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Impact of Prescription Drug Diversion Control Systems on Medical Practice and Patient Care

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PREFACE

In the spring of 1990, the White House Office of National Drug Control Policy (ONDCP) was evaluating the merits of the triplicate prescription system, already implemented in ten states, in an effort to determine whether ONDCP should encourage other states to develop similar prescription drug diversion control systems. In 1989, the previous administration had supported this method as a means to reduce prescription drug diversion. Hence, ONDCP sought the advice and counsel of both the Department of Health and Human Services (DHHS) and the Department of Justice regarding the relative risk and benefits of the triplicate prescription system. In May 1990, DHHS indicated that it could not support or recommend the use of such programs to states at that time since there was a paucity of research data on which to determine the risks, benefits, or superiority of any particular drug diversion control system. However, the Office of the Secretary instructed the National Institute on Drug Abuse (MDA) to immediately undertake an evaluation study of existing data on the relative merits and disadvantages of all existing drug diversion control methods and to submit their findings for deliberation at a subsequent technical review. In response, MDA, in collaboration with Brandeis University, undertook a review of available data on the effectiveness of existing drug diversion control systems and their impact on medical practice and patient care.

The specific objectives of this study were:

1. To identify and describe the most prominent diversion control systems currently in use at the State or Federal levels. The systems of control which are reviewed include:

- o Automated Reports and Consolidated Orders System
- o Drug Investigational Units
- o Electronic Point of Sale Systems
- o Medicaid Fraud and Abuse Systems

- o Multiple Copy Prescription Programs

- o Prescription Abuse Data Synthesis

2. To critique the existing literature on these systems to assess their impact on medical practice

3. To develop an assessment framework by proposing criteria by which the various systems can be examined within a system type and compared across different systems

4. To assess each diversion control system in terms of the proposed criteria

5. To review the concerns of groups impacted by and involved in drug diversion control

6. To evaluate the availability of data that could be used to carry out a rigorous evaluation of diversion control systems with particular emphasis on the impact on medical practice, and

7. To identify the gaps in our knowledge about diversion control systems and to propose one or more studies needed to fully analyze the impact of drug diversion control systems.

In planning for the Brandeis study, a preliminary literature search revealed a dearth of published scientific data on the effectiveness of the various drug diversion control systems in reducing prescription drug diversion or their relative cost or impact on medical practice and patient care. Nonetheless, reasonable people, using identical data bases, made sharply differing interpretations of the same data to argue for–or against–the magnitude of prescription drug diversion, the effectiveness of a particular drug diversion control system or the impact of these systems on medical practice and patient care. Likewise, definitions of drug abuse varied and often were ill defined. For example, some considered the use of psychoactive medications for unapproved indications or for chronic use a measure of drug abuse. Others included intentional use of psychoactive medicines in successful or unsuccessful suicide attempts as measure of prescription drug abuse. In view of the relatively small literature base and the lack of agreement regarding definitions and outcomes, a NIDA Technical Review was planned subsequent to the completion of the Brandeis evaluation study.

NIDA staff invited to the Technical Review relevant and knowledgeable people in medical therapeutics, law enforcement, State regulatory agencies, and representatives from professional associations and advocacy groups. We attempted to include many of those who had done research on therapeutic uses of drugs with an abuse potential, those known to represent a specific therapeutic bias or those supporting or opposing particular drug diversion control methods. Various presentations were made on the following six issues:

1. The medical usefulness of the four major classes of psychoactive therapeutic drugs for both FDA approved and unapproved uses

2. The nature, extent and consequences of prescription drug abuse and the relevant magnitude of the different sources of retail diversion

3. The advantages and limitations of existing drug diversion control systems

4. The impact of drug diversion control systems on medical practice and patient care

5. The findings from the Brandeis University evaluation of the scientific rigor of existing data supporting or refuting the cost and effectiveness of these various drug diversion control systems and their impact on medical practice and patient care

6. Areas needing additional research

There was an opportunity during the technical review for all participants to present their points of view and question the validity of each others data.

A special note of gratitude is made to Drs. Herbert Kleber and Daniel X. Freedman and Mr. Stanley Morris. Without the support and active participation of Dr. Kleber and Mr. Morris, this comprehensive review would not have been possible. Dr. Freedman's leadership at the Technical Review encouraged a candid and focused discussion among participants with disparate data, attitudes and beliefs.

This monograph contains most of the information presented at the technical review. Not all participants provided manuscripts for publication. Two major sections from the final Brandeis Report, which were presented at the Technical Review, are also included. The Summary of the MDA Technical Review attempts to incorporate the essence of the differing opinions exchanged during the open discussions between participants and the audience. The papers in the Abuse and Diversion Section illustrate the marked differences in data interpretation related to the nature and magnitude of prescription drug abuse and retail diversion. Likewise, the specific reasons for supporting or opposing a particular diversion control system(s) are made by the various enforcement and regulatory officials, professional associations and advocacy groups. The lack of consensus can in large part be attributed to the differences in perception of the nature, extent and consequences of prescription drug abuse and retail diversion, and the therapeutic usefulness of these various classes of psychoactive drugs.

Clearly there is no current consensus on the most appropriate design or methodologies for evaluating the impact of these various drug diversion control systems on drug abuse prevalence or on medical practice and patient care. Most studies have had serious weaknesses in design. Many fail to consider alternative factors that might affect abuse or prescribing practices. Likewise there was no consensus reached on defining accepted medical use, particularly as it relates to prescribing psychoactive medicines for unapproved indications or for long-term use. However, we now have a basis on which to design a research program to answer these questions. Furthermore, NIDA convened a research advisory panel to discuss design and methodological questions arising from the NIDA Technical Review and to recommend specific research priorities. The paper by Dr. Dorynne Czechowicz highlights the outcome of those discussions. NIDA encourages the submission of research projects in some of the identified research areas.

James R. Cooper, M.D., Editor

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The Impact of Prescription Drug Control Systems on Medical Practice and Patient Care: A Summary of the NIDA Technical Review

INTRODUCTION

In his opening remarks, the meeting chairman stressed this technical review was *not* a consensus conference. Rather, its objective was to enable the National Institute on Drug Abuse to meet its responsibilities in advising the Department of Health and Human Services of what is known–and not known –about prescription drug diversion control systems and their impact on medical practice and patient care. The Deputy Director for Demand Reduction in the Office of National Drug Control Policy (ONDCP) noted in his introductory remarks that arriving at a policy to control prescription drug diversion requires developing effective ways to prevent diversion while at the same time minimizing their impact on medical practice and patient care. The Deputy Director of ONDCP charged with drug supply reduction cited a "street price" of Dilaudid 40 to 50 times higher than its retail price as one indication of the success of prescription drug diversion control efforts, but urged the participants to give the topic their most serious consideration.

INTERNATIONAL TREATIES, FEDERAL AND STATE LAWS

An overview of international treaties, Federal and State laws, and regulations governing controlled psychoactive drugs prefaced the technical review. These treaties and laws are intended to ensure the continuing benefits of medical use of these drugs while minimizing their non-medical use. An underlying principle of international, Federal and State law is to limit drug production of these drugs to the amounts needed for medical and scientific purposes. However, in 1990, the World Health Organization's Expert Committee on Pain Relief expressed concern that improved methods for controlling inappropriate use not inhibit appropriate prescribing (WHO Expert Committee Report 1990). In developing federal drug control legislation, the congressional intent was also not to interfere with medical practice or to limit the medical purposes for which these drugs are to be used. Regulating medical practice is a responsibility reserved to the individual States. State

laws are usually based on the 1970 Uniform Controlled Substances Act (UCSA), a model law developed to provide a unified drug control policy. Because the 1970 UCSA failed to take into account the role of medicine and science in drug control decisions, new model legislation addressing this and other deficiencies was prepared in 1990.

State laws are often more restrictive and regulate practitioners in ways Federal legislation does not. For example, some States limit the number of dosage units of a drug that may be prescribed. Patients who have become physically dependent on medically justified prescribed drugs are also sometimes defined as "addicted" and must be reported to the State regulatory agency. In one State (South Carolina), prescribing controlled substances for other than FDA-approved purposes is restricted. State laws governing Multiple Copy Prescription Programs are also not based on the UCSA model.

PREVALENCE OF MEDICAL USE OF PSYCHOACTIVE DRUGS

Use of prescription psychoactive drugs within the general population was described (Balter 1991). Several national surveys of prescription drug use in the general population have been conducted. To date, these surveys have yielded a uniform conclusion: the vast majority of prescribed use of these drugs is conservative, therapeutically appropriate, and limited to short periods of time (<3 months). The usual source of medication (>95 percent) is through a physician's prescription; less than 5 percent of users obtained these drugs from a nonprescription source (usually a friend or relative). Consumer attitudes toward taking psychoactive prescription drugs are also conservative. Less than one third of a general population sample surveyed in 1990 were willing to use such drugs to offset a major emotional problem interfering with work, down from the 55 percent who indicated they would do so in 1970. There has also been a significant decline in use by those for whom use is medically appropriate. The overall conclusion drawn was that the benefit-to-risk ratio for these substances is positive with little epidemiological evidence that abusive use of prescribed medication is common. Populations taking prescribed psychoactive drugs show little overlap with abuser populations. Chronic medical use of prescribed psychoactive drugs rarely leads to addiction and addicts have significantly different characteristics from medical users.

THERAPEUTIC RATIONALE FOR USE

The treatment rationales for using analgesic, anxiolytic, hypnotic, and stimulant drugs were reviewed by medical experts in each drug area. An expert on pain relief discussed analgesics with primary emphasis on opioid drugs (Portenoy 1991). Despite an armamentarium of drugs that can provide adequate pain relief in 70 to 85 percent of cancer patients (Schug et al. 1990; Ventafridda et al. 1985, 1987), unrelieved pain continues to be common. Apart from truly refractory pain, this can be attributed to patient-related and clinician-related factors. Among the patient-related factors are inadequate symptom reporting because of stoicism, the belief that pain is inevitable, a desire to be liked (by medical staff), a fear of opiates, and the cost of drugs or other factors which limit their availability. Clinician-related factors include uncertainty about the appropriate role of opioid therapy and undertreatment. Undertreatment results from inadequate medical assessment, knowledge and skill deficiencies, overestimating the risk of using opiates, and the impact of drug regulations. The treatment of chronic pain is often a neglected topic; the standard therapeutic drug reference text, *Physicians' Desk Reference,* is notably deficient in addressing this problem.

Several examples were given of ways in which regulations can lead to undertreatment. These include prohibiting the use of stimulant drugs to offset the sedative effects of opiates, limiting amounts that can be prescribed in a single prescription or as an emergency supply, and the refusal of pharmacies to fill prescriptions that omit such minor details as the patient's age or ZIP code. Although little formal data can be cited, physicians are concerned about possible sanctions, peer pressure, being investigated for their prescribing habits and having these habits reviewed by regulators unfamiliar with current clinical practice. There is, the reviewer noted, a need to reassure clinicians that their appropriate use of multiple drugs, of opiates, of parenterally administered drugs, and escalating doses for prolonged periods will not result in their being investigated or having sanctions applied. Advances in the understanding of pain mechanisms and of improved pain management based on work with cancer patients also suggests the belief there is a high risk of addiction in the long term treatment of nonmalignant chronic pain is overstated. Several studies dealing with long-term use of analgesics have concluded that problems of toxicity or abuse of these drugs by chronic pain patients rarely occur (Chapman and Hill 1989; Kanner and Foley 1982; Perry and Heidrich 1982; Porter and Jick, 1980). Although the potential risk of addiction resulting from medical treatment is probably exaggerated, it is a medical issue which should be carefully considered when prescribing for pa-

tients with a history of drug dependence. However, since these patients also need appropriate pain management, a balance must be struck between the need to control pain as well as to avoid possible drug abuse. The need for better communication between physicians and regulators was stressed by this speaker and several other conference participants.

Two physicians reviewed the role of anxiolytic drugs in current medical practice with particular emphasis on the benzodiazepines (Rickels 1991; Salzman 1991). Among the many clinical indications for employing such drugs are status epilepticus, movement disorders, as muscle relaxants, for physical injury or trauma, as preanesthetic agents or as anesthetic adjuncts (to reduce the need for less safe agents), for transient, and short- and long-term treatment of anxiety, and for panic disorders. The treatment of panic disorder is particularly important since panic disorder is the second leading cause of suicide and failure to control its symptoms can seriously increase the risk of suicide. Since anxiety is common in many physical illnesses and occurs in response to many acute life stresses, benzodiazepines play an important role in modern therapeutics. Their relative safety, low abuse potential, and effectiveness must be balanced, however, against possible adverse effects on memory, tolerance development, possible cumulative toxicity (especially in the elderly), and, when use is discontinued, withdrawal symptoms and the return of the original symptoms in more severe form (symptom rebound). Withdrawal is affected both by pharmacologic characteristics of the drugs used (e.g., their half life) as well as patient characteristics such as concurrent alcohol or other drug abuse, psychiatric and medical comorbidity, personality, and diagnosis. The rate at which doses are reduced when treatment is discontinued also affects the severity of withdrawal. The use of benzodiazepines for treating older patients with chronic illnesses accompanied by anxiety, pain, and sleep disturbance is well established (Rickels 1991). Since these patients rarely abuse these medications or escalate their doses, benefits significantly exceed the risks. In treating panic disorders and agoraphobia, the benefit-to-risk ratio is somewhat less favorable since these disorders often require higher drug doses, and relapse or symptom rebound often occurs following termination of treatment. For patients with dysphoria or personality disorders, benzociiazepines offer sporadic relief although the benefit-to-risk ratio is less favorable since these patients may escalate doses, self-medicate, or abuse these drugs. With two other groups, patients with psychoses or chronic sleep disturbances, the risks outweigh the benefits and use probably should be avoided. There is little evidence that benzodiazepines are effective for these problems.

Overall, there is little question that benzodiazepines are therapeutically useful, especially for the short-term treatment of a range of disorders in which anxiety plays a role. Questions regarding the differences among the benzodiazepines and the possibility that high-potency and short-acting benzodiazepines pose greater withdrawal and dependency risks need to be studied. The implications of more stringent regulation of these medications on medical practice and patient care should also be examined, the reviewers concluded.

The review of hypnotics (Greenblatt 1991) also emphasized that epidemiological data do not suggest we are an overmedicated society. In the past decade, a range of shorter half-life hypnotic medications have been developed, providing physicians with a wider range of therapeutic alternatives. Some of the newer drugs are less likely to result in daytime sedation and impaired performance, although they may affect memory and lose their effectiveness more quickly. A third of Americans suffer from insomnia; about one in six can be classified as having a serious sleep disorder. The use of hypnotics for treating either transient or short-term insomnia (i.e., sleeplessness lasting as long as a few weeks) is clearly justified, although treating chronic insomnia (lasting months) is not. Both animal data and clinical observation suggest the efficacy of hypnotics diminishes over time and that rebound and withdrawal effects are common.

The therapeutic rationale for the use of stimulants was described by a psychiatrist experienced in this area (Cole 1991). Because of the "speed" epidemic of the mid-1960s and later concern about stimulant abuses in weight reduction programs, strict controls and intensive prescriber education were instituted. Most stimulant abuse now involves illicitly manufactured methamphetamine, not licit stimulants. The therapeutic use of these drugs for all but attention-deficit hyperactivity disorder (ADHD) in children and narcolepsy has come to be regarded as questionable. This may represent an overreaction since there is a body of clinical opinion, confirmed by physician surveys, suggesting stimulants are selectively useful for treating adult residuals of ADHD, chronic fatigue, treatment-resistant depression, AIDS-related brain dysfunction, idiopathic hypersomnia, and chronic pain (adjunctive use with analgesics to counteract their sedative effects). A review of 28 long-term patients (with from 1 to 27 years of prescribed use) who were judged to derive substantial benefit from stimulant maintenance therapy was described (Cole 1991). Fifteen had received the drug for depression, five for attention deficit disorder, three to suppress bulimia, two for fatigue, two for idiopathic hypersomnia, and one for panic disorder. These 28 patients maintained a

stable response without developing either tolerance or evidence of drug abuse.

During the ensuing discussion of the papers addressing the therapeutic uses of analgesic, anxiolytic, hypnotic and stimulant drugs, it was noted that the benefit-to-risk paradigm is a useful framework for thinking about these medications. The danger of confounding drug abusing populations with clinical populations for whom psychoactive drugs are prescribed for therapeutic purposes was reiterated. For example, only 4 out of a recent sample of 11,882 patients who received morphine therapeutically became addicted (Chapman and Hill 1989). Other studies also support this observation (Kanner and Foley 1982; Perry and Heidrich 1982; Porter and Jick, 1980).

Other salient points were made. The rate of use of a drug is a poor index of risk; the appropriateness of its medical use is a more relevant criterion. Another relevant aspect is the limited attractiveness of psychoactive prescription drugs to abusers. Most psychotherapeutic drugs are not highly sought after by addicts. Psychoactive prescription drugs are rarely "starter" drugs. In a Baltimore study of addicts (Nurco and Balter. 1990), the average age for beginning use of these drugs (if they were used) was over 18 compared to age 15 or younger for the initial use of alcohol, inhalants, and marijuana. There was also little evidence of their compulsive use and they were used infrequently compared to other, more preferred drugs of abuse. It was argued that the burden of proof should be upon regulators to demonstrate a need for regulation rather than upon practitioners to prove further controls are not needed.

Concern was also expressed that patient complaints that lack a visible physical basis are less likely to be taken seriously. The psychic pain of anxiety disorders as well as chronic pain associated with nonmalignant disorders is sometimes trivialized. However, adequate treatment of patients experiencing chronic pain can markedly improve their quality of life.

ABUSE AND ASSOCIATED CONSEQUENCES

Relevant data derived from NIDA's National Household Survey on Drug Abuse were summarized (Adams 1991). Among 18- to 25-year olds, the age range for peak drug abuse, 3.6 to 3.9 percent of those surveyed acknowledged having used nonprescribed stimulants, sedatives and tranquilizers in the month preceding the 1990 survey. By contrast, 12.7 percent of this age group

had used marijuana in the month preceding the survey and 14.7 of this age group acknowledged current use of any illicit drug.

The Drug Abuse Warning Network (DAWN), which tracks drug-related emergency room episodes, found a decrease of 20 percent in the number of reported episodes involving controlled prescription drugs between 1985 and 1989. There is little evidence of a causal relationship between the extent of drug diversion and changes in DAWN data. Moreover, the extent to which emergency room episodes are related to drug diversion is also unclear. In half the incidents reported, the source of the prescription drug was not noted. Another limitation is that suicide attempts, accounting for a large percentage of the DAWN-reported incidents, are not an indicator of drug diversion since most of these suicide attempts involved prescribed medications. DAWN is also a poor indicator of prescribed drug abuse since it provides no indication of the proportion of those receiving prescribed drugs who experience adverse consequences from their use. An unknown percentage of patients tracked by the DAWN system are likely to be "repeaters," not new cases. These limitations, some participants noted, render DAWN data of still less value for establishing the extent of prescription drug diversion.

Other conference participants, in their roles as prescription drug diversion regulators, stressed that control systems have had a positive impact on medical practice and patient care by reducing irresponsible prescribing (e.g., by establishing minimum standards for patient care) and by limiting the availability of dangerous drugs (Haislip 1991). Examples cited included sharply restricting amphetamines and methaqualone when they were being prescribed in "obesity and stress clinics" in excess of any legitimate medical need. The decrease in DAWN mentions involving prescription psychoactive drugs, it was argued, is one piece of evidence suggesting that improved control methods are reducing drug diversion. Despite this reduction, regulators maintained that the continued diversion of licit drugs into the illicit drug traffic is a major component of the national drug abuse problem. The fact that one in three DAWN emergency room mentions in 1990 was for a licitly manufactured drug was offered as one indication of this (Haislip 1991). While restrictions on prescribing have allegedly been detrimental to pain control, regulators noted that the quotas for narcotic production, have been steadily increased (e.g., morphine by 400 percent) over the past decade. Diversion control continues to be important since even a small number of prescription drug diverters can flood a community with hazardous drugs. Examples of this were cited (Haislip 1991).

During an ensuing discussion, participants pointed out that changing trends in psychoactive drug prescribing reflect many factors other than the impact of regulatory changes. Prescribing practices are significantly altered by physician education, the introduction of new drugs, and by programs such as cancer pain initiatives, which result in more appropriate patient care. The sheer number of prescriptions for a drug provides no evidence that it is being used inappropriately. Similarly, decreased prescribing of a specific drug may be the result of substituting other drugs rather than of improved treatment standards.

METHODS FOR IDENTIFYING DRUG DIVERSION

Methods for identifying drug diversion, their strengths and limitations, were also described. The many ways in which individuals fraudulently obtain drugs at the retail level were also described.

ARCOS

ARCOS–the Automation of Reports and Consolidated Order Systems–is a Drug Enforcement Administration data base auditing Schedule II controlled drug transactions at the manufacturing and wholesale distribution level. ARCOS can be used to identify geographic areas in which diversion is occurring and the drugs involved. It is federally run and causes minimal interference with medical practice since no patient or physician data are collected (unless the practitioner obtains drugs wholesale). It has reduced wholesale drug diversion to the point that most diversion is now at the retail level which is not directly monitored by ARCOS (Gitchel 1991).

Drug Investigational Units (DIUs)

DIUs were State units set up with Federal aid (from 1972 to the early 1980s) to assist in controlling Schedule II drug diversion. DIUs brought together individuals and agencies with a shared concern about retail drug diversion in order to facilitate more effective investigation of the problem. The units were often successful in improving drug diversion control and some DIUs were continued even after Federal support for them ended. Their major drawback is that labor intensive surveys and pharmacy audits are still required to obtain needed evidence to pursue criminal prosecutions (Bulla 1991).

PADS

The Prescription Abuse Data System (PADS) was a system of drug control developed at the State level with the assistance of the American Medical Association. The objective was to integrate State data bases to better target diversion. State agencies and private organizations, aided by a consultant provided by the AMA, formed a task force consisting of technical, regulatory/enforcement, and professional association components. This task force then made recommendations to a State PADS policy group to improve diversion control and professional education. Although a systematic evaluation of their effectiveness has not been done, PADS had the advantage of acting as a catalyst to encourage regulatory and professional groups to work together more effectively. PADS II was an AMA computer-based initiative to assist states in identifying high prescribers reimbursed under the Medicaid program, but was never implemented (Ambre, 1991a).

MEDICAID

Medicaid drug diversion control software to assist States in auditing their Medicaid system was also developed by the Office of the Inspector General of the Department of Health and Human Services and is now used in 18 states. It analyzes physicians' drug prescribing, pharmacies' dispensing, and patients' drug use whenever Medicaid reimbursement is involved and identifies statistically exceptional prescription drug patterns, which may justify further scrutiny (Roslewicz 1991).

An Electronic Point of Sale System–OSTAR

The electronic point of sale system is the newest of the drug diversion control systems and has just been implemented in Oklahoma under the acronym OSTAR (Oklahoma Schedule Two Abuse Reduction). OSTAR requires pharmacists to submit basic information concerning patients and the Schedule II drug prescriptions they have filled by electronic means or, alternatively, using a Universal Claim Form. Patients are identified by their drivers' license numbers. Problems of confidentiality have not arisen in the first several months of operation. The data being collected were previously available to investigators (by auditing pharmacy records), but are now much more easily obtained. Information is carefully restricted and only divulged in criminal cases. Any other uses of the data are subject to severe penalties. OSTAR was described as a fast, accurate tracking system for Schedule II prescriptions. During its first several months of operation, the State Medical

Association reported no physician complaints about OSTAR or any reports it had negative effects on medical practice. However, no formal evaluation has been conducted (Dodd 1991).

Multiple Copy Prescription Programs (MCCP)

Ten states (California, Hawaii, Idaho, Illinois, Indiana, Michigan New York, Rhode Island, Texas, and Washington) currently operate multiple copy prescription programs. The first MCPP was initiated in California in 1939. The systems of Illinois, New York, and Washington State were described by representatives of each (Bishop 1991; Eadie 1991; Williams 1991). The Illinois program is unique in being housed in the Department of Alcoholism and Substance Abuse rather than in a law enforcement or medical setting. Washington State's system requires triplicate forms be used only by practitioners who have been previously disciplined for their prescribing behavior.

The various drug control systems were also compared by a representative of the Bigel Institute for Health Policy at Brandeis University (Horgan 1991). This group has prepared a report reviewing prescription control methods for NIDA (Horgan et al. 1991). The report is based on a literature review and interviews with individuals involved with the various systems. The Bigel Institute systematically reviewed all currently used systems, including MCPPs, and the relevant literature, although no new data comparing the systems was collected. Most MCPPs share the advantages of simultaneously targeting physicians, pharmacies, and patients, and of including all population groups in the State. Their disadvantages include extra work for practitioners as well as dispensers, the fact that not all psychoactive medications can be tracked (e.g., some substituted drugs may not be included) and that MCPPs require labor-intensive data entry. State MCPPs vary widely in the agencies and licensing boards involved and in how well they cooperate with each other and with law enforcement agencies. These systems are, however, not static. The timeliness of their data can be improved as can the cooperation between professional associations and law enforcement agencies. Increased involvement of practitioner organizations can also lead to a greater emphasis on professional education to reduce diversion and more effective use of peer review methods.

POSITIONS OF PROFESSIONAL ORGANIZATIONS

Seven participants presented the positions of their respective professional associations. These included the American Medical Association (Ambre, 1991b), the American Nurses' Association (Naegle 1991), the American Pharmaceutical Association (Webb 1991), the American Psychiatric Association (Peele 1991), the American Society of Addiction Medicine (Geller 1991), the American Academy of Child and Adolescent Psychiatry (Rock 1991), and the Empire State Medical Association of the National Medical Association (Deas 1991). The first six generally oppose a Federal MCPP because of its possible effects on professional practice, concerns about confidentiality, the lack of convincing evidence of need, and/or because the proposed system either duplicates existing systems or is not state-of-the-art. As a group, the professional associations' representatives stressed the importance of professional education in preventing diversion and inappropriate prescribing and the need to focus primarily on impaired practitioners and those few dishonest or incompetent practitioners who require serious intervention and sanctions. Concern was expressed about regulators monitoring medical practice arbitrarily because of a lack of adequate understanding of current clinical practice. The professional association representatives emphasized treatment decisions should be made by qualified practitioners, not by regulatory agencies. The American Nurses' Association's representative expressed special concern about the possible impact of the proposed system on prescribing by nurse-practitioners working in medically underserved areas. The Federal triplicate prescription system may have a deleterious effect on the treatment of the patients whom nurse-practitioners serve. The Empire State Medical Association representative discussed the danger of attention being diverted by the drug control issue from more fundamental concerns about medical care for the poor. These include providing adequate medical aid for inner city residents, dealing with their sense of hopelessness, and not relying on band aid solutions to respond to such fundamental problems as lack of access to medical care and the wide disparities in the care the poor receive. He stressed the Empire State Medical Association's position that New York State's triplicate prescription program has produced a dramatic decline in the illicit diversion of prescription drugs, concluding that its overall impact on medical practice was positive.

ADVOCACY GROUP POSITIONS

Representatives of the American Narcolepsy Association, Wisconsin Cancer Pain Initiative, and the Public Citizen Health Research Group discussed the positions of their groups as well. A treatment program perspective was provided by a medical director from one of the programs.

The representative of the Narcolepsy Association described the nature of narcolepsy, pointing out that as many as 375,000 persons may suffer from this disorder, although only 50,000 have actually been diagnosed and are being treated (Piscopo 1991). Since the disorder is incurable, stimulant drugs are required on a lifetime basis. Present regulations sometimes result in patients having difficulty in finding a physician willing to prescribe stimulants and may result in the investigation of prescribers, pharmacists, and patients for "inappropriate" prescribing, dispensing, or use. Restrictions on the quantities that can be prescribed and a low priority on ensuring an adequate supply has also sometimes made these essential medications hard to obtain. The Chairperson of the Wisconsin Pain Initiative emphasized that group's concern about inadequate treatment of cancer pain (Dahl 1991). "Opiophobia" on the part of patients, their families, and the physicians who treat them often interferes with adequate pain relief. This can lead to serious impairment in patients' quality of life, a more rapid disease progression, and to higher medical costs. She concluded that there is a need to educate all concerned groups, to examine whether better prescription drug diversion monitoring systems are really needed, and to determine the potential impact of those systems on patient care.

The medical director of a private alcohol and drug treatment program expressed concern that the benzodiazepines can produce dependence even when used in the recommended dosages and that the effects of aging on drug response are not taken into account by many practitioners (O'Connor 1991). Benzodiazepine dependence can also complicate other substance abuse problems such as alcoholism. Withdrawal from benzodiazepines can lead to difficulties in cognitive functioning, memory difficulties, feelings of depersonalization, psychosis, tremors, insomnia, and other symptoms which contribute to their continued use. The combined abuse of alcohol and benzodiazepines is not an uncommon problem in his facility. He was in favor of triplicate prescription programs because he believes they serve as a deterrent to excessive and inappropriate prescribing of these drugs.

The physician representing the Public Citizen Health Research Group indicated they strongly support a Federal triplicate prescription program to curb 1) drug diversion through "pill mills" that indiscriminately prescribe psychoactive drugs, 2) inappropriate long term use of benzodiazepines, and 3) the prescribing of these drugs to cope with everyday problems for which their use is medically inappropriate (Wolfe 1991). While developing practice parameters is desirable, it is not enough to deter use. He felt the evidence that regulations interfere with appropriate prescribing is poorly founded. With respect to patient confidentiality, he pointed out, there is no evidence that pharmacists have breached confidentiality and little reason to believe law enforcement personnel are more likely to do so.

IMPACT OF MULTIPLE COPY PRESCRIPTION SYSTEMS ON MEDICAL PRACTICE AND PATIENT CARE

On the final day of the 3-day conference, several participants evaluated the impact of the triplicate prescription system on medical practice and patient care, particularly in New York State where data are available on physicians' prescribing behavior both before and after benzodiazepines were added to the State's triplicate prescription program on January 1, 1989.

The director of the New York State system emphasized the following:

- Data on triplicate prescribing is accorded the highest degree of medical confidentiality.
- There is no evidence that the triplicate prescription requirement has adversely affected medical practice.
- Although fewer benzodiazepine prescriptions are now being written, for every 100 fewer prescriptions, only 10 new prescriptions have been written for other drugs (Eadie 1991).

Overall, he noted, the data suggests that physicians may be exercising greater discretion in prescribing benzodiazepines. The widely publicized myth that New York State requires patients to be seen every 30 days if they are receiving a Schedule II drug is not true, he also stressed. A patient should be seen prior to initially receiving a triplicate prescription, but after that, it is up to the individual physician to determine how often the patient is seen.

A physician from the Department of Community and Preventive Medicine at the University of Rochester interpreted the New York data somewhat differently (Weintraub 1991). In January 1989, the first month of the

triplicate requirement for benzodiazepines, there was an overall decrease of 44 percent in the number of prescriptions written for the drug. A similar, although smaller, decline (30 percent) was noted by the Blue Cross/Blue Shield program. There was also an increase in the use of alternative drugs. For example, the prescribing of meprobamate, a nonbenzodiazepine antianxiety agent, more than doubled in New York following the change in regulations, although it decreased nationwide. However, the increase in alternative prescriptions in no way compensated for the decrease in benzodiazepine prescribing. An attempt was also made to relate the decrease in benzodiazepine prescribing to a change in the hip fracture rate, but the results were inconclusive because of the small numbers involved. There is, this speaker pointed out, professional concern about adding the benzodiazepines to the triplicate prescription system, since it is still unclear what the public health implications of doing so are. He concluded that more research is needed.

The impact of triplicate prescriptions in New York was also examined in a nursing home population (Gengo 1991). The records of 1,200 nursing home residents were examined. Of the 170 patients who had been taking benzodiazepines 6 months before the change, 62 were taken off the drug. Their doses were typically not gradually reduced and withdrawal symptoms were recorded for nearly a quarter of these patients within 1 week of stopping use. More than half were changed to other medications and most of the substitute drugs were regarded as less safe and effective than the medications they replaced.

Data from New York State also indicates that the use of hypnotics declined following the introduction of the triplicate prescription system. This may indicate a reduction in their appropriate medical use and possible inappropriate use of alternative drugs (Greenblatt 1991).

In Rhode Island, a multiple copy prescription program has existed since 1979 although it is limited to Schedule II drugs. In that State, if a practitioner makes the "top 5" in prescribing these drugs, a utilization review is undertaken by a three-member physician review group. An oncologist so classified would be unlikely to create concern; a family practitioner in the "top 5" prescribers is likely to be more carefully scrutinized. A survey of 3,000 Rhode Island practitioners (MDs, DDSs, DVMs) was conducted; 22.2 percent of those contacted responded to the written questionnaire (80 percent were physicians). Nearly two-thirds of the respondents (64.1 percent) agreed that the law reduced abuse and that it reduced prescription forgeries (62.4

percent). Three out of four (74 percent) reported no problem with patients getting their prescriptions filled. Over half (53.4 percent) reported they would not choose an alternative drug if a Schedule II drug was needed, although a third (32.8%) said they would (Campbell 1991).

LIMITATIONS OF EXISTING RESEARCH

A deputy director of the NIDA-sponsored review of prescription drug diversion control systems discussed the limitations of existing research in determining the extent to which drug diversion is controlled, at what cost, and with what impact on prescribing (Prottas 1991). His conclusion was that most of the studies have had serious weaknesses, asked the wrong questions, or failed to consider alternative factors impacting on prescribing. He noted that this is a new area of inquiry, one characterized by strongly partisan feelings. There is no consensus for operationalizing concepts or methodology. Most of the data available concerns MCPPs; much less with other drug diversion control programs. The MCPP data is, however, difficult to interpret. For example, attempts to evaluate MCPPs in terms of the number of disciplinary actions before and after introduction or changes in these systems ignore the deterrent effect of these systems on inappropriate prescribing. It is also difficult to know what level of disciplinary action is justified. The number of physicians ordering forms, especially at intermediate levels, is also hard to interpret. Street prices of prescribed drugs vary in response to multiple factors, making it difficult to tease out the effects of regulation. Epidemiological studies involving the DAWN system have serious shortcomings. The data are many steps removed from the impact of any specific drug diversion control program, making any connections obscure. The meaning of decreases or changes in prescription patterns is also difficult to interpret. While effects on drug substitution are important, studies of this aspect are methodologically inadequate in that only a limited data analysis has been done. In the absence of clinical information, it is difficult to know whether changes that resulted were desirable or not. In short, both the quantification and the trade-offs involved in drug diversion control are uncertain. Finally, the existing literature does not deal with the mechanisms involved in changes in drug prescribing, an important issue if the impact of regulatory changes is to be gauged.

During a discussion following these presentations, several points were made. A more adequate inventory and analysis of State laws would be useful, particularly if it included clear descriptions of the ways in which the various systems actually work, who reviews prescribing practices, and the criteria

employed in doing so. A level of analysis which includes the patient and his or her clinical diagnosis and medical history would be desirable. The lack of adequate clinical data on which to draw conclusions about the impact of diversion control systems on clinical practice is a serious deficiency.

NEEDED RESEARCH

The final afternoon was devoted to describing a needed research agenda based upon the Bigel Institute's review of the area (Tompkins 1991) and comments from the meeting participants during a general discussion. Further research was urged in order to better specify ongoing diversion control activities, to consider the possible outcomes from multiple perspectives, and to get beyond the limitations of anecdotal and impressionistic reports. The data on the magnitude of diversion is neither very good nor recent, and many of the underlying assumptions can be questioned (e.g., the source of street drugs may be diversion, but it can also be illegal importation or illegal manufacture). Trade-offs involve both positive and negative aspects. These include not only minimizing diversion, but the costs of doing so both in financial terms and in terms of medical and social consequences of the systems employed. The reviewer emphasized that "settling debates regarding the pros and cons of diversion systems [will] require something beyond aggregate, proxy variables." Researchers need to specify dependent variables that accurately reflect the concepts of both medical diversion and acceptable medical practice. Empirical findings can confirm or refute specific hypotheses with respect to diversion reduction or to the patterns of medical practice that are associated with alternative control systems.

In the concluding discussion, several points were raised. A former regulator said Wisconsin crime lab exhibits have been found to be a useful measure of drug diversion trends. Other participants pointed out that crime lab data are affected by changing enforcement patterns and only imperfectly reflect actual prescription drug diversion patterns. The need for a well-thought out set of indicators that includes patient care and a more detailed exploration of the basis for physicians' therapeutic decision-making was repeatedly emphasized. It may be desirable to devise some form of composite prescription drug diversion control system rather than limiting choices to the currently available alternatives.

In discussing the various control systems, several other major points were made by participants. There was some agreement that policy must be made despite the absence of adequate relevant data. There is no question that a

drug diversion problem exists, although the indicators of its seriousness and sources are imprecise and sometimes difficult to interpret. Similarly, there is little question that drug diversion control systems have impact on medical practice, although the extent of that impact is also difficult to determine. Although anecdotal accounts can be cited in defense of one or another diversion control position, definitive data do not presently exist.

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Guiding Principles of International and Federal Laws Pertaining to Medical Use and Diversion of Controlled Substances

David E. Joranson

INTRODUCTION

The title of this technical review, "Evaluation of the Impact of Prescription Drug Diversion Control Systems on Medical Practice and Patient Care: Possible Implications for Future Research," poses the question of whether efforts to reduce diversion of therapeutically useful controlled substances interfere with their appropriate medical use in patient care.

This paper will examine several sets of laws that shape public policy in this critical area. These laws create and limit the authority of government to (a) regulate medical practice, (b) make drugs available for medical use, and (c) control drug abuse and diversion. Developed over decades of democratic process, these laws establish the legal principles that determine the desirable relationship between control of drug diversion and the use of drugs in medical practice and patient care.

At the outset, it should be recalled that the use of controlled substances has an indispensable beneficial effect on public health. When controlled substances are used for legitimate medical purposes, they improve the quality of life for millions of Americans with debilitating diseases and conditions. However, when controlled substances are diverted from the legitimate distribution system, their abuse can lead to serious public health problems. Consequently, it is in the interest of public health to (a) promote and protect the appropriate medical and scientific uses of controlled substances, and (b) prevent their diversion and abuse. As will be seen, the laws of the United States direct that efforts by government to control drug abuse should not interfere with the legitimate practice of medicine or the availability of controlled substances for patient care. Achieving both purposes under the law will be referred to as "balance" (Joranson and Dahl 1990).

LAWS RELATING TO MEDICAL PRACTICE, DRUG AVAILABILITY, AND DIVERSION

Three classes of separate but related law establish a hierarchy of policy that governs medical use, drug availability, and diversion of controlled substances. The most fundamental of these laws will be discussed first.

State Law Regulates Medical Practice

The terms "medical practice" or "practice of medicine" as used in this paper refer to legitimate medical activities that involve the diagnosis and treatment of disease within a bona fide physician-patient relationship. These activities include medical decisions such as choice of therapy, choice of drug(s), amount prescribed, directions for use, and duration of therapy.

The professional practice of medicine is a privilege granted by law in each of the 50 State legislatures (Federation of State Medical Boards 1988). A physician's legal ability to prescribe drugs that are controlled substances depends on having a license to practice medicine, but also requires a separate Federal, and in some jurisdictions a State, controlled substances registration. State licensing and disciplinary boards administer the medical practice laws and have the principal governmental responsibility to protect the public health from improper, incompetent, and unlawful practices. Medical boards define activities that constitute unprofessional conduct, including prescribing controlled substances for purposes outside of the legitimate practice of medicine.

Federal Law Approves Drugs for Medical Use

The Federal Food, Drug, and Cosmetic Act (FFDCA) is a Federal law that approves drugs for commercial marketing and medical use in the United States. This approval concludes an often lengthy process of testing to determine that a drug is effective for use in treatment of a medical condition and that it is safe to use in a human population. FFDCA drugs are available only by prescription and include the stimulants, sedative/hypnotics, hallucinogens, and opioids. These particular drugs have an abuse liability because they can produce physical and psychological dependence. Consequently, they are also subject to controlled substances law.

The following elements of the FFDCA determine the relationship between the Federal government and medical practice, and define the basic

parameters of how an FFDCA drug may be used by individuals who have been licensed by the States to practice medicine.

FDA Does Not Regulate Medical Practice

Although drugs are made available under the FFDCA for use in medical practice, the Food and Drug Administration (FDA) has repeatedly determined that neither the FDA nor Congress regulates medical practice "as between the physician and patient" (Federal Register 1972). FDA policy is that good medical practice and patient interest require that physicians be free to use drugs according to their best knowledge and judgment (Federal Register 1975). The Federal courts have supported the principle that FDA does not regulate medical practice (U.S. vs. Evers 1981).

FDA Does Not Restrict "Off-label" Uses

The foreword to the *Physician's Desk Reference* recognizes that the FFDCA does not limit the manner in which a physician may use an approved drug. Once a product has been approved under the FFDCA for marketing, a physician may prescribe it (although it may not be advertised or promoted) for uses or in treatment regimens or patient populations that are not included in the approved labeling (Federal Register 1983).

> New uses for drugs are often discovered, reported in medical journals and at medical meetings, and subsequently may be widely used by the medical profession.... When physicians go beyond the directions given in the package insert it does not mean they are acting illegally or unethically, and Congress does not intend to empower the FDA to interfere with medical practice by limiting the ability of physicians to prescribe according to their best judgment. (U.S. vs. Evers 1981)

LAWS THAT ESTABLISH DRUG DIVERSION POLICY

Three tiers of law establish policy on diversion of therapeutic drugs to nonmedical uses.

International treaties

Treaties establish the legal framework for control of international and domestic production and distribution of drugs that have an abuse liability. The principal treaties are the Single Convention on Narcotic Drugs, 1961, and the 1971 Convention on Psychotropic Substances. As a party to a treaty, a government agrees to adopt domestic laws that carry out the provisions of the treaty. Both treaties clearly recognize that many drugs with abuse liability are indispensable to the public health and that their availability for legitimate medical and scientific purposes must be ensured.

Two agencies of the United Nations have expressed concern about the effect of a country's drug laws on availability of drugs for medical purposes. The International Narcotics Control Board (INCB), the agency of the United Nations that is responsible for monitoring governments' implementation of the treaties, has concluded that opioids are not sufficiently available for legitimate medical purposes throughout the world (INCB 1989). A number of important economic and social factors are responsible, including antidrug abuse laws and regulations that unduly restrict the availability of opioids for medical use. The INCB recommended that individual governments identify these factors and take corrective action.

A World Health Organization (WHO) Expert Committee has observed that concern about drug abuse has curtailed appropriate medical use of opioids for the treatment of pain (WHO, 1990). In discussing regulatory impediments, the Expert Committee expressed concern that the legal framework adopted by individual governments may govern prescribing so strictly as to impede the proper medical use of opioids.

Federal Controlled Substances Act

While the FFDCA establishes national policy for availability of drugs for medical purposes, the Federal Controlled Substances Act (CSA) establishes a security system to prevent these drugs from being diverted from the legitimate distribution system. Congress designed the CSA with the intent that efforts by the Federal government to control diversion should not interfere with medical practice or supersede FFDCA authority over availability of approved drugs for patient care (U.S. House of Representatives 1970).

The Congress adopted the following laws in order to achieve a balanced approach to national antidrug abuse policy:

1. The CSA clearly recognizes the public health value of controlled substances. Many controlled substances are necessary to the public health. (21 U.S. Code, Section 801)

2. The CSA does not interfere with the practice of medicine.

This policy is implemented in several significant ways:

a. The authority of law enforcement to regulate controlled substances depends on scientific and medical determinations.

1) Under the CSA the Attorney General (AG) must, before initiating any proceeding to control a drug in the schedules of the CSA, request a scientific and medical evaluation of the drug from the Secretary of the Department of Health and Human Services, along with a recommendation as to whether the drug should be controlled. Congress determined in 1970 that the recommendation of the Secretary is binding on the Attorney General in regard to scientific and medical matters, as is a recommendation by the Secretary that a drug not be controlled. (21 U.S. Code, Section 811-(b))

2) The authority of the AG to register practitioners to prescribe and dispense controlled substances depends upon prior licensing of a practitioner by State boards. With the exception of limitations on refills, the CSA does not regulate medical decisions such as the choice of drug, the prescription or the duration of therapy.

3) The authority of the AG does not extend to the routine review and monitoring of physician prescribing. Under the CSA, prescribers are not required to maintain prescribing records. (21 U.S. Code, Section 827 (c))

4) The CSA also provides joint authority for registration and revocation of practitioners who dispense narcotic drugs for maintenance or detoxification treatment of narcotic addicts. While the Attorney General must register an applicant, the Secretary must first determine that the applicant is qualified

and will comply with treatment standards. (21 U.S. Code, Section 823 (g))

5) The authority of the AG to investigate practitioners diversion is directed exclusively at the non-medical use of controlled substances.

Under the CSA, it is unlawful for a practitioner to prescribe or dispense a controlled substance except in the course of professional practice. The term "in the course of professional practice" defines the boundaries of practitioner investigations and prosecutions for DEA. According to the DEA, acts of prescribing or dispensing of controlled substances which are done within the course of the registrant's professional practice are, for purposes of the Controlled Substances Act, lawful. It matters not that such acts might constitute terrible medicine or malpractice. They may reflect the grossest form of medical misconduct or negligence. They are nevertheless legal. On the other hand, any act of prescribing, dispensing or distributing of a controlled substance other than in the course of the registrant's professional practice is an illegal distribution of that controlled substance, subject to the same penalties as if the drug were sold by the lowest pusher on the street. (Stone 1983)

The Congress created a "closed distribution system" to help DEA identify individuals who divert controlled substances to nonmedical uses. It should be noted that this system authorized the Federal government to monitor distribution only to the retail level, just short of where the physician-patient relationship begins. The system consists of registration of all handlers of controlled substances, order forms, record keeping, security requirements and penalties for unlawful activities.

A computerized information system tracks distribution of many controlled substances to the retail level and allows identification of unusual patterns of use which may, upon audit of required records, be found to involve diversion. These tools are intended to provide the Federal government with the information to detect leaks from the drug distribution pipeline into the illicit market, and the authority to hold individual registrants responsible for diversion.

Amendments to the CSA have strengthened the information available to detect diversion. In 1980, Congress said that it "believes that through vigorous and imaginative use of the ARCOS system, in conjunction with other

drug diversion/abuse indicators such as DAWN, retail diversion activities can be identified and the individuals involved apprehended and prosecuted." (Infant Formula Act 1980)

In 1984, the Attorney General was given additional authority to deny practitioner registrations in the public interest, "to work with the States, which license and regulate physicians," to assess State diversion control capabilities, provide advice on how to strengthen controls against diversion, and establish cooperative investigations. (Dangerous Drug Diversion Control Act 1984)

The CSA is not intended to interfere with patient care or confidentiality. Patients, the last link in the distribution chain, are defined as "ultimate users" under the CSA, and are recognized as being lawfully in possession of controlled substances (21 U.S. Code, Section 801 (26)). Ultimate users are not regulated parties under the CSA and are not intended to be objects of diversion monitoring systems.

Congress also recognized the importance of patient confidentiality. Under Federal laws, patient identity may not be released to the Attorney General in cases where a Federal agency or a State or local government has acted to protect confidentiality (21 U.S. Code, Section 873 (b)).

Under the CSA, it is outside of the professional practice of medicine (and, therefore unlawful) for a physician to prescribe a narcotic drug to maintain an addict, unless the physician is separately registered to treat addiction. Congress defined "addict" as a person who is a danger to society. Thus, "addict" does not include a patient who is simply being treated with a controlled substance. This is the case even though the patient may be physically dependent on an opioid analgesic as a result of medical treatment for pain, a situation that can be mistaken for "addiction." DEA regulations and publications make it clear that a physician who prescribes opioids to treat intractable pain over extended periods is considered to be acting within the professional practice of medicine. (Code of Federal Regulations, DEA Physician's Manual)

The CSA is not intended to interfere with the availability of FDCA drugs for patient care.

The CSA authorizes the Attorney General to set an annual production quota for Schedule II drugs, including many FDA-approved stimulants, sedative/-hypnotics, hallucinogens and opioids. The quota must allow for sufficient

quantities to meet legitimate medical and scientific needs in the United States (21 U.S. Code, Section 826).

In a 1988 Federal administrative law proceeding, the administrator of the DEA acknowledged that his agency had set the production quota for methylphenidate (Ritalin) below the level of legitimate medical need. The official record showed that patients with legitimate prescriptions for methylphenidate had been unable to have them filled. The administrator directed his agency to recalculate the production quota, and stated:

> The CSA requirement for a determination of legitimate medical need is based on the undisputed proposition that patients and pharmacies should be able to obtain sufficient quantities of methylphenidate, or of any Schedule II drug, to fill prescriptions. A therapeutic drug should be available to patients when they need it...the harshest impact of actual and threatened shortages falls on the patients who must take methylphenidate, not on the manufacturers to whom the quotas directly apply. Actual drug shortages, or even threatened ones, can seriously interfere with patients' lives and those of their families. Potential shortages encourage stockpiling by patients and their families as well as by wholesalers and retailers...diversion of methylphenidate is a serious problem which DEA must take into account in setting quotas. However, the evidence of diversion of methylphenidate in 1986 does not support the need for as "lean a pipeline" as was created by the way the quotas were set in 1986. (Federal Register 1988)

The intent of Congress to avoid interference with medical practice and drug availability was restated in 1978 when Congress enacted the Psychotropic Substances Act to satisfy U.S. obligations under the Convention on Psychotropic Substances. Congress amended the CSA to say that control of psychotropic substances in the United States "should be accomplished within the framework of the procedures and criteria for classification of substances provided in the (CSA)" to ensure that "availability [of FFDCA drugs]...for useful and legitimate medical and scientific purposes will not be unduly restricted...." Furthermore, the Congress said that nothing in the treaties is to "interfere with ethical medical practice in this country as determined by the

Secretary of Health and Human Services on the basis of a consensus of the American medical and scientific community" (21 U.S. Code, section 801).

State Controlled Substances Laws

Most State controlled substances laws are based on a model called the Uniform Controlled Substances Act (UCSA). The UCSA was prepared by the National Conference of Commissioners on Uniform State Laws in 1970. The NCCUSL is a 100-year old national organization of governor-appointed lawyers who have drafted numerous model laws that have been adopted by the States. The purpose of the 1970 UCSA was to replace a plethora of anti-drug abuse laws that States had adopted since the turn of the century with a single unified framework in order to achieve consistency in national drug control policy between the Federal government and the States (Uniform Controlled Substances Act 1970)

The UCSA was intended to provide the States with a policy framework that would complement the Federal law. For instance, the UCSA contained a closed distribution system to monitor drug distribution only to the retail level, parallel to the Federal system. The importance of maintaining the confidentiality of patient (ultimate user) identity was recognized; a provision stated that a physician is not required to reveal patient identity to a State agency or in any State or local civil, criminal, administrative, legislative, or other proceeding (Uniform Controlled Substances Act 1970).

However, the UCSA did not recognize the public health benefits of controlled substances as did the CSA. Nor did the UCSA require that scientific and medical determinations be made by a competent authority–a responsibility that Congress ultimately gave to the Secretary of the Department of Health and Human Services instead of to the Attorney General. How this came to pass is of some historical interest.

The UCSA was modeled after proposed legislation in the U.S. Senate rather than the final law. The Senate bill, which was the Nixon Administration's proposal prepared by the Justice Department, sought to make the Attorney General responsible for medical and scientific decisions concerning control of drugs. Considerable controversy arose in the Congress during the summer of 1970 after the medical and scientific communities learned of this plan. When Congress adopted the final version of the CSA in October 1970, the Secretary of Health, Education, and Welfare, and not the Attorney General,

had been given the responsibility for making medical and scientific decisions concerning drug control (Joranson 1990).

> As Members may recall, the scientific and medical community of this Nation were greatly upset over the fact that scientific and medical decisions in the Senate bill were centered in the Department of Justice, with the Attorney General having the responsibility to make scientific and medical determinations which were not in the competency of the Department, and admittedly so. We have changed that so that the Department of Health, Education, and Welfare will determine scientific and medical decisions. This is a most important change in the whole approach as it came from the Senate.
>
> Congressman Paul Rogers, Congressional Record, September 23, 1970.

The UCSA had, however, been adopted by the NCCUSL 3 months earlier.

Consequently, while most State controlled substances laws are similar in regulatory structure to the Federal CSA and the UCSA, they do not define authority in such a way as to achieve the balance between law enforcement and medical science that is the hallmark of Federal law. Furthermore, a number of States have not repealed narcotics statutes that were adopted in the early 1900s.

A preliminary review of State controlled substances laws has identified a number of provisions that conflict with the principles established by international, Federal, and uniform law (Joranson February, 1990). Some of these provisions limit medical decisions and regulate or restrict prescribing and dispensing of FFDCA drugs in ways that would not be regulated under the laws of the Federal government and most other States. A summary of these provisions follows.

1. Prescription monitoring

Multiple Copy Prescription Programs (MCPPs), or "triplicate" prescription programs, began in the United States as early as 1913 with the program in New York. MCPPs are amendments to controlled substances laws that require physicians to use special prescriptions. MCPPs allow government

agencies to monitor the appropriateness of prescribing and dispensing of controlled substances to patients. These programs generally require physicians to reveal patient identity to an agency of State government that is principally concerned with drug abuse.

MCPP legislation may also require application of Schedule II controls to prescribing a drug without placement of the drug in Schedule II. Schedule II prescription controls require that every prescription be in writing (as opposed to being called in and reduced to writing by the pharmacist) and prohibit refills. In New York, for instance, when benzodiazepines (Schedule IV drugs) were added to the triplicate program, Schedule II prescription controls were imposed on prescribers, dispensers, and patients without the public procedure to determine the need for increased scheduling that is ordinarily required under the CSA or UCSA (Resource Guide 1990).

The WHO Expert Committee has commented on multiple copy prescription programs that are used in some countries and in several States in the United States. Acknowledging that while these programs may reduce careless prescribing and "multiple doctoring," the Expert Committee said "the extent to which these programmes restrict or inhibit the prescribing of opioids to patients who need them should be questioned." Further, the Expert Committee expressed concerns about regulation scrutiny when it said:

> Health care workers may be reluctant to prescribe, stock or dispense opioids if they feel that there is a possibility of their professional licenses being suspended or revoked by the governing authority in cases where large quantities of opioids are provided to an individual, even though the medical need for such drugs can be proved. (WHO 1990)

2. Restricted use of approved drugs

South Carolina's controlled substances law prohibits the prescribing of any controlled substance for a use which is not specifically approved by the FDA and included in the approved labeling (South Carolina Health Code).

3. Restrictions on prescription quantities

A number of State controlled substances laws or regulations limit the amount of an FFDCA drug that can be dispensed at one time to as little as 100 dosage units or a 5 day supply. These provisions can impede drug availability

to patients with chronic conditions that require extended therapy with controlled substances.

4. Inappropriate definitions

Some States define "addict" or "drug dependent person" to include patients who are physically dependent on opioids or other controlled substances.

5. Reporting of patients

Several States require physicians to report to the government any patients who have been treated for more than several months with a Schedule II controlled substance. New York requires these patients to be reported as addicts. Failure to report patients as addicts is a violation of State law.

Revision of the Uniform Controlled Substances Act (1990)

The NCCUSL revised the UCSA in 1990 and urged States to bring their laws up to date with many changes that had been made to the CSA since 1970. The 1990 UCSA updates and refines the basic drug abuse control framework, provides new legal tools to address drug trafficking, and also addresses several shortcomings of the 1970 UCSA with regard to medical uses of controlled substances (Uniform Controlled Substances Act 1990).

1. Benefits of drugs are recognized

The 1990 USCA recognizes that controlled substances are essential to public health in the prefatory note, although not in the statutory language. NCCUSL drafting rules generally do not permit the inclusion of findings and declarations as appear in the Federal CSA. A suggestion for statutory language for a findings and declarations section has been made (Joranson 1990).

2. Patients are not confused with addicts

As in 1970, the term "addict" is not used. However, since some States still use such terms, a comment which follows the definition section of the 1990 UCSA urges States to assure that definitions in its controlled substances laws do not allow patients who are physically dependent on opioids for the treatment of pain to be confused with addicts, habitual users, or drug dependent persons.

3. Use of opioids for intractable pain is recognized

The 1990 UCSA contains a provision which clarifies that opioid treatment of intractable pain is, for the purposes of controlled substances law, considered part of the professional practice of medicine and therefore outside the scope of controlled substances law.

4. A diversion control program is created

A new statutory provision creates an interagency diversion control program to focus the information and authority of Federal and State agencies on identification and prosecution of individuals who are responsible for diverting controlled substances to illicit uses. This provision will assist States to make efficient use of existing resources before considering new and expensive prescription monitoring programs.

5. Confidentiality is protected

A 1970 UCSA provision that recognized the confidentiality of patient records is included once again. This provision states that a practitioner is not required to report the identity of patients to a State agency.

The 1990 UCSA has been provided to the legislature in each State for consideration. Consideration of the 1990 UCSA by a legislature is an opportunity for health professionals to help to improve their State's overall approach to drug abuse and to address and correct any problems with an unbalanced approach to the medical use of controlled substances.

SUMMARY OF GUIDING PRINCIPLES

Several guiding principles can be distilled from the laws that govern medical practice, drug availability, and diversion.

1. A primary purpose of controlled substances laws is to decrease diversion of the FFDCA drugs that have an abuse liability. These laws and their enforcement must not interfere in the practice of medicine or unduly restrict the availability of therapeutic drugs for legitimate medical and scientific purposes.

2. The purpose of law enforcement is to administer the controlled substances law, in some cases jointly with health authorities; to use the information

provided by law to identify individuals who divert controlled substances outside of the lawful practice of medicine; and to use the authority provided by law to bring violators to justice.

3. The purpose of health authorities is to make all scientific and medical determinations under controlled substances law. If an issue arises concerning the appropriate medical use of an FDA-approved drug, it should be resolved within the medical and scientific community, not by law enforcement agencies.

4. If additional restriction of the prescribing or dispensing of drugs beyond the level of control associated with a particular schedule is deemed necessary, such additional control should be accomplished using CSA/UCSA drug control procedures to increase scheduling. This will assure compliance with the intent of Congress that the appropriateness of controls on therapeutic drugs be guided by competent medical and scientific expertise.

5. Although State laws are generally permitted to be more restrictive than Federal law, States have been urged to use uniform law to achieve a consistent national drug policy framework that balances drug control and drug availability.

6. The confidentiality of patient-identifying information should be respected.

CONCEPTUAL FRAMEWORK FOR EVALUATING DIVERSION CONTROL PROGRAMS

From the foregoing, two general standards can be proposed for use in evaluating the diversion control programs that will be discussed during this technical review. One writer has commented that if it is in the public interest that drugs meet rigorous standards of effectiveness and safety, it should be of equal interest to public health that drug laws and regulations be held to the same standards (Woods 1990). The answers to the following questions will help to gauge the effectiveness and safety of diversion control programs.

Effectiveness

Is the diversion program aimed directly at identifying and stopping diverters? How effective is the program? Is the program designed to make use of the information, authority, and resources that are available from a number of State and Federal agencies? Is there a cooperative agreement to coordinate

the use of these resources? Does implementation of the diversion program result in reductions in valid measures of diversion and abuse of prescribed controlled substances? Are these reductions significant?

Safety

How safe is the diversion program? Does the program philosophy and design complement the basic principles of balance as previously outlined? Or, does the program extend controlled substances law into monitoring prescribing and ultimate users? Does the program aim to decrease the availability of controlled drugs or to regulate medical decisions? Does it shift patterns of prescribing or diversion to other drugs which may be less safe or effective? Do monitoring and enforcement activities result in identification of "false positives," i.e., reporting of patients as addicts, or investigation or prosecution of practitioners who are simply prescribing according to medical need?

CONCLUSION

International and Federal law recognize the public health value of controlled substances and establish a clear expectation that government efforts to reduce diversion of these drugs should not interfere with their beneficial medical uses. The overarching purpose is to improve the public health; the war on drug abuse must not impede the prevention and treatment of disease, pain and suffering.

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Therapeutic Use of Opioids: Prescribing and Control Issues

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INTRODUCTION

The medical use of prescription opioids can relieve human suffering by ameliorating a particularly compelling symptom, severe pain; illicit use or misuse damages individuals and contributes to the larger substance abuse problem in our society. These widely divergent outcomes are emphasized differently by professional groups whose perspectives derive from the nature of the problems they must address. Medical practitioners observe that inadequate treatment of pain is an immense public health problem and support intensive educational efforts that would, if successful, increase opioid prescribing. Those in regulatory agencies and law enforcement view illicit use and misuse as the more significant problems and support policies that limit these activities, usually without careful evaluation of their impact on medical use.

Although it is evident that the goals of these groups need not be in conflict, there has been a growing perception that conflicts exist. This is so despite acceptance by both the clinical and regulatory communities of the need for balance between the imperatives of clinical practice and the requirements of opioid regulation. The clinical endorsement of the efforts to achieve this balance is affirmed in a survey of practitioners (Berina et al. 1985) and policy statements of the American Medical Association (1990); the regulatory viewpoint is noted in the recognition of opioids as medically essential drugs by the International Narcotics Control Board and the United States Commission for the Development of Uniform State Laws (Joranson 1990). The lack of fundamental disagreement suggests that enhanced communication between those whose primary goal is the improved clinical use of opioids and those who monitor this use can lead to enlightened regulatory policies that reduce abuse without compromising the care of patients.

To accomplish this goal, those in regulatory agencies and law enforcement must become aware of the scope and complexity of clinical pain, the role of

opioid therapy in its management, and the types of problems encountered by legitimate prescribers as they attempt to conform to current regulations. These issues are discussed in the present review.

THE ROLE OF OPIOID THERAPY IN CLINICAL PRACTICE

Pain is a universal experience and the most common complaint presented to physicians. lt is an inherently subjective perception, with remarkably varied manifestations. Although opioids are indisputably effective analgesic drugs, their acceptability as a primary therapy depends on the clinical setting and numerous variables specific to the patient and situation. In the broadest analysis, three clinical settings are relevant: (1) acute pain, (2) chronic cancer pain, and (3) chronic nonmalignant pain.

Acute pain, which can be defined as pain that has had a recent onset and has been short-lived or is anticipated to be short-lived, is extraordinarily prevalent and occurs in association with numerous clinical disorders. Of those acute pains commonly considered for opioid treatment, postoperative pain is most prevalent, but other types are prominent as well, including posttraumatic pain and pain associated with a variety of medical diseases, including sickle cell anemia, hemophilia, some types of arthritis (such as gout), inflammatory bowel disease, and others. There are no comprehensive prevalence data that take into account the large number of clinical situations in which acute severe pain presents, but the extraordinary frequency with which clinicians encounter patients with this complaint can be appreciated.

Opioids are generally accepted as appropriate agents for the management of acute severe pain. With few exceptions, clinicians accept the use of these drugs for a period that is usually measured in days, during which the process that incited the pain resolves. Given recent evidence of the important physiological benefits that may occur with the adequate relief of acute pain (Yeager et al. 1987), it is clear that the need for opioids in this setting derives from **sound** medical goals, as well as the ethical imperative to provide comfort when the means to do so safely exist.

Cancer-related pain is also a highly prevalent clinical entity. Numerous surveys have demonstrated that pain is experienced by 30-50 percent of ambulatory patients or those actively receiving antineoplastic therapies, and by 75-90 percent of those with advanced disease (Portenoy 1989). Uncontrolled pain in this population has dire consequences. It compromises the

physical and psychosocial functioning of the patient and may profoundly worsen the suffering caused by progressive disease and the efforts to treat it.

The use of opioids to manage chronic cancer pain is also widely accepted, particularly among those patients with advanced disease (American College of Physicians 1983; Foley 1985; McGivney and Crooks 1984; National Institutes of Health 1987; Twycross and Lack 1983; World Health Organization 1986). Clinical observation suggests, however, that there may be reluctance to administer effective doses of opioid drugs to patients with limited disease and those who experience chronic cancer-related pain following remission or cure of the disease. This reticence may derive from the perception that the functional status and long life expectancies of these patients equate them with the chronic nonmalignant pain population, wherein the use of opioids is far more controversial. Cancer pain experts reject the view that therapeutic decisions should be based solely on life expectancy and have a strong bias in favor of opioid use in the latter groups, particularly those who have early or limited cancer. Although it is true that some patients with chronic cancer-related pain in the absence of active disease (e.g., due to cancer treatment) can be likened to those with nonmalignant pain, most cancer pain experts would not exclude a role for opioid therapy on this basis alone.

Chronic nonmalignant pain is an extremely prevalent problem. An estimate based on epidemiologic data drawn from a variety of sources suggests that more than one-third of the U.S. population has chronic pain and that 50-60 percent of these patients are partially or totally disabled by pain for periods of days or longer; in 1986, this disability resulted in more than 400 million work days lost, and this loss, combined with the costs for health care, compensation, litigation and unproved remedies, approximated $79 billion for that year (Bonica 1991). A extraordinarily diverse group of disorders may present with chronic pain. The associated physical and psychosocial impairments vary enormously, both among these disorders and among different patients afflicted with the same disease. These differences must be considered in therapeutic decision making.

Traditionally, chronic opioid therapy for nonmalignant pain has been rejected by the medical community. In recent years, however, there have been efforts to critically reevaluate this view (Portenoy 1990), a process driven by advances in the scientific understanding of pain physiology and opioid pharmacology, extensive experience with long-term opioid therapy for cancer pain, a small published experience describing chronic opioid treatment of

patients without cancer, and increasing recognition that nonmedical influences (including regulatory policies) may be having an undue influence on therapeutic decisions that should be fundamentally medical. As discussed further below, the use of opioid therapy for chronic nonmalignant pain remains controversial, but is no longer rejected, a priori, by a substantial segment of the medical community. The lack of consensus about this therapeutic approach presents the most difficult challenge for those engaged in the regulation of opioid drugs, who must assess the potential for illicit activity through an evaluation of prescribing practices.

OPTIMAL OPIOID THERAPY

The foregoing comments indicate the enormous magnitude of clinical pain and the potential use of opioids to manage it. Regulatory policies must be evaluated to confirm that they recognize the extent of the clinical need and accommodate the prescribing practices that have developed in response. Since the need to evaluate regulatory policy, or any other factor that may influence opioid prescribing, would be obviated by evidence that current prescribing practices were adequate, it is first necessary to compare the actual efficacy of opioid therapy with the potential of this approach in different settings. It is most illuminating to assess therapeutic efficacy in those settings that fully accept the need for opioid therapy, specifically, acute pain and chronic cancer pain treatment settings.

It is widely acknowledged that the optimal administration of an opioid drug is an extremely effective treatment for acute pain. Studies of patient-controlled analgesia, for example, document that there is a very strong potential for adequate pain relief from opioids in the postoperative setting (Lehmann 1990). Given this efficacy, the prevalence of unrelieved pain in surveys of routine postoperative care, which ranges from 30-70 percent (Edwards 1990), is striking.

A high prevalence of unrelieved pain also characterizes the cancer population. The optimal administration of a pharmacologic regimen is capable of providing adequate relief of pain in 70-85 percent of cancer patients (Schug et al. 1990; Ventafridda et al. 1985, 1987). Unfortunately, this potential efficacy is not achieved in routine clinical settings (Brescia et al. 1990; Marks and Sachar 1973; Miransky et al. 1991; Parkes 1978; Portenoy 1989; Schug et al. 1990; Twycross and Fairfield 1982). For example, a sample of 1,103 patients admitted to a hospital specializing in the management of advanced cancer patients observed that 78 percent reported pain on

presentation and 38 percent reported severe pain (Brescia et al. 1990). Unrelieved cancer pain, like acute pain, is highly prevalent despite the availability of the means to manage it successfully in most patients.

DETERMINANTS OF UNRELIEVED PAIN

Clinical observation suggests that a variety of factors may contribute to a poor therapeutic outcome, among which are regulatory influences. There are few data to clarify this issue, but hypotheses that relate specific factors to inadequate results can be fashioned, and this process can help clarify the potential role of regulation.

Factors contributing to the high prevalence of unrelieved pain include those related to patient behavior and those related to clinician behavior. Patient-related factors are seldom discussed, but probably play an important role. Patients may choose to deemphasize symptoms in discourse with their physicians due to any of several reasons, including stoicism, a desire to focus attention on the underlying disease, the need to please the staff, or the perception that pain is an inevitable consequence of the disease. These factors may combine with noncompliance, which itself may be induced by a variety of phenomena. Noncompliance with opioids may be related to the same factors that undermine other treatments, including cost, complexity of the therapeutic regimen, and concern about side effects. Additionally, opioid prescription generates the unique fear of addiction, which is almost universal and undoubtedly contributes to patient noncompliance as well.

The degree to which the patient-related influences hamper adequate opioid therapy is net known. It is generally perceived, however, that clinician behavior is the more important determinant of unrelieved pain. Although it is likely that the reluctance to prescribe opioids in some situations (e.g., chronic nonmalignant pain) derives from justifiable doubts about the role of this therapy, undertreatment is probably the major cause in those clinical settings that sanction the use of these drugs.

Surveys suggest that a variety of problems contribute to the systematic undertreatment of pain. Pam is seldom assessed and most clinicians lack adequate knowledge of opioid pharmacology (Charap 1978; Donovan et al. 1987; Grossman and Sheidler 1985; Marks and Sachar 1973). The degree of concern about adverse pharmacologic reactions is great and is perceived by pain specialists to far exceed the actual risks associated with appropriate therapy. Fear of producing addiction is very prevalent, notwithstanding data

demonstrating that the risk of this outcome in medical patients prescribed opioids for painful disease is extraordinarily low (Chapman and Hill 1989; Kanner and Foley 1982; Perry and Heidrich 1982; Porter and Jick 1980).

Regulatory policies that are not sensitive to the requirements of clinical practice may become another impediment to optimal opioid administration. Although it is true that there are no regulations that specifically limit the physician's right to administer an opioid drug for legitimate clinical purposes, there is a strong perception that the existence of some policies impedes appropriate prescribing.

THE IMPACT OF REGULATORY POLICIES ON LEGITIMATE PRESCRIBING

Empirical research is needed to evaluate specific hypotheses that relate regulatory influences to prescribing practices. Few data are currently available, but reasonable hypotheses can be developed from those extant and clinical observation. Specifically, it is likely that the regulatory policies worsen undertreatment by either limiting patient access to needed drugs or by negatively influencing prescribing behavior.

Policies Limiting Access to Controlled Prescription Drugs

Policies that limit access to opioids or other controlled drugs used commonly during opioid therapy can directly prevent appropriate prescribing or exaggerate the propensity to undertreat by increasing the burden on the patient and clinician. These policies limit the quantities of drugs that may be prescribed or prohibit the use of drugs commonly administered in combination with opioids.

Some States maintain a 120 dosage unit rule for opioid drugs, which has been interpreted to mean that no more than 120 tablets can be dispensed to a patient at any one time. For patients receiving high opioid doses, this regulation may necessitate very frequent prescription renewals. For example, a cancer patient receiving the opioid hydromorphone at a dose of 24 mg every 4 hours must consume 6 tablets per dose, or a total of 36 tablets per day. The 120 dosage unit rule mandates a new prescription for this therapy approximately every 4 days, an onerous requirement for both the patient and the physician.

Although less problematic than the 120 dosage unit rule, a 30-day maximum prescription period for opioids can also pose difficulties for some patients with chronic pain. Patients whose medical condition and pain are stable may present no medical reason for the monthly visit that may be required as part of this regulation. This visit increases the cost of medical care for the patient and is an unnecessary burden for those who live at a distance from the physician.

Although opioids are not prohibited by any State, some restrict the use of other controlled drugs that are now considered to be appropriate cotherapy in some clinical settings. For example, some States prohibit the use of amphetamine drugs for all but a few conditions, despite their widespread acceptance as an important adjunctive therapy in the management of opioid-induced sedation in cancer patients (Bruera 1989).

Policies That Negatively Influence Prescribing Behavior

Probably a more important determinant of undertreatment than policies that directly limit access to controlled prescription drugs are regulatory influences that indirectly reduce appropriate prescribing. Physicians are discomforted by the knowledge that their prescribing practices are intensely scrutinized by State and Federal authorities. It may be hypothesized that this discomfort is generated by a "perceived risk of sanctions," a perception that some personal risk accrues from the prescribing of these controlled substances. This perception of personal risk may increase underprescribing.

The perceived risk of sanctions may be sustained by several factors. Most important, physicians are not confident that those monitoring prescribing are knowledgeable about opioid pharmacotherapy. Prescribing behavior can be evaluated fairly only if regulators have a clear notion about the specific practices that constitute appropriate therapy. Current regulatory policies do not include a mechanism by which legitimate prescribers can be reassured about the level of training offered those monitoring prescribing or the specific guidelines used to decide on the need for further investigation or sanction. These guidelines do not appear in the medical literature, are not issued or overseen by clinicians who are expert in opioid pharmacotherapy, and are subject to change without warning. In such an environment, physicians have no way of knowing whether their therapeutic decisions could lead to suspicions that might result in the need for uncomfortable and costly interaction with regulatory agencies. This perception is enhanced by published reports in the lay press and medical literature that describe physicians who have been

investigated for the manner in which they administered opioids (Kofoed et al. 1989; Rose 1987).

It is probable that the perceived risk of sanctions interacts with other factors that influence opioid prescribing. Given the widespread acceptance of opioid therapy for patients with far-advanced cancer and those with acute tissue injury, undertreatment in these settings is probably less related to concerns about drug regulation than other factors, such as a lack of pain assessment or inadequate expertise in opioid pharmacotherapy. In contrast, it is likely that the perceived risk of sanctions contributes far more to the negative appraisal of opioid therapy in patients with chronic nonmalignant pain and the reticence to prescribe opioids when patients demonstrate an atypical course, such as the patient with postoperative pain that continues beyond the expected duration (Edwards 1990).

The perception of risk that may be associated with opioid regulation probably derives most strongly from State policies. Although there may be other sources for the concerns experienced by physicians, including Federal regulation, hospital-based review committees and the implicit threat of malpractice litigation, state oversight is most important for the legitimate physician. As an informative, albeit controversial, example of the potential impact from state regulatory policies, it is useful to evaluate the multiple copy prescription program, which is now active in nine States.

Multiple Copy Prescription Programs

Each State implementing a multiple copy prescription program has noted a greater than 50 percent decline in statewide prescribing of the controlled drugs covered by the regulation (U.S. Department of Justice 1987). These data have been adduced by proponents of such programs as evidence that they reduce illicit or inappropriate prescribing. There is no evidence to support this conclusion, however, other than the lack of formal complaints from patients or clinicians in the states involved. Data from the Federal Drug Abuse Warning Network do not confirm a decline in prescription drug abuse in these states (Jacob 1990) and one study observed that legitimate prescribers reduced their use of Schedule II drugs and increased the use of non-Schedule II drugs following the start of such a program (Sigler et al. 1984).

These data strongly suggest that the reduction in prescribing induced by multiple copy prescription programs can be attributed, at least in part, to a decline in legitimate prescribing of opioids and other controlled drugs. This effect may have several explanations. As the most visible reminder of the intense scrutiny that accompanies the administration of opioids and other controlled drugs, these programs may exacerbate undertreatment by enhancing the perception that some personal risk accrues to the legitimate physician who prescribes these drugs. Alternatively, legitimate prescribing may be reduced through the burden of paperwork associated with these programs, the cost of the prescriptions, or the potential loss of privacy for patients.

There is a disturbing irony in the debate surrounding multiple copy prescription programs. Proponents of these programs use data demonstrating a reduction in statewide prescribing to suggest that there has been a reduction in the abuse of controlled prescription drugs. Presumably, those who subscribe to this view in regulatory agencies and law enforcement would favor additional declines of this type, and contrariwise, would perceive an increase in statewide prescribing as a possible indicator of expanding illicit use. In contrast, opponents of multiple copy prescription programs, particularly those concerned about the undertreatment of cancer pain, strongly believe that opioids are underused and that improvement in clinical practice will require substantial increments in overall prescribing levels. The latter argument is supported by experience in the State of Wisconsin. Coincident with the success of an educational program in the area of cancer pain, known as the Wisconsin Cancer Pain Initiative, there has been a steady increase in statewide opioid prescribing while standard abuse indicators simultaneously continue a decline that began prior to the start of this program (Joranson et al. 1990). These data provide a direct contradiction to the argument linking levels of statewide prescribing to illicit use and suggest that educational programs directed at legitimate prescribers could potentially lessen undertreatment and increase opioid use, a pattern that would be welcomed by experts in pain management.

ISSUES IN SPECIFIC SETTINGS

As observed previously, the potential influence of opioid regulation on clinical outcome probably varies across the clinical settings in which these drugs are administered. Some issues in this area are relatively specific for one or another clinical setting, as follows:

Treatment of Cancer Pain

The undertreatment of cancer pain is widespread, and regulatory influences that unintentionally limit access to controlled prescription drugs or increase the physician's perception of personal risk from prescribing are among numerous contributing factors. In the setting of cancer pain management, physicians may become particularly concerned about the risk of investigation or sanction because they are aware that the prescribing patterns necessary in this population are those that can raise suspicion among regulators (Coyle et al. 1990; Foley 1985; Twycross and Lack 1983; Schug et al. 1990; Ventafridda et al. 1987; World Health Organization 1986).

Patients with cancer pain are often prescribed more than one controlled prescription drug, such as an opioid plus an amphetamine, and administration over many months or years is commonplace. Many patients require parenteral administration. Opioid doses are often high and dose escalation over time is frequently necessary. Some patients need more than one opioid or route of administration.

Given the requirements of cancer pain management, regulators who monitor prescribing patterns to identify opioid misuse or illicit use face a difficult challenge. Although some cases of diversion may be obvious, the prescribing behavior of a clinician who appropriately administers multiple controlled drugs at high doses to patients with cancer pain may be difficult to evaluate, unless there is adequate foreknowledge of state-of-the-art prescribing practices. The problem becomes greater when the treating clinician manages relatively few cancer patients (and, hence, has not become known to the regulators) and when the clinician is not registered with the State as an oncologist. Those in regulatory agencies and law enforcement could facilitate improvements in cancer pain management by addressing this challenge and providing a method to reassure clinicians that the system established to evaluate drug use is knowledgeable about recommended prescribing practices in cancer pain management.

Treatment of Acute Pain

Most patients with acute postoperative pain will recluire opioid analgesics for several days or less. Prescribing takes place in a hospital environment, and clinical observation suggests that practitioners are relatively unconcerned about regulatory influences in the routine administration of this therapy. Undertreatment during this period is highly prevalent nonetheless (Donovan

1987) an observation that provides confirmatory evidence of the multiple determinants of prescribing behavior.

Regulatory influences could potentially become important, however, in patients who develop an atypical course for the pain. It has been observed anecdotally that undertreatment is likely in those with acute pain that requires higher opioid doses for relief or persists beyond the usual period for the injury in question (Edwards 1990). Despite the enormous variability in both the pain experienced following acute tissue injury and the pharmacokinetics and pharmacodynamics of the opioids used to manage it (Austin et al. 1980; Lehmann 1990), many clinicians treat these pains with an inflexible opioid regimen. Studies are needed to isolate the impact of regulatory influences on this type of inappropriate prescribing behavior.

The impact of regulatory policies on the opioid management of other types of acute pain, particularly recurrent acute pains associated with medical disorders (such as sickle cell anemia, hemophilia, inflammatory bowel disease, and others) has also never been evaluated empirically. It may be speculated, however, that the influence of regulatory policies varies in these patients with the frequency of painful episodes and the specific opioid requirements during each. It is likely that some patients raise concerns that are similar to those encountered in the treatment of chronic nonmalignant pain,

Treatment of Chronic Nonmalignant Pain

As noted previously, there has been growing interest among clinicians in a reevaluation of the role of opioid therapy for nonmalignant pain. This interest has been evidenced by recent symposia at national scientific meetings (e.g., American Pain Society, International Association for the Study of Pain, American Academy of Neurology, and American Society of Addiction Medicine) and numerous papers in the medical literature. This literature now includes many clinical series that describe the successful management of opioid therapy in patients with chronic nonmalignant pain.

On the basis of this interchange, it may now be justifiably concluded that the traditional rejection of chronic opioid therapy for nonmalignant pain has been replaced by a true lack of consensus among responsible medical authorities. Those who eschew the approach are now balanced by experts in pain management who endorse the view that long-term opioid therapy may be an appropriate intervention in a selected subpopulation of patients with chronic nonmalignant pain (Green and Coyle 1989; France et al. 1984;

Portenoy 1989; Portenoy 1990, 1991; Portenoy in press; Portenoy and Foley 1986; Taub 1982; Tennant and Uelman 1983; Tennant et al. 1988; Turk and Brody 1991; Urban et al. 1986; Wan Lu et al. 1988; Zenz et al. in press).

Regulators who have previously subscribed to the view that any long-term prescribing of opioids to a patient without cancer is, a priori, evidence of misuse must now recognize a changing clinical ambiance, in which a segment of the medical community accepts a limited role for this treatment. This clearly places great pressure on the regulatory community, who must develop guidelines for the monitoring of prescribing practices that are sensitive to current medical thinking. To avoid inappropriate investigations of legitimate prescribers who are applying a therapy recommended by some authorities, the nature of opioid prescribing must be examined much as it is when the clinical context is cancer pain and the prescriber is identified as an oncologist. Therapeutic guidelines for chronic opioid therapy in nonmalignant pain have been proffered in the medical literature (Portenoy 1990) and these may begin to provide a basis for the kinds of guidelines that should be developed by regulators. For example, a physician's decision to administer morphine to a patient with postherpetic neuralgia cannot by itself be construed as inappropriate, but the administration of a 6-month supply of this drug is likely to be in conflict with accepted clinical practice and might be identified as such by regulators.

The need for better communication between clinicians and those in regulatory agencies and law enforcement is underscored by the potential for expanded use of opioid drugs in the management of patients with chronic nonmalignant pain. The inclination of regulators to react negatively to the mere prescription of an opioid will not diminish until the clinical approach to opioid therapy is defined by physicians, and the perception of personal risk that physicians experience when prescribing will not decline unless regulators make clear their willingness to sanction this approach when it is performed in an appropriate manner. The interaction that must ensue over this issue may well benefit the clinical use of opioids in other settings, such as cancer pain.

CONCLUSION

The inadequate administration of opioids is highly prevalent, leading to unnecessary pain even in those clinical settings in which the use of these drugs is widely approved. Although opioid regulation is not intended to interfere with any form of clinical practice, there is evidence that it

contributes to this outcome. Regulatory policies may reduce patient access to needed drugs or increase the tendency of practitioners to prescribe in ways that are clinically suboptimal. Enlightened regulatory policy should recognize that these outcomes are possible and include efforts to reassure prescribers that the administration of opioids in clinically appropriate ways will not result in investigation or sanction. To do this, those in regulatory agencies and law enforcement must become knowledgeable about currently accepted practices in opioid pharmacotherapy. Communication must improve, so that clinicians become aware of the guidelines used by regulators and regulators can become aware of changing clinical practice. The most challenging area for the future will be the development of regulatory approaches that recognize the potential acceptability of chronic opioid therapy for some patients with nonmalignant pain.

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Anxiolytics: Indications, Benefits, and Risks of Short- and Long-Term Benzodiazepine Therapy: Current Research Data

Karl Rickels and Edward Schweizer

For the past 30 years the benzodiazepines (BZs) have been the most frequently prescribed anxiolytics and hypnotics in medical practice. They long ago replaced the barbiturates, bromides, meprobamate, and the neuroleptics as drugs of choice for the treatment of anxiety (Greenblatt et al. 1983). Over the last decade several new classes of drugs such as the $5HT_{1A}$ partial agonists, have also been developed for the treatment of anxiety (Rickels 1990). This class of drugs offers the first pharmacologic alternative to the benzodiazepines, but they have not replaced them. Although lacking many 01 the risks of the benzodiazepines, they do not provide all their therapeutic benefits. Thus, the benzodiazepines remain for many indications an important treatment option. This is as true today as it was 20 years ago. In several tables we have summarized both the indications and some of the benefits that may be derived from the use of benzodiazepines. One main indication for using these agents is in the short-term treatment of situational anxiety and insomnia (table 1). They may also be used to provide palliative relief for anxiety associated with such acute stresses as impending surgery, physical illness or trauma, or temporary psychosocial stresses. Acute situational uses of benzodiazepines constitute an estimated 85 percent of all prescriptions written (Mellinger and Balter 1981), especially by nonpsychiatric physicians, who prescribe more than three fourths of all benzodiazepines (Beardsley et al. 1988). This indication for benzodiazepines is the least well-studied. Benzodiazepines are also indicated for the management of many patients suffering from more classic anxiety disorders, such as generalized anxiety disorder (GAD) and panic. GAD has a lifetime prevalence of 3.8 percent, with an average duration of more than 5 years (Robins and Regier 1990). GAD has a high comorbidity both with other anxiety disorders, such as panic, and with affective illness. This means that any use of BZs beyond 6-8 weeks must be constantly reevaluated. For patients suffering from panic disorder the benzodiazepine, alprazolam, is the only FDA approved drug, though other BZs (e.g., lorazepam and clonazepam), in addition to tricyclic antidepressants (e.g., imipramine) and monoamine oxidase inhibiting (MAOI) antidepressants (e.g., phenelzine), have also demonstrated comparable

efficacy. Panic disorder also has a high comorbidity with GAD and major depressive disorder and panic patients frequently experience a chronic and intermittent course of their illness, which tends to be more disabling than GAD.

In addition to these primary psychiatric indications for the use of benzodiazepines, there are several other relevant and important indications. There is, for example, the adjunctive use of benzodiazepines in the acute management of agitated psychoses, both in manic and schizophrenic patients. This short-term use represents a rapid and humane way of calming agitated patients without risking the neurological side effects from neuroleptics. The benzodiazepines are also the treatment of choice as preanesthetic agents, both because of their muscle relaxing sedative and anesthetic properties and because they potentiate the effects of standard anesthetic agents.

Clonazepam has an approved indication for the treatment of epilepsy and diazepam for the use in status epilepticus. Some of the benzodiazepines are also used for the treatment of mood disorders. For example, alprazolam is used for the treatment of major depression (Feighner et al. 1983) and clonazepam for bipolar disorder (Chouinard 1988; Aronson et al. 1989), though more research is needed before benefit for these indications can be confirmed. Finally, diazepam is indicated in movement disorders.

Thus, benzodiazepines are prescribed for a large range of indications, for some of which better, safer, and more efficacious drugs are not yet available. Naturally, drugs that are so widely used and beneficial for so many indications also have certain risks. For acute therapy, these risks include primarily sedation, psychomotor impairment, cognitive or other CNS effects, and the behavioral effects of combined use with alcohol (table 2). These acute adverse effects are generally quite manageable since tolerance tends to develop within 4 to 6 weeks. The possible contribution of BZs to an increase in auto accidents is of concern, and patients should certainly be cautioned, but an etiologic link has yet to be established (Skegg et al. 1977; Rickels 1981). In fact, highly anxious or panicking patients who suddenly feel faint or who believe a heart attack is impending while driving may be a larger contributor to car accidents than patients on BZ treatment.

In the past decade, the most controversial issues concerning therapy with BZs relate to their long-term use, with more than 2 percent of the adult population on BZs daily for at least 6 months (Woods et al. 1988). The risks of physical dependence and withdrawal should be discussed with each patient

prior to initiating even acute therapy, since clear evidence exists that problems may develop as early as 4-12 weeks (Fontaine et al. 1985; Rickels et al. 1988). All marketed benzodiazepines appear to possess relatively low abuse potential, and are rarely the drugs of choice for drug abusers (Woods et al. 1988), but they do frequently produce varying degrees of physical dependence (Winokur et al. 1980; Petursson and Lader 1981; Busto et al. 1986; Rickels et al. 1990; Schweizer et al. 1990). Once benzodiazepines are used for the longer term–that is over 4-6 months–a majority of patients do experience a physical dependence phenomenon, even at very low therapeutic doses, which manifests itself via a withdrawal syndrome that occurs during and/or after abrupt or tapered benzodiazepine discontinuation (table 3).

After acute benzodiazepine treatment of only 4-6 weeks for anxiety, some patients, particularly those treated with short half-life benzodiazepines may experience a rebound of anxiety upon abrupt benzodiazepine treatment discontinuation (table 4). Such rebound consists of the appearance of the same symptomatology, but frequently of greater intensity than that present at pretreatment, and represents clearly a transient phenomenon. Rebound symptoms may occur with rapid taper in as many as 30 to 50 percent of patients after a short course of therapy with short half-life benzodiazepines. To a lesser degree, these symptoms may also occur with long half-life benzodiazepines. The symptoms may be more severe than before treatment, are often very frightening to the patient, but usually peak within a few days and generally disappear within 7 days after the patient has become medication-free. Rebound insomnia persisting for l-3 days may occur after less than 1 week of therapy with a short half-life hypnotic benzodiazepine. Tapering the hypnotic medication will reduce such rebound insomnia (Kales et al. 1978).

In contrast to rebound and withdrawal phenomena, relapse represents a return of the original illness, which usually manifests itself as a more gradual return of the symptoms of anxiety, and is reported to occur in 20 to 80 percent of patients treated for various periods of time. Relapse usually has a gradual onset, though it may be triggered by an episode of rebound anxiety occurring transiently in the immediate post discontinuation phase (table 5). Most patients improve if treatment is resumed either with the same or with another medication or alternatively, if cognitive-behavioral therapies are initiated (Michelson and Marchione 1991). It should be stressed that relapse is a return of anxiety symptoms present before treatment. Unlike rebound anxiety or panic, relapse has a temporal progression that is not acute and

transient but appears more gradually over time and persists without additional therapy.

For BZ therapy of anxiety disorders, there is as yet no good evidence of a prophylactic benefit from long-term maintenance therapy. In fact, we found in a study of GAD patients who were treated for 6 months with diazepam, that at 1 year followup 65 percent of improved patients reported a return of anxiety during the followup period, and 45 percent suffered from moderate to marked anxiety at the time of the followup (Rickels et al. 1986). Clearly, these findings indicate that many GAD conditions are of a chronic nature.

The longer the anxious patient is treated continuously with a benzodiazepine, the higher the daily dosage (frequently required for panic therapy); and the shorter the BZ half-life, the more likely it is that a patient will experience a withdrawal syndrome (Rickels et al. 1990). After 4-6 months of daily therapy, a BZ withdrawal syndrome is detectable in at least 50 percent of patients (Rickels et al. 1983). Gradual taper serves to reduce the differential effect of short versus long half-life BZs on withdrawal severity (Schweizer et al. 1990). Table 6 summarizes some of the drug and patient factors which contribute to the severity of the BZ withdrawal syndrome. Some of the most commonly reported withdrawal symptoms are given in table 7.

The steps to be taken when discontinuing benzodiazepine therapy are discussed in table 8. One should taper even after short-term use, and the longer the treatment, the more gradual the taper. The first 50 percent dose reduction may be relatively swift, whereas the last 25 percent reduction usually is much more difficult and protracted.

If the taper period is too extended, discontinuation symptoms may be hard to distinguish from relapse of the original illness, and one should remember that gradual taper does not prevent discontinuation symptoms, it only makes them less intense. During BZ discontinuation, it is frequently beneficial to treat insomnia, which is often perceived as very disturbing to the patient, with sedating antidepressants such as doxepin or trazodone. It is also important to treat psychiatric comorbidity, especially depression and panic, prior to undertaking BZ taper. One should also consider treatment with adjunctive medications such as imipramine, buspirone or carbamazepine even in patients without obvious comorbidity (Schweizer et al. 1991; Rickels et al. 1990). Pretreatment of patients for several weeks before initiating taper appears, at present, to be the most effective approach.

Benzodiazepine discontinuation after long-term use results in one of four outcomes: (1) some patients experience minimal to no discontinuation symptoms and suffer no relapse of their illness; (2) some patients experience benzodiazepine withdrawal, with or without rebound, but this resolves in 2-4 weeks with no illness relapse, allowing them to remain BZ-free; (3) some patients will be unable to discontinue BZ therapy fully, either because of withdrawal severity, return of original symptoms, or because of personality factors; and (4) all patients, whether they successfully discontinue their BZ or only partially reduce their dose, may at some time after taper experience a relapse of their original illness.

The question then should be raised: What are some of the reasons why benzodiazepines should be discontinued? These are summarized in table 9. Especially important are either poor or good clinical response. It has been demonstrated that of chronically anxious patients treated for only 4-6 weeks, 50 percent remain symptom free for at least 3 months (Rickels et al. 1983). Thus, a fair percentage of even chronically anxious patients do not necessarily require long-term therapy. Furthermore, patients on maintenance BZ therapy who have been symptom-free for several months probably deserve a medication-free trial to assess their continued need for BZ therapy. A subset of patients, even those with a history of chronic anxiety, benefit most from intermittent rather than continuous therapy.

SUMMARY

Benzodiazepines are some of the most widely used drugs in medicine today. There exist appropriate and clear-cut indications which range from generalized anxiety and panic disorder to such medical conditions as status epilepticus and use as a preanesthetic agent. Until new replacement drugs are found, the BZs will continue to represent important tools in the physician's armamentarium for managing the many indications discussed in this paper. They do, however, have liabilities. These liabilities become particularly obvious during long-term therapy of chronic conditions. For patients treated for short-term anxiety, the risks are primarily those of a sedative nature and the accompanying impairment of psychomotor performance and cognition. Patients usually become tolerant to these side effects while maintaining desirable antianxiety or antipanic effects.

It is when one treats patients for prolonged periods of time that many patients develop symptoms of low-dose physical dependence. It should be stressed that when stopping a patient after only a few weeks of therapy,

whether the patient is treated for anxiety or insomnia, a short taper of the medications should be carried out to discontinue therapy in order to prevent rebound insomnia (Kales et al. 1978) or rebound anxiety (Fontaine et al. 1985; Rickels et al. 1988). Astute physicians try to minimize the problems of physical dependence by using drugs intermittently. However, treating patients intermittently necessitates patients experiencing at periodic intervals some withdrawal symptomatology. This occurs when the drug is discontinued temporarily during its intermittent administration. Even carefully tapered patients frequently experience some withdrawal symptoms such as insomnia, agitation, restlessness, fatigue, nausea, sweating, and, at times, even depersonalization and perceptual disturbances. In addition, for the management of chronic conditions such as generalized anxiety disorder, some of the newer anxiolytics such as buspirone may be preferred because of comparable efficacy and possible absence of dependence potential (Rickels et al. 1988).

For the chronic treatment of panic disorder, if patients and doctors are concerned about the development of physical dependence with benzodiazepines, they can use other effective agents such as imipramine or phenelzine. However, the use of these medications also entails risk. Their side effects are often intolerable and many patients would rather accept the risk of developing physical dependence than use these agents for the treatment of panic disorder. Though many patients suffering from anxiety disorders may benefit from long-term maintenance therapy with BZs, still the risks of such use dictate that every attempt be made to first try intermittent therapy. In either case, the benefit and risk of various treatment options should be discussed with the patient prior to initiating pharmacotherapy.

Table 1

Benzodiazepines
- Benefits -

Treatment of Short-term Anxiety and Insomnia

- Acute stress from various life situations may become severe and incapacitating
- Impending surgery, physical illness, or trauma
- Temporary psychosocial stressors
- PRN use for palliative relief of transient episodes of anxiety

Treatment of Generalized Anxiety Disorder (GAD)

- Excessive anxiety and worry that is pervasive, persistent and highly distressing
- Frequently fluctuates in intensity and is commonly associated with various autonomic, motor tension, or arousal symptoms
- Frequent co-morbidity
- Chronic, intermittent course which may benefit from long term use of BZs

Treatment of Panic Disorder (PD)

- Unpredictable episodes of panic and dread
- Prominent somatic symptoms and/or phobic avoidance
- Frequent comorbidity as secondary disability
- Chronic-intermittent course which may benefit from long term use of BZs

Acute Treatment of Agitated Psychosis

- Acute manic or schizophrenic
- Rapid and humane way of calming agitated patients without risking neurological side effects observed with neuroleptics

Table 1 continued

Use As Preanesthetic Agents

- Muscle relaxing, sedative, and amnestic properties

Use As Anesthetic Agents During Surgery

- Allows for lower doses of other anesthetics

Treatment of Epilepsy

- Emergency treatment of status epilepticus
- Use of clonazepam to prophylactically treat various forms of epilepsy (akinetic, myoclonic, petit mal)

Treatment of Movement Disorders

- Muscle relaxants
- Stiff man syndrome

Table 2

Risks of Treatment with Benzodiazepines

Effect	*Time of Use*	*Risk*
Sedation	Acute chronic	Moderate Minimal
Psychomotor impairment	Acute chronic	Moderate Minimal
Cognitive/memory impairment	Acute chronic	Moderate Minimal to moderate
Abuse potential	Acute chronic	Minimal* Minimal*
Physical dependence	Acute chronic	Some rebound after 4-6 weeks Moderate to marked withdrawal after 4-6 months

* Except in patients with history of substance abuse

Table 3

Withdrawal Syndrome After BZ Discontiuation

- Occurs in 40-80% of patients treated for >= 4-6 months, even after extended taper.
- Occurs with long and short half-life BZs.
- Consists of old (rebound) and new (withdrawal) symptoms.
- Peaks toward end of taper and has mainly disappeared within weeks.

Table 4

Rebound After BZ Discontiuation

- Definition

  Rebound Insomnia - Hypnotic BZ
  Rebound Anxiety - Anxiolytic BZ
  Rebound Panic - Antipanic BZ

- Occurs with abrupt or rapid taper in as many as 30-50 percent of patients after short term (4-8 weeks) anxiolytic therapy, primarily with short half-life BZs.
- Sudden symptom return, frequently with greater intensity than pre-treatment.
- Symptoms are often frightening to patient and may lead to resumption of BZ intake, mistaking temporary rebound symptoms as a return of original anxiety.
- Symptoms peak at the end of taper and generally disappear within 1 week.
- Symptoms are transient; therefore, do not represent a relapse.

Table 5

Relapse After BZ Discontinuation

- Rebound relapse rates range from 20 to 80 percent.
- Relapse usually gradual onset and symptoms remain stable without therapy.
- Relapse to the same symptoms that necessitated initial therapy.
- Most patients improve if medication is resumed.

Table 6

Drug and Patient Factors Contributing to Withdrawal Severity

Drug Factors

- Higher daily dose of BZ
- Shorter BZ half-life
- Longer duration of daily BZ therapy
- Faster rate of taper

Patient Factors

- Higher pretaper levels of anxious and depressive symptomatology
- Higher levels of personality psychopathology (e.g., dependency, neuroticism)
- Younger age
- Concomitant alcohol and substance abuse

Table 7

BZ Withdrawal Syndrome Symptoms

- Anxiety/nervousness
- Restlessness/agitation
- Lethargy/fatigue/lack of energy
- Nausea/upset stomach
- Loss of appetite
- Diaphoresis
- Insomnia
- Faintness/dizziness
- Tremor
- Tinnitus
- Increased acuity to stimuli
- Muscle cramps/twitches
- Poor coordination
- Difficulty concentrating
- Paresthesias
- Perceptual distortions
- Depersonalization
- Confusion

Note: If drug administration is stopped abruptly, possible convulsion, delirium, psychotic reactions may occur.

Table 8

Discontinuation of Benzodiazepine Therapy

- Taper even after short-term use.
- The longer the treatment, the more gradual the taper.
- The higher the daily dose, the more gradual the taper.
- The shorter the half-life, the more gradual the taper.
- The first 50 percent reduction occurs relatively swiftly; last 2.5 percent reduction takes the longest period of time
- If taper period is too extended, discontinuation symptoms may be hard to distinguish from illness relapse.
- Gradual taper does not prevent discontinuation symptoms, it only makes them less intense.
- Treat insomnia during taper with sedating antidepressants such as doxepin or trazodone.
- Important: Only a 3-5 weeks' benzodiazepine-free period will allow clearly distinguishing between rebound, withdrawal symptomatology and illness relapse.
- Relapse has a gradual onset; rebound and withdrawal have a more rapid onset, greatly determined by drug half-life.
- Rebound and withdrawal, but not relapse, are transient, temporary phenomena.
- Treat comorbidity prior to or during taper with appropriate medications such as imipramine or buspirone, or appropriate psychosocial therapy.
- Consider adjunctive medication use, even without obvious co-morbidity, of imipramine, buspirone, or carbamazepine.

Table 9

Reasons for BZ Discontinuation

- Persistent adverse effects which outweigh clinical benefit
- Pregnancy or wish to become pregnant
- Apparent sustained remission of anxiety disorder
- Concomitant alcohol and/or drug abuse
- Patient's wish to be "drug-free"
- Family and social pressure
- Poor clinical response

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Issues and Controversies Regarding Benzodiazepine Use

Carl Salzman

INTRODUCTION

This paper reviews the following aspects of benzodiazepine use:

(1) The prevalence of anxiety and anxiety-related disorders as a way of understanding the context of benzodiazepine prescription

(2) The appropriate length of therapy, focussing especially on the appropriate and inappropriate uses of long-term benzodiazepine treatment

(3) Current controversies regarding the prescription of benzodiazepines in the United States

(4) Suggestions for future research

EPIDEMIOLOGY OF ANXIETY DISORDERS

Anxiety is a ubiquitous human experience. In mild degrees of severity, anxiety can be a motivating force and enhance performance. At higher levels of severity, anxiety interferes with performance and becomes an inhibiting and even disabling symptom. Anxiety may develop acutely following a stressful situation or it can become chronic and worsen over time. Contemporary diagnostic classification schemes now consider anxiety as a disorder with several disorders (including general anxiety disorder, panic disorder, agoraphobia, social phobia, simple phobia, obsessive compulsive disorder, and posttraumatic stress disorder). Considerable information has been gathered concerning the prevalence of these disorders in the United States as well as in other countries. Most of the United States data are based on five community surveys of adults aged 18 and older who were interviewed (Eaton et al. 1984). The total sample size was 18,571; 7.3 percent of the adults surveyed had one or more of these disorders (Regier et al. 1990), most commonly phobic disorders (6.2 percent), followed by obsessive compulsive

disorder (1.3 percent), and panic disorder (0.5 percent). If one combines all categories into anxiety disorder, the 1-month prevalence increases to 7.3 percent with women being nearly twice as likely (9.7 percent) as males (4.7 percent) to develop this disorder. Interestingly, men who are 65 or older have a decline in 1-month prevalence of anxiety (see below). The 1-month prevalence of anxiety disorders varies markedly in other countries. Compared with the 7.3 percent in the U.S., the rates are 2.9 percent in London, 3.5 percent in Australia, 8.2 percent in Athens, 2.8 percent in Edinburgh, and 3.4 percent among female Ugandans (Regier et al. 1990).

Anxiety may arise *de novo,* but is more commonly associated with life stress. Following bereavement, for example, ECA survey data indicate that there is an overall rate of 22.9 percent in the first 6 months increasing to 38.9 percent for the next 6 months after bereavement. Panic disorder rates go from 6.3 percent to 13 percent and social phobia goes from 0 prevalence in the first 6 months to 3.7 percent in the second 6 months. Conversely, simple phobia starts at 10.5 percent and decreases to 0, and obsessive compulsive disorder starts at 2.1 percent and goes to 0 (Jacobs et al. 1990). Anxiety in individuals and in families is common after severe traumatic events (Terr 1991) and is a regular feature of posttraumatic stress disorder (van der Kolk, 1987). A lifetime prevalence of 1 percent has been associated with PTSD (Helser et al. 1987).

Anxiety is commonly associated with physical illness as well: HIV infection syndrome (Fernandez 1989); severe pain associated with cancer (Holland 1989); alcoholism (Linnoila 1989); and coronary heart disease (Rahe 1989). Overall, 5 to 20 percent of medical inpatients and 4 to 14 percent of general medical outpatients suffer from anxiety states with anxiety disorders diagnosed in approximately 6 percent of inpatients (Wise and Taylor 1990; Strain et al. 1981). Anxiety and depression commonly occur with each other, and, in fact, may be confused with each other. Approximately 66 percent of patients with panic disorder have a major depression (Clayton 1990; Stein and Uhde 1988) and 60 percent of patients with depression also report anxiety symptoms, with 20 to 30 percent of these having clear anxiety attacks (Clayton 1987). Having several anxiety disorders concurrently, such as general anxiety and OCD, or social phobias and panic disorder, increases the likelihood of concurrent depression (Clayton 1990). The comorbidity of depression and anxiety is especially high in panic disorder patients. Patients with major depression also often have panic disorder and anxiety, and in the ECA survey data, 1.9 percent of the population had a diagnosis of both

anxiety and depression, anxiety being present in 33 percent of those with affective disorders.

Anxiety disorders, especially panic disorders, are commonly seen by primary care physicians. Depending on one's diagnostic criteria, a large percentage of patients with adjustment disorder have a psychiatric diagnosis (47 percent) and more than two-thirds of these have anxious or depressed mood (Schatzberg 1990).

Among elderly patients, anxiety tends to be less common as an initial symptom and also is less prevalent (albeit not uncommon) in older people (Blazer 1991), although it is a common component of physical illness in the elderly (Cohen 1990) and is a frequent side effect of medications used by the elderly. Anxiety is common in depression in the elderly, and vice versa, and, indeed, may be difficult to distinguish between the primacy of either symptom. Anxiety is commonly seen in dementia, and may be also associated with alcohol use. The lower rate of anxiety in older men may reflect a developmental change for men who "settle down" and learn to drink responsibly (Liptzin 1990).

APPROPRIATE LENGTH OF TREATMENT WITH BENZODIAZEPINES

In the United States, most benzodiazepine prescription is in the setting of acute stress, with the drugs being given for short periods of time. National household survey data for the United States in 1979 and 1981 showed that 45 percent of benzodiazepines were used for only 1 or 2 days at a time, and in most cases, for 30 days or less. For 80 percent of all anxiolytic users, the longest period of daily use was less than 4 months and for 67 percent the longest use was less than 1 month (APA Task Force 1990). Although there are no data specifically examining the acute use of benzodiazepines, worldwide clinical experience suggests that these drugs are remarkably efficacious and unusually safe as a treatment for acute anxiety, stress, and insomnia. Their use in general hospitals by physicians, family practitioners, and surgeons is widespread, and there are no data to suggest that such use leads to prolonged use, dependence, dose escalation, or abuse (APA Task Force 1990). Concern, however, has been expressed both in medical publications as well as the lay press regarding long-term use of benzodiazepines, and the benefit versus risk of long-term use must be carefully examined.

The United States household survey data describe the benzodiazepine usage patterns of patients who took these drugs on a regular or an occasional basis,

and thus provide baseline data for estimating the potential incidence of dependence on a therapeutic dose of a *medically supervised* benzodiazepine prescription. The 1979 household survey also reported that approximately 3.5 percent of the total population took benzodiazepines one or more times that were *not prescribed* for them (Mellinger et al. 1981; Uhlenhuth et al. 1984). These pills were usually borrowed from a friend or spouse. In a later survey, this figure increased to 5 percent (Miller et al. 1983; Smith and Nacev 1978). Almost all these people took benzodiazepines for symptom relief rather than recreational purposes, and almost all took the pills only once or twice.

Although data on annual volume of benzodiazepine prescribing and household survey studies of prevalence and pattern of use do not suggest either a recent increase in the amount of medication consumed or an increase in the prevalence of use, there is a continuing public perception that benzodiazepine use is too widespread in the United States as well as in European countries.

In the United States, long-term users (12 months or longer) can be distinguished from shorter term users. They tend to be older, have substantial psychological distress (including depression), and have significant somatic health problems, especially cardiovascular disorders and arthritis (Mellinger et al. 1984*a* 1984b). Three recent surveys of long-term benzodiazepine prescription in Britain also demonstrated that most long-term benzodiazepine users were elderly, female, and suffered from physical illness and depressive symptoms (Catalan et al. 1988; Nolan and O'Malley 1988; Rodrigo et al. 1988).

There appear to be at least live groups of long-term regular benzodiazepine users. The drugs are prescribed for specific purposes to patients within each of these groups, although, for some, the rationale for long-term use is less clear than for others.

The first and most clearly defined group of long-term users consists of patients who tend to be older (but not necessarily elderly) who suffer from medical disease. These patients often have chronic illness, are in pain, are dysphoric or depressed as well as anxious, and have trouble sleeping. They make many more visits to their physicians than other age-matched people, and their overall psychosocial as well as physical functioning is compromised. These patients also take other medications. However, there is no evidence to suggest they have a dependence associated with their long-term use of benzodiazepines. The side effects of benzodiazepines or drug interactions represent a clinical problem for these patients. As a group, they tend to

scrupulously abide by the doctor's prescriptions, and never escalate their dose. They do not abuse benzodiazepines, mix them with alcohol or other sedative hypnotics, nor have toxic consequences from drug interactions. Rather, patients, as well as their physicians and family members, consider benzodiazepine treatment to be a beneficial and therapeutic part of an overall treatment program (Salzman 1991*b;* Rickels et al. 1984, 1987). In terms of benefit versus risk, therefore, the benefits of long-term benzodiazepine use clearly outweigh any limited risks for these patients.

The second group of chronic benzodiazepine users are patients who are treated primarily by psychiatrists for panic and agoraphobic symptoms. Since panic and agoraphobic disorder is chronic and recurrent, patients who take benzodiazepines for symptomatic reduction are usually treated on a chronic long-term basis, and the doses of benzodiazepines necessary for symptomatic reduction of panic and agoraphobic anxiety are considerably higher than the usual anxiolytic doses. Most clinical studies suggest that these patients do not abuse their medication or escalate their dose. However, concern has been expressed regarding the development of dependence and possible toxicity from such long-term high-dose use. There is evidence that discontinuation from long-term high-dose benzodiazepine use among panic and agoraphobic disorder patients is accompanied by frequent discontinuance symptoms, sometimes severe (Fyer et al. 1987, Pecknold et al. 1982, 1988). Consequently, the benefits compared to risks for these patients are not as great as with the first group. Furthermore, since panic and agoraphobic disorder can be treated with drugs other than benzodiazepines (and possibly treated better), clinicians must carefully consider benefit versus risk for beginning a patient on long-term high-dose benzodiazepine treatment. For some, these drugs may be the most appropriate and least toxic way to reduce symptoms. For others, however, alternative treatments may be more successful, limiting the role of benzodiazepines as an adjunct to other treatments.

Those patients with chronic anxiety and dysphoric symptoms, sometimes with associated personality disorders, appear more typically in psychiatric practice. There are no survey data specifically focusing on this second population of patients, and estimates of the number of these patients and their actual benzodiazepine using habits are not available. Clinical experience suggests that these chronically dysphoric patients seek regular psychiatric attention or regular medical attention, and have their benzodiazepine prescriptions continually renewed. They do not increase their dose (Balmer et al, 1981), and experimental data suggest that anxietyper se does not increase the risk of benzodiazepine dependence (de Wit et al. 1986; Winstead et al. 1974).

Patients with personality disorder may have greater difficulty discontinuing benzodiazepines than patients without personality disorders (Golombok et al. 1987; Tyrer et al. 1983).

For the first two groups of patients, the medically ill and the chronic panic/-agoraphobic group, long-term use appears to be a rational medical therapy. However, depending on one's medical opinion, it may be that some of the third group of long-term users, the chronically dysphoric (a significant number of people), do not have clear cut indications for ongoing regular benzodiazepine therapy. Controversy regarding risk versus benefits of long-term benzodiazepine use centers around this very point: Those who emphasize the therapeutic benefit for the majority of long-term user patients versus those who emphasize the risks of long-term use without clear medical indication and the development of dependence. One review suggests that the evidence for long-term anxiolytic efficacy of benzodiazepines is not sufficiently compelling (Rickels 1987) to warrant continuous, uninterrupted use for months or years. Other authors emphasize the clinical benefit of ongoing benzodiazepine treatment, especially for the medically ill and clinically dysphoric, with little risk of serious toxicity (Marks 1985).

A fourth group of patients who take benzodiazepines chronically are those with sleep disorder. Some patients with chronic insomnia take benzodiazepines on a nightly basis: 2.6 percent of the general population use a medically prescribed hypnotic during the course of the year, and 0.3 percent of all adults have used hypnotics regularly for 12 months or more (Mellinger et al. 1985). Benzodiazepines given to promote sleep may be associated with the development of dependence and signs and symptoms of discontinuance. Furthermore, there is no evidence to suggest that benzodiazepine hypnotics retain their efficacy after more than 30 continuous nights of use. Nevertheless, nightly benzodiazepine prescriptions are commonly found in nursing homes (Allen 1988; Buch 1988; Avorn et al. 1989) and in general hospital inpatients (Salzman and van der Kolk 1979; Salzman 1981). Since dependence and discontinuance phenomena may promote ongoing benzodiazepine use beyond a period of clear efficacy, it is necessary to determine whether such long-term use is also associated with toxicity. Numerous data attest to the effect of benzodiazepines in compromising cognitive function, especially in the elderly. Recent data suggest that chronic benzodiazepine use produces a cognitive syndrome that resembles mild to moderate dementia that is reversible when the benzodiazepines are discontinued (Salzman et al. 1991). Consequently, for chronic sleep disturbance there is limited benefit with

demonstrable risk suggesting that the benefit to risk ratio does not favor routine long-term administration of benzodiazepines for hypnotic purposes.

The fifth group of long-term benzodiazepine users are psychiatric patients with chronic psychotic illness, usually schizophrenia, who are being treated primarily with nonbenzodiazepine medications, but who are also being given benzodiazepines for treatment of coexisting anxiety, for adjunctive antipsychotic effect, for diminution of extrapyramidal symptoms, or for treatment of tardive dyskinesia. The use of benzodiazepines for control of behavioral disruption has been well established (Modell et al. 1985; Greenfield et al. 1987; Santos and Morton 1990; Salzman et al. 1991) but there are no data to suggest that long-term maintenance use of benzodiazepines prevents additional disruptive behavior. There are no data to suggest that benzodiazepines by themselves exert antipsychotic effect, even in high doses, and there are only limited data to suggest that benzodiazepines in conjunction with neuroleptics permit the use of lower doses of the latter drug over a long period of time. The risks of long-term benzodiazepine use in this population are those of dependence, potential withdrawal, excessive sedation, and, in elderly psychotic patients, cognitive impairment. Consequently, although the risks are not as considerable as in the long-term hypnotic users or the long-term dysphoric patients, the benefits do not clearly outweigh the risks, suggesting that chronic benzodiazepine use in psychotic patients probably should be avoided.

In summary, it seems clear that short-term use of benzodiazepines for acute anxiety/stress situations and some long-term use of benzodiazepines is therapeutic and relatively risk-free compared with other anxiolytic drugs such as meprobamate, CNS sedatives, and antidepressants. An argument can be made that many patients with symptoms of anxiety and/or depression are in fact *undermedicated* with benzodiazepines: 60 percent of patients who are legitimate candidates for antianxiety treatment do not seek or obtain treatment for any of their psychological problems (Balter 1988). In cases of both major depression and generalized anxiety, the treatment rate with these drugs is under 40 percent (Uhlenhuth et al. 1983, 1984, 1988). Consequently, anxiolytics may actually be underprescribed to anxious patients (Nagy 1987) and a substantial majority of patients who report high levels of distress do not use medically prescribed psychotherapeutic drugs (Mellinger et al. 1974).

The question of whether benzodiazepines are appropriately prescribed or underprescribed or overprescribed, however, depends both on the physician's as well as the patient's philosophic perspective. Although some patients with

anxiety and stress are undermedicated, the question of whether all patients who have anxiety and stress should be treated with benzodiazepines cannot be easily answered. For stress or anxiety symptoms that are overwhelming or compromise clinical function, acute or long-term benzodiazepine treatment may be considerably more therapeutic than harmful. For less severe states, or for symptoms that are due to underlying psychological conflict, ongoing situational distress, etc., medication of any kind may not be indicated. For some patients, such as the group of chronic dysphoric psychiatric patients, long-term use of benzodiazepines may actually be antitherapeutic. Consequently, there is probably some truth that although for some patients benzodiazepines are underprescribed, for others they are overprescribed. For the majority of acute and medically ill long-term users, however, the benefits of benzodiazepines seem to substantially outweigh their risks.

ISSUES AND CONTROVERSIES

There are at least four controversial issues regarding benzodiazepine use and effect that require discussion. These are:

(1) The misinterpretation and overevaluation of certain benefits other than anxiolytic and antipanic effects. Examples include their supposed antidepressant and antipsychotic efficacy.

(2) The concern about rampant overprescribing of benzodiazepines by physicians, abuse of benzodiazepines by patients and nonpatients alike, and the misinterpretation of the drug's risk versus benefit.

(3) The questions of whether the long-term use and/or high-dose use of some benzodiazepines is more likely to produce dependence, toxicity, and severe withdrawal than other benzodiazepines.

(4) The increasing regulation and perhaps overregulation of benzodiazepine prescription and the consequent underuse of these drugs in legitimate circumstances and the reappearance of more toxic drugs to substitute for benzodiazepines.

The misinterpretation and over evaluation of the therapeutic effects of benzodiazepines

In addition to the well-established antianxiety, hypnotic, and antipanic effects of benzodiazepines, these drugs have been used to treat other psychiatric

conditions. Most prominently, benzodiazepines have been thought to have antipsychotic and antidepressant properties.

1. Antipsychotic properties

Studies with benzodiazepines at high doses have suggested significant therapeutic antipsychotic effect (Nestoros et al. 1983). An initial trial of alprazolam, for example, was shown to have beneficial effect on negative symptoms in chronic schizophrenic patients (Wolkowitz et al. 1988). This result has not been replicated (Csernansky et al. 1988). As a general conclusion, benzodiazepines by themselves probably do not exert any antipsychotic effect although they may modulate the dopamine system and allow for slight reduction in total antipsychotic drug dosages (Douyon et al. 1989).

The interpretation of data suggesting that benzodiazepines have antipsychotic properties illustrates some of the problems that can be found in benzodiazepine research for atypical indications such as psychosis and depression. In earlier studies, patient samples were small, and diagnostic and outcome criteria insufficiently described and established. In more recent studies, the diagnostic and outcome criteria are very specific, but the interpretation of the results is somewhat questionable. Statistically significant changes in rating scale scores may have little clinical meaning. For example, BPRS scores following alprazolam administration decreased by approximately 5 points (Wolkowitz et al. 1988), but this decrease does not translate to meaningful clinical improvement in patient's thought, affect or behavior. Benzodiazepines have been clearly shown to have adjunctive effect in the control of disruptive behavior associated with psychosis. Retrospective and prospective studies have demonstrated that psychotic patients who are out of control can be effectively managed by adding low doses of a benzodiazepine (usually the high potency lorazepam given intramuscularly) along with low doses of a neuroleptic. In fact, this combined treatment of severe agitation and behavioral disruption has become standard throughout many parts of the United States (Salzman et al. 1991). However, clinical practice has misinterpreted this therapeutic effect to suggest that continued benzodiazepine use might prevent recurrence of disruptive behavior. There are no data to support the prophylactic effect of benzodiazepines on behavioral disruption. Furthermore, benzodiazepines have been shown to be associated with irritability, hostility, and even aggression in some patients, especially under conditions of frustration (Salzman et al. 1974; Kochansky et al. 1975; Gardner and Cowdry 1985; Dietch and Jennings 1988). Therefore, one must question whether or not continued benzodiazepine use for this purpose is justified.

2. Treatment of depression

Benzodiazepines have been thought to therapeutically affect depressive symptoms for many years, and these observations have been supported by limited data (Salzman et al. 1975). More recently, benzodiazepines with a triazolo-ring have been thought to have more specific antidepressant effects. These clinical observations have been supported by double-blind placebo-controlled research. A review of 20 controlled studies of benzodiazepines as antidepressants concluded that these drugs alone are effective in relieving anxiety associated with depression and thereby elevate mood somewhat, but provide little benefit for the core symptoms of major depression (Schatzberg and Cole 1978). Nevertheless, the triazolo group of benzodiazepines still has the reputation of therapeutic antidepressant efficacy.

Examination of the data from some of these studies of antidepressant effectiveness illustrates some of the possibilities of misinterpreting these data. In one study, for example, alprazolam and imipramine, as compared with placebo, significantly reduced Hamilton depression ratings; it was concluded that alprazolam was as effective as imipramine for the treatment of depression, both significantly more effective than placebo (Feigher et al. 1983). Although a statistically correct conclusion, its clinical significance is questionable for three reasons. First, the total Hamilton depression scale score was reduced to only 15 which indicates a lack of clinically significant antidepressant effect. Second, most of the Hamilton depression score items that showed improvement were items associated with anxiety, agitation, or sleep, whereas the core symptoms of depression only changed slightly. Third, the study was only 6 weeks in duration. The patients who received tricyclics might have improved more than those who took the benzodiazepine if the study had been continued for a longer period of time. Similar conclusions can be drawn from a study of alprazolam compared with amitriptyline and doxepin with virtually identical data (Feigner 1982).

Controversy regarding the role of benzodiazepines for psychosis and depression continues today. As noted, the antiagitation effect of benzodiazepines is established, and there may be a further role in the reduction of neuroleptic doses and diminution of some extrapyramidal side effects. For depression, it is clear that benzodiazepines are useful drugs to promote sleep and decrease anxiety and agitation. It may be that the secondary consequences of improved sleep and decreased anxiety is some elevation of mood, but there are few data to support a meaningful antidepressant effect of these drugs on core symptoms of depression. Nevertheless, it seems that these drugs and the

triazolo derivatives, in particular, are still thought to possess antidepressant properties. For example, a recent study of estazolam, a benzodiazepine hypnotic with triazolo-ring structure, was shown to have antidepressant effect by significantly reducing total scores on the Hamilton depression rating scale (Ferguson et al. 1990). The authors concluded that these data further supported the hypothesis that triazolo benzodiazepines possessed antidepressant effect. Examination of Hamilton scores, however, reveal interpretive problems similar to the previous depression studies cited. The total Hamilton score only decreased to approximately 15, and virtually all of the items showing improvement with estazolam were on sleep, anxiety, and agitation items.

It may be true that triazolo benzodiazepines have some antidepressant properties, but the data are not yet available. Furthermore, clinical experience suggests that benzodiazepines, regardless of their structure, while not good drugs for use as primary antidepressants, may be useful adjuncts for treating related anxiety, insomnia, and agitation.

Are There Differences Among Benzodiazepines?

Until recently, it was axiomatic that all benzodiazepines were essentially therapeutically equivalent for the treatment of anxiety as long as doses were equalized. The high-potency benzodiazepines were shown to be more effective for treatment of panic disorder, although the low-potency drugs may also be effective if higher than usual anxiolytic doses are used. The question of benzodiazepine equivalence with regard to side effects has been controversial. It has also been axiomatic that all benzodiazepines share common side effects, and all produce a dependence and discontinuance syndrome following their long-term use. Although the onset of this discontinuance syndrome is more rapid with short half-life drugs, there may be no difference in the symptomatic components of the discontinuance syndrome nor in its intensity between high- versus low-potency benzodiazepines.

Whether or not there were pharmacologic as well as toxic differences between high- and low-potency benzodiazepines was discussed at considerable length by the APA Task Force members (1990) without clear resolution. From the pharmacologic perspective, some task force members pointed out the lack of data suggesting differential receptor binding affinity, and emphasized that the only difference was in the pharmacokinetic property of elimination half-life. On this basis, short half-life drugs are more likely to produce a severe discontinuance syndrome when abruptly discontinued than

are long half-life benzodiazepines regardless of the clinical potency of the benzodiazepine being used. Other task force members noted that clinical experience has suggested otherwise. Alprazolam and triazolam, in particular, (possibly clonazepam and lorazepam as well) seem to be commonly associated in the clinical setting with severe dependence and more difficult discontinuance. Many patients find it difficult to wean themselves from these drugs, and even with gradual dose discontinuation, severe rebound symptoms are not unusual (Fyer et al. 1987, 1988).

This controversy persists right up to the present. Practicing clinicians are concerned that the prescription of high-potency benzodiazepines, regardless of their elimination half-life, may be associated with difficult discontinuation if the drugs are given for more than a brief period of time, e.g., more than 1 to 4 months. However, research studies have not shown any difference in dependence and discontinuance between high- and low-potency drugs when both are gradually discontinued. The controversy is significant not only from a scientific perspective, but because of the implications for public confidence in physicians prescribing benzodiazepines and for possible legal consequences of prescribing these drugs. Critics of benzodiazepine use emphasize the dependence and difficult discontinuance associated with high potency benzodiazepines. Researchers emphasize the lack of evidence supporting a true difference between high and low potency drugs. Furthermore, some patients who may benefit from high-potency benzodiazepines may be reluctant to take them out of concern they will become dependent on them. Consequently, the question of risk versus benefit again becomes central for the use of these medications.

Recent data have suggested that there may be more than one subtype of benzodiazepine receptor, and that benzodiazepine receptors and their subtypes may be differentially located throughout the central nervous system. Furthermore, differential benzodiazepine-GABA receptor complex sensitivity may exist in different parts of the brain, suggesting that there may be some pharmacologic basis for different therapeutic efficacy, toxicity, and dependence among benzodiazepines.

Government Regulation of Benzodiazepine Prescription

As noted, benzodiazepines are widely available in the United States, but tend to be used either primarily for short periods of time or chronically for specific groups of limited numbers of people. There are also data clearly indicating that benzodiazepines are not abusable compounds (APA Task

Force 1990), although they are widely used among substance abusers who are taking other drugs of abuse and/or alcohol. Since benzodiazepine use by substance abusers tends to be highly visible, some public health and drug enforcement officials have concluded that benzodiazepine misuse and abuse was widespread. This conclusion may be also bolstered by the apparent existence of some physicians or physicians' groups that tend to prescribe large amounts of benzodiazepines for large numbers of patients, usually for people treated in clinics supported by Medicaid.

As a consequence, drug enforcement programs have sought to limit the availability of benzodiazepines by making their prescription more difficult. In New York State this has led to the use of triplicate forms for benzodiazepine prescriptions, resulting in reduced benzodiazepine prescribing, especially in nursing homes and in cancer treatment facilities. However, this regulation has interfered with legitimate prescribing of benzodiazepines so that some patients may now have more difficult access to treatment. Nursing home patients in New York State, for example, are now being prescribed greater numbers of neuroleptics for control of agitation or insomnia, with consequent increases in extrapyramidal and cardiotoxic side effects. Cancer patients and others with chronic disease (a group who are legitimate chronic users of benzodiazepines) are increasingly being prescribed alternate anxiolytics such as meprobamate and non-barbiturate sedative hypnotics, two classes of compounds that are far more toxic and dependence-inducing than benzodiazepines. Physician surveys report a growing reluctance to prescribe medications even for appropriate patients, for fear of prescription auditing. Furthermore, the attempt at regulation has failed to affect the primary target populations, i.e., substance abusers, and there has been no change in the street availability of these drugs (Schwarz 1991).

There is obviously a controversy regarding whether these compounds are ultimately helpful or harmful. The clinical perspective, articulated by the APA Task Force, suggests that although benzodiazepines may be sometimes overprescribed for certain patient subgroups, and occasionally misprescribed and misused by some physicians and patients, they are primarily used for appropriate clinical indications. Furthermore, they are not abused by legitimate patient populations, and with the exception of dependence and discontinuance, are relatively risk-free compared to the considerable therapeutic potential. From the public safety perspective, however, these drugs are apparently seen quite differently: they are considered to be abusable, widely misused, and overly prescribed, thus requiring careful regulation (Salzman 1991*c*).

FUTURE RESEARCH

The controversies discussed above clearly point to the need for further research. In addition to the burgeoning pharmacologic data on benzodiazepine receptors, pharmacodynamics, and pharmacokinetics, research is necessary to resolve these controversies.

A. Differences Among Benzodiazepines

It is likely that all benzodiazepines, if given in sufficient doses for sufficient periods of time, have the potential for producing a discontinuance syndrome when their use is abruptly terminated. Data from one series of research studies (Rickels et al. 1984) suggests that approximately four months of daily therapeutic doses is necessary to produce a state of dependence as defined by a clinically meaningful discontinuance syndrome. Anecdotal reports, however, indicate that there may be a broad duration of treatment during which some patients quickly become dependent, whereas others apparently never do or do not develop dependency for many months. The APA Task Force Report reviewed factors that may predispose to dependence, such as prior dependence on sedative hypnotics and advanced age, but there are still insufficient data to reliably predict the timing of onset of clinically meaningful dependence when therapeutic doses of benzodiazepines are given over a period of time.

Three research questions thus arise. First is the need for data timing the onset of dependence, as defined by appearance of discontinuance symptoms at different dosage levels, in patients with anxiety symptoms as compared with panic symptoms. A second perplexing question not resolved by the APA Task Force Report concerns potential differences among benzodiazepines in producing dependence and severe discontinuance symptoms. The task force reviewed the growing body of clinical experience suggesting that short half-life benzodiazepines are more likely to produce dependence at any given dose and duration of treatment than are long half-life benzodiazepines. It seems clear that abrupt discontinuation of short half-life benzodiazepines produces more severe rebound and withdrawal symptoms (and earlier onset of symptoms). The question of whether high-potency benzodiazepines are more likely to produce dependence and serious discontinuance problems than low-potency compounds remains unresolved.

The third related question concerns differences among benzodiazepines in causing withdrawal seizures following their abrupt discontinuation. The task

force review suggests that seizures are a serious, although relatively infrequent, withdrawal symptom that occur almost exclusively after abruptly discontinuing long-term benzodiazepines use, especially of short half-life compounds. However, FDA information based on anecdotal reports provided to the task force, suggests that alprazolam is more likely to be associated with withdrawal seizures than other benzodiazepines (Nelson 1987). However, there are no research data controlling for dose, duration of treatment, or presence of other drugs, that compares the relative potential for withdrawal seizures among different benzodiazepines. Anecdotal reports should not be taken as a measure of withdrawal seizure frequency or prevalence because of differential use patterns and reporting rates that may exist for alprazolam. Therefore, a comparative study of benzodiazepine withdrawal seizures would have considerable public health significance.

B. Long-term Benzodiazepine Use and Abnormal Brain Imaging

While the task force was preparing its report, several publications suggested that long-term benzodiazepine use is occasionally associated with cerebral atrophy as observed on CT scan (Lader et al. 1984; Schmauss et al. 1987). These observations were criticized because of the small number of patients, the lack of control of benzodiazepine doses and of concomitant substance use especially alcohol (Perera et al. 1987; Poser et al. 1983). The task force concluded that there was no reliable evidence to suggest that long-term benzodiazepine use was associated with structural or functional central nervous system damage. Nevertheless, these findings of possible brain damage continue to be cited by critics of long-term benzodiazepine use. Further evidence either to refute these conclusions, or in support of the APA Task Force conclusions is needed. Future studies, however, must be conducted in patients who have not previously used psychotropic drugs, substances of abuse, or alcohol.

C. Effects of Long-term Benzodiazepine Use on Cognitive Function

Therapeutic benzodiazepine use may cause an acute decrement of cognitive functions. There are no data to suggest that long-term benzodiazepine use is associated with permanent cognitive impairment. Pilot data in older patients suggest that cognitive impairment associated with benzodiazepine use of more than several months is reversible when the drugs are discontinued (Salzman 1991). However, because benzodiazepines may be used chronically by some older patients, it is of considerable public health importance to study the

effect of long-term use on cognitive function. In addition, discontinuance studies should be done to determine whether or not there is improvement or lack of improvement in cognitive function when long-term use is terminated.

D. Continued Consequences of Benzodiazepine Regulation

Although a reduction of widespread benzodiazepine use in elderly residents of nursing homes is to be applauded, the clinical consequences of such a reduction and the possible worsening of care from the use of more toxic substances must be carefully investigated. What are the consequences of no benzodiazepine treatment or the use of more toxic replacement drugs in patients for whom chronic benzodiazepine use is most appropriate, i.e., the older medically ill patient? Will there be increased benzodiazepine withdrawal (and even seizures) as more clinicians discontinue benzodiazepines in those patients who had been chronically treated?

Preliminary information suggests that triplicate prescription has not been entirely successful and may have limited the legitimate use of these drugs. However, States other than New York are also considering the use of triplicate forms for benzodiazepine prescription. Careful studies of the benefit to risk ratio of such regulation is necessary.

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Stimulant Drugs-Medical Needs, Alternative Indications, and Related Problems

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INTRODUCTION

This review of the medical uses of Schedule II stimulant drugs has been prepared for a meeting to evaluate the impact of prescription drug diversion control systems on medical practice and patient care. The stimulant drugs used in conditions other than appetite control–chiefly dextroamphetamine (Dexedrine), methamphetamine (Desoxyn) and methylphenidate (Ritalin)–fall under a major diversion control system based on the Controlled Substances Act of 1970. This act placed these drugs in Schedule II, made refillable prescriptions illegal, and placed controls and quotas on their manufacture. This has already had a massive effect on the extent of use of these drugs in medicine. One source (Grinspoon and Hedblom 1975) claims that over ten billion tablets of amphetamine-like drugs were made in the United States in 1970. Although no relevant figures or current production or sales of stimulant drugs are available, at least a 90 percent decrease in availability for prescription purposes in the United States seems likely. This massive reduction in use has been accompanied by great reluctance on the part of most physicians to prescribe stimulants, even when the medical indication is very clear or when the patient's clinical history clearly documents complete failure to respond to any other noncontrolled medication.

Clinical studies of the efficacy of Class II stimulants in psychiatric conditions, other than attentional deficit hyperactivity disorder (ADHD), have almost completely disappeared over the 20 years since stimulants were moved to Schedule II. Only recently have there been a small number of papers describing excellent response to stimulants in depressed or severely anergic medically ill patients in general hospitals, as well as in the treatment of depression-fatigue-cognitive impairment in patients with AIDS. There is also a modest revival of interest in and experience with the use of stimulants in treatment refractory depressions. A few studies also look at adult patients with residual ADHD symptoms. At the same time, one hears anecdotal

reports from patients with narcolepsy, adult ADHD, and chronic depression who have done excellently on stable stimulant medication for years. They complain that they are frequently unable to find a new physician to prescribe the stimulant once their original doctor moves, dies, or retires. The general position taken by this review is that stimulant medication is currently substantially underutilized in American medicine, and that the current level of control is certainly adequate to prevent any major abuse of prescribed stimulant drugs. In fact, since most patients who really benefit from stimulant therapy require maintenance medication for years, the currently nonrefillable monthly prescription causes frequent problems to patients, physicians and pharmacists. A special provision allowing selected documented patients requiring long term stimulant therapy to receive refillable prescriptions of the sort available under Schedule III would be very helpful. This paper will consider a number of relevant areas:

I. Changes in stimulant abuse between the 1940s and the present.

II. Available evidence on the way stimulants are currently being used, viz.:

A. Physician survey data for both Ritalin and Dexedrine from their respective manufacturers.
B. A mail questionnaire survey of the members of the Massachusetts Psychiatric Association with respect to stimulant prescribing to adults, conducted by the authors in the fall of 1990.
C. A description of 28 patients (evaluated or treated by the senior author) who have been maintained on stimulants for 1 to 30 years.

III. The principal officially approved as well as the medically reasonable indications for the prescription use of stimulants, with estimates of the number of patients who might reasonably receive trials of stimulant therapy and the number likely to be receiving such therapy.

IV. Medical need for stimulants

V. The probable impact of new diversion control systems

I. STIMULANT ABUSE–THEN AND NOW

McLean Hospital, a 300 bed private psychiatric hospital in the Boston area with a substance abuse program, has not admitted a patient with a discharge diagnosis of primary stimulant abuse or dependence (other than cocaine) in 10 years. Patients admitted in the preceding 10 years with this diagnosis were few and marginal, often chronic depressives who had done well on stimulants and whose physicians were worried about prescribing further stimulants for them. Real abuse of prescribed stimulants, except by a few younger poly-substance abusers, appears to have disappeared from our inpatient service. Informal checks with other Veterans Administration and university psychiatric services reveals the same general picture. Abuse of prescribed stimulants leading to amphetamine psychosis, violence, or overuse to elicit euphoria seems to have disappeared. When one reads overviews such as that in Grinspoon and Hedblom's 1975 volume, *The Speed Control,* the world seems to have been very different in the period before 1970. When amphetamines were freely and widely prescribed and almost anyone could get legitimate stimulant medication in enough volume for serious abuse, major problems occurred in some truckers, prisoners, and drug abusing delinquents. Some housewives and students also got into serious trouble. Unfortunately, the available literature cited by authors like Grinspoon and Hedbloom is biased. There are no extensive studies of large samples of patients prescribed stimulants for obesity, fatigue or depression in the course of ordinary practice which could yield any estimates of the proportion of thes patients who eventually got into serious trouble with stimulants.

The Grinspoon and Hedblom book begins with a distressing self-report of a man who began using amphetamines to perform better in college and eventually destroyed years of his life because of a massive, prolonged amphetamine addiction. Many, many college students then, and sometimes now, used stimulants for a night or a few nights to cram for exams without ever going on to malignant abuse of the drugs. The use of drugs to relieve fatigue and enhance performance on an occasional basis may, in fact, be useful in some cases, benign in others, and lead to dependence in others, but this type of use has never been seriously studied. The Armed Services in World War II used stimulants to avert fatigue in pilots and other personnel. This may have been unwise or it may, in fact, have been useful to the men taking the drugs some of the time. We'll never know. Similarly, we'll never know what proportion of the patients prescribed amphetamines for a wide range of psychiatric and medical complaints in the 1940s and 1950s were helped, what proportion used them wisely, and what proportion ended up

abusing them. One suspects the proportion who got into serious trouble was quite small. The only available study of the clinical patterns of stimulant use in the period before 1970, a survey of the use of stimulants by family physicians, was reported in 1962 (Brandon and Smith 1962).

This study was carried out in the United Kingdom. Thirty three doctors (members of the NE Faculty of the College of General Practitioners) completed data sheets on all patients receiving an amphetamine-like medication over a 3-month period. The drugs prescribed were Drinamyl (d-amphetamine plus amobarbital) (35 percent), d-amphetamine (21 percent), Durophet (probably a d-amphetamine spansule) (13 percent), and Preludin (9 percent). Dose averaged 10 mg a day and almost never exceeded 20 mg d-amphetamine or the equivalent a day. Six hundred and twenty (0.8 percent) of the 79,300 patients covered by the practices received an amphetamine. The main indications were: obesity (35 percent), depression (20 percent), tiredness (18 percent), anxiety (14 percent), and lack of confidence (5 percent). Rates of prescribing were much higher for women (85 percent) than for men (15 percent). Prescribing was highest in the age range 36-55. No cases of psychosis, toxicity, or dose escalation were observed, the authors state. One hundred and twenty-seven (20 percent) of the patients had been receiving stimulants for over two years, mostly for depression or other psychiatric reasons. The participating practitioners were asked to identify patients they judged to be "habituated." Sometimes the authors add the term "addicted". No criteria for this judgement were provided. Seventy-three patients (12 percent) were said to be habituated. Most of these did not fall into the "psychiatric disability" or "depressed" groups. Of the "habituated" patients, all but 17 of the 73 were over 35 years of age and 31 were over 65. At a guess, physicians called patients "habituated" if they felt the patients wanted to continue the drug but the doctor was not sure it was clinically useful.

Since Haight-Asbury, most of the serious noncocaine stimulant abuse has not been of prescription stimulants but rather of illicitly manufactured methamphetamine, once provided as a powder and now in smokable crystals. Putting severe diversion controls on prescribed stimulants to decrease "street" use of methamphetamine is an excellent example of a cure that does not fit the disease.

II. AVAILABLE EVIDENCE ON CURRENT USE

A. Manufacturers' Survey of Reasons for Stimulant Prescribing

Data provided by CIBA-Geigy based on market data from IMS International, presumably from prescription audits from panels of cooperating physicians, give figures on the reasons for prescribing methylphenidate for 1987, 1988 and 1989. For 1989, 47 percent of the prescriptions were for unspecified disorders of conduct, 31 percent for ADHD, 6 percent for depression and 5 percent for narcolepsy and cataplexy. These figures leave 11 percent of these patients undescribed.

Smith-Kline Beecham has conducted a nationwide, random sample telephone survey of Dexedrine use involving 50 pediatricians (30 percent used Dexedrine), 25 adult psychiatrists (12 percent used Dexedrine) and 23 child psychiatrists (39 percent used Dexedrine). They then interviewed 100 physicians, all of whom used Dexedrine, including the above three groups plus primary care physicians and neurologists.

The indications for which these 100 physicians prescribed Dexedrine were: ADHD (74), narcolepsy (29), weight control (5), ADHD-residual type (17), depression (13), fatigue (3), AIDS-related brain dysfunction (1), enuresis (2) stroke (1), and idiopathic edema (1).

B. Survey of the Massachusetts Psychiatric Society

A questionnaire was mailed to the 1,599 members of the Massachusetts Psychiatric Society in October 1990. Four hundred and thirty or 27 percent, responded. Two hundred of the 430 responders indicated they were currently treating patients over 18 with stimulants. Thus, 12.5 percent of the membership or 47 percent of those responding indicated current use of stimulants. Numbers of patients in various diagnostic categories were reported. A total of 655 patients were receiving stimulants: 377 for depression, 188 for ADHD-residual type, 55 for chronic fatigue, 28 to counteract sedation due to other drugs, 17 for narcolepsy, 18 for medical illnesses with depression, 14 for organic brain syndromes (10 due to AIDS), 6 for bulimia, 4 for obsessive-compulsive disorder and 4 for various anxiety disorders. A number of patients had more than one diagnosis, e.g., depression plus chronic fatigue or ADHD, or depression with a medical illness, such as AIDS. An additional 37 responders said they were not currently treating anyone with stimulants but had done so in the past, and 11

were using stimulants only in children with ADHD. Several also noted occasional brief stimulant use in hospitalized medical or surgical patients.

C. Patients on Maintenance Stimulant Therapy

The senior author is currently following or has done a detailed evaluation on 28 patients who, in his clinical judgement, derive substantial benefit from maintenance stimulant therapy. All of these patients have maintained a stable response without developing tolerance and without any evidence of drug abuse for periods of between 1 and 27 years. Twenty-one of these patients have received formal diagnostic reassessments in the last 2 years, including a SCID-P interview, while seven received a less detailed assessment. Most patients seen off stimulants originally met criteria for full major depressive disorder or had been hospitalized for such a severe depression in the past. One patient had been started on methylphenidate for "fatigue" 27 years earlier by an internist and no records of her state at that time could be retrieved; she may well have been depressed then. This patient plus a patient with pure panic disorder are the only ones without a significant history of depression or dysthymia. However, if one selects one major target symptom per patient, three have received stimulants primarily to suppress bulimia, two for fatigue, two for idiopathic hypersomnia, five for attentional deficit disorder (with or without hyperactivity), 15 for depression and one for panic disorder. However, two of the depressions also had bulimia, two had some form of attentional deficit disorder and two had idiopathic hypersomnia. Of note, three of the depressed patients had also had manic episodes at some time in the past but never on stimulants. All patients had failed on at least two antidepressant therapies before, during or after being started on stimulants. They average six unsuccessful antidepressant trials. Eight of the patients had first received stimulants in the 1960s before these drugs were rescheduled. Three of these had used illicit amphetamines bought in Mexico or on the street when they could not obtain licit medication.

Defining drug abuse for patients whose medical condition or symptoms clearly benefit from prolonged use of a controlled drug is a problem. Such patients do not meet current DSM-III-R criteria for substance abuse or dependence because they, legitimately, do not believe the drugs they are taking are harmful. Dr. Richard Blum of Long Island, New York (verbal communication 1990) has suggested the following criteria for abuse of prescription of drugs:

(1) Dosage out of physician's control
(2) Use causes overt problems (e.g. auto accidents, fights, loss of job)
(3) Patient denies problems obvious to others
(4) Problems increase over time
(5) Quality of life declines on the drug

By these criteria, none of the 28 patients described above have had any suggestion of drug abuse since they have been receiving reasonable dosages of prescribed stimulants.

It should be noted that response to stimulants in this population can be very specific to a single stimulant. Dexedrine will work well, while Ritalin is either ineffective or highly dysphoric. Pemoline will occasionally suffice. One patient only responds to biphetamine, one only to methamphetamine. Some take one pill at a time, two or three times a day. Others take the whole daily dose on arising and notice no obvious stimulating effect at all. Several patients have been off stimulants for 1 or more years at a time and stayed miserable on all other antidepressant therapies, but regained euthymia when placed back on stimulants. A few patients had fair to good responses to standard antidepressants but the response had faded after a few months. Stimulant response in this sample has been maintained for years, a rare phenomenon in treatment-resistant depression.

III. MEDICAL USES OF STIMULANTS

The Class II stimulants have FDA-approved indications in the treatment of attentional deficit-hyperactivity disorder (ADHD) and narcolepsy. Some amphetamines also have an approved indication in the treatment of obesity. Their use as anorectics will be ignored in this paper on the grounds that, although placebo-controlled studies document drug-related weight loss of about two pounds a week, there is little evidence that prolonged use does (or does not) benefit obese patients. Other approaches to obesity are available and are probably preferable.

As with many other psychoactive and nonpsychoactive drugs, stimulants are commonly used for indications beyond the approved labeling. These uses will be discussed. Since one of the goals of this paper is to estimate medical need, this will be attempted. These estimates will be exceedingly crude since the conditions treated are, by and large, relatively uncommon and some-such as chronic fatigue, adult ADHD (residual type), or AIDS-related neurasthenia -have never been the subject of any systematic study of prevalence, much less

incidence, in any defined population. The authors have conversed with experts and experienced clinicians in the relevant areas.

A. Narcolepsy

Classical narcolepsy is manifested by involuntarily falling asleep during the day plus chronic sleepiness, which can interfere with performance when the patient is awake. About half of the patients are said to also have cataplexy (sudden loss of muscle strength under stress), sleep paralysis and hypnogogic hallucinations (Mitler et al. 1990). Such patients show rapid onset of REM sleep when studied in sleep laboratories. Since the available prevalence studies were done on the basis of clinical judgement, not supported by polysomnography, they probably include an unknown proportion of patients with idiopathic hypersomnia (IH). Patients with IH suffer from recurrent sleepiness during the day, probably less severe than in Narcolepsy but nevertheless troublesome. They lack the rapid onset REM. Estimates of the prevalence of hypersomnia range from 5 to 29 per 1,000 (Roth 1980; Bixler et al. 1979). Both groups of patients benefit uniquely from stimulants and the vast majority take medication faithfully and sensibly without abuse or side effects for years.

One excellent study of narcoleptic patients by Mitler (1987) shows that Ritalin prevents sleep attacks and improves performance when awake, while Cylert improves performance when awake without preventing sleep periods. An antidepressant did neither; tricyclics do prevent cataplexy which stimulants do not help (Mitler and Hajdukovic 1991). Behavioral approaches to both narcolepsy and IH have been proposed. Several naps a day are said to prevent unexpected sleep attacks in narcolepsy. Some IH patients may not be sleepy during the day if they sleep 12 hours a night. Neither treatment approach is helpful for patients leading ordinary lives with ordinary jobs and social lives. The quality of daytime performance during these non-drug treatments has not been assessed. Given current knowledge, all patients with diagnosed or presumed narcolepsy deserve long-term maintenance stimulant therapy. Cylert, currently still in Schedule IV, may work in some IH patients. On the basis of a little personal clinical experience and conversations with two clinicians treating large numbers of such patients, I propose for the treatment of narcolepsy that 10 percent might be on Cylert and 90 percent on Schedule II drugs. One clinic following 250 such patients has not had any problems with stimulant misuse or abuse (Mitler personal communication).

Dement et al. (1973) give a prevalence of one per 1,000 for narcolepsy. Other figures for the United States are one in 10,000 (Roth 1980). A study of the rate of diagnosis of new cases done by the Mayo Clinic is said to give an incidence figure of 5 per 10,000 per year (Piscopo 1991). Piscopo estimates there are 12,500 new cases of narcolepsy a year for the United States, based on the unpublished Mayo Clinic data, and proposed a prevalence rate of 0.15 percent for narcolepsy or 375,00 narcoleptics in the United States. Epidemiological studies in the San Francisco area (Dement et al. 1972) and in Los Angeles (Dement et al. 1973) give total U.S. estimates of about 115,000, averaging the two studies. Narcolepsy has its onset, on the average, at age 25 and stimulant therapy is required indefinitely for the life span. Narcoleptics are the only group of patients with organized national associations and, therefore, the only source of any data at all on the problems patients face in obtaining reliable, indefinitely prolonged, stimulant therapy. The acute shortage of Dexedrine from the spring until the fall of 1990 caused substantial chaos for patients needing stimulants and for physicians prescribing them. Apparently Smith-Kline Beecham failed to manufacture either Dexedrine tablets or Dexedrine spansules (5 mg, 10 mg or 15 mg size) in time to prevent a massive supply problem. Patients and doctors had to go to several pharmacies (while the 4-day limit on Schedule II prescriptions expired), had to get prescriptions rewritten because the pharmacy only had 5 mg spansules, not 5 mg tablets, etc.

The person answering the phone at Smith-Kline Beecham in the summer of 1990 claimed this was only a supply problem, but there was a chronic suspicion by local clinicians that the Drug Enforcement Administration may have been somehow responsible. Certainly the drought lasted for many months. It caused anxiety, aggravation, and extra work in the Boston area, but most patients eventually found some pills of some size somewhere. Independent of where the blame for all this should really fall, it is inconceivable that such a shortage would have been allowed to occur if the drug were imipramine or propranolol or even morphine. The Schedule II almost orphan drug status of stimulants must have contributed to the unreasonable delay with which the problem was handled at the manufacturer's end. A similar shortage of methylphenidate occurred in 1986 (Federal Register 1988).

There is no available data on large groups of patients giving actual doses of Class II stimulants used in either narcolepsy or IH. However, there are two papers providing information on stimulant dosages needed over the long periods by narcoleptic patients by Daly and Yoss (1974) and by Honda et al.

(1979). Daly and Yoss assert that patients with moderately severe narcolepsy require about 100 mg of methylphenidate a day, with a few requiring up to 200 mg. For methamphetamine, which they observe to be better tolerated and more effective than d-amphetamine, they use daily doses of 25 mg for mild narcolepsy and more than 100 mg for severe cases. Honda et al., reporting on Japanese narcoleptics, note usual daily doses of methylphenidate of 20 to 60 mg. Both papers state that stimulants work well for years without any evidence of tolerance and with very little evidence of abuse or of psychiatric adverse effects. These papers suggest that average required doses for narcolepsy may be higher than for ADHD.

B. Attentional Deficit-Hyperactivity Disorder (ADHD)

This condition, manifested by a variety of behavioral and affective symptoms, was first shown to respond to amphetamine in the late 1930's. It affects predominantly male children from ages 2 to 15, with some amelioration of the symptoms when these patients reach their teens. Controlled clinical trials of the efficacy of Dexedrine, Ritalin and Cylert are almost invariably positive, though only a portion, perhaps 30 percent of the affected children, have excellent drug response, while another 30 percent show some clinical benefit. Cylert is less generally effective than the Schedule II drugs. Some children respond well to one stimulant but not to others. Prevalence is estimated at about 3-5 percent of school-age children or 1. 5 million cases in the United States (Biederman and Steingard 1989). Two follow-up studies on children with ADHD note that 30-50 percent still met criteria for ADHD in adolescence. Wender, who has published the majority of the papers on ADHD in adults, estimates that a third of the patients with childhood ADHD continue to have significant manifestations of the disorder in adulthood (Wender, personal communication 1991). Hyperactivity may be less of a problem than difficulties with sustained attention, mood lability, irritability, and disorganization. In his studies, adult ADHD patients improve substantially on stimulants but often are less aware of the improvement than their family members. They often stop the medication unwisely and the old behaviors return (Wender et al. 1981).

There is a related group of children and adults who have attentional deficit without hyperactivity (ADD). Some of the dysphoric adults evaluated at McLean who receive stimulant therapy with benefit appear to have something resembling ADD. They can think more clearly, do organized reading and work for the first time, and manage their lives and responsibilities much better. Some depressed patients who benefit from stimulants note that they

can go to work, hold jobs, and pay income taxes much more effectively on stimulants, but that their sad mood is less improved than their coping ability. As Rapaport (1983) showed, normal children also show improved performance on stimulants. The effects of stimulants on fatigue-induced performance is well documented (Weiss and Laties 1962). The stimulants are, therefore, likely to improve cognitive and behavioral functioning in conditions without obvious relationship to childhood ADD without hyperactivity. This overlap area will be discussed below.

The area of stimulant use in children with ADHD is an area of chronic controversy. From time to time, pressure groups try to prevent all stimulant treatment of children, raising specters of massive chemical restraint or poisoning of hordes of children. Currently, the evidence that many children with carefully diagnosed ADHD benefit from stimulants is overwhelmingly positive, based on information from patients and teachers as well as physicians. If anything, stimulants may be underprescribed because of inadequate mental health services for children. It is also likely that stimulant therapy is stopped prematurely in adolescents when hyperactivity is less prominent but concentration and adjustment are still poor. The diagnosis and stimulant treatment of adults with histories of ADHD in childhood and significant continuing problems is relatively rare and poorly studied. The survey of Massachusetts psychiatrists described above did, however, show that 29 percent of the patients over 18 receiving stimulants were assigned this category, suggesting that this use may now be more widespread. However, the exigencies of prescribing controlled stimulants in Massachusetts may facilitate the assignment of this “approved” diagnosis.

C. Depression

Although the literature on the efficacy of stimulants in depression remains equivocal, most controlled, double-blind studies are negative or weakly positive (Cole and Chiarello 1987); open studies are strongly and convincingly positive. Pooling of data from several studies using a single dose of Dexedrine or Ritalin in depressed patients as a diagnostic challenge yields a positive mood-improving response in 280 out of 4% patients (Goff 1986). There are also 19 recent case reports of rapid, excellent antidepressant response in depressed patients in general hospitals (Satel and Nelson 1990). Discussions with psychiatrists from two large local general hospitals suggest that such excellent responses occur in about half the patients so treated.

From our survey of Massachusetts psychiatrists, it appears that 58 percent of the adult patients receiving stimulants are being treated for depression. In the 1962 British survey of family practitioners, 20 percent of the patients were being given stimulants for depression. Most of the patients receiving stimulants for more than 2 years had depression or other psychiatric conditions. Interestingly, three quarters of these patients were not judged to be "habituated or addicted" by their doctors, suggesting that the stimulant was judged to be appropriate treatment for the depression. The senior author's experience is consistent with this general proposition. Some patients with depression respond uniquely to stimulants after failing to improve on or to tolerate standard therapies. In the senior author's series he considers the resilience of the improvement–no tolerance, no loss of efficacy over 2 to 28 years–remarkable.

In short, there exists a proportion of depressed patients who fail on standard therapies but respond very well to stimulants. A few of these have partial response to standard antidepressants and do very well on the combination of a standard drug and stimulant. In addition, there are chronically depressed patients who fail on many, many drugs but obtain limited benefit from stimulants–able to do a little more, feel less fatigued but are not markedly improved. Schedule II stimulants occupy a place in the treatment of depression at least equivalent to that of electroconvulsive therapy–a valuable option in patients who fail to respond or fail to continue to respond to standard antidepressants. Stimulants are much more useful than ECT, because ECT response is often brief while stimulants can provide excellent maintenance therapy. Since a 20 percent relapse in over 2 years is about as good an outcome as any antidepressant trial has ever shown (Frank et al. 1990), and a 50 percent relapse in 2 years and 80-90 percent in 3-10 years is more likely (Cole et al. 1986), excellent maintenance therapies are hard to find. At a conservative estimate, one fifth of the treatment resistant depressions will show a good response to one or another stimulant and most such depressions deserve such trials. Among treatment-resistant depressions referred to the Affective Disorders Clinic at McLean Hospital, only a third have had a stimulant trial (even though they average nine previous different drug trials), and this third have usually only received one stimulant, often at a dose which had no discernible effect. Such patients might well respond to a larger dose or to a different stimulant.

Psychiatrists are, in general, reluctant to start new patients on stimulants. Perhaps 80 percent of depressions are treated by primary care physicians; it seems likely that these nonpsychiatrists are even less prone to initiate

stimulant trials. One can assume that there are six million cases of depression in the United States in any given year and that three million actually receive treatment. Of those receiving treatment, 20 percent will turn out not to improve on at least three adequate trials on standard antidepressants. This leaves about 600,000 patients for whom stimulant therapy would be clinically reasonable. If one guesses that 20 percent would do well enough to warrant long-term stimulant treatment, 120,000 patients in the United States ought to be receiving stimulant therapy.

D. Chronic Fatigue Syndrome

Patients with chronic, disabling fatigue as a primary symptom have been described by clinicians for a century. The old diagnosis of neurasthenia is no longer part of DSM-III or DSM III-R, but the patients exist. Interest in the syndrome as a possible consequence of chronic viral infection has reawakened attention to the condition recently. Some such patients, with or without daytime sleepiness, do respond well to stimulants. Where other therapies have failed and stimulants provide substantial symptomatic relief, improve functioning, and are not abused, the use of stimulants is clinically justified.

At a crude guess, such patients are about one-tenth as common as patients with treatment-resistant depression and one-third will respond to stimulants, yielding a national figure of 6,000 patients.

E. AIDS

Patients with AIDS can develop a mixture of depression, fatigue, and cognitive impairment which leaves them more incapacitated than their general physical status appears to warrant. Perhaps this condition is related to viral involvement of the basal ganglia. In any event, clinicians in centers treating AIDS patients, at least in San Francisco, Boston, Miami and Houston, report using methylphenidate or d-amphetamine to treat such chronic states (Jones, personal communication 1991; Forstein, personal communication 1991; Cohen, personal communication 1991; Holmes et al. 1989). The dose may need to be increased from 20 mg of Ritalin a day to 80 to 100 mg a day as the disease progresses (Forstein, personal communication 1991). There are currently almost 200,000 known AIDS cases in the United States. Perhaps 10 percent of AIDS patients will have such a syndrome and benefit from a Class II stimulant for about a year during the course of their disease. Such patients,

even those in methadone programs for heroin addicts, are not observed to abuse or misuse their stimulant medication.

F. Medical-Surgical Patients

Some local general hospitals (Massachusetts General Hospital, Tufts-New England Medical Center) have Consultation Liaison Psychiatric Services which often prescribe stimulants for depressed or inert and apathetic medical-surgical patients whose psychiatric status appears more incapacitating than their original medical problem (Woods et al. 1986; Katon and Raskind 1980; Fisch 1985,86). In about half such patients, stimulants cause a rapid and impressive improvement within 1 to 2 days. AIDS patients also often are first prescribed stimulants in the same situation, during a hospitalization for an acute medical complication; they respond equally rapidly. Even if a standard antidepressant would be eventually as effective, their onset of action is far slower and they are more likely to cause cognitive difficulties or delirium in medically ill or brain-impaired patients.

Most medical-surgical non-AIDS patients may stay psychiatrically improved after a week to a month on stimulants, but perhaps a third may require long-term stimulant therapy to keep depression at bay.

G. Drug-Induced Sedation

Some psychiatric patients require long-term treatment with either anti-psychotic or antidepressant drugs that relieve depression or psychosis but leave the patient chronically oversedated. Lowering the dose of the sedative drug causes return of symptoms, changing to a less sedative antidepressant or antipsychotic does not help, and caffeine does not relieve the sedation. In such patients, stimulants can counteract the sedation and provide an optimal mix of drug effects.

H. Other Psychiatric Conditions

Occasionally a range of psychiatric conditions will respond uniquely to stimulants when other standard treatments fail to be of help. Some of these, bulimia, panic disorder, and obsessive-compulsive disorder, may be helped because these conditions bear some biological relationship to affective disorders. In the case of bulimia, perhaps the appetite decreasing effects of stimulant drugs is relevant. Other stimulant-responsive patients have a mixture of symptoms-fatigue, trouble thinking or organizing thought or

action, impulsivity, or mild brain damage; in these patients perhaps stimulants are acting in the same way they do in ADHD even though these atypical patients usually have no history of childhood ADHD. Perhaps brain changes occurring later in life respond in a similar manner to the brain deficit present in children with ADHD.

I. Perfomance Enhancement

Some patients with chronic mild dysthymia or concentration difficulty use stimulants in the same way some college students use them to write term papers or study for tests. They may or may not need maintenance stimulant therapy, but they either use higher doses or only use stimulants when they need to perform at a higher level for a few days to write papers or cope with unusual stresses or workloads. When used only occasionally for such purposes, such use does not lead to escalating use or abuse.

Whether or not such stimulant use is legitimate depends on one's viewpoint. Pharmacological Calvinists certainly would view such use with great concern. However, if such occasional use averts failures in professional school or loss of high-level jobs, the use seems reasonable.

IV. MEDICAL NEED FOR STIMULANTS

Stimulants are still viewed by many physicians as suspect, even illegal drugs. A survey of doctors' attitudes toward the use of stimulants by other doctors done around 1970 by Lewis (1971) is illustrative. Two-thirds of the physicians surveyed believed that other physicians overprescribed stimulants. Such attitudes are presumably still common. Some psychiatrists, faced with difficult, treatment resistant patients, or patients with a convincing history of past good response to stimulants, will prescribe them to a few patients. Others will refuse to prescribe stimulants even to patients with classical presentations of narcolepsy or ADHD, much less to treatment-resistant depression or bulimia. The hopelessness of dealing with AIDS patients and the pressures to shorten hospital stays in medical-surgical patients have probably contributed to the recent apparent increase in the use of stimulants in medically ill patients with or without AIDS on metastatic cancer (Massie and Holland 1990).

In the absence of knowledge of the current volume of use of prescribed stimulants, the figures proposed below may be higher or lower than the current quotas provide. They are:

Narcolepsy = 350,000
Idiopathic Hypersomnia = 350,000
Child and Adolescent ADHD = l,000,000
Attentional Deficit Disorder Without
Hyperactivity, Child and Adult = 250,000
Treatment-Resistant Depression = 120,000
Chronic Fatigue Syndrome = 20,000
AIDS-Related Depression and Fatigue = 20,000
Depression in Medical Patients = 20,000
Other Psychiatric Conditions = 15,000

Total number requiring maintenance stimulant therapy in a year = 1,145,000

Average Stimulant Dose: Ritalin 40 mg
Dexedrine 20 mg
methamphetamine 20 mg

It is impossible to say what proportion of patients should be on each Schedule II stimulant. Currently Ritalin is viewed as less "bad" and therefore prescribed a good deal more. However, in ADHD, surveys suggest that non-responders on Ritalin do better on Dexedrine, while the reverse is less likely to occur. The spansule form of methamphetamine may have a more even, prolonged action than equivalent forms of Dexedrine (Wender, personal communication, 1990).

The average useful dose is only an estimate. Some patients do well on a single tablet a day, a few need very large doses if any physician has the courage to go above 80 mg of Ritalin or 40 mg of Dexedrine–upper limits cited in some texts.

It is impossible to go from current data on prescription use of stimulants to firm figures on the numbers and types of patients, much less the range of dosages needed, if one assumes the drugs are used overconservatively at present. Current use should substantially underestimate real clinical need.

V. THE PROBABLE IMPACT OF NEW DIVERSION CONTROL SYSTEMS

If, as we believe, many patients with a variety of conditions could benefit clinically from reasonable, well-monitored prescribing of stimulants and most of these patients would not do as well on other psychiatric treatments, then

any new, aversive program which makes physicians feel that stimulant prescribing will bring a narcotics agent pounding on their door will, of necessity, decrease the use of stimulants substantially. Even under current Federal and State regulations, prescribing stimulants is difficult for both doctor and patient. Many drugstores do not carry d-amphetamine or methylphenidate. Druggists sometimes make patients feel as if they are drug addicts to the extent that they prefer pemoline to a Schedule II drug even though the Schedule II drug helps them a lot more. Most patients eventually find a friendly pharmacist and stay with him for years. If supplies of stimulants dry up, as they have twice in the last 5 years, then chasing from drugstore to drugstore becomes an agony. When drug enforcement personnel are believed to be punitive, as seemed to be true on Cape Cod in Massachusetts several years ago, it was impossible to get any doctors on the Cape to prescribe a stimulant or to get a drug store there to fill a prescription.

On the other hand, at least two psychiatrists in California who work with AIDS patients feel very comfortable prescribing Ritalin or Dexedrine, having lived with a triplicate prescription system for years and, thus, feeling secure that their prescribing behaviors do not bring the wrath of narcotics agents upon them. Physicians already comfortable prescribing stimulants to a number of patients will probably not change their prescribing when a new diversion control program is imposed on them if the new program does not attack them. Physicians who occasionally might consider prescribing a stimulant with trepidation would probably avoid actually prescribing one if they imagined that a new triplicate prescription system would leave them open to attack or censure. If the diversion control system means buying special prescriptions to use Schedule II drugs, many psychiatrists who never use opiates might never buy any and, therefore, could not prescribe Schedule II stimulants. As with many systems in the world, the response to a new system will be determined initially by the doctor's fantasies and expectations. Later, the response will be determined by what he or she hears, reads or believes about the way the system is actually run.

A triplicate prescription system that is mainly used to detect patients getting controlled substances from two or more physicians would be viewed as a good thing. A system that threatens well-intentioned, reasonable physicians with loss of license will spread panic and produce excessive caution in prescribing. If the system criticizes every physician who prescribes stimulants to any patient who does not have clearly documented narcolepsy or ADHD, it will penalize a large number of patients with other conditions which

respond well for years to stimulants. If the same standards are applied, but less aggressively, tired or sleepy depressions will be called narcolepsy and agitated or muddled patients will be called ADHD just so the patient can actually get the drug the doctor believes will help him. The issue of confidentiality will frighten away another group of doctors and also patients. The idea that one's name is in some State or Federal computer as a "drug addict" or "drug pusher" can be quite aversive. If the computer records are actually used to prosecute or investigate patients or doctors and the prosecutions are not perceived as unreasonable, then even more doctors and patients will be deprived of valuable drug options.

The issue of FDA-approved indications is another vexing problem for the use of Schedule II stimulants. The approved uses miss a substantial number of responsive patients. Unfortunately, double-blind studies showing efficacy in well-controlled clinical trials are not available for treatment-resistant depression, depression in medically ill or AIDS patients, chronic fatigue syndrome, idiopathic hypersomnia, or even adult ADHD. However, the patients who respond well do so within a few days and respond dramatically. The evidence of efficacy for these diagnostic groups as a whole is weak. For individual patients, the evidence is compelling. Any new diversion control system must take such evidence into account.

There is no published evidence of the risk of abuse or illicit distribution of prescribed stimulants. Anecdotally, Ritalin is obtained in Baltimore by drug abusers who claim they have ADHD children. The Ritalin is then dissolved and injected intravenously, causing talc deposits in the lungs and serious respiratory disease. "Ice" abuse is increasing on the west coast, but this form of methamphetamine is illicitly manufactured and outside any pharmacy-based diversion control system. If clear ground rules could be promulgated for the legitimate use and monitoring of Schedule II stimulants in a wide range of psychiatric and medical conditions including, but not restricted to, currently approved indications, then physicians could feel more secure in prescribing stimulants where standard therapies don't work as well as for FDA-approved indications. If the system then allowed for refillable prescriptions on patients who had done well on stimulants for a year, the lives of both doctors and patients would be greatly simplified. If the purpose of expensive, computer-based, statewide or Federal triplicate prescription systems is to reduce diversion or abuse of Schedule II drugs, we know of no evidence that more rigorous controls are currently needed for Schedule II stimulants. Their medical use has dropped dramatically since 1970 and the shortages of Ritalin in 1986 and Dexedrine in 1990 suggest that current

controls or quotas are already too restrictive. Patients who would do well on stimulants or have in the past done well on stimulants are likely not to get them. Underprescribing is more of a problem than overprescribing. Ominous sounding new diversion control systems are likely to cause even less appropriate use unless combined with benign enforcement procedures and extensive education of doctors about the right way to use stimulants in patients with legitimate but non-FDA-approved indications.

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The Nonmedical Use of Prescription Drugs in the United States

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Pharmaceuticals have brought major changes in the health and quality of life of the population of the United States and the world. Among these changes have been such milestones as the eradication of polio and small pox, and, on a broader spectrum, the ability to cure infections with antibiotics. The development of psychoactive drugs has brought similar benefits, ranging from the effective relief of pain to the control of mental illness to a point where massive deinstitutionalization became possible.

Each year, more than 1.5 billion prescriptions or an average of 6.7 prescriptions per person are dispensed from drug stores in the United States. The psychotherapeutic drugs, analgesics (excluding nonnarcotic analgesics) and sedative hypnotics account for approximately 215 million prescriptions a year (Burke et al. 1991). There is no doubt that these potent psychoactive medications are abused by some people. These drugs may be diverted from the manufacturing or distribution levels obtained through dishonest or duped doctors or from dishonest or duped pharmacists. They may also be obtained via pharmacy thefts, prescription forgery, or by illegal importation from foreign sources.

Data from the National Household Survey on Drug Abuse (NHSDA), the primary measure of the use and abuse of drugs in the United States, indicate that in the United States in 1991, approximately 172 million household residents reported that they had ever used alcohol, 68 million reported the use of marijuana, 25 million reported ever using any psychotherapeutic drug, and 24 million reported ever using cocaine (NHSDA Population Estimate 1991). If current use (any use in the past month) is considered, 103 million used alcohol, approximately 10 million used marijuana, 3 million used a psychotherapeutic drug and approximately 2 million used cocaine. It should be noted that the psychotherapeutic category is summed over four classes of medicinal agents: stimulants, sedatives, tranquilizers, and analgesics. Of these, only the current use of analgesics (1.4 million) exceeds 1 million.

The issue has been raised regarding the extent to which these data reflect abuse. In the NHSDA, the question on nonmedical use of drugs is phrased as follows:

> This is a very important point about the next set of questions. We are interested in the nonmedical use of these prescription type drugs. Nonmedical use of these drugs is any use on your own, that is either: without a doctors prescription, in greater amounts than prescribed, more often than prescribed, or for any reasons other than a doctor said you should take them-such as for kicks, to get high, to feel good, or curiosity about the pills effect.

The breadth of this definition has caused some to question whether self-medication is being measured rather than abuse.

This paper uses data from the NHSDA and the Drug Abuse Warning Network (DAWN). The primary measures associated with drug abuse are used to describe the current prevalence of abuse of illicit psychotherapeutic agents. The NHSDA also attempts to measure the consequences associated with drug use by collecting data on self-reported problems attributed to selected drugs. These problems include such things as becoming depressed or losing interest in things, having arguments or fights with family and friends, feeling alone or isolated and other problems. In total, eleven types of problems are included.

NATIONAL HOUSEHOLD SURVEY ON DRUG ABUSE

The NHSDA has been conducted since 1971 and sponsored by MDA since 1974. The 1991 survey represents the 11th survey in the series. A significant change in 1991 was an increase in the sample size so that data were collected from over 32,000 individuals, compared to approximately 9,000 interviews in 1990. Other changes in 1991 include the collection of data from persons living in some group quarters, e.g., civilians living at military installations, those living in college dormitories, and homeless shelters (homeless people not in shelters were not included). Also, Alaska and Hawaii were included for the first time. The response rate of approximately 84 percent is consistent with the response rates obtained with previous surveys. As in the past, the data are based on self-reports and do not include incarcerated populations.

More than 37 percent of the household population in the United States have tried drugs. The seriousness of the drug problem in the United States is reflected in part in polls conducted in the early 1970's as well as the early 1990's that cite drug abuse as one of the major problems facing our country. The good news is that while drug abuse remains a significant problem, the size of the problem appears to be diminishing. However, in some cases the gains of the last several years appear to have stabilized. For example, the estimates of any current illicit drug use in the population were the same in 1991 as in 1990; this was also true for marijuana and cocaine. This should be interpreted with some caution since the time period covered is only one year. The same is true of the nonmedical use of any psychotherapeutic agent. The significant decrease in past year use of these agents between 1988 and 1990 was not maintained in 1991.

Table 1

Trends in Nonmedical Use of Any Psychotherapeutic Agents
1988 - 1991

	1988		1990		1991	
	Number*	%	Number*	%	Number*	%
Lifetime	23,536	11.9	24,025	11.9	25,463	12.6
Past Year	11,399	5.7	8,567	4.3	9,161	4.5
Past Month	3,393	1.7	2,858	1.4	3,062	1.5

* In thousands Source: NIDA National Household Survey on Drug Abuse Population Estimates 1989, 1990, 1991

This pattern of stability is also exhibited for each of the classes of psychotherapeutic agents. In 1991, there were no significant changes in either the past month or past year's use in stimulants, sedatives, tranquilizers, or analgesics between 1990 and 1991.

Table 2

Trends in Past Month Use of Selected Psychotherapeutic Agents
1988 - 1991

	1988		1990		1991	
	Number*	%	Number*	%	Number*	%
Stimulants	1,755	0.9	957	0.5	668	0.3
Sedatives	784	0.4	568	0.3	755	0.4
Tranquilizers	1,174	0.6	568	0.3	889	0.4
Analgesics	1,151	0.6	1,534	0.8	1,403	0.7

* In thousands

Source: NIDA National Household Survey on Drug Abuse Population Estimates 1989, 1990, 1991

Table 3

Trends in Past-Year Use of Licit Psychotherapeutic Agents
1988 - 1990

	1988		1990		1991	
	Number*	%	Number*	%	Number*	%
Stimulants	4,957	2.5	3,109	1.5	2,709	1.3
Sedatives	3,099	1.6	2,233	1.1	2,130	1.0
Tranquilizers	4,407	2.2	2,538	1.3	3,408	1.7
Analgesics	5,342	2.7	4,999	2.5	5,090	2.5

* In thousands

Source: NIDA National Household Survey on Drug Abuse Population Estimates 1989, 1990, 1991

DRUG ABUSE WARNING NETWORK

DAWN collects data on drug-related emergency episodes in the total coterminous United States and 21 metropolitan areas. In 1986, the conversion of DAWN to a probability sample was initiated. Weighted data are currently available from 1988 forward, making long term trend analysis impossible. Previous analyses of long-term trends using consistent reporting panels indicated an increase in the number of total DAWN episodes between 1985 and 1989, but a decrease in the number of episodes associated with controlled prescription drugs (Table 4) (Adams 1991). In 1985, controlled prescription drugs accounted for approximately 38 percent of the episodes compared to 21 percent in 1989.

Table 4

Emergency Room Data: Total Number of Emergency Room Episodes and Episodes Associated With Controlled Prescription Drugs According to Year 1985-1989*

	1985	1986	1987	1988	1989
Total DAWN Episodes	76,391	87,388	103,500	114,411	109,400
Controlled Prescription Drug Episodes	28,840	27,430	27,219	25,292	23,020

* Based on data from 441 consistently reporting facilities with adjustments for nonresponse.

Table 5 shows the top 20 drugs reported to the DAWN in 1990. Included in the top 20 are 15 licit pharmaceutical products, including over the counter products such as aspirin and acetaminophen.

Table 5

Drug Abuse Warning Network Weighted Emergency Room Estimates, 1990

Drug Name	*# of Mentions*	*# of Suicide Mentions*	*Revised # Mentions*
Alcohol-in-combination	115,162	49,125	66,037
Cocaine	80,355	5,203	75,152
Heroin/Morphine	33,884	1,154	37,720
Acetaminophen	25,422	20,938	4,484
Aspirin	19,188	15,525	3,663
Ibuprofen	16,299	N/A	N/A
Alprazolam	15,846	10,976	4,870
Marijuana/Hashish	15,706	1,124	14,582
Diazepam	14,836	8,604	6,232
Amitriptyline	8,642	6,535	2,107
Acetaminophen with Codeine	8,222	N/A	N/A
O.T.C. Sleep Aids	7,984	6,733	1,251
Lorzepam	7,625	4,857	2,768
D-Propoxyphene	7,417	1,164	6,253
Fluoxetine	6,917	6,205	712
Diphenhydramine	6,483	5,059	1,424
Methamphetamine/ Speed	5,236	661	4,571
Oxycodone	4,526	2,528	2,076
PCP and PCP Combinations	4,408	244	4,154
Lithium Carbonate	44,025	N/A	N/A

Source: DAWN Annual Emergency Room Data 1990

These data are often cited as evidence of the diversion and abuse of these products. In fact, the inclusion of many of these agents in the top 20 is due to an anomaly in DAWN that, unfortunately may now be more misleading than informative. The anomaly occurs because the DAWN data include suicide attempts and gestures as one of the motivations listed for DAWN cases. So, while DAWN data are often quoted as reflecting diversion and prevalence of abuse, they reflect neither. The impact of the suicide attempts and gestures category on the top 20, especially licit pharmaceutical agents, is apparent from Table 5. For example, the number of acetaminophen cases drops from 25,422 to 4,484 and fluoxetine drops from 6,917 to 712. The arguments for excluding suicide cases from the analysis of DAWN data have been expressed previously (Adams 1988, 1991). Furthermore, the DAWN data are a measure of the consequences of abuse and not prevalence, as is sometimes implied. Increases in DAWN cases may reflect an increase in the number of users, but they may just as well reflect a shift in patterns of use (e.g., from snorted cocaine to smoked crack).

Other Consequences

As previously noted, the NHSDA contains a measure of the problems associated with the use of drugs. The problems range from health, work or school problems to drug-related problems with other people, feelings of depression, isolation, anxiety, and irritability. Respondents were asked to identify the specific drugs which caused any identified problem. These data are summarized in Table 6. A review of the data suggests an internal consistency between the pharmacology of the drug and the problems reported. For example, difficulty in thinking clearly and having arguments and lights with family and friends are mentioned more frequently for alcohol than feeling nervous and anxious and irritable and upset for cocaine. Among past year cocaine users almost 15 percent reported one or more of these problems in the 1990 NHSDA. For the licit psycho-therapeutic agents, it was necessary to combine the data from 1988 and 1990 in order to get reliable estimates of the problems attributed to these agents. Only 0.2 percent of past year sedative users and 0.1 percent of past year tranquilizer users reported at least one of the 11 problems. Two percent of past year stimulant users experienced at least one problem, while problems reported by analgesic users were so infrequent that the estimates were unreliable, even with the 2-year file.

Table 6

Problems Associated with Past Year Drug Use

Drug	Percent Reporting at Least One of Eleven Problems
Cocaine (1990)	15%
Psychotherapeutic Agents (1988-1990)	
Analgesics	*
Tranquilizers	0.1%
Sedatives	0.2%
Stimulants	2.0%

* Estimate unreliable
Source: National Household Survey on Drug Abuse

DISCUSSION

The use and abuse of licit psychotherapeutic agents obtained outside of normal medical channels is part of the drug abuse problem in this country. In 1991, an estimated 3 million Americans reported the nonmedical use of one of these agents at least once during the month prior to being interviewed. A critical question regarding this number is the proportion that reflects "abuse," however abuse is defined.

The report of the Shafer Commission includes data from a survey of 3,291 persons age 12 and above conducted in the fall of 1972 (National Commission on Marihuana and Drug Abuse 1973). Respondents were asked to identify various situations as drug abuse or not drug abuse. The report concluded that there was a tendency to identify nearly any situation as drug abuse. For example, 82 percent of the respondents said taking more of a nonprescription medication than the label directed was drug abuse, while 35 percent said that having a cocktail or highball with lunch or dinner and in the evening was abuse. However, the following were most often connected with abuse: use for pleasure, use to help cope with the day, taking more than prescribed or directed, and occasional use of heroin.

The current definition of nonmedical use includes the references to taking a drug in greater amounts than prescribed or more often than prescribed. It seems likely that a significant proportion of people reporting nonmedical use in the NHSDA may be obtaining the psychotherapeutic agents through licit channels. If abuse is related to problems attributed to the use of these agents, then the overall problem from a health perspective is relatively small. The problems are a fraction of those associated with marijuana, cocaine, alcohol or tobacco. The DAWN data are supposed to reflect consequences associated with the abuse of drugs, but for the licit psychotherapeutics they are misleading. The primary reason for this is the inclusion of suicides as described above.

From a law enforcement perspective, the diversion of these licit psychotherapeutic agents from legitimate practice, whether through forgeries, scams, or theft, is illegal. Representatives of the law enforcement and health communities often cite, albeit inappropriately, DAWN data as evidence of the size of the prescription drug abuse problem.

The importance of understanding the magnitude of the problem and the source from which the drugs are obtained is reflected by the fact that unlike heroin, for example, these are licit products that are subject to varying degrees of bureaucratic regulation and control. In fact, ten or more States are now spending millions of dollars in attempting to control the diversion of these products through the monitoring of physicians and patients.

In States where multiple copy prescription programs have been implemented, 35 to 50 percent reductions in the prescribing of the medicinal agents covered by the program have been noted. Some have argued that the reduction reflected the extent of overprescribing, while others argue that there is a chilling effect that is having a negative impact on patient care. Oklahoma has implemented an electronic data transfer program that does not require the use of a special form although the information sent to the State is the same as in a triplicate program. Preliminary analysis seems to suggest that this program does not have a chilling effect on prescribing.

To date, the only empirical evidence would seem to suggest that a chilling effect does, in fact, exist and that there is a negative impact on patient care. In Texas, a study demonstrated a reduction in the prescribing of Schedule II drugs and a corresponding increase in the prescribing of Schedule III analgesics (Sigler et al. 1984). In New York State there has been an increase in the prescribing of outdated, less effective, and more lethal drugs such as

meprobamate and chloralhydrate instead of benzodiazepines (Weintraub et al. 1991). In another study conducted in New York, two-thirds of the population felt that sending copies of prescriptions to the State was a violation of privacy, and 30 percent of the respondents stated that they would not take the best drug prescribed if it fell under the triplicate prescription program (Adams and Palmerini 1992).

Unfortunately, there is a paucity of data either at the national or State level that can address these issues. The current circumstances only reinforce the need for the health and law enforcement communities to work in concert. They must agree on the data that is needed, the best way to collect it and use it, and to design programs that effectively reduce prescription drug abuse without impairing health care.

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Drug Diversion Control Systems, Medical Practice, and Patient Care

Gene R. Haislip

INTRODUCTION

In recent years, some persons and corporate representatives have expressed concern that government-imposed controlled substances controls, especially multiple copy prescription systems, adversely affect the quality of patient care. The experience and available information, however, support the position that the reverse is the case, that such controls help ensure the quality of patient care and that it is negligent and criminal prescribing that supports excess drug sales, which are adversely affected. Research in every area affecting the health and welfare of citizens is desirable and it is no less the case in the area under review. However, this should not obscure the fact that a great store of knowledge, wisdom, and experience exists, nor should it be misused as an excuse to delay needed social action. Moreover, to evaluate drug diversion control systems on the basis of their impact on medical practitioners tends to obscure the correct focus of these systems. Their impact on medical practitioners and patient care is only one part of a larger purpose, which is to protect the public from the consequences of drug traffic and abuse. Nevertheless, control systems do have an impact on improving medical practice and patient care and it is worthy of attention. But, before proceeding in this area, it is desirable to focus at least briefly on the principal concern for which control systems are created.

THE PROBLEM OF DIVERSION

The diversion of licit drugs into the illicit drug traffic continues to be a major component of the national drug problem. Evidence of this can be found by looking at national estimates of hospital emergency room mentions for the top 20 controlled substances from the Drug Abuse Warning Network (DAWN). Approximately one out of every three mentions (33.5 percent) In 1990 was for a licitly manufactured substance. The dominant group for licit drugs continues to be the benzodiazepines. In 1990, there were eight among the fourteen licit drugs. Over the past few years, they have accounted for

approximately 60-65 percent of the mentions for licit drugs. However, there are also four narcotic analgesics among the top 20 controlled drugs. One of these is hydrocodone, which has shown a 56 percent increase in mentions in 1990. The influx of licit drugs into illicit channels is further demonstrated by examining emergency room episodes for cocaine and heroin. Among the drugs mentioned most often in combination with these are diazepam, alprazolam, methadone, and oxycodone. This statistical evidence is further corroborated by the Community Epidemiology Work Group and actual day-to-day State and DEA case investigations.

FEDERAL AND STATE CRIMINAL INVESTIGATIONS

Today there are approximately 845,000 DEA registrants that fall within the closed system of distribution of controlled substances. The overwhelming majority take their responsibilities seriously. Unfortunately, however, a small percentage of registrants break their public trust and engage in supplying the lucrative illicit market. The basis of this market is, as every pharmacologist knows, that these legitimate drugs produce consequences essentially identical to the purely illicit drugs and are sold for the same extraordinary profit. Relatively few Federal, State, and local law enforcement resources are dedicated to apprehending diverters of controlled pharmaceuticals, and yet we have some notable statistics to share. In 1987, DEA diversion investigators, often working in conjunction with their State and local counterparts, reported 63 criminal convictions. In 1990, the number of convictions grew to 192. Several recent examples of these investigations are included at the end of this paper. Further, in 1990, criminal court fines levied against pharmaceutical diverters exceeded $2 million. Finally, another gauge of the extent of diversion of controlled pharmaceuticals and the cooperative Federal and State response is the number of civil actions against registrations. From October 1987 through September 1990, the DEA's Office of Chief Counsel handled over 1,000 show cause proceedings to revoke, suspend, or deny Federal controlled substances registrations.

THE FUNCTION OF STANDARDS AND CONTROLS

Before proceeding to examine the impact of the laws designed to control the distribution of these drugs, it is appropriate to mention the principles on which they are based. The basic function of government-imposed standards and controls is to improve the quality of goods and services by establishing minimum requirements to protect the public from inferior, negligent, or

fraudulent practices, e.g., automobiles which malfunction, drugs which do more harm than good, airline pilots who fly under the influence of intoxicants, or physicians who improperly prescribe or profiteer from the weakness or ignorance of the public, etc. Controls are limited, however, to establishing a minimum acceptable level of goods and services and do not guarantee excellence. Nevertheless, excellence in good medicine is encouraged when it does not have to compete with unlicensed service which may be offered at a much reduced price.

An additional issue that is of concern to governments and taxpayers is cost-effectiveness. This is a socioeconomic issue which relates to cost as compared with (1) other alternatives, (2) the availability of funds for the intended purpose, and (3) the severity of the social problem which they are intended to correct.

These are principles to bear in mind in any examination of the issues under discussion. It is evident that any future research will be dealing with some aspect of the application of these principles. It is also evident that the possibilities for such research are enormous and could consume the work of decades. It is for this reason that decisions of the day, as always, must inevitably be made on the basis of experience, wisdom. and the best available evidence.

OVERSUPPLY AND EXCESSIVE DEMAND

When we behold the diversity of the world and its history, we must stand in awe. Not one thing is simple. Not one thing can be damned but what some useful result can be made of it. Not one thing can be praised but what some evil or stupidity can be found in it. It is no less so in the matters under review. We have in view a complex process of controls and standards operating within a dynamic and complex socioeconomic system consisting of industry, commerce, the health professions, the public, and government. Although it may not have been scientifically validated, I am confident in asserting that virtually all people hate to be sick or to feel bad. Those who are, or fear the possibility, hunger after health and happiness and its assurance. Medicine is viewed as the panacea; medicine for What ails, medicine to prevent the possibility of ailment.

This need for medicine has led scientists and doctors to produce wonders in the world, the virtual elimination of smallpox, polio, and numerous other sources of tragedy and horror. It is estimated that U.S. companies alone

spend approximately $8 billion per year to support these efforts. This desire for medicine has led even larger numbers of people into avenues of profiteering, some of which were bogus and some of which were destructive: the sale of addictive medicines, "fat clinics" whose activity produces amphetamine dependence and brain damage, heroin for morphine addiction, "stress clinics" whose trade results in addiction, stress management for young women which produces middle-aged benzodiazepine 'junkies," or the dumping in developing countries of out-of-date surplus antibiotics which destroy livers while providing corporate tax deductions. The excessive desire for medication has often led to an equally excessive supply. A couple of recent examples relating to the consumption and utilization of controlled substances will help to illustrate this latter point.

Prior to the passage of the Federal laws, it was estimated that approximately eight billion 10 mg doses of amphetamine and methamphetamine were manufactured, prescribed and consumed in the United States. This resulted in the massive abuse of stimulants throughout the country. They were obviously available everywhere and under all sorts of conditions, particularly through weight reduction clinics. As a result of the application of quota reductions and a variety of enforcement measures, the quantity now available within the legitimate sector is approximately one-half of 1 percent of the previous amount. This has had tremendous impact on patient care as well as general protection of the public. Consider the vast numbers of persons who have not become drug-dependent, have not been killed in accidents, do not pose social problems, have not wasted their money, or died of overdose. The tremendous quantities of these stimulants which were previously available would equate to 6 to 20 million stimulant-dependent persons, depending upon dosage per day. This compares with present figures of 29 to 115 *thousand* persons for whom they are currently prescribed. Thus, the impact of controls on patient care has truly been significant.

The drug methaqualone provides another interesting example. At one point, in 1981, the number of deaths and injuries which were reported in connection with this drug were equal to those involving heroin. It was soon discovered that the great majority (perhaps 95 percent) of the worlds legitimate production of this substance was being sold into the illicit traffic under the pretext and assumption of legitimacy. During the late 1970s and early 1980s, a phenomenon known as "stress clinics" operated in the United States. The financiers behind these clinics were nonmedical personnel who sought to profiteer from the prescription and sale of Quaaludes under the guise of treating patient stress. Clinics were set up in Chicago, New York, Ft. Lee

(NJ), Boston, Miami, Los Angeles, and in other cities. Doctors were hired at all these clinics to write prescriptions for one drug–Quaaludes. Again, the evidence was clear that most of the Nation's legitimate manufacture was actually being used for this disguised illicit purpose.

After extensive investigation over many years, and after many arrests of doctors, pharmacists, and other conspirators, three ringleaders were convicted in March of 1983 of operating a Continuing Criminal Enterprise (CCE) and sentenced to 15, 12, and 10 years in prison with no possibility of parole. Finally, the drug was taken off the market by Act of Congress In 1984.

THE IMPACT OF COMMERCIAL INTERESTS

Mind-altering drugs create dependence and a desire on the part of substantial numbers of persons to engage in their habitual consumption in the absence, and in excess, of any legitimate medical need, with resulting injury and costs to both the society and the individual. This social behavior is the basis of a demand for such substances in excess of need. This is precisely illustrated in the examples cited. If permitted to do so, the market will expand production and sales to meet this demand, thus generating profits far in excess of those associated with legitimate medical and social needs.

This fact is the basis on which all substance controls are predicated. Control\ act to reduce the permissible circumstances for consumption, thus restricting the volume of sales, and thereby conflicting with powerful commercial interests. Thus, we often see that commercial interests seek to resist or reduce controls, utilizing all the arguments and tactics clever lawyers can devise. A good example of this was the Federal effort to bring benzodiazepines under control. This action was first proposed in January 1966 and due to a series of hearings, delays, legal motions, and appeals, was not finalized until July of 1975, only a short time before the patent expired. Oftentimes much of the industry involved in the supply of controlled substances behaves In this way. Such generalizations have to be qualified since the pharmaceutical industry is by no means homogenous. For example, some manufacturer-s have occasionally sought appropriate control status for new products. The attitudes of corporate management are as diverse as those of individuals, and the behavior of some should not be used to characterize all. In the area of controlled substances, commercial interests sometimes manifest themselves in several important ways that may threaten the integrity of the health professions and the quality of patient care. These include (1) extensive organized efforts to influence physician behavior, (2) large expenditures on advertising,

and (3) well financed political networking and lobbying activities to influence government at all levels.

The relationship between the medical practitioner, the drug manufacturer, and patient drug consumption is complex. Companies use a variety of techniques to increase product utilization by medical practitioners. In the case of new drugs, this is inevitable because the developer possesses the majority of the knowledge concerning the product and has usually performed all or most of the research concerning it. However, promotion is largely the work of corporate sales departments, advertising, and detail men. Available studies show that this activity often goes far beyond technical explanation regarding indication for use of the drug, into all of the marketing techniques associated with non-drug products. According to the recent report of the AMA Council on Ethical and Judicial Affairs (1990), companies sponsor medical conferences that may include free lunches, dinners, hospitality suites, cash payments to attenders, or full cost of family transportation to a resort area with extra days for vacation. Some companies have provided gifts or cash payments for every patient who was started on a particular drug. In 1987, the pharmaceutical industry spent $5,000 per U.S. physician to promote its products, or 25 percent of total sales revenues. Moreover, in recent years some firms have shown a strong desire to extend prescription drug advertising directly to the consumer in order to stimulate sales. Thus, we see the persistence of commercial pressure to extend prescription drug consumption through a variety of techniques that go well beyond professional education.

Political networking is another means of protecting sales and especially of resisting control measures which threaten them. Thus, for example, most of the lobbying activity in opposition to control measures such as the multiple copy prescription systems is organized and initiated by manufacturers. This includes the sponsorship of seminars and meetings and other devices designed to create the appearance of alarm on the part of the medical professional, which might otherwise be absent. The availability of financial resources allows the employment of consultants whose reputation and influence within organized medicine and government facilitate these efforts. These are all practices which should be further researched by those concerned with patient care and public welfare.

A resort to dilatory tactics is the final defense of commercial interest professionals and executives. This may take the form of involved legal proceedings to contest control actions or perhaps simply a call for more research. In the present circumstances, for example, there is now a great

desire to research the impact of multiple copy prescription programs prior to any further legislative action. These systems have existed since 1940 and have been further enacted throughout the 1980s, but this sudden concern has arisen only since the action of the State of New York in now including benzodiazepines under its triplicate prescription requirement. It is now obvious that this action dramatically reduced the sale and utilization of these drugs. Some of their manufacturers claim that this is because many physicians are now intimidated in prescribing them by fear of government oppression. But New York State's action only created a reporting requirement. It did not change either State or Federal medical standards or In any way affect the approval for marketing of benzodiazepines.

Claims of reduced availability of drugs have, in fact, been made regarding the impact of controls on the prescribing and dispensing of narcotics for the treatment of cancer pain. Yet, the record discloses national quotas for production of narcotics have steadily increased over the past 10 years. In the case of morphine, the increase has been by more than 400 percent. It appears that these claims, as they relate to drug controls, are bogus and designed to play upon our natural sympathies.

FEAR OF DISCLOSURE

Although demands for research are sometimes used as a dilatory tactic, some are fearful of what the collection of data might actually disclose. For example, not long ago I had occasion to address a conference concerned with the administration of methadone maintenance programs, a difficult undertaking requiring the highest degree of patience, dedication and professionalism. In the course of my remarks, I reminded the conferees of the high number of death and injury reports in the DAWN system associated with methadone, an entirely legal drug under stringent quota control, all of which is supposed to be prescribed for medical need. The evidence does indeed suggest that it may be the most lethal of controlled drugs, legitimate or otherwise, on a dosage level kilogram-for-kilogram basis. It is not a popular thing to say, but it nevertheless needs to be examined and appreciated especially by those who utilize the drug. I subsequently learned that these remarks were not appreciated by some, and that one large, well-known institution which conducts maintenance programs thereafter declined to participate in the DAWN data collection system, citing my remarks as a reason not doing so.

Certainly we have ample evidence that some practitioners fear the creation of data systems which wilt expose the nature of their prescribing activity. This is because a small percentage of such persons may flood a community with diverted drugs through profiteering or excessive prescribing contrary to legitimate medical standards. For example, by utilizing national drug distribution data, we discovered an area in Texas which reported an enormous consumption of the Schedule II stimulant known as Pretudtn. A certain Dr. Thomas was the subject of a lengthy DEA/Texas Department of Public Safety investigation which disclosed that he was responsible for the dispensing of 46 percent of Preludin in the State, or approximately 33,600 dosage units per month. Prescriptions were issued at the physician's office in Nacogdoches, Texas, or from various motels in the Dallas, Texas area. On April 15, 1983, John Halt Thomas, M.D. a physician from Nacogdoches, Texas, was sentenced to five years in prison following his conviction for illegally prescribing Pretudin.

In 1986, national distribution data disclosed that Pennsylvania accounted for the consumption of approximately 25 percent of all Schedule II amphetamine and methamphetamine manufactured tn the U.S. and nearly 33 percent of all the Schedule II phenmetrazine (Preludin) although it had only 4.8 percent of the Nation's population.

Operation Quaker State was initiated by the DEA to reverse the upward spiraling trend. Between 1986 and 1988, over 43 separate investigations were initiated and completed against Pennsylvania physicians and pharmacies. Over 60 onsite investigations were conducted after the new 1987 Pennsylvania anorectic law was passed as a result of this DEA initiative. In addition to numerous criminal and civil convictions, a number of highly successful registrant cancellations were accomplished. By 1989, distribution of these drugs in Pennsylvania had returned to a normal level.

From the above, it may be seen that there are quite a few persons interested in hiding their activity from official scrutiny. The collection of prescription data does have an inhibiting effect on their activities, but not for the reasons usually cited by critics of data collection. These systems make more visible the malpractice and criminal profiteering which were previously safety hidden from authorities. The accomplices and wilting victims of such persons never complain to authorities and may operate without discovery indefinitely without such data systems. Filling out forms for the use of government and law enforcement personnel can never be popular with anyone, whether it is for income taxes or controlled drugs. But it is only those who have no

legitimate justification for their income or behavior who are inhibited by them.

In summary, then, experience supports the following conclusions with regard to the impact of drug controls on patient care:

1. The actual and potential demand for controlled substances exceeds legitimate need, thus necessitating the application of a variety of controls to ensure that production, sales, and supply do not exceed this need. The dependence-producing character of controlled substances and the potential for profits for both licit and illicit suppliers creates pressure to expand their availability beyond need, as illustrated In the examples cited.

2. Controls are intended to protect the entire public, of which patients are a smaller but critically important subset.

3. Controls should accord with the standards of legitimate patient care and medical practice.

4. Administrative and enforcement practices should not exceed these parameters.

5. Controls serve to protect patients from either willful or negligent abuse and excess, even though they may be willing to consent to such conduct by virtue of ignorance or dependence.

6. Controls help establish minimum standards of patient care and help sustain the public trust in the medical professions.

7. Data requirements relating to drug distribution, prescribing, and utilization do not establish standards of medical care, but do assist enforcement and licensing authorities in discovering incidents in which they are not being adhered to.

ADDITIONAL ILLUSTRATIONS OF PRACTITIONER-LEVEL DIVERSION

John X, M.D.

On May 8, 1991, physician John X was convicted on four counts of violation of 21 U.S.C. 841(a)(1), charging illegal sale of Schedule IV controlled substances (Valium). Despite multiple high quality undercover buys, the jury acquitted Dr. X on eight of the twelve counts of the indictment. Dr. X was portrayed by the defense as a decent small-town physician being harassed by the Federal Government. Dr. X was the subject of a 20-month DEA investigation which disclosed he was a significant source of Schedules III through V controlled substances in the rural Georgia community of Alma. Valium was the drug named In the indictment, although he was known as an "easy mark" for generally any drug in the lower schedules. Dr. X is currently awaiting sentencing.

Buy More Drugs

On December 7, 1990, Peter Doe, the previous owner of "Buy More Drugs", a pharmacy in Louisville, Kentucky, was convicted of ten counts each of illegal distribution and aiding and abetting (21 U.S.C. 841(a)(1) and 21 U.S.C. 843(a)(3)). The investigation by the Louisville Resident Office Diversion Group disclosed that Mr. Doe was illegally distributing Schedules III through V controlled substances to the addict community in Louisville. Mr. Doe was charged with illegal distribution of approximately 70,000 dosage units, primarily of Tylenol with codeine and Valium. Controlled substances were illegally dispensed to addicts by the pharmacist upon request without authorization by physicians. Several physicians testified to nonauthorized prescriptions which were on file at the subject pharmacy. On April 17, 1991, Peter Doe was sentenced to 51 months confinement and a $10,000 fine.

Michael Y, M.D.

On May 8, 1991, Buffalo physician Michael Y was found guilty in U.S. District Court on 11 separate counts of unlawful distribution of Schedule IV benzodiazepines. Sentencing is scheduled for July 18, 1991.

A convicted dope peddler/witness explained during the trial how prescriptions written by Dr. Y supplied his busy drug ring. He also explained how taxpayers-through the Medicaid system-footed the bills.

The witness testified that he made payoffs to the doctor in exchange for bogus prescriptions that allowed the witness and his associates to buy drugs at various Buffalo area drugstores. Medicaid cards were used to get the drugs at tax payer expense and the drugs were, in turn, sold on the street for many times their commercial value. Dr. Y received up to $1,000 per week from this one witness.

Basically the doctor took payoffs from several individuals to prescribe drugs hundreds of times for "patients" the doctor had never even met, much less examined. Drug of choice-Valium.

Robert Z., M.D. et al.

Three co-conspirators of Dr. Z recruited indigent people and took them to the doctor's office to receive Schedule II controlled substances prescriptions (Biphetamine, Dexedrine and Tuinal) for nonmedical reasons, These "patients" were then taken to a pharmacy to have the prescriptions filled, paid a fee, and relieved of the controlled substances which were then resold.

Dr. Z was indicted on 101 felony counts. In August 1990, he was found guilty in U.S. District Court, Southern District of Texas (Houston), on 89 of the counts (2 for conspiracy, 1 for obstruction of justice, 28 for Medicaid fraud, and 58 for illegal distribution). One of the co-conspirators was also found guilty of conspiracy. The other co-conspirators previously pleaded guilty to one count of conspiracy to distribute controlled substances.

On November 2, 1990, Dr. Z was sentenced to a maximum of 7 years imprisonment, a $100,000 fine, and $6,400 reimbursement to Medicaid. Action against Dr. Z's DEA registration has been initiated and is currently pending.

This case represented a cooperative effort of the Houston Diversion Group, the Houston Police Department, and the Medicaid Fraud Unit of the Texas Attorney General's Office.

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Existing Methods to Identify Retail Drug Diversion

G. Thomas Gitchel

CONTROL SYSTEM GOALS

Diversion of pharmaceutical drugs into the hands of dealers or abusers can potentially occur at each point in the "closed system of distribution"; thus, various degrees of control are dictated for participants in the system, from the manufacturer/distributor through the wholesaler, to the pharmacy, and on to the patient. The Controlled Substances Act of 1970 (CSA) is the Federal legislation enforced by the U.S. Drug Enforcement Administration (DEA) designed to create the closed system of distribution within which a controlled substance must be secured and accounted for throughout its journey from creation to consumption. Ideally, the system allows the drug to be traced backward or forward through a trail of controls and accountability requirements.

The CSA brought together various methods and procedures employed since the Harrison Narcotics Act of 1914 to prevent the diversion of licit pharmaceuticals into the hands of abusers through the establishment of a closed system of distribution. Each of the act's provisions was designed to limit an abuser's access to abusable drugs. A fully successful control system would be self-enforcing and totally prevent access to those without a legitimate need.

Control systems have two basic goals: first, to limit access to the controlled substances only to those with a legitimate need for access; and second, to establish, through records and reporting, the ability to track and identify instances in which the access controls are compromised. Some information systems assist in the latter–identification after the crime has occurred-which is, of course, essential for law enforcement to do its job. Some information systems also prevent or deter simply because some people won't take the chance of committing illegal activity for fear of detection. However, few record or reporting systems actually prevent access to the drug by the abuser. At the manufacturer/distributor level of control, preventing access to persons without a legitimate need is relatively clear-cut and strict, that is, vaults and alarms are required. However, at the dispensing level, finding the balance

between preventing or limiting access to the abuser without limiting access to the legitimate patient is much more difficult. Therefore, as we identify methods of drug diversion and systems to deal with them, let's consider them as *access control* or *identification systems,* or both.

The Controlled Substances Act

The first access control of the CSA is registration. It is designed to restrict access to controlled substances to those with the training, responsibility, and background needed to handle controlled substances. Prior to granting DEA registration, at the top of the control system is the background (eligibility) and security (location, access control) check. This includes the requirement for extensive vault, alarm, and cage security, along with employee screening procedures-all to provide access control to prevent employees, visitors, and burglars from obtaining controlled substances for unauthorized purposes. Quite obviously, similar restricted access controls do not exist at the retail level for the pharmacist or doctor.

A second major provision of the CSA is a records requirement. Registrants must keep track of all transfers of the drug-they must ensure that the transfer is either to another registrant or to a legitimate patient with a medical need for the drug. The "certification" for all persons in the chain except the patient is the registration number. The certification for the final delivery in the journey from creation to consumption-that of pharmacist to patient-is the prescription order by a registered medical practitioner.

Another record and access control provision of the CSA for Schedule II controlled substances is the three-part order form, or 222 form, which continues to be a primary self-enforcing access and identification control, All transfers of Schedule II controlled substances between registrants must be pursuant to a three-part control form preprinted at time of issue by DEA with the name, address, and registration number of the registrant. Schedule II drugs may only be shipped to the address shown on the form and the 222 is the only official and acceptable legal accounting record of the transfer. Such a form has been required for over 50 years for Schedule II drugs to provide limited access control and identification. The sole exception is the final transfer-from pharmacy to end user.

The final transfer authorization in this last link in the closed system of distribution is unique in another significant way. Unlike all other transfers which essentially involve two parties, this last transfer, at the most critical

level for protecting the drug from escaping into the hands of abusers, involves three parties. The pharmacist cannot distribute to the end user without specific instruction (a prescription) from a registered practitioner. Thus at the retail level, there are *four essential elements* to the transfer of a controlled substance: (1) the doctor, or authorizer; (2) the pharmacist, or dispenser; (3) the patient, or consumer; and (4) the prescription, or the authorization for the transfer of the controlled drug.

It is evident, by all available measures, that the tight access and accountability controls at the wholesale level have all but eliminated diversion at that level, but that the major problems of diversion occur at the retail level, again beginning with the "patient" or abuser either in collaboration with, or through manipulation of, the dispenser/prescriber. When diversion occurs at the retail level, a determination must be made as to where among the four elements the breach has occurred. Control systems must be examined to look, first, at the effectiveness to prevent unauthorized access, second, at the ability to provide information to correct the breach; and third, to identify where a system can do *both.*

Methods of Diversion

In order to apply this principle, let us examine several ways in which controlled substances exit the closed system of distribution at the retail level. First, there is prescription forgery, which can take several forms. These include legitimate prescriptions which are altered to increase the quantity; prescriptions written on blanks stolen from a doctor, which are not missed since these authorizations are not accountable; and the creation of false prescription pads.

This latter form of forgery is most insidious-prescription pads can be printed at any print shop with any name, address, and phone number requested, with no verification required. The forms are then "passed" by runners operating independently or in organized groups. If a pharmacist even attempts to verify the prescription by calling the physician's phone number on the prescription, the runner's cohort answers "doctor's office" and verifies the prescription. This is now even done with cellular phones, so the cohort can sit outside the pharmacy and alert the runner to any police activity. In this form of diversion, where among the above mentioned four elements has the breach occurred? (1) The doctor–no, because a legitimate doctor's name may be used although there is no authorization to dispense; (2) the pharmacist-no, because unless the pharmacist has other indications that the prescription is a

forgery, the dispensing occurs pursuant to a false authorization; (3) the end user-there is no legitimate patient here; and (4) the prescription-here is the key to preventing the activity. The abuser has created the authorization without a physician. The prescription itself is that part of the control system where the breach has occurred.

A second diversion scheme involves the pharmacist who sells controlled substances illicitly. In order to cover the illicit sales, the pharmacist takes blank prescription forms available in the store, looks through the files to identify legitimate patients of legitimate doctors, and simply writes out enough prescriptions in those names to cover the illicit sales. If the pharmacist uses enough doctor and patient names, this activity is almost impossible to detect by looking through the records or reports of the pharmacy because no one patient or doctor appears unusual. This type of diversion can only be documented by direct contact with the doctors and patients listed to verify that they did not authorize or receive the drugs. Where did the breach occur? (1) The doctor-none involved, although legitimate practitioners' names may be used without their knowledge; (2) the pharmacist-the primary source of the illicit sale with the access to the blank authorization to hide the illegal transaction; (3) the end user-the name on the prescription is a legitimate patient who never received the drug; (4) the prescription-here, again, is the key to preventing the activity. The pharmacist has created the authorization to cover the illicit sale without a doctor or patient.

A third scenario is the "doctor shopper." There are numerous scams frequently encountered to defraud a doctor into authorizing the dispensing of a controlled substance. These scams vary widely, such as claims of badly rotted teeth, lower back pain, hyperactive children, and old war wounds. One such despicable scheme involved an organizer who located several elderly cancer patients on fixed incomes who had difficulty meeting their bills. Each day the organizer loaded the patients into a van and went to various cities in a 3-State area to visit several doctors. The patients took their medical records and told the doctors they had come to the city to live out the last days of their lives with a relative in the city. In the move, they lost their pain medicine. They asked the doctor to take them on as a patient, and they would make an appointment to come back after he had checked with their doctor "back home," but could he please prescribe some hydromorphone until then. The patients collected 15-20 prescriptions per day, or 300 to 600 hydromorphone tablets per day, worth $50-$60 per pill. Again, where was the breach in the system? (1) The doctor-in this case the doctor wrote an

apparently legitimate prescription for a patient with an apparent medical need; (2) the pharmacist-the drug is dispensed pursuant to an apparently legitimate order; (3) the end user-using either a legitimate or feigned ailment, the user has obtained drugs for illegal safe or abuse through fraud; (4) the prescription-this is the link between the fraudulent patient, the prescriber/dispenser, and the method to detect the fraudulent end user visiting multiple doctors.

A fourth scenario is the one most people think of when the word diversion is mentioned-the illegal prescriber, or the indiscriminate prescriber. The indiscriminate prescriber prescribes even though it is apparent the drug is for abuse purposes. The doctor is an "easy touch" or too rushed to verify the patient claims, or simply writes the prescription to get the abuser out of the office. The illegal prescriber makes little or no pretext of medical practice; the practice consists of selling prescriptions. Variations include thinly veiled specializations to cover a drug selling operation, such as the "stress," weight, or lower back pain clinic in which every "patient" leaves with the same prescription for the same drug. Where among the elements did the breach occur in this scenario? (1) The doctor–the doctor is part of the diversion and issues an authorization without a clear medical need; (2) the pharmacist-unless the pharmacist questions the authorization, it will generally be dispensed; (3) the end user–again, the abuser seeks out such doctors to obtain drugs for abuse, not medical treatment; (4) the prescription–this is the authorization common among the other three elements that clearly documents the pattern of illicit activity.

Diversion Control Systems

This was a brief look at the complexity of retail diversion, not touching on additional areas such as hospital or nursing home pilferage. Now I would like to examine diversion control systems vis-a-vis the two issues of access control and information collection for targeting breaches of the controls.

First, Automation of Reports and Consolidated Order Systems, or ARCOS, which I will discuss in more detail later. ARCOS is a reporting system operated by the Drug Enforcement Administration (DEA) in its current form since about 1979. Briefly, it requires all manufacturers and distributors of controlled substances in Schedule II and narcotics in Schedule III, and limited other drugs required by treaty, to report all transfers of these drugs. From reported data, DEA produces information related to distribution by State, ZIP code, and per capita distribution. It provides absolutely *no*

information about doctors unless they buy drugs directly from a wholesaler. It provides no information about the end user or the prescription. ARCOS has little impact on access or on preventing diversion at the retail level. With respect to providing information to identify possible diversion after it has occurred, ARCOS is one of the best systems for identifying trends, targeting geographic areas, and identifying possible sources of illegal dispensing. However, ARCOS does nothing to assist in determining which of the four elements of retail diversion should be focused upon. ARCOS is invisible to the doctor, pharmacist, and end user.

The next diversion control system listed on the program is PADS, the Prescription Abuse Data System. Frequently, there is confusion between PADS and PADS II, both programs of the American Medical Association. Rather than a control system, the original PADS program is more appropriately considered an administrative approach to addressing diversion at the State level. This approach brought together, at the State level, private and government concerns with an interest in diversion issues to look at various systems and resources in the State such as ARCOS, Medicaid, treatment program information, and DAWN. The parties attempted to define the nature and extent of the problem within a State and to identify legislative or administrative approaches to deal with the problem. PADS II was a theoretical program to collect voluntary submissions from chain drug stores, Medicaid, and worker's compensation systems to identify the top five percent of prescribers in the State. Due to the voluntary nature of the submissions, the utility of the system was questionable, and due to legal, technical, and administrative problems the system was never effectively implemented in any State.

Another State system, the DIU, or Diversion Investigation Unit, is a specialized, staffed unit to investigate diversion, rather than a control system as such. As with any crime, medical, public health, or safety issue, attacking a problem is more effective if dedicated and trained resources are devoted. Unless we can design self-enforcing control systems which absolutely limit illicit access and thus prevent diversion, a dedicated and trained work force is essential. A DIU is the primary user of the information systems designed to control diversion, and examines the distribution system to identify breaches in the "closed system." The DIU is a hybrid State unit with elements of the State police, and boards of pharmacy and medicine, which examines the nature of the diversion and determines whether the approach should be a criminal investigation or licensing board action. Knowledge that such a unit

exists within the State and publication of its actions is a deterrent to criminal activity; thus, there is a preventive element to DIUs.

A very new diversion control system is OSTAR–the system for Oklahoma Schedule II Abuse Reduction. This is a welcome approach to providing potential diversion information not available previously due to the lack of computer capabilities at the pharmacy level. Basically, this system requires the electronic transfer of information on prescriptions filled to a contract firm employed by the State, information which is then used to identify questionable practices. The data, including online access, is provided to the State enforcement agency. This system is a major advancement in the ability of the State to identify and attack sources of diversion on a timely basis. Widespread adoption of the electronic transfer of prescription information should be encouraged. However, in considering the elements of a control system, this, as most systems, primarily provides information to identify where the closed system has been compromised, but does not prevent it or provide access control. The forgeries are still filled, are reported, and are not readily detectable; the pharmacist creating false prescriptions to cover illegal sales still reports them, and they are not readily detectable; and the doctor writing illegal prescriptions continues, but will hopefully be detected before too much damage is done.

The MADAS, or Medicaid system, is a recent and welcome innovation. Similar to the other systems described, it reviews information regarding Medicaid prescriptions of controlled substances in all schedules which have been filled to identify unusual or excessive prescribing. Again, this information is very useful, important, and helpful in identifying possible leaks in the closed system, but it does not provide access control or prevent diversion. First, information is limited to Medicaid claims. Second, the system can be evaded by paying cash for the controlled drug, so the transaction is not reported in the system, yet Medicaid is billed for services or drugs which were not provided. Third, forgeries and false prescriptions created by pharmacists are still reported and are not easily detectable.

Lastly, I would like to discuss multiple copy prescription programs (MCPPs), or accountable prescription programs. Generally, under these programs, prescriptions for designated drugs must be written on State-issued, serially numbered prescription blanks preprinted with the doctor's name, address, and registration number. Under a triplicate prescription system, one copy is retained by the doctor, one by the pharmacy, and one copy is sent by the pharmacy to the State. Under a duplicate system, the doctor does not retain

a copy. Several States are considering a program in which a single-copy serialized prescription is written by the doctor, retained by the pharmacy, and electronically reported to the State, thus combining the control/prevention aspects of the MCPP and the timely reporting of the OSTAR. MCPP programs are in place in nine States covering approximately 40 percent of the practitioners in the United States, and seven of the nine State programs have been in existence for 10 years or more.

Unlike any of the above-mentioned control programs, the MCPP provides a major element of diversion prevention or access control in addition to its ability to provide information to identify breaches in the closed system. Forgeries are essentially eliminated–the prescription blank is a control document similar to the Federal order form used at all other levels of distribution. It cannot be altered or falsely printed without easy detection *prior* to dispensing. In addition, the pharmacist seeking to create false prescriptions to cover illegal sales is eliminated-he does not have access to the authorization document. The pharmacist may still sell illegally but is substantially deterred since there is no way of covering up the illegal sale with false records. Also, the illegal or indiscriminate prescriber is substantially deterred. Only under this control system is the prescriber, at the time of putting pen to paper, reminded that this prescription is directly accountable to the prescriber. Illegal prescribers have no doubt that their activity is now readily detectable. Regarding "doctor shoppers," the system does not improve the prevention aspects any better than other systems, but the patterns are readily identifiable, and the "evidence"–the prescription-does not have to be randomly searched for throughout the pharmacies in the State. Nothing in the MCPP dictates, stipulates, regulates, or manipulates the doctor's medical judgment. It simply requires that certain controlled substance prescriptions be recorded on a different authorization document.

Finally, in examining controls, there are those who imply that the problem of pharmaceutical abuse is declining and, thus, current diversion control efforts are sufficient. It must be recognized that the problem is declining as a direct and traceable result of these controls. The attitude that current efforts are sufficient because of a decline in the problem implies that the United States is approaching some threshold level of diversion and abuse that is acceptable. The only appropriate response is that there is no excuse for accepting diversion that experience has proven to be preventable. Independent of any other success which may be achieved in reducing the abuse of illicit drugs such as heroin, cocaine, or LSD, the pressure to divert and the powerful abuse potential for pharmaceutical drugs will always be with us, because we

must ensure that necessary medication is readily accessible to all. But in consideration of the constant and potentially increasing pressure to divert pharmaceuticals, it is essential that appropriate access controls be employed to prevent diversion and abuse. Unlike dealing with illicit drugs of abuse, in attacking pharmaceutical diversion, we don't have to deal with helicopters, foreign diplomacy, and jungle laboratories. The sources of these drugs are here in this country, listed in the "yellow pages," and we give them a Federal and State license. Preventing the diversion of pharmaceutical drugs is the one abuse problem that is within our direct ability and jurisdiction to control in the United States, if we have the necessary resolve.

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PADS Approach to Preventing Prescription Drug Diversion

John J. Ambre

PADS is an acronym for Prescription Abuse Data Synthesis. This acronym or label has been used since 1982 to highlight the American Medical Association's response to public concern about drug abuse as a national problem and the impression that diversion of prescription medications was one source of supply of drugs to the "street" market. I will give a brief historical overview. I should point out that I am not a figure in that history since I have been with the AMA only a few months.

The PADS activity involved the use of the resources and influence of the AMA to aid States in developing a program for evaluation and approach to the problem of medication diversion within the State. This activity had several elements:

1) Enhance cooperation among State agencies involved in licensing, regulation and drug enforcement activities. This took the form of aid in creation of State task forces and interagency committees through the drafting of interagency agreements and memoranda of understanding. It involved the organization of meetings of various State agencies such as the State Department of Health, the State drug abuse agency, the agency administering Medicaid, police and law enforcement agencies, the field office of the Drug Enforcement Agency (DEA) in the State, and State medical and pharmacy Associations. The design was to facilitate the sharing of information from the Drug Enforcement Agency (DEA) that was already available to various agencies within the State, primarily ARCOS reports, i.e., reports of wholesale distribution of prescription drugs to pharmacies or other retailers. Information might also include Medicaid Management Information System Reports (MMIS) and some pharmacy audit data from State boards of pharmacy but these were much smaller databases.

2) Improve medical professional education and awareness regarding the mode of operations of drug diverters posing as patients and identify refreshed courses on the clinical pharmacology of analgesic and psychotherapeutic

medications (the major group of controlled substances and abused drugs) for physicians identified as needing such. PADS also assisted in the production of conferences and continuing educational materials for physicians and other medical professionals-for example, the publication of practice guidelines and up-to-date information about prescription medications through the *AMA Drug Evaluations* textbook.

3) Aid the investigation and prosecution of practitioners suspected of drug diverting activities. This was accomplished by operation of the AMA master file for biographic and disciplinary information on physicians.

4) Development of model legislation for diversion control, including involvement in the drafting of a new Uniform Controlled Substances Act that would include provisions for cooperative interaction of State agencies.

5) Sponsorship of national conferences on impaired health practitioners and identification of model programs for referral and treatment of these individuals.

In other words, PADS represented the formalization of AMA staff activities appropriate for a national professional organization properly concerned about the public health–specifically a national problem of substance abuse-and the quality of medical practice.

Over the last few years, considerable effort was devoted to development of the *PADS II* concept. This included the development of computer software for manipulation of electronic databases consisting of medication dispensing records from State Medicaid systems. Data acquired from pharmacy transactions would be used to generate prescriber and patient specific prescription profiles. Input would consist of patient identifier, drug code, quantity and dose information, pharmacy, and prescriber identifying numbers for each prescription Reports would consist of quantity data on each drug or drug class, such as total weight or dosage units of a drug prescribed, units per prescription or patient, total weight or dosage units received by a patient, and others, which would allow retrospective review of prescribing volumes and the detection of gross fraud and abuse by prescriber or patient. As I mentioned, the database of pharmacy transactions to be used would consist of the data acquired by the State Medicaid system. The database includes all drugs paid for under the Medicaid program, but PADS would focus only on the controlled substances.

Such a program would collect the same information as other electronic prescription systems. An analysis would be made in terms of the mass balance sheet: How much of each product has changed hands. The so-called "drug exception report" would identify physicians or pharmacists whose prescribing or dispensing of a particular drug placed them in the top few percent of all prescribers or dispensers in the preceding quarter. A listing of frequent recipients would identify patients who filled the most prescriptions for a particular drug and those who obtained the drugs from various different dispensers or prescribers. The difference would have been how and by whom the reports would be reviewed. I will discuss this later when I describe the principles of utilization review applied to controlled substances. The PADS II program has not been implemented, although a test project using this software system may eventually take place in Colorado.

Because the general PADS activities I described earlier are not, in the main, directed at identification of individual cases of drug diversion, it is difficult to evaluate their effectiveness. It would not be appropriate to use (as they have been) total drug mention data from DAWN as an index of the impact of various programs on prescription drug diversion. Changes, for example, in Schedule II drug mentions in emergency room visits would include cocaine mentions, since cocaine is in schedule II. The supply of cocaine to the street is certainly not from diverted prescriptions. It also is not appropriate to look simply at changes in volume of Schedule II prescriptions to evaluate the effectiveness of various alternative programs such as MCPP on drug diversion because drug use patterns change periodically due to other factors such as introduction of new alternative medications and new information about old ones. For example, zomepirac was widely used as a supplement to opioid analgesics in severe pain until its withdrawal from the market because of liver toxicity. A new nonsteroidal potent analgesic, ketorolac, may have a similar impact. The lack of data addressing the question is no reason to use other data inappropriately.

We do not intend to use the PADS acronym in the future, other than to refer to past AMA activities. Evolution of the larger issue of quality assurance in drug therapy dictates a modification in approach. Under the recently enacted Omnibus Budget Reconciliation Act of 1990, Federal Medicaid payments for outpatient prescription drugs will be conditioned on State development of a Drug Utilization Review (DUR) program by January 1, 1993. A number of programs, using computers and electronic data collection, are already in place. DUR computer programs that generate patient and physician medication profiles would also have the capability of identifying inappropriate or

illicit usage patterns for controlled substances. Such programs often have parallel components called Surveillance Utilization Review (SUR) that deal exclusively with fraud and abuse. Since the PADS II program described above would be identical, using the same database, the AMA plans to incorporate the objectives of the PADS program i.e., include SUR in the overall DUR initiative that addresses the prescribing of all drugs (including all controlled substances). The AMA strategy on DUR is presently taking shape, working with Pharmacy organizations and Federal and State Government agencies, and will look to programs that have the primary goal of improving the quality of patient care through improved physician prescribing, pharmacist dispensing, and patient compliance, and that are reasonable and fair to physicians. Model programs will use more complex algorithms for screening cases rather than simple statistics on script volume. False positives in the screening process translate into inappropriate investigation, intimidation and even harassment of conscientious and competent physicians. Therefore, every attempt should be made to prevent false positives.

The AMA has been involved in many important and potentially effective activities, formalized under PADS, that collectively constituted a source of information and education for physicians and had impact on controlling diversion of prescription medications. These activities will continue, insofar as the resources of the AMA permit, but in the future will be part of a general drug utilization initiative.

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Diversion Investigation Units–Methods, Utilities, and Limitations

R. Keith Bulla

Any discussion of diversion should begin with some identification of the different levels of activity. I break it down as follows:

Activities usually addressed by regulatory action

Overprescribing (long-term use)
Misuse
Abuse

Activities usually addressed by criminal action

Doctor shopping
Prescription forgery
Sale (including practitioner prescription sale)
Embezzlement
Theft

If we compare prescription drug activity with "street" drug activity, we find the motivation is similar. It is the use of the drug or the sale of the drug, or a combination of the two. The source is very different. Prescription drugs begin with legal distribution and access, and at some point the activity steps outside the legal course. In contrast, the "street" drug source is completely illegal.

The possession of a prescription drug can be legal or illegal; its sale can also be legal or illegal. The possession of a "street" drug is illegal and its sale is illegal. If an individual is found to have heroin in his or her possession, the person is in violation of the Controlled Substances Act. That same individual with a bottle of Dilaudid in his pocket poses a different problem. How was it obtained? What did the person tell the practitioner?

The control approach must be different for street drugs versus prescribed substances. With street drugs, we strive to eliminate the *supply* and the *demand.* With prescription drugs, we cannot eliminate the supply *or* the demand. Therefore, we must develop a better control system, a system which ensures the drug's availability to those with medical problems requiring it but, at the same time, identifying those without a medical need. A very critical element of this system must be adequately training practitioners and pharmacists to practice their professions. This training must include their learning to recognize substance abusers and the various ploys they use to obtain abusable prescribed drugs.

We also need to increase the awareness of the general public that tablets and capsules in the local pharmacy are drugs. Most people draw a very distinct difference between medicine and drugs. They do not understand that it is the use circumstances, not the substance, which distinguishes between medicine and drugs.

Prior to 1972, there was virtually no law enforcement effort directed at drug diversion in this country. Many physicians wrote/sold prescriptions with no hint of the practice of medicine.

The Drug Investigation Unit-DIU-program was developed in 1972 with a pilot project in three States. In 1974 the program expanded with Federal funding to more than 30 States. Then, with the decline of Federal funds, the program also declined. Once again we saw law enforcement directing most of its resources at street drugs because it was the most visible problem. Another factor-maybe the most influential-was that the enforcement of street drug laws was easier.

Some States continued the DIU program in one form or another as did North Carolina. Even with the decline of identified DIUs we saw an increasing awareness of the problem. The medical profession in particular has made great progress. I observe a great reduction in the number of "script doctors." Since the mid-1980s we have seen several effective programs introduced to reduce diversion. However, no single program solves all the prescription drug diversion problems.

North Carolina began a DIU in 1974 with Federal funds and received State funding in 1976. It still operates today and has the responsibility for criminal diversion.

If the problem is the "bad practice of medicine," then it is not a DIU problem but one for the State Medical Board. On the other hand, if there is no legitimate medical need *and* the prescribing is not done in the normal course of professional practice, then the activity is criminal and a law enforcement and regulatory board problem.

A third example which occurs more and more frequently, is the "patient" conning the practitioner. That is also a law enforcement problem. I see "doctor shopping" as the fastest growing source of drugs in the country. People are obtaining drugs under the color of medical need and trying to use patient-physician confidentiality as a shield against exposure. The physician does not even realize he or she has been conned. This situation places the practitioner in a difficult position if the particular State fails to distinguish between a bona fide and bogus patient-physician relationship.

Our responsibility in North Carolina is to conduct criminal investigations of diversion. At the conclusion of the investigation, the information is made available to the appropriate regulatory board and court if a health care professional is involved. If, during the course of the investigation, it is determined that a criminal violation did not occur but a practice issue was involved, the information is given to the appropriate regulatory board for followup or whatever action it deems to be necessary.

The Diversion Investigation Unit operates statewide under one office. This structure ensures consistent response, action and interpretation across the State.

I feel a model State approach to diversion should include a six-step process:

> (1) Improving the education of health-care professionals, particularly their formal training. We are seeing medical, pharmacy, and nursing students who had substance abuse problems the day they graduated from school and took their State boards. No one recognized the problem. There must be time in the curriculum for substance abuse training.
>
> (2) Good, strong, consistent regulatory boards. They should have an impaired professional program. They should support enforcement action when necessary.

(3) There should be a system to identify and track problem prescriptions.

(4) Good law enforcement response to prescription drug diversion should include:

a. Support of regulatory boards.

b. Recognition of the role of education and treatment.

c. Clear guidelines for operation (law enforcement must receive specific training before conducting diversion investigations)

d. Access to the records and prescription files.

e. Statutory authority and laws addressing "doctor shopping" and embezzlement (diversion).

(5) Court recognition of the diversion problem.

(6) The medical and law enforcement communities must learn to work together. The most autonomous profession (medicine) and the most reviewed profession (law enforcement) need not butt heads; instead, they should complement one another's roles in preventing abuse.

North Carolina is now in the fourth phase of investigative activity with the DIU. Initially, Phase I was directed at practitioners. We used undercover investigations and surveys of prescription files. We initiated an educational program for physicians on controlled substance prescribing. The regulatory boards increased their activity as they recognized problems in the professions they regulated.

Phase II was directed at pharmacies and pharmacists. Using ARCOS and other data sources, we initiated undercover and audit investigations of selected targeets. From its inception to date, the DIU in North Carolina has not conducted any random investigations. Nor have we allowed medical

complaints to be used in undercover stories without specific authorization from my office. There is only one circumstance in which I give that authorization.

Phase III carried us into organized groups of "doctor shoppers" and prescription forgery rings. The "doctor shoppers" seemed to develop as the practitioners responded to education, board actions, and law enforcement investigations of diversion. In short, it became harder for abusers to get drugs by just asking for them.

Phase IV now has us in the most difficult and unanticipated investigations, those involving health-care professionals diluting, substituting, denying and embezzling drugs from facilities and patients. While this activity does not account for the greatest volume of drugs diverted, it has the potential for the greatest harm to trusting, vulnerable, and unsuspecting patients.

No health-care facility is immune to this problem, although many fail to recognize it. The problem may occur in any area of the hospital, from the pharmacy to the operating room.

Approximately 50 percent of our cases in the last year involved health professionals diverting drugs by dilution or substitution. We have increased our educational programs for nursing schools and for hospital administration and hospital professional staff. Our program includes identification of tampering techniques and profiles of diverters.

A Diversion Investigative Unit is not a diversion control system. It is an identified mechanism for conducting investigations based on some form of information or complaint. I can suggest two advantages of using a DIU in a State: First, it should provide consistent methods, criteria, and evaluations for investigations. Second, it probably has the best chance of ensuring continual emphasis/attention on diversion problems. It is very tempting for law enforcement to apply its resources to the street drug problem.

A weakness of the DIU concept is that, alone, it has no built-in system for identifying potential problems. It is limited by the information to which it has access. A data system is needed. Some options are ARCOS, pharmacy surveys, excessive purchase reports, multiple copy systems, and electronic transfer of prescription data. Each system varies in effectiveness-from ARCOS to multiple copy prescription systems, with surveys and electronic transfer of data falling between the two. But each system serves only as a

pointer to possible problems which then must be investigated. The real key bit of information is the prescription; most investigations will involve some examination of the prescription data.

I have heard speakers say that a multiple copy system is an invasion of the patient's confidentiality. I fail to see the difference between sending a copy of a prescription to some State office, allowing investigators to examine prescription information in a pharmacy's files, or obtaining it by electronic data transfer; it is the same information.

I have heard speakers say that a multiple copy system will cause physicians to hesitate to prescribe their drug of choice for the patient. I think that is selling physicians short.

As we examine the opposition to prescription data reporting systems, I do not find individual physicians complaining. On the contrary, I find physicians are surprised we do not have automated access to prescription files. I also find the opposition (dollars) to be the drug industry and a national association of physicians setting the policy for State associations.

In closing, I see drug prices going up. Users and dealers are inventing new ways to get physicians to write prescriptions through subterfuge. Our health messages are working. Drugs are dangerous, intravenous drug use is risky, and street drugs are unsafe. People are therefore turning to prescription drugs. I feel diversion attempts will continue to increase.

Again, we need a system to identify problems, and a defined investigative process and action when appropriate. This can occur without restricting prescribing for legitimate medical purposes. Law enforcement is not trying to tell physicians how to practice medicine; we simply say practice medicine with an awareness of the problem of prescription drug diversion.

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OSTAR–Oklahoma Schedule II Abuse Reduction: An Electronic Point of Sale Diversion Control System

Elaine Dodd

HISTORICAL OVERVIEW

For several years, Oklahoma law enforcement officials attempted to obtain approval of legislation for a Multiple Copy Prescription (MCP) program. The sheer numbers of fraud, forgery, and doctor scam cases made it clear that some sort of tracking program was essential to curb the great numbers of licit drugs diverted to street use.

Oklahoma narcotic agents continued to see large amounts of legal manufactured drugs available for sale on the street. Manpower for diversion investigations is limited in Oklahoma, and there are manpower shortages across the Nation. For an investigator to follow leads on a diversion care, he or she had to second-guess which of the 900 pharmacies in Oklahoma might have prescriptions, then spend days manually reviewing files. If someone had a prescription filled in the panhandle of Oklahoma, it required at least 5 hours of driving time from central Oklahoma to visit those pharmacies. One felony investigation on a physician required two investigators 3 weeks just to determine where the pertinent prescriptions were. As it turned out, all of the prescriptions in question were in the metropolitan Oklahoma City area. Diversion investigators were facing an impossible task in trying to identify locations of prescriptions and ultimate consumers of those prescriptions.

From 1986 through 1989, different versions of MCP programs were presented to the Oklahoma Legislature, and each attempt failed dismally. Such a program was strongly opposed by drug manufacturers and physicians, and it became clear that passage of MCP was not likely. Some opposing physicians made statements to the effect they were uncertain as to the basis for their opposition and even admitted they felt some sort of tracking program would deter diversion.

In preparation for the 1990 legislative session, a study was contracted by the University of Oklahoma which confirmed the belief that Oklahoma was

extremely high in the use of several Schedule II drugs, including amphetamines, and there was no logical rationale behind these high numbers. A meeting between the Governor and his staff, the Oklahoma Bureau of Narcotics (OBN), State health regulatory boards, the Drug Enforcement Administration (DEA), and professional associations was held to discuss any proposed legislation. Oklahoma Pharmacy Board Executive Director Bryan Potter suggested that electronic transmittal of Schedule II information might be a viable alternative to MCP. The decision was made to study the feasibility of such a system.

The Oklahoma Department of Corrections computer experts assisted OBN in a study of whether the electronic transmission concept would work in our State. Expertise was also drawn from many other sources, including a major third-party claims adjudicator. Other systems were reviewed to rule out the possibility of using existing data systems. There was no existing system within Oklahoma (or any combination of existing systems) which would serve to identify the groups which scam physicians and pharmacies to divert controlled drugs. Any combination of systems excluded persons who pay cash for drugs, which are then diverted. In the final analysis, OBN came to the decision that OSTAR was a concept that was both needed and could be wholeheartedly supported. The change from MCP to OSTAR legislation allowed various groups, which had previously been entrenched in "camps", to unite in support of a system which could benefit all parties. Legislation was passed on May 15, 1990, and OSTAR became effective January 1, 1991, with little or no opposition.

OBN first considered an in-house program but, due to the lack of a large internal computer system, on-staff programmers, and technicians capable of handling phone line difficulties, it was determined that OSTAR could be handled more efficiently and with less expense by an outside vendor. Development of an in-house program would also have slowed its initiation by the several years that would have been required to develop programs which were already in existence in companies handling third-party pharmacy payments.

Prior to the beginning of this system, bids were accepted for an outside vendor. The main criteria for selection included the ability to function in a "real-time" environment and flexibility in reporting. A Bureau of Justice Federal Assistance block grant was secured by OBN, which paid 75 percent of the $270,000 committed for first-year operation. In this period, Argus Health Systems agreed to process all Schedule II prescriptions, pay all line

costs and generate all necessary reports. Of these monies, $100,000 were considered as front-end development costs, and $40,000 of this total was set aside for payments to software vendors with existing programs in Oklahoma pharmacies after they had proven modification. (Unless a State mandates strictly electronic transmission, software vendors are not obligated to modify. Because we did not choose to mandate only electronic transmission, we added this as an incentive.) It should be noted the American Society for Automation in Pharmacy (ASAP) was instrumental in providing communication between the State program and vendors, and helping to see that industry standards were incorporated. Software updates are crucial to this system as they not only allow for quicker transmission but also reduce the work required of each pharmacist in order to submit this information.

CRITICAL ELEMENTS OF THE PROGRAM

The Anti-Drug Diversion Bill required all Oklahoma pharmacists and dispensing physicians to submit information on all Schedule II controlled drugs dispensed. The bill was framed in such a manner to be as noninvasive to the pharmacists as possible, allowing for transmission by means of computer (through modem, disk or tape), by "black box" (intelligent modem), or by Universal Claim Form. The ability to submit by paper was considered necessary at the inception of the program for pharmacies that have very few Schedule 11 prescriptions per month and may never be computerized. It also allowed for a means of transmission at the onset of the program for the pharmacies that had not yet received the computer modifications to transmit electronically.

Information may be submitted by point-of-sale (real time) and must be submitted within a 14-day time period. If a pharmacy fails to submit, there are civil penalties.

All information is submitted to Argus Health Systems, a Kansas City private vendor who has had extensive experience with medical claims processing. Argus was selected through the State bidding process and is responsible for the generation of exception reports. These reports are received on a monthly and quarterly basis. A computer at OBN headquarters allows online accessibility to the data.

Information submitted conforms to NCPDP standards and includes:

1. Patient ID number (driver's license number followed by two-digit numeric State code, which requires pharmacist to obtain positive identification through photo ID)

2. NDC (National Drug Code, which also tells strength and form)

3. Date prescription is filled

4. Amount dispensed

5. Pharmacy ID number (National Association of Boards of Pharmacy number)

6. Prescriber ID number (DEA number)

By far, the most difficult issue revolved around whether to try to transmit alpha characters to capture the name and, if not, what number would be most useful as an identifier. A number of pharmacies are using the actual black boxes and the transmission of alpha characters by this means is very difficult and would place an unfair burden on those pharmacists. It was finally determined that the State driver's license number, followed by the two-digit State code, would be a number that could be identified by law enforcement officials while enhancing confidentiality, since information about individuals cannot be easily interpreted by other sources using this number. The State code was made available to the pharmacists in a manual distributed by OBN. Persons from other countries are identified by a 98 suffix. If the patient is terminally ill or home bound, the pharmacy identifies this customer using a 99 suffix.

DEA numbers and NABP numbers are translated into actual names for investigators through the use of look-up tables. Other look-up tables identify the practitioners by medical specialty, with this information being provided by the medical boards.

Questions of confidentiality have not arisen, in part because law enforcement is simply accessing information that was previously available but much harder to obtain. Access to the on-line OSTAR computer is limited to just three agents and records are kept of requests. If the agent does not know the requester personally, a callback is made to the police agency or health regulatory board where they are employed. Information from this system is only divulged in

criminal cases; other use of the data is prohibited by State law, with severe penalties for violation.

OSTAR queries are possible by member number, pharmacy name or NABP number, or by physician name or DEA number. Exception reports are generated based on a number of factors, with the most active category at present being patients with multiple physicians/ multiple pharmacies. Meetings have been held with a committee of regulators and other professionals formed by the enabling legislation to determine which reports are most effective. As more data becomes available, additional parameters will be set by this group for reports on physicians by specialty.

EVALUATION OF SYSTEM

Although the OSTAR system has been operational for only a few months, there are clear indicators that the system is a successful tool for the prevention of licit drug diversion. In the past, physicians have been frustrated in their efforts to attempt to determine whether a "patient" is only in their office to obtain CDS. A phone call to law enforcement officials would be successful if the possible scammer was already known to that officer, or had a history which included arrests and convictions. Even with a criminal history, officers would have to use a combination of intuition and blind luck to locate the multiple pharmacies from which this person had been obtaining drugs to build a viable case for prosecution. The OSTAR program provides a means to identify the pharmacies and physicians that the scammer has frequented.

A recent lecture concerning appropriate prescribing and scams before a group of Oklahoma physicians prompted two phone calls the next day. Both physicians gave a patient's name and their reasons for their suspicions. Both names were queried through OSTAR by driver's license number. Each had a history of obtaining controlled drugs from multiple pharmacies and physicians (more than 10 each in less than 3 months). Criminal cases were opened on both subjects, and will be investigated in a minimal amount of time, as the pharmacy locations are already pinpointed for the case agents.

Involvement in cases such as these has increased the support of the physician and pharmacy communities and gained their support for maintaining, and possibly increasing, the reporting of possible "scammers" to OBN.

A full 4-month collation of data (with only one full quarterly report) does not lend itself well to statistical evaluation of OSTAR, as there was no similar data

base in the past. However, attempts have been made to survey other State data bases to establish what impact OSTAR has had on Schedule II dispensation. The State insurance system compared a 3-month period in 1990 with the first quarter of 1991. This data showed large decreases in oxycodone, methylphenidate and morphine sulfate. The Medicaid data for the same period is directly contradictory, indicating large *increases* in oxycodone, methlylphenidate and hydromorphone (with a small decrease in morphine sulfate). Both programs were affected by external factors unrelated to the OSTAR program, but strong enough to skew the data for purposes of using it for verification of OSTAR. State insurance changed from a co-pay system to an 80-20 percent split and established a drug utilization review. The Medicaid system opened its formulary in September of 1990 and payments were drastically increased in all categories (not just Schedule II). Efforts are currently being made to cormpare data in other existing data bases to verify whether OSTAR has changed statewide prescribing. At this time, the argument can simply be made that negative "chilling effects" do not appear to have occurred under the new system.

A study on a much smaller scale was conducted by a pharmacy in an area of Oklahoma which has always had a large diversion problem, including numerous groups of doctor scammers. This small study showed a decrease in all Schedule II prescriptions since the inception of OSTAR, and the pharmacist indicated he had not seen a corresponding increase in Schedule III prescriptions. This particular pharmacy is an interesting case because of its geographic location. In the 75 days preceding OSTAR, it filled 128 prescriptions for Schedule II drugs, for 4,848 total dosage units. During the first 75 days of 1991, that pharmacy filled 62 Schedule II prescriptions, totalling 2,314 dosage units. Practitioners were not writing each prescription for higher totals (in both periods an average 37.5 dosage units per prescription was prescribed). This pharmacist felt this validates the theory that there has not been a chilling effect on the physicians' prescribing, but the results simply reflect a drop in the number filled for scammers and forgers. Intelligence from informants shows that "patient" scammers are now keenly aware of the new tracking system.

OSTAR, like MCP programs, is limited by the geographic boundaries in which it has jurisdiction. As in the past, when patient scammers came north from Texas to fill prescriptions in Oklahoma in hopes of avoiding detection in their triplicate system, we now expect Oklahomans to move their illegal activities to border States. This could easily be solved by a nationwide uniform tracking system.

SUMMARY

In its short history, OSTAR has proven to be a fast, accurate tracking system for Schedule II prescriptions within Oklahoma. Information is available immediately in many cases and, having been entered into the system by the pharmacist, is very accurate, Approximately SO percent of the information is being transmitted through electronic means at this time, and that percentage is increasing daily due to software companies making modifications to their pharmacy programs.

System deficiencies have proven to be minimal, even less than anticipated. Efforts are still underway to ensure that data is received in a uniform manner; i.e., some data systems include zeros at the end of the patient number, which causes investigators to have to query in more than one form. These pharmacies and companies are currently being notified and are making the necessary changes. The technical problems usually encountered with a new system have been limited, and data has been useful from the first month of the program.

Feedback from impaired physicians has indicated they would not have been so free to divert Schedule II substances through prescriptions if this system had been in place. OBN has active cases involving a large number of physician scammers that are a direct result of OSTAR and it has enhanced cases on at least one physician and provided valuable information for search warrants. Agents are able to make better cases for prosecutors while completing investigations in much shorter periods of time. Local law enforcement personnel who have accessed OSTAR have become convinced that it is a most effective tool, and use of the system has complemented their investigations.

OSTAR has coalesced the various groups in Oklahoma, each having a reason to prevent diversion of controlled drugs and allowed all alternative which all felt they could leave their diverse "camps" to support. Physician and pharmacy support increases with each successful case completed using this system. At long last, there is a means by which ultimate consumers/potential abusers can be tracked in Oklahoma.

There is no corollary indication that OSTAR has had any "chilling effect" on prescribing for valid pain. This can be attributed to the fact that physicians will continue to use their best judgment in prescribing for those in need of medication. Educational efforts by OBN continue to stress that our goal is never to prohibit a patient who truly needs medication from receiving it, but instead, to encourage appropriate prescribing while discouraging diversion for

abuse and resale. As of May 1991, the Oklahoma State Medical Association had yet to receive a single complaint from a physician regarding OSTAR and any supposed negative effects on their practice.

OSTAR addresses the much-needed informational gap in Schedule II dispensation in Oklahoma, which could not have been solved by the use of existing data systems or even by greatly increased manpower alone. It is an experiment in technology that works better than was anticipated and is one of the most productive programs in antidrug diversion law enforcement today.

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The Illinois Experience in Achieving the Medical/Regulatory Balance Required to Control Prescription Drug Diversion

Mark T. Bishop and Ronald J. Vlasty

INTRODUCTION

Each year, thousands of Illinois patients are treated for a variety of diseases. Their treatment regimen may include the use of prescription drugs whose therapeutic benefits are often accompanied by psychoactive effects. While these drugs have positive and effective medical uses, misuse or abuse of these drugs can produce a variety of adverse consequences such as drug dependence, overdose, and death.

In an effort to strengthen controls over prescription drug misuse and abuse, Illinois revitalized its Triplicate Prescription Control Program in 1984 by transferring the operation of the program from the Illinois Department of Registration and Education to the Illinois Department of Alcoholism and Substance Abuse (DASA). The new program was created to achieve a balance between the appropriate medical availability of "designated product" Schedule II prescription drugs and the need to limit their potential for diversion and abuse. This program has virtually eliminated forgeries and mechanical alterations by requiring that Schedule II drugs only be prescribed on official forms which are serially numbered on counterfeit-proof paper and registered to an individual physician. By controlling the form, the Triplicate Program has reduced the number of stolen and stolen/cashed prescriptions. The program has also been able to significantly reduce the fraudulent acquisition of hydromorphone (Dilaudid) and phenmetrazine (Preludin), two of the most sought after "street" prescription drugs in Illinois.

The Triplicate Program has also served to deter indiscriminate prescribing. When physicians are required to complete the necessary prescription form, they often evaluate whether another equally effective drug might be suitable for their patient, yet offer the patient less risk of dependence or abuse.

The department has operated the Triplicate Program since July 1, 1984, and has achieved the following remarkable results:

- In 1984, Illinois added the drug glutethimide (Doriden) to the Triplicate Program and, in effect, virtually eliminated deaths attributed to the overdose of this drug. Between 1982 and 1984, 36 deaths had been reported in the 3 years prior to the rescheduling of glutethimide. Since then, only one death has been reported in Illinois which is in clear contrast to the rest of the Nation which reported 523 deaths during the same time period. Recently, the Federal Government followed Illinois' lead and reclassified glutethimide under Schedule II to increase control over this drug.

- A 90 percent reduction in the amount of hydromorphone (Dilaudid) diverted through fraudulent use of the triplicate form.

- A 100 percent reduction in the amount of fraudulently diverted phenmetrazine (Preludin).

- A 90 percent reduction in the fraudulent cashing of triplicate prescription forms.

- Developed and implemented the Pharmacy Inventory Control (PIC) Program which enabled the Department to track and monitor activities of out-of-State medical practitioners who issue Schedule II controlled substance prescription orders that are filled by licensed Illinois pharmacies.

This program has caused a number of States outside of Illinois to initiate regulatory actions and it has blocked out-of-State physician avoidance of home State prescribing constraints. In the part, some physicians took the opportunity to have their patients fill illicit prescriptions "across the border" in Illinois to avoid detection in their local State.

- Provided data targeting practitioners involved in illicit or illegal prescribing/dispensing activities. To date, 140 cases have resulted in licensure sanctions.

- Provided research data to the Illinois State Medical Society and the Illinois Pharmacists Association to contribute to the development of

educational programs on the prescribing responsibilities associated with controlled substances, anorectic drugs, benzodiazepines, and anabolic steroids.

- Participated at the national level on prescription drug control policy forums. The Illinois program has been recognized as a national model. Indiana and Michigan, which have recently installed triplicate programs, have designed significant portions of their programs based on the Illinois model.

- On an annual basis, it is estimated that the Triplicate Prescription Control Program saves other local, State and Federal agencies an estimated $170,000 annually in administrative costs that ordinarily would have been spent on laborious onsite prescription file and medical record reviews.

- Identified a self-dispensing physician who was averaging over 300 prescriptions/500,000 mg of amphetamines. Some of this physician's patients had received amphetamine prescriptions for periods iii excess of three years. After further investigation, this physician received 2-years' probation against his medical license because of his indiscriminate prescribing practices.

- Identified one physician in southern Illinois who was selling his triplicate prescription blanks to "professional patients" from the Chicago area. The physician originally reported that his prescription forms had been stolen, but after reviewing the forms received from the pharmacy, it was found that the physician was actually writing these prescriptions. This physician was eventually arrested and sanctioned for his illegal activity.

- Provided information to the Drug Enforcement Administration (DEA) on four Illinois physicians who have been prescribing large quantities of Dilaudid for "professional patients" over the past 3 years. It is estimated that the drugs diverted through these prescriptions have a street value totalling over $12 million. The DEA is confident that these four physicians will be indicted for their illegal activity.

- Provided data targeting 150 to 200 criminal drug traffickers who regularly prey on unsuspecting Illinois physicians. These known drug

diverters "score" from 60-100 prescriptions per month and have been known to make in excess of $200,000 annually which is, of course, also "unreported" income. Illinois now estimates that only 25 "doctor shoppers" are still active in this State, a 90 percent reduction since 1985.

- The Illinois Triplicate Program is the only program of its kind in the nation with the full support of its State medical society and its State pharmacy association.

HISTORY OF THE ILLINOIS TRIPLICATE PROGRAM

The Illinois Triplicate Prescription Control Program was enacted in 1961 under the administrative authority of the Illinois Bureau of Investigation (IBI). The IBI was superseded by the Department of Law Enforcement (DLE), which, in 1984, again had its name changed to the Department of State Police (DSP). In 1974, as a result of reports on widespread fraud and illegal prescribing and dispensing of prescription drugs in Illinois, an Illinois Legislative Investigating Commission recommended that this program would be more capably administered by the agency that was responsible for the regulation of professional licenses issued in accordance with the Illinois Medical Practice Act and the Illinois Pharmacy Practice Act. In 1975, the responsibility for the administration of the Triplicate Program was transferred from the Department of Law Enforcement to the Department of Registration and Education (DRE), which, in 1987, was subsequently renamed the Department of Professional Regulation (DPR).

In 1982, and in response to media investigations of blatant Medicaid prescription fraud and diversion, Governor Jim Thompson's convened a Prescription Drug Abuse Task Force. The Task Force recommended that the Illinois Dangerous Drugs Commission be charged with the responsibility of developing a new automated triplicate system to provide for the more efficient distribution, receipt, and tracking of triplicate prescription forms and information. On July 1, 1984, the Department of Alcoholism and Substance Abuse (DASA) was created to address growing concerns over the problems of alcoholism and substance abuse in the State of Illinois. The Dangerous Drugs Commission and the operation of the Triplicate Prescription Control Program were incorporated under the mandate of the new department and immediate implementation of the new system began. Additionally, placing the administrative authority for the Triplicate Program with DASA ensured

that there would be a balance between the law enforcement community and the medical professions.

The Triplicate Prescription Control Program was designed to deter the misuse, abuse, and diversion of Schedule II "designated product" prescription drugs in Illinois. The prescription drugs in Schedule II of the Illinois Controlled Substances Act have a currently accepted medical use for treatment, but also have an extremely high potential for abuse that may lead to severe psychological and physiological dependence. A drug with "designated product" status requires the use of an official triplicate prescription form and includes narcotics, amphetamine, phenmetrazine, methamphetamine, glutethimide, and pentazocine. There are also "nondesignated product" prescription drugs under Illinois' Schedule II classification, which include amobarbital, pentobarbital, secobarbital, and methylphenidate, and these drugs *do not* require the use of the triplicate prescription form.

PROGRAM PARTICIPATION

The Illinois Controlled Substances Act (III. Rev. Stat. 1988, ch. 56 1/2) provides that physicians/surgeons, dentists, podiatrists, and veterinarians are the only medical practitioners who can prescribe Schedule II controlled substances. The Department of Professional Regulation (DPR) currently licenses 43,794 of these practitioners, of whom 36,929 hold Controlled Substances licenses. Since August of 1985, DASA has issued triplicate prescription forms to 23,917 practitioners in Illinois. DPR also currently licenses 11,731 pharmacists and 2,824 pharmacies that participate in the triplicate prescription program. Excluding retirees, teaching, and all other nonpracticing physicians, approximately 90 percent of licensed Illinois physicians participate in the program.

PROGRAM OPERATIONS

Forms Issuance

In August 1985, DASA developed an inventory subsystem which permitted the Triplicate Program to issue preprinted triplicate forms to all requesting medical practitioners in the State. The use of this new form has eliminated many of the previous problems encountered with forged and stolen blanks. To date, DASA has issued over 5 million forms to Illinois medical practitioners and has collected over $465,570 in issuance fees.

Forms Processing

In September 1986, the development of a new automated triplicate form processing system was completed. It allowed the collection of timely and accurate information based on prescription data submitted by Illinois pharmacies. This data is being used to more accurately identify and analyze patterns of drug use and misuse. To date, DASA has processed over one milion triplicate forms. On average, medical practitioners, issue 11 triplicate prescriptions per year, pharmacies fill 66, and pharmacists dispense 15.

Since DASA assumed responsibility for the triplicate prescription program on July 1, 1984, the total number of prescriptions for Schedule II designated product prescription drugs has remained relatively constant. While FY 1991 statistics indicate a decrease in the total amount of triplicate prescriptions compared to FY 1985, triplicate prescriptions written for analgesia and cancer pain management have significantly increased. Morphine sulfate prescriptions increased from 10,841 in FY 1985 to 36,489 in FY 1991. Oxycodone with acetaminophen also increased from 26,012 prescriptions in FY 1985 to 39,046 in FY 1991. Increases also occurred in the total number of milligrams prescribed per prescription.

Changes resulting from effects of the new program and other concurrent factors (e.g., professional education, improved pain control) on the prescribing of analgesics to control chronic/cancer pain has been mixed.

- The number of prescriptions for morphine sulfate has steadily risen–from 10,841 in FY 1985 to 36,489 in FY 1991.
- The number of prescriptions for oxycodone/acetaminophen preparations rose from 26,012 in FY 1985 to a peak of 41,164 in FY 1988 and has slightly declined since to 39,046 in FY 1991.

Reductions in the number of triplicate prescriptions are most noticeable with respect to the target drugs–amphetamines, glutethimide and hydromorphone. Regulatory efforts initiated against the diversion of these drugs account for a reduction of 11,264 triplicate prescriptions from FY 1985 levels.

Reductions attributed to regulatory initiatives are indicated in the following tables; they demonstrate the rankings of the top ten Schedule II designated product prescription drugs according to the number of prescriptions written as well as the total milligrams dispensed:

TOP 10 SCHEDULE II PRESCRIPTION DRUGS
NUMBER OF TRIPLICATE PRESCRIPTIONS ISSUED*

DRUG NAME	FY 1985	FY 1986	FY 1987	FY 1988	FY 1989	FY 1990	FY 1991
AMPHETAMINES	19.5	18.2	15.5	13.9	12.4	11.8	12.9
CODEINE	2.2	2.3	2.0	2.1	2.0	1.8	1.6
DOLOPHINE	5.4	5.0	4.5	4.5	3.9	3.0	2.4
GLUTETHIMIDE	2.7	2.7	1.9	1.5	.97	.79	.56
HYDROMORPHONE	16.3	16.7	16.7	16.1	14.6	13.1	13.8
MEPERIDINE	22.7	24.6	22.2	21.8	19.2	18.3	16.8
MORPHINE SULFATE	10.8	14.8	17.4	22.6	26.0	31.7	36.5
OXYCODONE/ASPIRIN	43.0	41.7	35.5	31.8	27.5	22.0	19.7
OXYCODONE/ACET.	26.0	33.6	36.5	41.2	40.3	39.3	39.0
PENTAZOCINE	5.8	3.1	.71	.68	.42	.45	.3

Numbers are in thousands

TOP 10 SCHEDULE II PRESCRIPTION DRUGS
TOTAL DRUG AMOUNT
(IN MGS)*

Years are fiscal years

DRUG NAME	1986	1987	1988	1989	1990	1991
AMPHETAMINES	6,487	12,054	11,110	9,970	9,090	9,090
CODEINE	2,981	6,516	7,348	6,891	6,825	6,868
DOLOPHINE	1,761	3,406	3,379	3,063	2,298	1,993
GLUTETHIMIDE	29,610	54,551	45,804	31,456	27,023	20,433
HYDROMORPHONE	2,221	4,651	4,337	3,841	3,601	3,662
MEPERDINE	21,298	41,592	39,851	35,320	35,681	34,125
MORPHINE SULFATE	14,054	38,809	58,177	82,573	158,266	189,221
OXYCODONE/ ASPIRIN	4,305	8,301	7,682	6,593	5,481	4,784
OXYCODONE/ACET.	4,913	10,188	11,177	11,102	10,621	10,605
PENTAZOCINE	401	623	608	439	505	360

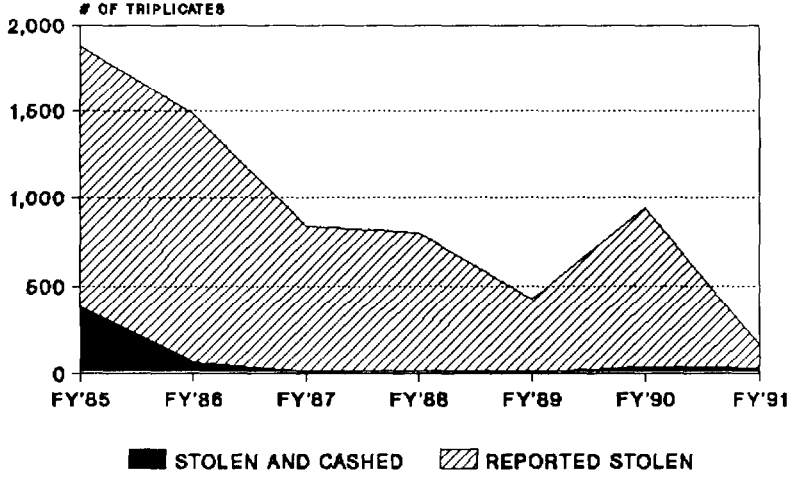
*Numbers are in thousands of MGS

PROGRAM EFFECTIVENESS

Stolen/Cashed Triplicates

The number of stolen triplicates which have been fraudulently cashed at Illinois pharmacies has dropped significantly over the past 7 years. Between fiscal year 1985 and fiscal year 1991, the number of fraudulently cashed prescriptions for all triplicate drugs decreased from 380 to 29. The 29 fraudulently cashed prescriptions reported in fiscal year 1991 have been traced back to a group of known drug traffickers who were working in collusion with a single physician, and DASA has forwarded this information to the Drug Enforcement Admininstration for further investigation. The overall reduction in diversion activities can be attributed to an aggressive program that provides timely and accurate stolen prescription information to the Drug Enforcement Administration, the Department of State Police, the Department of Professional Regulation, and to networks of Illinois pharmacies.

STOLEN TRIPLICATE PRESCRIPTIONS VERSUS
STOLEN AND CASHED TRIPLICATE FORMS

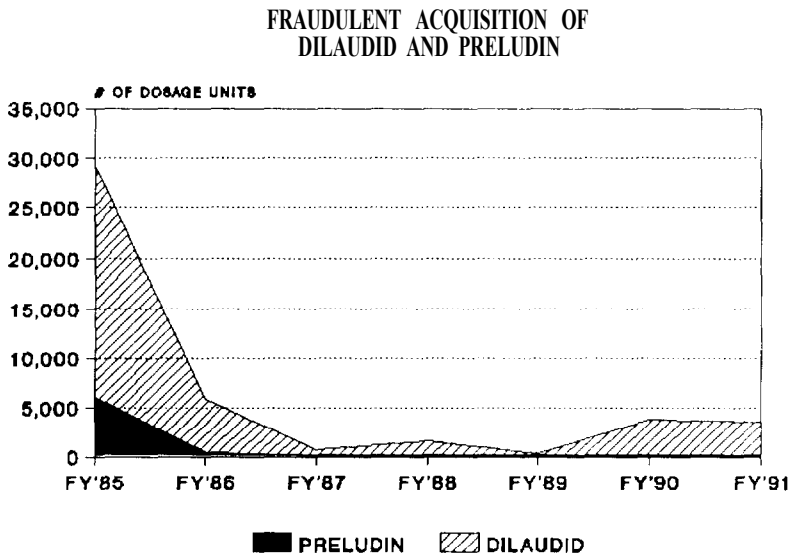


(ELEVEN PROFESSIONAL PATIENTS ACCOUNTED FOR ALL STOLEN/CASHED TRIPLICATE FORMS DURING FY'91)

Fraudulent Acquisition of Hydromorphone and Phenmetrazine

In a majority of cases, stolen triplicate prescriptions are used to acquire hydromorphone (Dilaudid) or phenmetrazine (Preludin), which are two of the most sought after "street" prescription drugs in Illinois. During the past 7 years there has been a dramatic reduction in the number of diverted dosage units (capsules, tablets, etc.) of these drugs compared to the total diverted dosage units in fiscal year 1985. Diverted hydromorphone dosage units dropped from 29,314 in FY 1985 to 3,600 dosage units in FY 1991. This was accomplished without limiting medical necessity of this drug for cancer pain treatment.

Similarly, diverted phenmetrazine dosage units, which totaled 6,090 in FY 1985, dropped to 0 in FY 1991. This reduction and complete elimination may be attributed to the fact that drug diversion rings in Illinois are continuing to experience the fear of arrest and prosecution. This is directly related to the stepped-up efforts and cooperation among Federal and State law enforcement and regulatory agencies.



(ELEVEN PROFESSIONAL PATIENTS ACCOUNTED FOR ALL STOLEN/CASHED TRIPLICATES FORMS DURING FY'91)

Pentazocine Epidemic

In 1977, the Illinois Dangerous Drug Commission began receiving isolated reports of intravenous pentazocine (Talwin) abuse from its licensed narcotic treatment programs. By mid-1977 most narcotic treatment programs located on the south and west sides of Chicago were reporting pentazocine abuse admissions. Pentazocine was being used intravenously with pyribenzamine (a combination commonly known as "T's and Blues"). The Dangerous Drugs Commission's Advisory Council examined the causative factors of this epidemic and recommended the classification of pentazocine under Schedule II of the Illinois Controlled Substances Act as a designated product, thus requiring the use of an official triplicate prescription blank. In Illinois, the drug pentazocine was classified under Schedule II in August of 1978. On the Federal level, pentazocine was and still remains under the Schedule IV classification. Due to the rescheduling actions of the Dangerous Drug Commission, the enforcement actions of the Department of Professional Regulation, the Chicago Police Department, and the Drug Enforcement Administration, and the introduction of pentazocine with naloxone (Talwin Nx) by Sterling-Winthrop Pharmaceutical, the pentazocine epidemic was eliminated in Illinois. The National Institute on Drug Abuse (NlDA) annually produces drug abuse profile information collected through the Drug Abuse Warning Network (DAWN) which includes emergency room and medical examiner facilities in 27 metropolitan statistical areas. An analysis of DAWN data for Illinois indicates that emergency room drug mentions for pentazocine decreased from 477 in 1978 to 15 in 1989.

Conversely, emergency room drug episodes for the total DAWN network show a decreasing pattern that significantly lags behind Illinois.

Glutethimide Problem

In 1982, the Illinois Dangerous Drugs Commission was faced with the widespread diversion and abuse of the drug glutethimide (Doriden), which at the time was classified under Schedule IV both in Illinois and federally. After a significant legal battle, it was reclassified under Schedule II of the lllinois Controlled Substances Act in 1984 and it was also made a "designated product" requiring the use of the official triplicate prescription form. An analysis of DAWN data for Illinois indicates that emergency room drug episodes for this drug decreased from 34 in 1984 to 0 in 1989 and, more importantly, medical examiner drug mentions (deaths) decreased from 36 in the 1982-1984 time period to 1 in the 5-year time period following the

rescheduling action. Conversely, national DAWN emergency room drug mentions have continued to demonstrate an increasing pattern of glutethimide overdoses and persistent reports of deaths.

Triplicate Program Involvement in Disciplinary Actions

Since 1985 the department has been an active participant in the Diversion Liaison Group (DLG) which acts as a forum for information sharing and coordination of investigative and regulatory activities. The DLG membership is comprised of representatives from the United States Drug Enforcement Administration (DEA), the Internal Revenue Service (IRS), the Illinois Department of State Police (ISP), the Illinois Department of Professional Regulation (IDPR), the Illinois Department of Public Aid (IDPA), the Chicago Police Department (CPD), and the Cook County States Attorney's Office (CCSAO). DASA provides support information to the DLG in which high volume prescribers, high-volume dispensers and suspicious patterns of distribution and consumption are identified. During FY 1991, DASA provided 846 investigative profile reports which led to an increase in sanctions on the professional and controlled substances licenses of medical practitioners, pharmacists, and pharmacies that have violated provisions of the Illinois Controlled Substances Act. Investigators from the various DLG agencies estimated that without the ability to receive automated tracking reports on the prescription activities of medical practitioners, pharmacies, pharmacists, and "doctor shoppers" they would spend a *minimum* of $200 pet investigation manually gathering the information. In addition, it would be virtually impossible for law enforcement or regulatory agencies to identify the activities of sophisticated "doctor shopper" rings without the Triplicate Prescription Control Program.

The estimated cost savings for FY'91 is calculated at 846 profiles multiplied by $200 or $169,200. Since 1985 DASA has been directly involved in the licensure sanctions of 95 medical practitioners, 33 pharmacists, and 30 pharmacies. Information provided by the department has also led to an increase in the number of arrests and prosecutions of professional patients or "doctor shoppers." Currently, the department reports that only 25 of the originally identified 200 "doctor shoppers" are still active today.

PHARMACY INVENTORY CONTROL PROGRAM

One of the major innovative features of Illinois' Triplicate Program is the Pharmacy Inventory Control (PIC) program. The PIC program tracks the filling of out-of-State Schedule II controlled substance prescription orders by Illinois pharmacies. The PIC Program was originally conceived to allow patients who live out-of-State in areas close to Illinois, the convenience of having their prescriptions filled in Illinois border towns. In order to accomplish this task, the Department of Professional Regulation developed and implemented the "Pharmacy Inventory Control" (PIC) form. Illinois pharmacists are required to use a PIC form to collect information similar to that required on the triplicate form, the only difference is that the physician does not issue the original prescription on this form.

PIC Program Participation

Since August 1, 1985, the DPR has issued over 135,700 PIC forms to licensed Illinois pharmacies. Pharmacists are required to submit an (original) completed PIC form to the Department by the 15th day of the month following the month in which the prescription was filled. Since August 1, 1985, the department has processed 81,890 PIC forms. During FY 1991 (July 1, 1990 - June 30, 1991), 2,824 pharmacies held licenses in the State of Illinois and 1,448 of these pharmacies utilized PIC forms.

PIC Program Monitoring and Reporting

Since implementation, the department has been monitoring and reporting on the dispensing of prescribed drugs pursuant to out-of-State Schedule II controlled substance prescription orders. We have been providing detailed Pharmacy Inventory Control Reports to regulatory and law enforcement officials in 48 states, the District of Columbia, and Puerto Rico. These reports contain the following information:

1. Practitioner DEA number: The Drug Enforcement Administration's registrant number assigned to the medical practitioner located in the State where the prescription order originated.

2. Drug code: The Department's internal drug code that identifies the Schedule II controlled substance that was prescribed, the dosage form and the strength of the drug.

3. Drug quantity: The quantity, in dosage units, of the drug dispensed.

4. Drug amount: The total quantity in milligrams of the controlled substance drug contained within the prescription

By providing PIC Reports to regulatory and law enforcement officials, a number of investigations have been initiated. The department has assisted the following agencies with drug diversion investigations:

- Denver Board of Medical Examiners
- Drug Enforcement Administration - St. Louis Office
- Drug Enforcement Administration - Chicago Office
- Kentucky Drug Control Branch
- North Carolina Bureau of Investigations
- West Virginia Board of Medicine
- Wyoming State Board of Pharmacy
- Nebraska State Police

PIC Program Data

During FY 1991, a total of 4,103 out-of-State medical practitioners had Schedule II controlled substance prescriptions presented at and fitted by Illinois pharmacies. Medical practitioners from the States that border Illinois are responsible for prescribing 81 percent of all out-of-State practitioners whose prescriptions have been fitted in Illinois.

Also during FY 1991, a total of 15,101 Schedule II controlled substance prescription orders from out-of-State medical practitioners were fitted by Illinois pharmacies. Over 92 percent of these prescription orders originated in the Stales that border Illinois.

ILLINOIS CONTROLLED SUBSTANCES MONITORING PROGRAM

The problem of prescription drug abuse still persists throughout the State of Illinois. Although the Department has made the Triplicate Prescription Control Program a major success in the deterrence of the diversion and abuse of Schedule II controlled substances, there remains a vast number of controlled substance prescription drugs which do not fall under triplicate-like reporting requirements.

In 1990, Drug Abuse Warning Network (DAWN) report for the Chicago metropolitan area indicated that controlled substance prescription drugs in Schedules III through V accounted for 1,100 emergency room episodes. An "emergency room episode" describes an incident in which a controlled substance prescription drug may have been abused by a person to the point where hospitalization was required. Further, the DAWN report indicated that controlled substance prescription drugs played a leading or contributing role in the deaths of 53 Illinois residents during the same time period.

Since prescription drug abuse is a serious problem in Illinois, and in other States as well, the department has recently established the Illinois Controlled Substances Monitoring Program. This program requires manufacturers and distributors of Schedule II and Schedule III narcotic prescription drugs to report transactions on direct sates to Illinois medical practitioners and pharmacies. The program will provide the following:

- An early warning system to detect suspicious purchases and distributions of controlled substance prescription drugs so that law enforcement and regularory agencies can be informed immediately of such activities.

- Support information for street drug use research projects intended to measure the incidence and prevalence of diversion, abuse, and dependence associated with controlled substance prescription drugs.

This program will also enhance the efficiency of law enforcement and regulatory agencies in their efforts to sanction the criminal/unprofessional activities of registrants. In addition, this program will strike a blow against the professional "doctor shoppers" in Illinois that plague our physicians and pharmacists with their well-planned and rehearsed scams that enable them to illegally obtain controlled substance prescription drugs.

Since January of 1991, we have received direct sales reports of controlled substances from 54 manufacturers and distributors. These reports include a total of 497,278 transactions.

PLANS FOR FUTURE ACTION

During FY 1993, the Department of Alcoholism and Substance Abuse plans to undertake the following activities to strengthen the State's control over prescription drug diversion and abuse:

A. The department will look toward expanding the Illinois Controlled Substances Monitoring Program in an effort to collect drug data to ascertain the public health risks associated with other groups of nontriplicate prescription drugs such as benzodiazepines, cough syrups, and methylphenidate (Ritalin).

B. The department will continue to work with the Illinois State Medical Society to identify physicians who prescribe Schedule II prescription drugs beyond the scope of their practice.

C. The department will continue to evaluate and provide consultation on the feasibility of proposed Federal legislation such as the "Prescription Accountability and Patient Care Improvement Act." This Act was designed to prevent and detect illegal drug distribution by allowing States to collect information on prescription drugs in all schedules. Pharmacies would be required to electronically transmit data on controlled substances prescriptions to a central repository in a designated State health agency.

D. The department will conduct research on the prescription drug methylphenidate (Ritalin), which is showing up more and more in reported substance abuse situations. This research will examine the drug's distribution and its impact on drug abuse treatment admissions.

E. The department will expand its participation at the national level to highlight the success of the Illinois Triplicate Program and to offer assistance to other States interested in implementing such a program.

F. The department will continue to evaluate and validate medical examiner reports as they pertain to drug overdose deaths caused by licit as well as illicit use of prescription drugs.

G. The department will attempt to integrate prescription drug data systems to better define the State's prescription drug abuse problem. This integration will include Triplicate Program data, DEA pharmacy theft reports, street drug data from the Illinois Community Epidemiology Work Group, toxicology data from drug abuse clients and criminal justice offenders, Medicaid reimbursement data for prescription drugs, and data on private

insurance company prescription drug reimbursements. The results of this integration will allow Illinois to compile a "prescription drug abuse profile system."

H. The department will continue to work with the Illinois State Medical Society and the Illinois Pharmacists Association to develop practitioner education programs with curricula specific to alcohol and other drug abuse and treatment.

CONCLUSION

In reviewing the past 7 years of operation, it is clear that the Illinois Triplicate Prescription Control Program continues to demonstrate significant success in controlling the diversion of Schedule II prescription drugs throughout the State. This success must be credited, to a great extent, to the level of communication and cooperation that has existed among medical professionals, pharmacy professionals, medical societies, pharmacy associations, and Federal and State agencies. Information sharing has been the most effective tool in the control of diversion.

However, there exists a continuing need to identify and sanction those unscrupulous professionals who prescribe and dispense dangerous drugs outside the law for personal gain. The Department of Alcoholism and Substance Abuse is committed to the effort of alleviating the suffering and pain caused by the abuse and misuse of prescription drugs. With cooperation and communication, DASA will continue to support the statewide effort to interdict the flow of criminally diverted Schedule II drugs.

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New York State's Triplicate Prescription Program

John L. Eadie

INTRODUCTION

New York State has found no program, system, or activity as effective in dealing with the diversion, abuse and misuse of controlled substances as the multiple copy prescription system. New York State is one of nine States that has such a system. Of these, Rhode Island and Hawaii have duplicate systems, while New York, California, Texas, Idaho, Illinois, Michigan, and Indiana have triplicate systems. Contrary to what opponents assert, triplicate systems do not interfere with the continued legitimate and necessary prescribing of those drugs to meet patients' needs.

The Triplicate Prescription System

In 1972, legislation was passed in New York State requiring that all Schedule II drugs be prescribed only upon a State-issued triplicate copy prescription form. Initially restrained by litigation, this legislation was promulgated in 1978 and became known as the Triplicate Prescription Program. This program requires that a copy of the triplicate prescription form be forwarded to the New York State Department of Health pursuant to dispensing the drug.

Prescribing of up to a three month supply is permitted on triplicate forms for a list of conditions where such long term use is medically indicated. Except for those conditions, prescriptions can only be written for a maximum of a 30-day supply. Refills are not permitted. Patients must receive a new prescription for additional drugs, although continued office visits are not required and are left to the physician's discretion in accordance with sound medical practice. Physicians may mail prescriptions to patients or their pharmacies, or make the prescriptions available for pickup in the office.

The items of information on a triplicate prescription form are the same as on a standard prescription except that check boxes are used to denote drug type and the patient's gender. The practitioner's name and address are imprinted on each prescription by the State. Certain areas of information have been converted to check boxes or machine readable numbers so the information

can be read by optical character readers, thus, expediting our processing of the volume of prescriptions.

The forms originate with licensed practitioners who retain one copy and forward the other two to the pharmacy. After dispensing, the pharmacist retains a copy and forwards the other to the Department of Health where the information is compiled by computer and analyzed.

The triplicate system stops prescription forgery and counterfeiting.

The New York State triplicate prescription forms are serially numbered and their distribution is controlled by the State. Only bona fide practitioners can obtain them as every order is screened by the State to verify its validity. The forms are printed with special paper, inks and artwork making counterfeiting, photocopying, and alterations nearly impossible. In contrast, anyone can print or photocopy thousands of standard prescription blanks and then forge a physician's signature.

There has been only one attempt in New York to counterfeit triplicate forms, and it was identified and quashed immediately. If triplicates are lost or stolen, the physician simply reports this to the Bureau of Controlled Substances and we notify all pharmacies of the missing forms' serial numbers. If the lost or stolen prescriptions are ever filled, they are immediately identified by the computer, enabling us to investigate.

In New York State before triplicates, 12.5 percent of prescriptions for Schedule II drugs were forgeries. In the first year of the triplicate system, only 0.5 percent of the filled prescriptions had been reported lost or stolen and by 1986, that had dropped to 0.06 percent and remains at that tiny fraction of 1 percent today.

In New York some have suggested that we consider a PADS II, Voluntary Drug Utilization Review System or electronic transfer of prescriptions without a State issued form. However, such systems do not prevent forgery and counterfeiting, they only count the scrips that are forged and counterfeited.

The triplicate prescription system stops drug diversion and abuse.

The triplicate prescription data is compiled by New York State to create profiles of prescribing practitioners and pharmacies. This data is used for

investigations by the State and the DEA and county medical societies have very responsibly used the data for peer review to correct improper prescribing by physicians.

State and Federal investigations and peer review have effectively eliminated major drug diversion and abuse as evidenced by the changes in abuse of amphetamines, barbiturates and benzodiazepines. The triplicate system identified 46 physicians writing more than 160,000 amphetamine prescriptions in 1978. Investigation and prosecutions of many, plus peer review led to a 94 percent reduction in prescribing of these highly abused drugs (Chart A). Simultaneously, drug abuse was reduced, as measured by the 95 percent decline in drug overdoses involving amphetamines, as reported for emergency room admissions in sample New York State hospitals to the National Institute of Drug Abuse's Drug Abuse Warning Network (DAWN) (Chart B).

Once barbiturates were placed on triplicate prescription in 1981, drug overdose ER admissions reported to DAWN declined by 94 percent while prescribing declined by 70 percent (Charts C and D).

In January 1989, New York placed benzodiazepines on the triplicate program, curtailing the massive diversion of these drugs into illicit use as evidenced by:

- A group of over 3,400 persons suspected of diverting benzodiazepines had been receiving as many as 20,000 prescriptions for these drugs each month, almost a quarter of a million annually. By May 1989, their prescription claims had been reduced by 95 percent, to only 1,070 scripts (Chart E).

- A group of pharmacies suspected of being "pill mills," that were diverting drugs into illicit use, have reduced benzodiazepine dispensing by 76 percent.

- "Street" prices for benzodiazepines have increased two to five times, indicating a major drying up of supplies "on the street" for illicit sale (Chart F).

- Emergency room admissions for drug overdoses involving benzodiazepines were reduced by 48 percent in New York City and Buffalo during the first year (1988 to 1989) while

simultaneously decreasing by only 5 percent in the rest of the country, as reported to the DAWN system and analyzed by MDA in their 3-year trend analysis. (Charts G reflects the change in the number of such admissions reported by all the DAWN sample hospitals in Buffalo and New York City SMSAs).

Overall, there appears to have been about a 50 percent decline in benzodiazepine prescribing since the regulation was enacted as exemplified in three publicly funded programs in New York State, the Elderly Pharmaceutical Insurance Coverage (EPIC) program, the Empire Plan (for public employees and dependents), and the Medicaid Program (Charts H-J). This change resulted in savings of approximately $12 million during 1989 and $15 million in 1990 for New York State's Medicaid Programs alone through reduced benzodiazepine prescribing (after accounting for increased use of alternative drugs).

In addition, greater savings in injuries and costs are expected as a result of decreased accidents, fractures, drug overdoses and impairment of the elderly.

These findings are more fully described in *Epidemiology Notes,* a publication of the New York State Department of Health (NYSDOH 1989, 1990).

The triplicate prescription system does not interfere with legitimate drug use.

In New York State virtually every physician who has a reason to prescribe a drug on triplicate forms does so. In 1989, more than 27,000 of the 31,000 physicians, or about 90 percent of those in active private practice had issued triplicate prescriptions. (Note: Not all physicians have a reason to prescribe these drugs, e.g., dermatologists and general pediatricians have little need to prescribe them). This data indicates that physicians continue to prescribe the drugs on triplicate prescription forms when needed by their patients (Chart K).

Opponents of New York's triplicate system have argued that the triplicate system results in physicians denying proper treatment to their patients, such as terminally ill cancer patients. This argument simply is not valid. It presumes that physicians will deny their patients proper medical care because they are afraid of being held accountable for their prescriptions.

In reality, the majority of physicians have not reacted inappropriately. The prescribing of the narcotic analgesics, Percodan, Percocet and their generic equivalents have been basically unaffected by New York's triplicate program as can be seen in the attached Chart L. Use of Dilaudid, a primary narcotic analgesic used for treating cancer patients, has actually increased while on the triplicate form (Chart M). What is particularly important is that the triplicate prescription system has allowed New York to prevent abuse of these drugs while their prescribing has been unimpeded, as reflected in the very low levels of DAWN reports of emergency room admissions involving these drugs (Charts N & O).

Further evidence of the lack of adverse impact on proper prescribing has been seen following placement of benzodiazepines on triplicate prescriptions. The use of the drug clonazepam, which is used for treatment of epilepsy, has not decreased while other benzodiazepines that were abused have decreased (Chart P).

Based upon New York State's experience with the triplicate system, physicians have not simply switched their patients to other lower scheduled or non-scheduled drugs, nor is their evidence patients have increased their alcohol use as a mode of self-medication.

New York has carefully tracked this issue as part of its implementation of the regulation placing benzodiazepine drugs on triplicate prescriptions. For example, in the Medicaid Program, for every 100 fewer benzodiazepine prescriptions written, only about 20 alternative drugs prescriptions were issued in 1989. Of these alternative prescriptions, only about 3 were for chloral hydrate or meprobamate, and could be questioned as to their therapeutic appropriateness. By 1990, the small number of alternative drug prescriptions began to decline. Chart Q demonstrates this information for the Medicaid program.

Also, contrary to claims by opponents, consumption of alcohol has declined in New York State since implementation of the triplicate program for benzodiazepines. The State Department of Taxation and Finance reports that beer sales declined 2.3 percent from 1988 to 1990, liquor sales declined 8.1 percent, and wine sales declined 12.8 percent.

Triplicate prescription systems protect patient confidentiality. They can do so better than third-party payers, physicians' offices, pharmacies, PADS 11, or voluntary DUR systems.

New York State Law protects triplicate prescription patient information. Public disclosure of the identity of patients is expressly prohibited and violators can be penalized by a year in prison and a $2,000 fine. In 12 years of operation, there has never been a breach of confidentiality.

In the case of Roe v. Whalen, the United States Supreme Court found the confidentiality safeguards in New York's triplicate prescription system acceptable. Since then, New York has added more protections. Triplicate prescription information is maintained on computer tapes, not online, and the tapes are only run with the computer in an offline status so no one can break into the data base. Patients' names are encrypted on the tapes and only deencrypted when reports requiring patient names are run, thus preventing inadvertent observation even by State staff. The triplicate tapes are randomly filed among thousands of other tapes to prevent unauthorized persons from finding the tapes. All patient identity is erased after 5 years. Additional security measures are also employed.

New York State has found no alternative system that is equal to the triplicate prescription system in controlling and preventing drug diversion.

Opponents of New York's triplicate system have suggested that New York substitute the American Medical Society's Prescription Abuse Data Synthesis (PADS II) system for our triplicate system. More recently, mention has been made of a voluntary Drug Utilization Review (DUR) system or electronic transfer of prescription data without a State issued form. While New York may consider such systems as supplementary adjuncts, we do not consider them a substitute for a triplicate system because:

- Triplicate prescription systems are in operation and have proven effective over many years of operation.

- Triplicate prescription systems are mandatory under law: every pharmacy must report every triplicate prescription. No law in New York State requires pharmacies or any other source to report data on PADS II, DUR, or electronic transfer. Pharmacies involved in drug diversion are certainly not going to volunteer to report. Under New York law, third-party payers have no legal obligation to report and may jeopardize their participants' right to privacy by reporting to PADS II or DUR. Even if all third-party payers cooperate,

they pay for only about 50 percent of prescriptions, so one-half the data would be missing.

- Triplicate prescription systems prevent forgery and counterfeiting of prescriptions as described earlier.

- Triplicate prescriptions are validated evidence of prescribing. The State has an actual copy of each prescription. The State can verify if the physician signing the prescription is the physician to whom it was issued by checking the serial number and signature. This not only prevents forgery but also vastly increases investigative efficiency. The State does not have to prove who wrote the prescription and does not have to go to multiple pharmacies to obtain copies of the prescriptions.

- Triplicate prescriptions prevent tampering and altering of prescriptions. They are printed on special paper with special inks that will readily disclose efforts to erase, eradicate ink, or otherwise alter the prescriptions. This prevents patients, pharmacy staff, or others from altering prescriptions to obtain larger amounts than those prescribed by the practitioner.

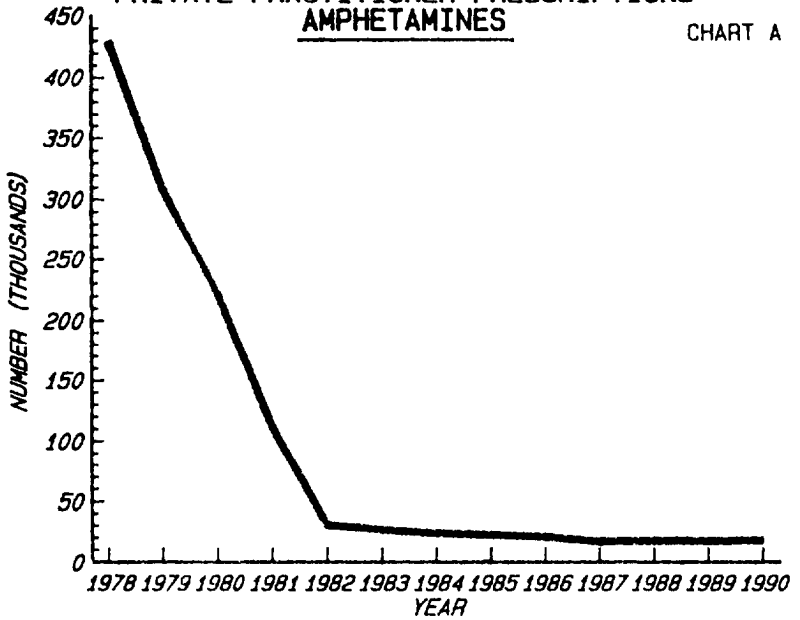
- Triplicate prescriptions prevent a convicted practitioner from prescribing drugs. The State simply does not issue triplicate forms to such practitioners and requires return of any forms previously issued. Without the forms, the practitioner cannot issue prescriptions that will be filled, saving patients from injury.

- Pharmacies are assisted by triplicate prescription systems for they have assurance when tilling such prescriptions that the prescribing practitioner is bona fide and qualified to write controlled substance prescriptions.

CHARTS

PRIVATE PRACTITIONER PRESCRIPTIONS
AMPHETAMINES

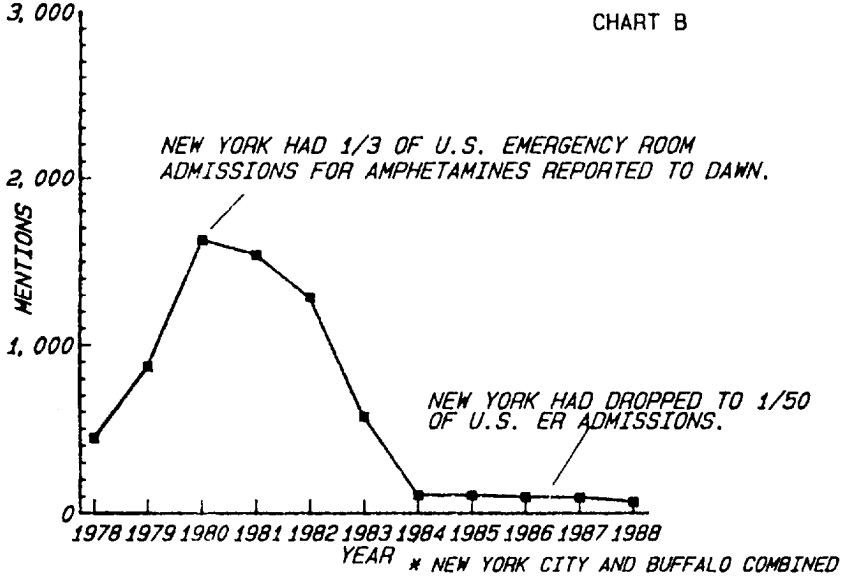
CHART A



DIVISION OF PUBLIC HEALTH PROTECTION
BUREAU OF CONTROLLED SUBSTANCES, DOH (1991)

NEW YORK STATE DAWN E.R. MENTIONS *
AMPHETAMINES

CHART B

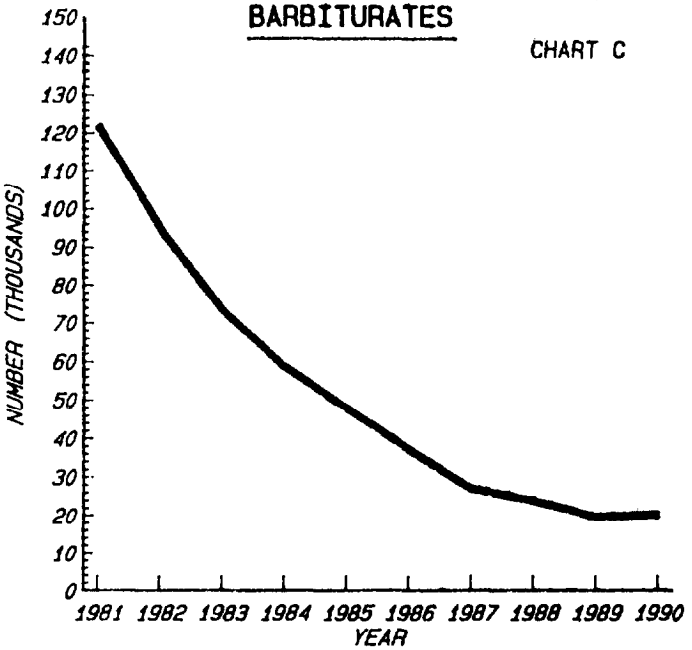


* NEW YORK CITY AND BUFFALO COMBINED

DIVISION OF PUBLIC HEALTH PROTECTION
BUREAU OF CONTROLLED SUBSTANCES, DOH (1991)

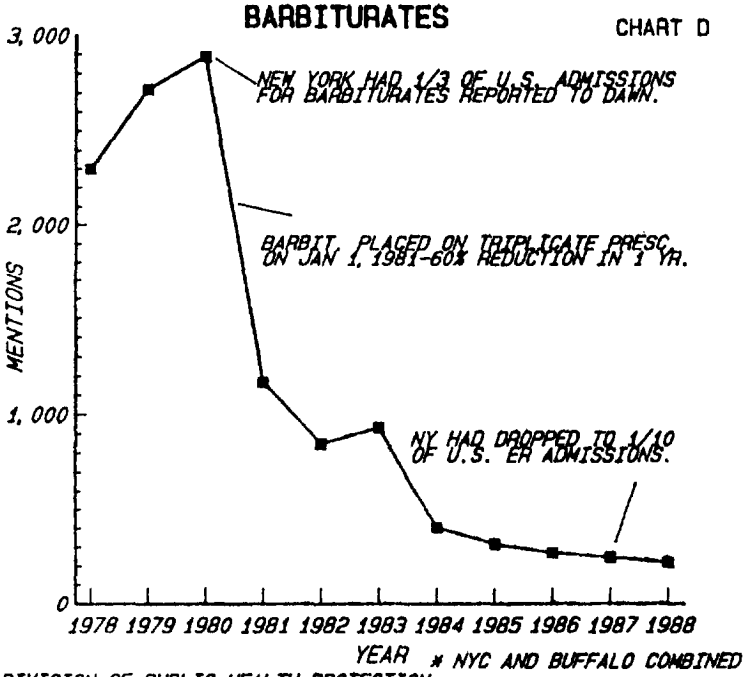
PRIVATE PRACTITIONER PRESCRIPTIONS
BARBITURATES

CHART C



NEW YORK STATE DAWN E.R. MENTIONS *
BARBITURATES

CHART D

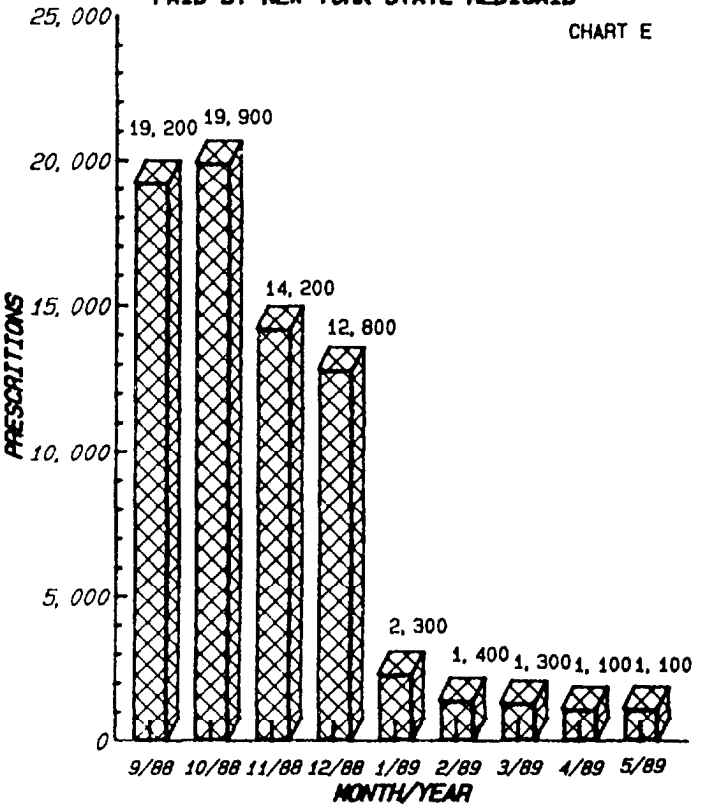


* NYC AND BUFFALO COMBINED

DIVISION OF PUBLIC HEALTH PROTECTION
BUREAU OF CONTROLLED SUBSTANCES, DOH (1991)

RECIPIENTS W/HIGH VOLUME OF PHARM. SVCS. BENZODIAZEPINE PRESCRIPTIONS PAID BY NEW YORK STATE MEDICAID

CHART E



Data from NYS Dept. of Social Services

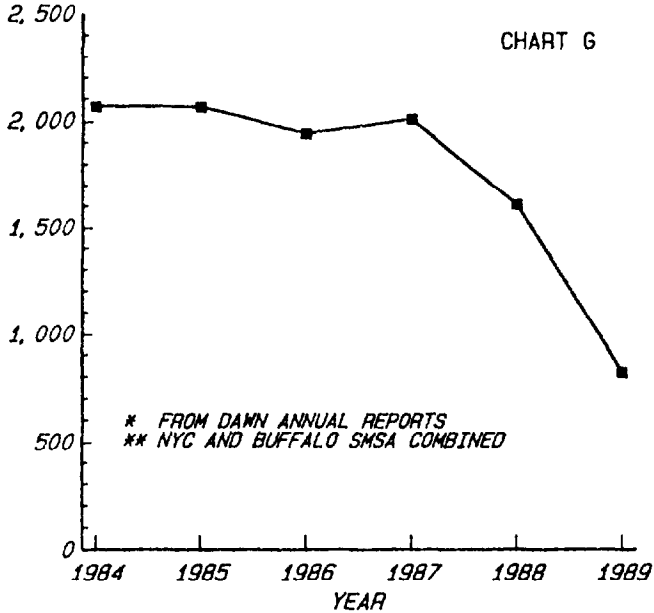
STREET PRICE PER PILL OF SELECTED BENZODIAZEPINES IN NEW YORK CITY

CHART F

DRUG		*DEC. '88*	*SEPT. '89*
ALPRAZOLAM (XANAX)	*1mg*	*$1.50*	*$8.00*
DIAZEPAM (VALIUM)	*5mg*	*$1.00-$1.25*	*$2.00-$3.00*
	10mg	*$2.00-$2.50*	*$4.50-$6.00*
LORAZEPAM (ATIVAN)	*0.5mg*	*$2.00-$2.50*	*$3.00-$4.00*

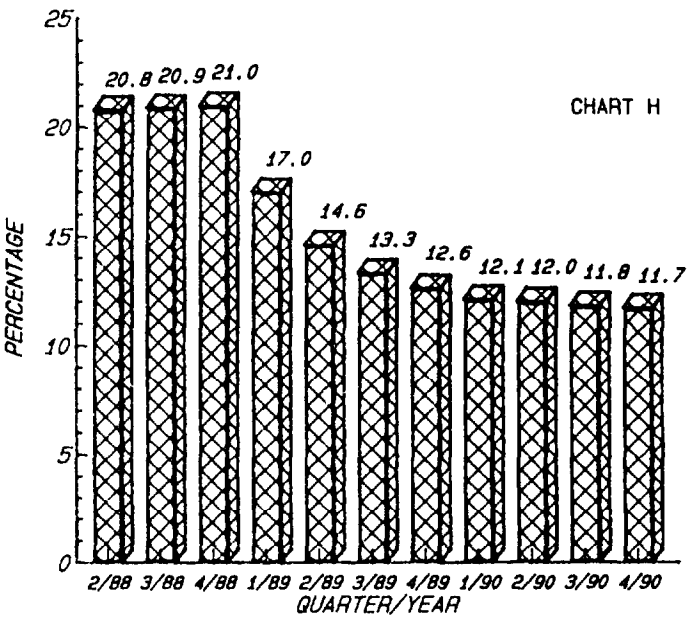
SOURCE: NYS Division of Substance Abuse Services

DAWN ER EPISODES *
NEW YORK STATE **



DIV. OF PUBLIC HLTH PROTECT.
BUREAU OF CONTROLLED SUB., DOH (1991)

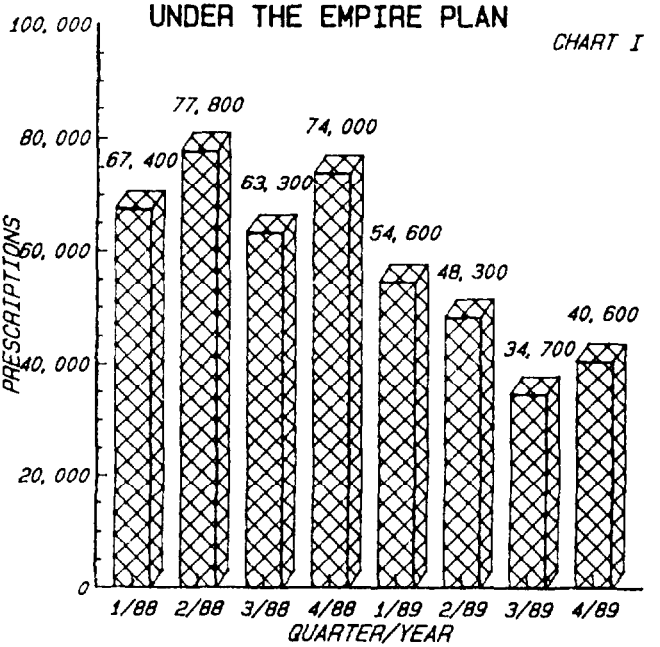
NEW YORK STATE EPIC PROGRAM
PARTICIPANTS WITH BENZODIAZEPINE CLAIMS



DIV. OF PUBLIC HLTH PROTECT.
BUREAU OF CONTROLLED SUB., DOH (1991)

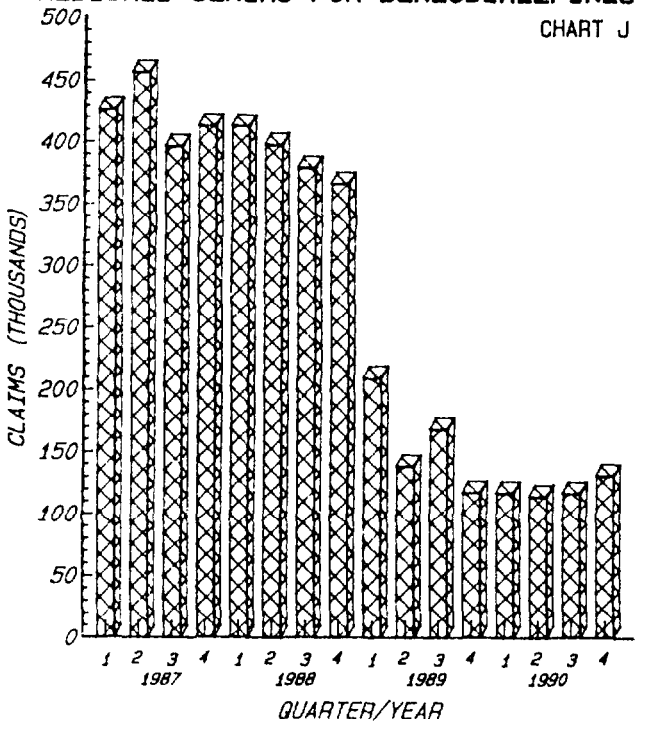
PRESCRIPTIONS FOR BENZODIAZEPINES
UNDER THE EMPIRE PLAN

CHART I

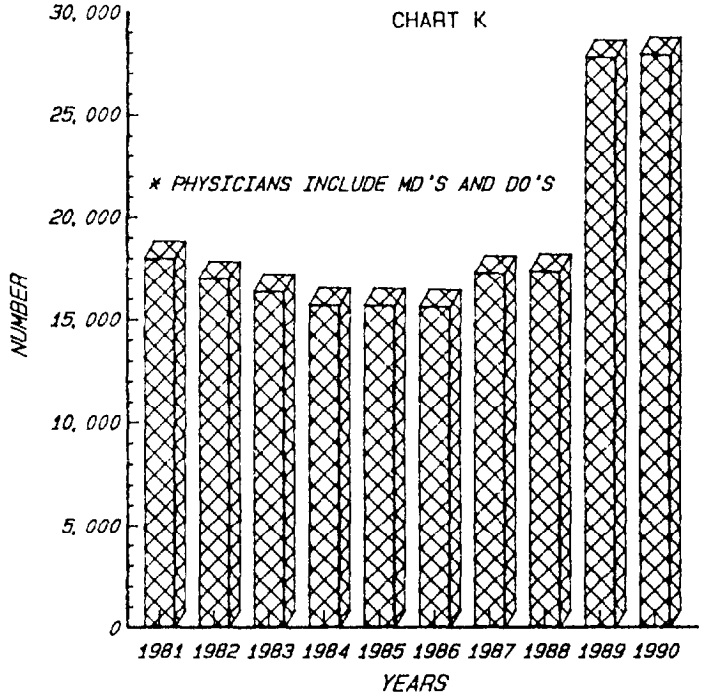


MEDICAID CLAIMS FOR BENZODIAZEPINES

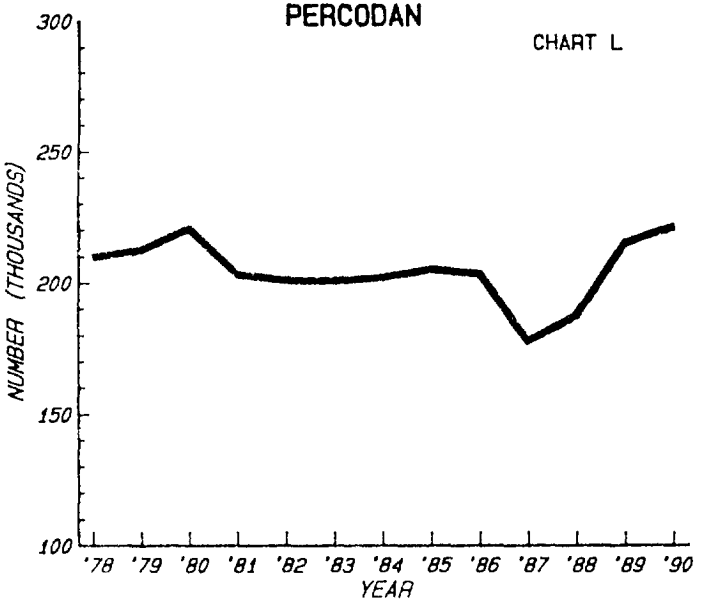
CHART J



PHYSICIANS PRESCRIBING ON PRIVATE PRACTITIONER TRIPLICATE PRESCRIPTION FORMS *



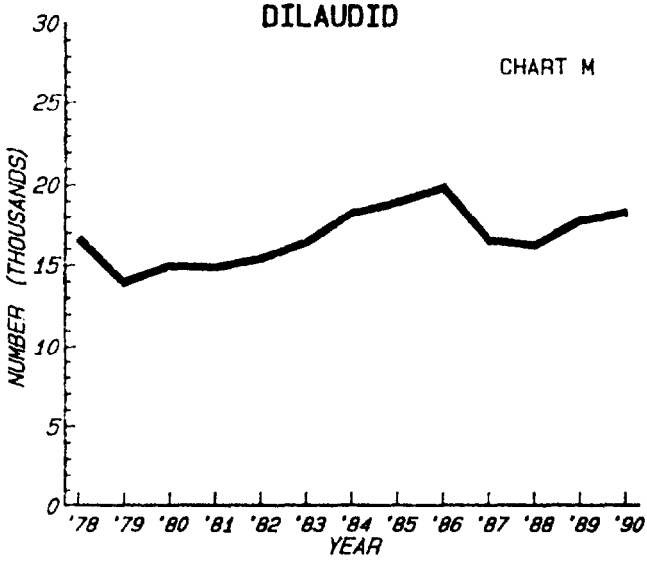
PRIVATE PRACTITIONER PRESCRIPTIONS PERCODAN



DIVISION OF PUBLIC HEALTH PROTECTION
BUREAU OF CONTROLLED SUBSTANCES, DOH (1991)

PRIVATE PRACTITIONER PRESCRIPTIONS
DILAUDID

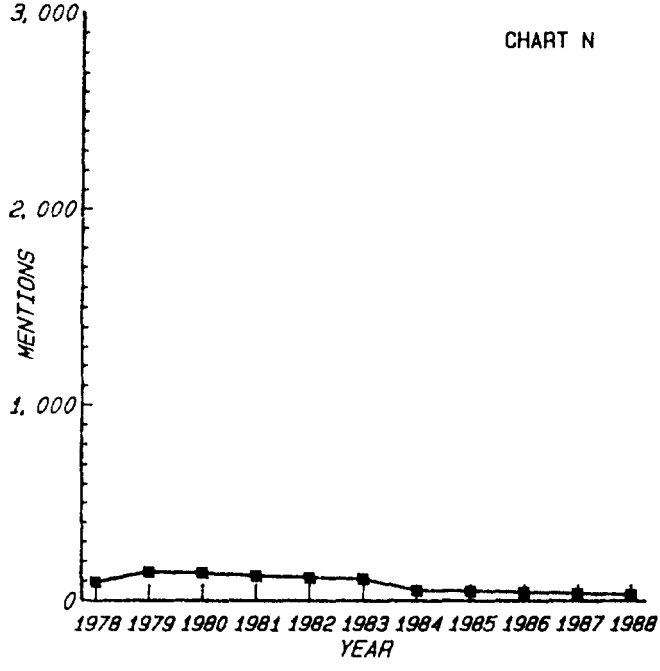
CHART M



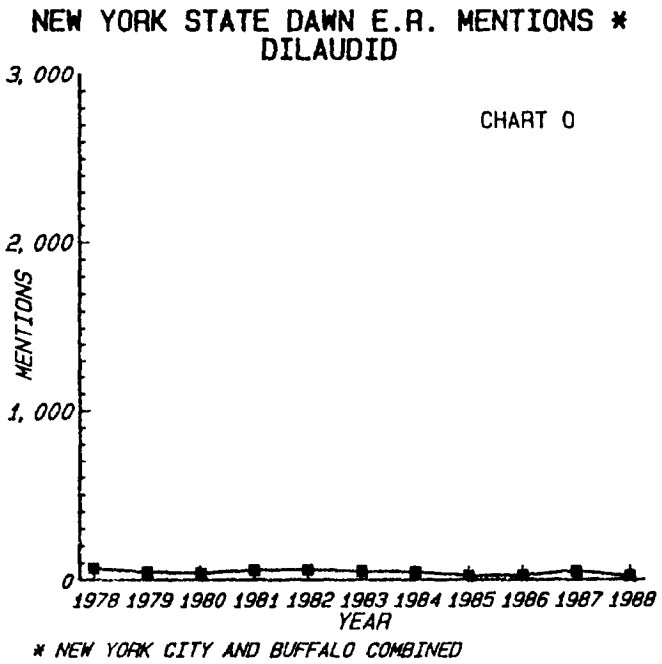
DIVISION OF PUBLIC HEALTH PROTECTION
BUREAU OF CONTROLLED SUBSTANCES, DOH (1991)

NEW YORK STATE DAWN E.R. MENTIONS *
PERCODAN

CHART N



* NEW YORK CITY AND BUFFALO COMBINED


NEW YORK STATE DAWN E.R. MENTIONS *
DILAUDID
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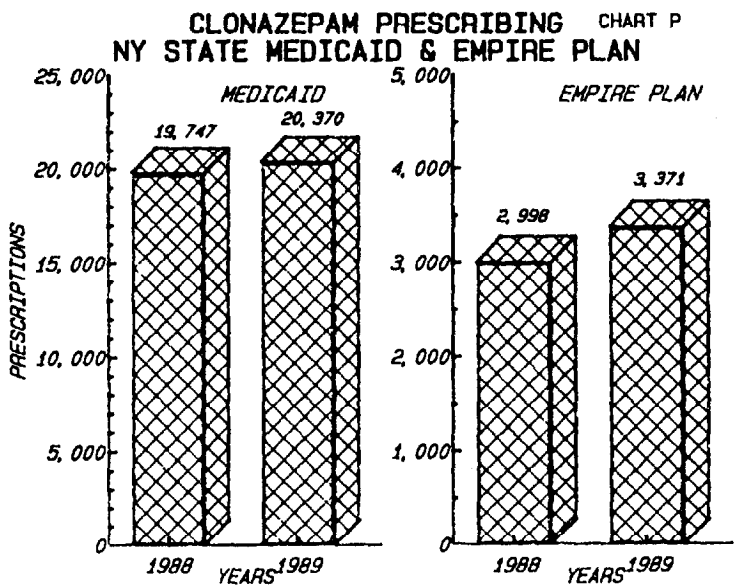
* NEW YORK CITY AND BUFFALO COMBINED


CLONAZEPAM PRESCRIBING
CHART P
NY STATE MEDICAID & EMPIRE PLAN
MEDICAID
EMPIRE PLAN
25, 000
20, 000
15, 000
10, 000
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PRESCRIPTIONS
19, 747
20, 370
2, 998
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5, 000
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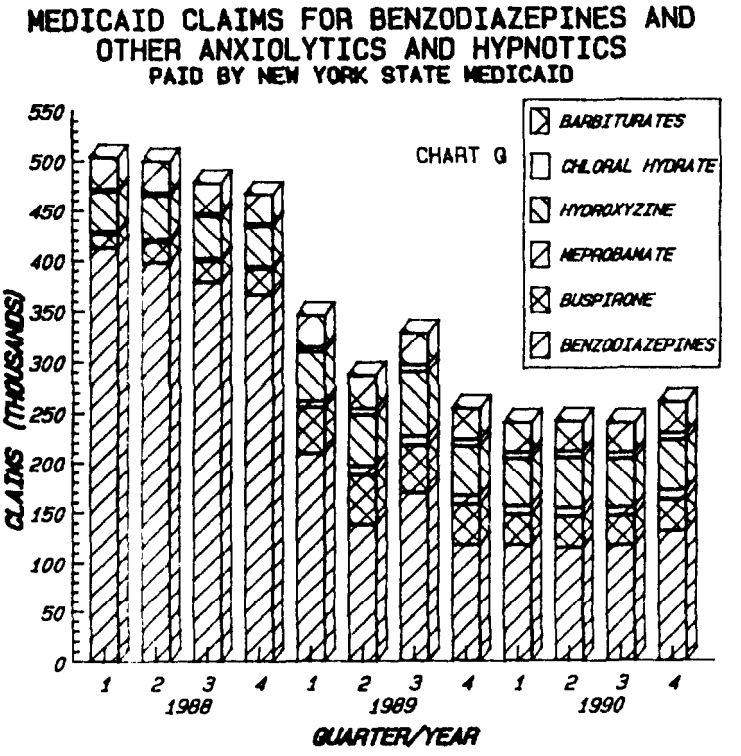
MEDICAID CLAIMS FOR BENZODIAZEPINES AND OTHER ANXIOLYTICS AND HYPNOTICS
PAID BY NEW YORK STATE MEDICAID
CHART G
BARBITURATES
CHLORAL HYDRATE
HYDROXYZINE
MEPROBAMATE
BUSPIRONE
BENZODIAZEPINES
CLAIMS (THOUSANDS)
550
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1988
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QUARTER/YEAR

DISCUSSION

The triplicate prescription system has given New York State an extremely effective and sensitive tool to control and prevent drug abuse and misuse while assuring the uninterrupted, legitimate use of controlled substance medications. The triplicate data permits the monitoring of drug use, education by peer review directed to the physicians who need it most, and efficient targeting of investigations with less governmental intrusion into practitioners' offices and pharmacies. Investigations and prosecutions are expedited because the prescriptions are already in the State's possession; the patterns of prescribing and dispensing are documented.

The controlled distribution of forms prevents forgery and counterfeiting by assuring that only bonafide practitioners can use the prescriptions. The privilege of having the forms can be revoked or restricted to specific drugs. Monitoring of such restrictions is automated. Pharmacies are assisted by the knowledge that a practitioner who has triplicate prescriptions has been verified by the Department of Health to possess a valid license and Drug Enforcement Administration (DEA) registration.

No other system offers to New York State the advantages of the triplicate prescription system in reducing prescription drug diversion, abuse, and misuse without interfering with physicians and other practitioners' ability to prescribe as they determine.

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Triplicate Prescriptions in Washington State

Donald H. Williams

BACKGROUND

The Washington State Board of Pharmacy serves as the drug control agency for the State of Washington. Besides the licensing of pharmacists, pharmacy technicians, pharmacies, drug manufacturers, and other drug distributors, the board also administers and enforces a variety of State drug laws. These laws include the Legend Drug Act, the Uniform Controlled Substances Act, the Food Drug And Cosmetic Act, the Controlled Substance Precursor Control Act, and several other drug laws and regulations. The board serves as the controlled substance scheduling authority and determines which drugs are prescription drugs and which may be sold over the counter. Also, the board investigative staff performs all drug-related investigations on all licensed health professionals. The results of these investigations are usually referred for disciplinary action to the board that is responsible for licensing the investigated practitioner. When the cases involve criminal law violations, these are referred either to the county prosecutor or to the United States assistant attorney for the jurisdiction in which the offense(s) took place. The investigators, all licensed pharmacists, are designated as law enforcement officers with the duty to enforce drug laws. This authority includes the power of arrest.

The Washington State Triplicate Prescription Program (TPP) had its origin in the Sunset Review Audit of the Washington State Board of Pharmacy, conducted by the Legislative Budget Committee during 1983. There is nothing like the threat of extinction to get a State agency moving. During the initial review, it was noted that, although the board was doing a good job of reacting to drug diversion issues, the board should be doing more to control the abuse of drugs. The reviewer suggested that the board convene a drug abuse task force to determine what activities the board and its staff might engage in to do a better job of controlling drug abuse in the State. The board followed this advice and invited the participation of licensing boards and professional associations whose members had drug prescribing, dispensing or administering authority (e.g., pharmacists, physicians, dentists, veterinarians, nurses, and podiatrists.) The Drug Enforcement Administration and the State Alcohol and Substance Abuse Agency also participated. After several meetings, the

task force made some recommendations. One recommendation was that the State should adopt a limited triplicate prescription program.

Although some task force members supported a full triplicate program, there was insufficient support to adopt this as a recommendation. In addition, the State was recovering from a recession and there was no source of funding for such a program. It should be noted that, as we enter another recession, there remains a funding shortfall that precludes adoption of a full triplicate prescription program by the State of Washington.

The recommendations of the Task Force were made a part of the final Sunset Review Report and this report was adopted by the 1984 Legislature. Many recommendations, including reauthorization of the Board of Pharmacy and the limited triplicate prescription program, were enacted into law by the Legislature during the 1984 Session (Chapter 69.50.311 RCW.). The law provided that each licensee with prescriptive authority agree, as a condition of licensure, to comply with a triplicate prescription program if imposed by the practitioner's disciplinary board.

Rules were to be adopted by the Department of Licensing, which was the parent agency at the time, for all the health professional licensing boards except the Board of Pharmacy. The Department of Licensing adopted implementing rules in May 1986 (WAC 308-250-010 to -050). (Note: On October 1, 1989, all the health professional licensing and disciplinary boards, including the Board of Pharmacy, were incorporated into the new Department of Health.)

The authority to determine which practitioners would be required to participate was left entirely to the disciplinary boards for the individual health professions. The cost of the prescription forms was made the responsibility of the practitioners. The original prescription is taken to the pharmacy, with the prescriber retaining one copy for his/her records and the other copy transmitted to the department. Unlike other multiple copy programs, the responsibility for transmitting a copy of the prescription to the State was assigned to the practitioner rather than to the pharmacist. If the drug is administered in the office or dispensed by the practitioner to the patient, both the original and the copy are sent to the department. The rules made provisions for emergencies so that the prescriber may issue an oral prescription but this is to be confirmed by delivering a written prescription to the pharmacy within 72 hours. The remaining copies are to be transmitted to the State or retained as with nonemergency prescriptions.

The first licensing board use of the program started in 1987 and there has been limited use since that time. Each licensing board has the responsibility for operating its own triplicate program, leading to some inconsistencies and other problems. The Board of Pharmacy developed a software program for data entry of prescription information into laptop computers so that board investigators could collect information at community pharmacies for later analysis using desktop computers. This system was described by Tony Zinicola at the American Medical Association symposium, "Balancing the Response to Prescription Drug Abuse," held in Washington, D.C. in December 1988. Modifications were made in this program to allow computer entry of the prescriptions that had been received by the Medical and Dental Disciplinary Boards. After entering the available data, an analysis of problems was performed and some recommendations for improvement of the program were made. Some of these problems included:

1. Boards were not exercising proper security control over the blank forms.
2. No record was maintained of which blanks went to which prescribers.
3. Completed prescriptions were not being reviewed upon receipt by the boards.
4. Prescribers were not writing on a solid surface so that the writing from one prescription carried through to the subsequent prescription, making it difficult to read.
5. Prescribers were using multiple forms of the same patient name causing difficulty in determining how many patients were treated. For example, prescriptions for William M. Smith were written variously as William Smith, W.M.Smith, Will Smith, Bill Smith, Willie Smith, etc.
6. Many prescriptions did not include addresses though this is required by DEA rule, 21 CFR 1306.05(a).
7. The prescriptions received by the boards were reviewed manually instead of being entered into a computer.

In 1990, the Pharmacy Board staff again gathered all the available completed triplicate prescription forms and entered them into the computer for analysis. This data was merged with the data collected in 1988. For this study, we produced reports to show each drug prescribed by the practitioners in the program. Although the numbers in our study are small, we believe that we have had some effect on the prescribing habits of these practitioners.

We have surveyed the prescribing of thirteen physicians and two dentists. Since one practitioner (Doctor No. 3) issued significantly more prescriptions than the others we computed the average number of prescriptions per prescriber both with and without these numbers. When this prescriber's data is included, the average number of prescriptions per practitioner is 442, but only 240 when excluded. The average number of prescriptions per patient is 2.5. Doctor No. 3's average of 7.7 Schedule II prescriptions per patient has been brought to the attention of the Medical Disciplinary Board, where we anticipate some additional action will be taken.

The reasons for practitioners being required to participate in the program range from inappropriate prescribing to personal use of drugs. A comparison of the number of drug-related cases referred to the disciplinary boards and the number of practitioners who have been placed in the program by their respective boards leads one to conclude the program is currently being underutilized by the boards as a disciplinary monitoring tool.

SUMMARY

In summary, I believe that this program, although limited in scope, has been of value to our State in controlling the inappropriate prescribing of controlled substances. We have identified several problems that have been or are being addressed in order to make the program even more effective. The program targets only those prescribers who have been identified as having drug use or prescribing problems rather than subjecting all practitioners to a program for the purpose of finding a relatively small number of violators. Thus, the intimidation factor alleged to be present in full triplicate programs is absent in the limited program. It is flexible since the drugs included in the monitoring can range from a single controlled substance schedule, all schedules, or even to all prescriptions. The program includes both prescribed drugs and those administered in the office or dispensed by the practitioner. The responsibility for compliance is placed on the prescribers, not on the pharmacists.

The way the law is written, the program could be expanded to include a sample of all prescribers, providing information that could be used to determine prescribing norms. Overprescribing appears to be in the eyes of the beholder. A pharmacist may view certain prescribing habits differently than a disciplinary board. The availability of norms would assist boards in making more scientific determinations regarding alleged overprescribing practices.

RECOMMENDATIONS

All States should adopt some type of program to identify and control the diversion and abuse of drugs. The limited triplicate prescription program described in this paper is one alternative that should be considered. If a program is adopted, it should be placed in an agency that does not have a vested interest in the practitioners. States, for example, should have a State controlled substance registration that can be administered by a controlled substance authority rather than by the individual licensing boards. This authority might be in a better position to make decisions regarding which practitioners should be required to participate in a triplicate program. In addition, there should be a thorough study of the current drug control programs to determine which programs are applicable to which problems. The reduction in the number of Schedule II prescriptions or doses dispensed after implementation of a triplicate prescription program is not necessarily a good measure of the effectiveness of such a program. The counterclaims of physician intimidation or inadequate therapy do not prove that multiple prescription programs automatically mean inferior patient care. After the electronic prescription data collection program, now being implemented in Oklahoma, has been in operation for at least a year, it, too, should be analyzed to see what effect it has had on controlling the inappropriate use of controlled substances. Claims for the AMA PADS II program also should be validated.

There is plenty of data available. Rather than saying, "Ours is the best program," we all need to work together to perform the necessary studies to determine which programs are proven to be most effective in meeting our needs and goals.

NOTE: The author wishes to thank the research analysts Diana Ehri and Tony Zinicola for the data analysis necessary to support the presentation of this paper.

A series of 11 charts providing a detailed analyses of the specific controlled drugs prescribed by physicians and dentists in Washington State, the 15 practitioners required to participate in the program's prescribing habits, and the disciplinary actions taken in these cases, is available from the author upon request.

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The Medicaid Prescription Drug Initiative

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I am Tom Roslewicz, Deputy Inspector General for Audit Services of the Department of Health and Human Services. With me is Pat Marion, an audit manager in our Philadelphia Regional Office. We have been invited here to discuss with you the nationwide Medicaid Prescription Drug Initiative being conducted jointly by the Office of Inspector General and numerous States. The objective of this initiative is to identify and take action against traffickers and abusers of prescription drugs purchased under the Medicaid program.

A computer program, which we developed with the help of the Drug Enforcement Administration (DEA) to identify targets for review and investigation, is the driving force behind this nationwide initiative. Pat Marion is the audit manager in charge and is available at any time to discuss this initiative. What I would like to do is to:

1. Provide background information on why and how the Office of Inspector General became involved in this initiative

2. Discuss the capabilities of our computer program

3. Provide examples of the targets identified by our program

4. Present my overall evaluation of the joint initiative to date

BACKGROUND

Why did the Office of Inspector General (OIG) become involved in this joint initiative? Our involvement goes back many years. In 1983 we made an audit of controls over prescription drugs purchased under the Medicaid program in the District of Columbia. We found those controls were weak. We recommended that the District strengthen its procedures for: (1) identifying recipients with the greatest potential for drug abuse or misuse, and (2) lock

these recipients into a single primary care physician to control their access to prescription drugs.

We did a followup review in 1990 and found that, although some improvements were made, controls of prescription drugs, for the most part, remained weak. Although our review was limited to the District, we suspected that the control problems were not restricted to the District. We also knew that the Medicaid program is susceptible to drug trafficking and abuse. The National Institute on Drug Abuse identified the top 20 abused drugs in this country. Only 5 of the top 20 are illegal drugs, while 15 are prescription drugs available through the Medicaid program.

We decided to broaden the scope of our review of prescription drugs to include not only controls over recipients but also controls over physicians who prescribe the drugs and the pharmacies that dispense them. We also decided to seek the assistance of the DEA to find a better way of identifying targets with the greatest potential for trafficking or otherwise abusing prescription drugs under the Medicaid program.

Working with the DEA, we developed a computer program to identify those physicians, pharmacies, and recipients most likely to be involved in the prescription drug trade. We tested the program in the District of Columbia and concluded that we had a pretty good product. We recognized, however, that the product was only as good as its user. Our program identifies targets. The user has to review and investigate these targets. This requires a commitment of time, personnel resources, and funds.

We recognized that we did not have the resources to do it alone. With that recognition, the joint OIG/State initiative was born. We decided to forgo the traditional audit approach and offer our computer program to those States that wanted to use it.

States are often wary of auditors offering something for nothing, so we started out slowly and carefully. Pat Marion attended national drug conferences and offered our computer program to those States in attendance. The response was good but we realized another, more expansive approach was needed. We tried something unique, at least unique to the Inspector General community. We made a 20-minute video in which I explained the merits of our computer program and we sent it to every State Medicaid agency and Medicaid fraud control unit in the country. The response to date has been excellent.

Eighteen States have, or shortly will have, run our computer program against their paid claims tiles. Arkansas, Florida, Montana, Minnesota, New Mexico, Oklahoma, Massachusetts, Pennsylvania, and Virginia have the program up and running. Delaware, Illinois, Kansas, Kentucky, Missouri, Nevada, Vermont, West Virginia, and South Dakota are in the process of doing so.

Twenty-one other States and the District of Columbia have requested technical data on the program. They are reviewing this data and comparing the capabilities of our program with their existing controls. These States will decide shortly whether or not they will use our program. The States are Alabama, Alaska, California, Connecticut, Georgia, Hawaii, Idaho, Indiana, Iowa, Louisiana, New Hampshire, New Jersey, New York, North Carolina, North Dakota, Ohio, Oregon, South Carolina, Texas, Utah, and Washington. Six States have responded that they have no interest in our computer program (Arizona, Maine, Maryland, Michigan, Nebraska, and Wisconsin) and five other States have not responded at all (Colorado, Mississippi, Rhode Island, Tennessee, and Wyoming).

We intend to keep the Health Care Financing Administration informed on the progress of this initiative so that it can direct its oversight resources to those States with the greatest risk of material internal control weaknesses over Medicaid prescription drugs.

OIG COMPUTER PROGRAM

I now want to talk about the computer program itself. The program basically has a single purpose–to monitor drug utilization patterns of prescribers, dispensers, and users of abusable drugs; and to identify targets with aberrant patterns in relation to their peers. Some of the main features of our computer program are:

1. The program focuses on Schedule II through V prescription drugs. We obtained and incorporated into the program over 50,000 national drug codes. These codes represent about 100 controlled substances, virtually all of which are considered by the DEA to be subject to abuse and diversion.

2. The program statistically analyzes by controlled substance the patterns of physicians, pharmacies, and recipients against the average of their peers and identifies those who exceed the peer average by two or more standard deviations. This

feature is very important in assuring that we are comparing apples with apples and not applying the standards of say Boise, Idaho, to New York City. The average is based on drug volume rather than the number of drug prescriptions.

3. The program prioritizes targets by number of drug parameters and standard deviations exceeded. This is a very important feature in that prioritization of targets allows user States to point their scarce investigative resources to those targets with the greatest potential for wrongdoing.

4. The program provides flexible targeting. It can target a specific drug, a specific combination of drugs, or a specific location–such as the city of Philadelphia where a review is underway. The program can also be modified to meet requirements of individual State programs.

In summary, our computer program can identify every physician, pharmacy, and recipient who exceeds the average drug patterns of peers by at least two standard deviations. Ideally, all should be reviewed to determine if their patterns are justified medically. Realistically, we cannot expect that because of a shortage of resources. This is where the capability of the program to prioritize targets comes into play. Targets that exceed a drug parameter by five or more standard deviations are clearly the highest volume prescribers, dispensers, or users of that drug, clearly aberrant in relation to their peers, and should be reviewed first.

TYPE OF TARGETS IDENTIFIED

Now for some examples of the targets identified by our computer program. New Mexico was the first State to request our assistance. Our computer program identified six physicians, or 5 percent of all physicians, who were major prescribers of 5 to 9 drugs. Let's look at two of these six.

Chart 1

This physician was one of two who exceeded the parameters for the three most abused prescription drugs: Valium, Xanax and codeine. He was the State's leading prescriber of:

- Xanax, accounting for 7.5 percent of all Medicaid prescriptions
- Codeine, accounting for 3.8 percent of all Medicaid prescriptions
- Percodan, accounting for 5.1 percent of all Medicaid prescriptions

He was also a major prescriber of five other drugs–Serax, Darvon, Talwin, Librium and a codeine mixture. The last we heard, the State was moving toward an indictment.

Chart 2

This physician was one of eight who exceeded parameters for two of the three most abused prescription drugs. Aside from being a major prescriber of Xanax, he was the State's leading prescriber of:

- Valium, accounting for 28.5 percent of Medicaid prescriptions
- Darvon, accounting for 26.9 percent of all Medicaid prescriptions
- Equinal, accounting for 25.5 percent of all Medicaid prescriptions
- Fiornal, accounting for 15.2 percent of all Medicaid prescriptions
- Serax, accounting for 15.2 percent of all Medicaid prescriptions

He was also among the leading prescribers of percodan. This physician also faces a State indictment.

EVALUATION OF INITIATIVE

I believe these two examples clearly demonstrate that our computer program can identify targets with great potential for involvement in drug trafficking and abuse of prescription drugs purchased under the Medicaid program. But I will be the first to tell you that our computer program is not the entire answer to eliminating fraud and abuse in the Medicaid prescription drug program. As I noted earlier, our program is just the first step in this process. There is still a tremendous amount of legwork required by utilization reviewers and investigators to follow up and investigate targets identified by our computer program to determine if actual trafficking or abuse had occurred. Unfortunately, this takes time.

Criminal investigations underway in Virginia and the District of Columbia are being conducted jointly by our Office of Investigations, the Federal Bureau of Investigation, and the DEA. We know their work continues, but can say no more about it.

Investigations in Pennsylvania, which were initially concentrated in Philadelphia, are being conducted by our Office of Investigations and the State Medicaid fraud control unit. On April 16, 1991, agents obtained search warrants for 10 physicians and 5 pharmacies. All warrants have been executed and the records seized from the physicians and pharmacies are currently being reviewed for criminal intent. The investigation, currently being expanded throughout Pennsylvania, indicates to us that the investigators are pleased with the results so far.

Is our computer program better than anything else now being used in the Medicaid program to detect prescription drug trafficking or abuse? We honestly do not know, but we are encouraged by the fact that 18 States are using the program as an internal control over prescription drugs. We are also encouraged that an additional 21 States and the District of Columbia have shown initial interest in our program and are now comparing its capabilities with those of their own internal control systems. This attention alone could lead to improvements in controls over prescription drugs.

We have asked all States to be honest with us. Tell us the program's strong points and tell us its failures. We expect it will be months before we receive all this information. At that time, we will analyze the results and make whatever improvements or modifications are needed to our computer program, and once again offer the program to the States and to the Health Care Financing Administration for use in their oversight functions.

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Summary and Conclusions of a Review of Prescription Drug Diversion Control Methods

Constance Horgan, Jeffrey Prottas, Christopher Tompkins, Linda Wastila, and Melissa Bowden

The purpose of this paper is to summarize the findings from a report reviewing diversion control systems prepared under a NIDA contract by the Center for Drug Abuse Services Research of the Bigel Institite for Health Policy at Brandeis University (Horgan et al. 1991). Four tables are included summarizing each of four broad criteria areas: impact on diversion, impact on medical practice, operational aspects, and cost aspects.

These criteria are provided to compare the advantages and disadvantages of each system on a standardized basis. These summary tables attempt to describe typical situations. There may be exceptions for some of the systems which would suggest another classification. Thus, when examining these tables, the possibility of exceptions should be considered. Because no operating Prescription Abuse Data Synthesis (PADS) systems were included in this review, PADS is not included in any of the summary tables.

A. Impact on Diversion

It should be remembered that this study did not empirically estimate the effects of these systems on diversion activities. Rather, these observations reflect what might reasonably be expected if evaluations of the roles and effectiveness of the various systems were undertaken. With regard to diversion control, alternative systems can be useful in any of three ways: prevention, identification, and investigation.

In many cases, these systems potentially overlap and could act as near substitutes. For example, an Electronic Point of Sale (EPOS) system may be weighed against a Multiple Copy Prescription Program (MCPP) by a State contemplating strengthening its diversion control capability. In other cases, the systems operate quite differently–often as complements. For example, the Automation of Reports and Consolidated Order System (ARCOS) is primarily a tool for identifying potential diversion, whereas a Drug Investigational Unit (DIU) is primarily an investigative arm of State law

enforcement. Many officials involved in diversion control, including DIUs, make use of ARCOS data. Table 1 provides a summary of prescription drug diversion control systems in terms of their likely impact on diversion.

Types of Diversion

Patient Intent This type of diversion describes situations in which the patient is culpable for the diversion activity and the prescriber unwittingly participates. "Doctor shopping" and feigning illness are common examples of patient pretense. Systems that collect patient-level data might be capable of detecting this type of activity.

The Medicaid claims systems (the Surveillance and Utilization Review System, or SURS, and the Medicaid Abusable Drug Audit System, or MADAS) can deal with this issue because collecting information at the individual patient level is part of the process of claims payment. Most MCPPs also collect information at the individual patient level. Some MCPPs rarely generate exception reports at the patient level, whereas others do so routinely. The EPOS system is similar to the MCPPs in that patient-level data can be collected and analyzed. Oklahoma, the only operational EPOS, does collect patient identification information, and routinely generates exception reports at the patient level. ARCOS does not capture patient-specific data. DIUs can identify potential patient level diversion through the use of labor-intensive audits of pharmacy records.

Prescriber Intent This type of diversion describes situations in which the prescriber ("script doctor") intentionally misprescribes in collusion with the patient, and both the patient and the prescriber are culpable. Systems that can organize data to show prescriber patterns can identify this type of activity. For example, excessive overall volumes of controlled substances prescribed or great numbers of patients receiving prescriptions for controlled substances can be indicative of possible illegal behavior.

The EPOS type of system, Medicaid claims systems, and MCPPs are all capable of identifying prescriber pretense because, typically, individual providers can be identified (e.g., by Drug Enforcement Administration (DEA) registration number). It should be noted that not all MCPPs use their data to identify aberrant prescribing patterns on a routine basis. In some MCPPs, the data are accessed and reports are generated only during preliminary or full-fledged investigations of prescribers already suspected of diversion. ARCOS does not capture direct information about prescribers

unless they are also dispensers. DIUs (and other law enforcement agencies) are able to investigate providers suspected of diversion, and can collect information about prescribing behavior through examination of prescription records stored at pharmacies.

Dispenser Intent This type of diversion describes situations in which licensed practitioners intentionally dispense controlled substances under unlawful circumstances. The dispenser may accept a prescription knowing that it is not proper or valid, or may sell controlled substances to people without any prescription form at all. To avoid being detected, the dispenser may fabricate prescription forms that appear legitimate. This activity involves collusion with the patient and sometimes with the prescriber. Systems that collect data on individual dispensers may be used to identify this type of activity, although in many cases it may be difficult to detect without actually examining prescription records and validating their authenticity.

The ability to recognize dispenser pretense is similar to the findings for prescriber pretense noted above, with DIUs, EPOS, Medicaid, and MCPPs all being able to target unusual activity which involves a prescription at this level. In particular, the controlled prescription forms used by most MCPPs probably severely hamper the ability of pharmacist diverters to make their records appear legitimate. Additionally, ARCOS is able to detect dispensers who order unusually high quantities of certain controlled substances.

Forgeries/Alterations In order to verify this type of activity, it is necessary for the system to have access to the actual prescription form or possibly a copy. Potential cases of diversion may be identified, however, by systems that allow analysis of individuals visiting multiple pharmacies for controlled substances. DIUs and other law enforcement officials can verify cases of forgery or alteration through investigations in the field.

MCPPs, in general, can detect prescriptions that are counterfeit through the serialized numbering system of the multiple copy pads, and that are altered through the use of tamper-proof pads. Some argue that the hindrance to counterfeiting or making alterations to prescriptions under MCPPs will lead to increased theft and forgery of prescription forms (Belizzi 1991). However, this was not raised as a problem by law enforcement officials whom we interviewed.

Table 1 Summary of Prescription Drug Diversion Control System

IMPACT ON DIVERSION

	ARCOS	DIUs	EPOS	MEDICAID	MCPPs	PADS
Patient pretense	No	Yes*	Yes*	Yes	Yes*	Sometimes
Prescriber pretense	No	Yes*	Yes	Yes	Yes	Sometimes
Dispenser pretense	Yes	Yes*	Yes	Yes	Yes	Sometimes
Forgeries/ Alteration	No	Yes*	No	No	Yes*	Sometimes
Theft/ smuggling	No	Yes*	No	No	No	Sometimes

Key: * = with caveats

Theft/Smuggling This type of diversion refers to the theft or robbery of controlled substances from retail supplies (with or without substitution of another substance) or the illegal transportation of controlled substances into an area. Most systems reviewed here are unable to deal with theft or smuggling because these activities do not involve retail transactions. ARCOS has been used to help detect theft within the distribution chain, but does not track the disposition of drugs after reaching elements of the retail market.

DIUs are authorized to investigate all types of criminal activity related to the diversion of pharmaceutical products. Law enforcement agencies, and DIUs in particular, are able to address diversion through theft or smuggling because of their investigatory capacity across all aspects of diversion.

B. Impact on Medical Practice

This section provides a summary of prescription drug diversion control systems in terms of their potential impact on medical practice, broadly defined to include many aspects of health service delivery and utilization. Table 2 summarizes many of these findings.

Administrative/Cost Burden on Practitioners If a diversion control system were to impose significant costs or administrative burdens on practitioners, then practitioners may seek to lessen their activities that invoke those burdens. Many of these systems are, in fact, rather transparent to practitioners and therefore may not interfere with decisions regarding appropriate treatments and services. Some systems, notably EPOS and MCPPs, do impose costs or other requirements on prescribers and/or dispensers, which may alter their decisions and behavior. DIUs or other investigation efforts can involve a burden on the pharmacy, such as when pharmacy records are audited.

MCPPs require the prescriber to obtain multiple copy pads and, in most States, maintain copies of these prescriptions. In some States there is a fee for the purchase of multiple copy pads. MCPPs are viewed by some as intrusive for prescribers because of these administrative and cost burdens. MCPPs also require the forwarding of a copy of the prescription to the appropriate State regulatory agency. This may be viewed by some as burdensome to the dispenser, although it did not surface as a problem in our interviews. The only operational EPOS does not involve physician collaboration, but pharmacists must enter prescription information electronically or forward it by mail. This may be burdensome to dispensers

in terms of time and administrative costs, but again, pharmacists in Oklahoma apparently do not currently perceive it as such.

Changes in Prescribing Patterns All diversion control systems reviewed in this study reported having a goal of not interfering in the legitimate and appropriate prescribing of controlled substances. The most controversy with respect to diversion control seems to involve the question of impact on legitimate prescribing patterns. In this context, changes in prescribing patterns refer to the following:

- reduction in careless or inappropriate prescribing
- decrease or increase in appropriate prescribing
- substitution of drugs not covered by system
- prescribing in different quantities and/or different durations

Some MCPPs and the one operational EPOS aim to affect what might be described as inappropriate prescribing by involving the peer review process in educating the prescriber. Unfortunately, there have been no evaluations of diversion control systems that could shed much light on either positive or negative effects on appropriate prescribing. If data collection or the potential for investigation by themselves were to affect prescribing patterns, then every system may cause changes in the utilization of controlled substances. If that were true, even ARCOS (which does not collect information at the prescriber level and, therefore, may not directly affect prescribers) may influence some pharmacies to limit their purchases of controlled substances. On the other hand, if active participation by practitioners is more likely to cause changes in prescribing patterns, then MCPPs may be more prone than other systems to bring about those changes.

Impact on Medical Care A related issue is whether utilization patterns of other health care services besides prescription drugs are affected by diversion control systems. Most diversion control systems have as a goal noninterference in other aspects of medical care, such as increase in physician office visits. It is unlikely that DIUs have an impact on this aspect of prescriber behavior. Although there are claims that MCPPs increase physician office visits, there are no studies to support this claim. Similarly, this issue has not been studied for EPOS and Medicaid systems.

Table 2 Summary of Prescription Drug Diversion Control Systems:

IMPACT ON MEDICAL PRACTICE

	ARCOS	DIUs	EPOS	MEDICAID	MCPPs	PADS
Administrative/Cost burden on practitioners	No	No	Yes	Yes	Yes	No
Changes in prescribing patterns	No	No	? *	?	?*	?
Impact on medical care	No	No	?	?	?	?

Key: * = with caveats
? = unknown

C. Operational Aspects

There are several issues related to the structure and process of diversion control systems that could influence their effectiveness or their potential for unintended effects. Table 3 summarizes several subcriteria related to the operational aspects of prescription drug diversion control systems.

Confidentiality Protection of patient, prescriber, and dispenser confidentiality is considered of paramount importance for diversion control systems. For some systems, particularly EPOS and MCPPs which involve construction of data bases with patient, prescriber, and dispenser identifiers, the confidentiality issue is most salient. Any system that collects or organizes sensitive information, including insurance claims or income tax records, must build in measures to safeguard confidentiality. All systems reviewed for this study had controls built in to limit access to information.

Not all MCPPs collect and/or enter patient identifier data. This reduces the threat to patient confidentiality, but also the usefulness of the system to detect "doctor-shopping" and "pharmacy hopping."

Comprehensiveness Two aspects of comprehensiveness are included as important operational aspects of a system: whether the system covers all patient population groups, and whether all controlled substances are included under the system.

ARCOS does not address patient level issues, and Medicaid only covers the population who have Medicaid coverage. The comprehensiveness of Medicaid is additionally a problem, since Medicaid beneficiaries can purchase drugs without using the Medicaid system.

Both EPOS and MCPPs cover dispensing for all individuals that takes place within the State. There is variation in how prescriptions written on State multiple copy forms are handled by mail service pharmacies which are located out of State.

Both ARCOS and DIUs are more comprehensive than other systems with respect to the proportion of all scheduled controlled substances involved. However, ARCOS does not cover all controlled substances, and law enforcement personnel interviewed for this study reported a lack of resources to target all controlled substances. The EPOS and MCPPs, with certain exceptions, most notably New York's inclusion of steroids and

Table 3 Summary of Prescription Drug Diversion Control Systems:

OPERATIONAL ASPECTS

	ARCOS	DIUs	EPOS	MEDICAID	MCPPs	PADS
Confidentiality	No	No	Yes*	Yes*	Yes*	Sometimes
Comprehensive-ness - Population - Drugs	No Yes	Yes Yes	Yes No	No Yes*	Yes No	Sometimes Sometimes
Timeliness	Yes	Yes	No	Yes	Sometimes	Sometimes
Integration	Sometimes	Yes	Yes	Sometimes	Yes	Yes
Education	No*	Yes	Yes	No*	Yes	Yes

Key: * = with caveats

benzodiazepines, cover only Schedule II drugs. Medicaid covers all controlled substances for which Medicaid pays; however, in some States certain drugs may not be on the State Medicaid formulary.

Timeliness A system should provide data quickly enough to aid in potential diversion identification. All systems, except for EPOS, suffer to a greater or lesser extent from a lack of timeliness. ARCOS has been widely criticized for the lateness of its reports. MCPPs vary with respect to timeliness, and speed may vary within a State from year to year related to the vagaries of the State budget. A major strength of the EPOS system is that most data are entered electronically at the point of sale, thus, report generation is expedited.

Integration The systems described in this review do not operate totally independently in a State setting. The degree of integration and collaboration among interested parties varies both within systems and across States.

ARCOS is a federally operated system and its integration into State diversion control activities is related to how actively a State chooses to use the ARCOS system. DIUs, EPOS, and MCPPs collaborate with law enforcement groups and State professional licensing boards. In some States, MCPPs conduct some or most investigatory activities.

Education There are two educational components of diversion control systems that have operational implications at the State level. The first relates to whether interested parties are given adequate explanations of the purposes for and operational details of the system, and the implication for patients, prescribers and dispensers. The second relates to whether questionable, but not illegal, behaviors of practitioners are referred to appropriate agencies for peer review.

DIUs, EPOS, and MCPPs all engage in educational activities to varying degrees. ARCOS and the Medicaid MADAS systems are Federal systems which may be used in different ways at the State level.

D. Cost Aspects

Certainly States need to weigh the costs imposed by a diversion control system against any benefits derived. Table 4 summarizes three subcriteria related to the cost aspects of prescription drug diversion control systems. In contrast to many operational aspects, cost data proved to be the more

difficult to obtain in this review. Thus, the table contains many entries where it is noted that assessment could not be done because the cost data were unknown or could not be presented in a manner that allowed comparisons.

Implementation The cost of bringing a program to an operational State is an important consideration for states that are considering similar systems. Whether a program can piggyback onto an existing system is one mechanism for reducing implementation costs. Purchase of computer equipment is a potentially high implementation cost for an MCPP or EPOS system.

The EPOS system in Oklahoma had lower implementation costs than might have been expected because it was able to piggyback onto the computer systems already in many pharmacies. This system is still phasing into its fully computerized state, as some pharmacies convert to the system. Thus, figures for implementation must be considered preliminary until this implementation phase is completed. The cost of implementing an EPOS type system in the future should decrease, as more pharmacies become computerized as part of their normal operation.

ARCOS and Medicaid systems have low implementation costs because the data are already collected for claims processing purposes. Development of MADAS was done by the Federal Government, thus, the only implementation costs are those associated with the software to run this specialized controlled substance system on the Medicaid claims data base.

Operation It was very difficult to identify operational costs in a comparative framework for several reasons. First, many programs, particularly MCPPs, were parts of a larger operation and their budgets were not separately available. Second, the activities of programs varied. For example, some MCPPs perform their own investigatory activities, while others refer all investigations out to other agencies. Third, even if investigatory costs are available separately, the costs may need to be adjusted to reflect differences in population size, etc. Virtually all programs that performed their own investigatory activities said that more cases could be investigated if there were greater resources. The largest component of operating budgets for programs such as DIUs, EPOS, and MCPPs is typically staff salaries.

The costs of operating systems such as Medicaid are relatively low because the data are already collected for other purposes. In the case of SURS, the

Table 4 Summary of Prescription Drug Diversion Control Systems:

COST ASPECTS

	ARCOS	DIUs	EPOS	MEDICAID	MCPPs	PADS
Implementation	?	?	?	Low	?	?
Operation	?	?	?	Low	?	?
Cost savings	?	?	Yes	Yes	Yes	?

Key: * = with caveats
? = unknown

mechanism for performing utilization review already exists as part of the review system for all Medicaid claims.

Cost Savings For this review, the discussion is limited to cost savings related to the operation of prescription drug diversion systems. As discussed previously, an examination of the costs to society of such programs, while important, is beyond the scope of this report.

Within diversion control systems, certain kinds of activities cut down on other costs. For example, both EPOS and MCPPs are capable of producing computerized summaries on several different dimensions, such as by prescriber, dispenser, patient, and geographic area, and thus cut down on the investigatory time which would have been required for gathering similar information through the process of pharmacy audits.

There also may be cost savings across systems. For example, under the only operational EPOS, pharmacists enter the required information directly into the computerized system without charge, thus eliminating labor costs associated with data entry. Under MCPPs, data must be entered after the prescription is received by the State, typically by data entry clerks.

E. Advantages and Disadvantages of Diversion Control Systems

This section provides a brief overview of the advantages and disadvantages of the six diversion control systems that were reviewed for this report.

1. *Automation of Reports and Consolidated Orders System (ARCOS)*

Advantages

- Targets the wholesale level
- Available at low cost to states
- Not intrusive into medical practice
- Can be used to pinpoint problem geographic areas or particular dispensers

Disadvantages

- Does not target the prescriber or patient level
- Usually more than 1 year before reports are available

2. *Diversion Investigational Units (DIUs)*

Advantages

- Deals with all aspects of diversion of prescribed drugs, including theft and forgeries
- Can be used to complement other systems
- Not intrusive into medical practice

Disadvantages

- Operation is labor intensive, particularly pharmacy audits
- Pharmacy audits follow prescriptions retrospectively, thus considerable time may have elapsed from the time of transactions

3. *Electronic Point-of-Sale (EPOS)*

Advantages

- Targets diversion activities at patient, prescriber and dispenser level
- Not burdensome to prescriber
- Includes all population groups in a State
- Electronic entry speeds report generation

Disadvantages

- Somewhat burdensome to dispenser even for selected drugs
- Would be more burdensome to dispensers if all prescribed controlled substances were included
- Not all pharmacies are computerized

4. *Medicaid Claims Systems (SURS and MADAS)*

Advantages

- Data are already collected through claims process
- Targets diversion activities at patient, prescriber and dispenser level

- Can target all prescribed controlled substances that Medicaid covers

Disadvantages

- Includes only Medicaid population
- Does not capture out-of-pocket transactions

5. *Multiple Copy Prescription Programs (MCPPs)*

Advantages

- Targets diversion activities at patient, prescriber and dispenser level
- Includes all population groups in a State
- Prevents or reduces prescription counterfeiting and alteration

Disadvantages

- Somewhat burdensome to prescriber and dispenser
- As currently implemented, does not include all prescribed controlled substances, and thus is not comprehensive
- Data entry at State level is labor intensive

6. *Prescription Abuse Data System (PADS)*

Advantages

- Not intrusive into medical practice
- Attempts to integrate best approaches in State

Disadvantages

- Impact idiosyncratic to particular states's approach
- Participation is voluntary

F. Conclusions

This final section provides some general comments on prescription drug diversion control systems.

First, because prescription drug diversion control systems are implemented at the State level, there is a great deal of variation in the same type of system from State to State. For example, MCPPs differ on several dimensions. There are differences regarding which controlled substances are included under each system and, in particular, only the State of New York includes benzodiazepines under its program. Not all MCPP States enter patient identification into the computerized system. MCPPs are located in different types of agencies, with some having a public health focus and others more oriented toward law enforcement. This may result in differing philosophical orientations, such as the public health type agencies having a stronger interest in inappropriate prescribing. Some MCPPs perform investigations internally; others identify potential cases of diversion but refer all investigatory activities to other agencies. Some MCPPs generate exception reports on a routine basis; others only use their systems to support an investigation.

Another example of State variation relates to the use of Medicaid claims data. Some States have well developed SURS programs for all aspects of medical care, including prescription drugs. Other States' SURS programs are less efficient and are not used to detect fraud and abuse related to controlled substances. For these States, a system such as MADAS, which is specific to controlled substances, can aid in developing a focus on prescription drug diversion.

Second, prescription drug diversion control systems do not work in isolation. Many States, including the MCPP states, use more than one approach. ARCOS was widely mentioned as a useful tool to complement other diversion control activities in a State. Most systems reported cooperation with many agencies, including the Drug Enforcement Administration, State police, and professional licensing boards.

Third, the age of a system is important to control for in assessment of programs. New systems or existing systems with new components will show larger changes in the short term than older established systems. Older systems have a tendency to move from one of identification of diversion to one of prevention of diversion activities. It is, therefore, problematic to use

measures such as numbers of investigations as a measure of program effectiveness.

Fourth, one should distinguish between aspects of a system that are truly inherent to the program and what is mutable. Systems can be altered to improve on what now may be viewed as disadvantages to the particular program. For example, ARCOS has been criticized for a lack of timeliness; however, computerization of this system would improve its speed. MCPPs and EPOS can add or delete certain drugs. EPOS could be designed to deal with the prescription counterfeiting and alteration issue without including multiple copy pads. This could include requiring that prescriptions be written on single-copy, tamperproof paper, linking the prescriber into the system by a computer terminal which would allow access to a patient's prescription drug profile, or by sending patient specific reports to prescribers for their review on a periodic basis.

Finally, the challenge of prescription drug diversion control systems is to develop techniques that maximize the prevention and identification of illicit prescribing and dispensing, while at the same time, minimizing any adverse impact on legitimate medical care. This can only be accomplished by considering this area of prescription drug diversion as one requiring a social algebra of striking a balance between these two goals.

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An American Medical Association Perspective on Preventing Prescription Drug Diversion

John J. Ambre

Programs to reduce or eliminate the diversion of medications with abuse liability are an important undertaking and the American Medical Association has been encouraging this effort. Although the magnitude of the diversion problem is undefined, diversion certainly occurs to some extent. Most physicians, as we heard many times from law enforcement agencys' representatives, are not involved as diverters but are prescribers of medications that are classified as controlled substances, because these agents represent such an essential therapeutic group. Therefore physicians in general are interested in the existent and proposed systems for control. I have been asked to comment on four specific aspects of the issue.

Practice parameters or clinical guidelines for the acute and chronic therapeutic use of drugs in the stimulant, sedative-hypnotic and analgesic groups are available and are well defined. Going back several years, the American Medical Association and other groups have published guidelines. The American Medical Association publication, Drug *Evalmuations* (AMA-DE), provides comparative evaluations of available medications and a suggested approach to therapy of medical diseases and syndromes. Consider, for example, the use of opioid analgesics in the long term therapy of chronic nonmalignant pain syndrome, a controversial topic. A few weeks ago I attended a symposium and panel discussion on this topic jointly sponsored by the addiction medicine and pain therapists societies. At the end of the day I distilled the days discussion into one paragraph (four points or guiding principles) that I felt represented the consensus of the panel. Reading the corresponding paragraph in the AMA-DE, I found each of the four points concisely stated. There are similar sections in the AMA-DE on the therapeutic use of stimulants and sedatives. Numerous other publications in the area of pain therapy exist such as the World Health Monograph on Cancer Pain Relief, the brochure from the American Pain Society on Principles of Analgesic Use, and others.

Concerns about the existing diversion control systems relate to their impact on medical practice and patient care. We heard earlier about these systems and they include, in addition to the ARCOS reports, the OSTAR system recently activated in Oklahoma, the DIU system outlined for the State of North Carolina and the MCPP systems operative in several states.

The OSTAR (Oklahoma Schedule II Abuse Reduction) system is based in a law enforcement agency (the Bureau of Narcotics and Dangerous Drugs) rather than the Department of Health. Obviously, the interdiction of criminal diverters is a law enforcement function and in some cases the evidence of diversion is blatant, but more often the selection of cases as indicative of diversion or inappropriate practice is a medical question. In the Oklahoma system, the criteria for case selection are unknown. They are the province of either (1) the law enforcement agent administering the system, who has no medical training, or (2) the commercial drug audit firm providing data manipulation, in which case, the criteria are considered proprietary, are unavailable for evaluation, and are of unknown specificity (some are known to have poor positive predictive value). Low specificity leads to many false positive decisions and unwarranted investigation of competent practitioners. Oklahoma officials claim to have convened a coordinating committee of the medical, dental, and pharmacy organizations, but the committee is apparently not actually involved in the process of case screening.

The Drug Investigation Unit (DIU) system would present similar concerns. Case selection for investigation is made by law enforcement agents without medical review. The "exception" report may be a low specificity index. This approach might be adequate for identifying a patient who is acquiring unreasonable amounts of opioid drugs, but it is not necessarily a valid indicator of the appropriateness of a physicians prescribing practice. An ethical and competent prescriber might appear at the top of a product volume list because of patient composition of his practice and/or his choice of opioid analgesic. In the same way the DEA record of production quotas showing a 4-fold increase in morphine over the last ten years does not mean that more morphine is being diverted to the street market. Instead, it probably reflects an improvement in knowledge of pharmacology on the part of physicians and recognition of the fact that morphine is the agent of first choice for patients requiring a strong opioid for pain relief (Bennett 1991; WHO 1986)

The Multiple Copy Prescription Program (MCPP) presents concerns addressed over the past 10 years by the AMA. Of particular concern is the equation of decreases in the volume of certain prescriptions with a salutary

effect on medical practice. The limited evidence available suggests that such may not be the case. Appropriate agents may be replaced by less effective, less safe agents. There are well founded concerns about patient confidentiality, a "chilling effect" on the appropriate use of opioid agents, and the additional unnecessary costs of a system that will be a duplication of emerging DUR systems.

POSITION OF THE AMA ON EXISTING SYSTEMS

The AMA has been and continues to be opposed to the institution of MCPP on the basis that they may have an adverse effect on appropriate medical therapy. Of particular concern is the possibility they exacerbate the documented underutilization of potent analgesics in the therapy of pain, a problem entwined in the social and legal milieu of the country, against which the medical profession has been working for a generation of practitioners. In addition, the AMA believes that such systems will be rendered obsolete by the developing DUR/SUR programs. They will be an unnecessary and costly duplication of drug therapy data bases and quality assurance programs mandated for the Medicaid system in 1993, and likely to expand subsequently.

The American Medical Association is in the process of drafting a set of principles of utilization review applied to controlled substances (SUR) that would set out the elements of the optimal program. Elements will likely include:

1) Recognizing that reducing diversion of drugs is paramount, there should be due consideration given to potential effects of the program on proper medical care.

2) Criteria or standards used in case identification and evaluation should be derived in cooperation with appropriate medical and professional groups. There should be particular sensitivity to effects on and efforts to reverse the documented underutilization of opioid analgesics in therapy of pain. Such criteria must be nonproprietary and open to evaluation and revision by a professional consensus process.

3) Interventions should have an educational focus where appropriate. In other words, it should be recognized that not all–in fact very little–practice resulting in diversion is the result of intentional misprescribing for profit motive.

4) Confidentiality of the patient-practitioner relationship must be protected.

Continued research is recommended on several aspects of these questions. Almost totally lacking is actual research on the impact of regulatory controls on the appropriate prescription of the controlled medications. The perception is that the condition of underprescription of opioid analgesics described in the landmark paper by Marks and Sachar (1973) is still prevalent (Max 1990). We need to understand better the reasons for this so that remedial action can be focused. Continued research on the pharmacology of analgesics and other drugs is important. The benefits of new understanding are perhaps exemplified by the recent study suggesting central analgesic action of acetaminophen but not aspirin (Pilette et al. 1991). Such information will almost certainly alter our thinking about what constitutes rational analgesic drug combinations. Likewise, recent studies on the association of defective codeine demethylation to its active metabolite morphine with lessened analgesic activity may enhance our understanding of variations in patient response to established medications.

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Prescription Drug Regulation: Implications for Nursing and Health Care Delivery–Response of the American Nurses' Association

Madeline A. Naegle

Prescribing practices by registered nurses have important implications for the nursing profession and for the accessibility of high-quality health care for the consumer. In recent years an increasing number of States have granted prescribing privileges to nurses identified as advanced practitioners. "Advanced practitioners" are nurses prepared at the graduate level, and/or nurses certified in particular specialties. Most often these specialty practice roles are nurse practitioner, nurse midwife, and nurse anesthetist. All nurses qualifying for prescribing privileges must validate advanced education in pharmacotherapeutics.

Individual States have regulated nursing practice in relation to prescribing in a variety of ways, since each is relatively autonomous in the regulation of the licensed professions. Prescribing authority can be granted through legislation, actions of the nursing, medical or pharmacy board, or through special regulations or waivers for certain circumstances, granted by the attorney general. Currently, over 35 States have granted prescriptive privileges to nurses, including authority to prescribe controlled substances. Such authority does not have the same scope in each State; some States have granted independent prescribing authority to selected groups of advanced practitioners, some authorize prescribing with physician supervision, and a few have granted nurses limited site-dependent authority (Pearson 1991).

Bigbee notes that most professions can clearly identify professional functioning that is germane or even unique to the discipline (Bigbee 1983). Drug prescribing, however, does not fall definitively within the boundaries of only one profession; dentistry, medicine, pharmacy, and nursing may "prescribe" not only drugs, but therapeutic regimens as well (Bigbee 1983). Issues of autonomy, control, responsibility, and competence then emerge around activities related to prescribing. How each profession negotiates such issues will depend on regulatory practices by the respective State, professional traditions, educational standards, and norms within professional communities. Achieving

prescribing authority has been an important agenda for nurses in advanced roles, particularly nurse practitioners, because the use of medications and appliances available only by prescription, such as contraceptive diaphragms, is an important adjunct to primary care and the management of long-term illness. Prescribing authority is essentially a tool which increases the scope of practice for the nurse practicing at a level beyond generalist preparation. It has been estimated that the health problems of 67 to 90 percent of people who seek primary care could be effectively managed by nurse practitioners (Coulihan and Sheedy 1973; Record 1979). Generally, nurse practitioners prescribe fewer drugs than physicians (Batey and Holland 1985), and anti-infective, respiratory agents, analgesics, and hormones accounted for 74.6 percent of all prescriptions in one study.

In addition, 70.5 percent of all prescriptions were given for health problems in five categories: infectious respiratory system conditions, common genito-urinary diseases, primarily infections, family planning and immunizations, and infections of the skin and cellular tissue. In surveying the mechanisms by which prescribing took place, it is notable that approximately 85.7 percent of these prescriptions were issued independent of physician involvement (Batey and Holland 1985). While the forgoing data was gleaned from only one study (of 89 nurse practitioners and 7,086 prescriptions), both practice patterns and prescribing trends are considered to typify the work of most nurse practitioners in adult and family practice. The American Nurses' Association, of which 6,700 nurse practitioners are members, emphasizes the importance of the scope of practice identified above and prescribing privileges in meeting consumer health needs. One nurse, residing in a rural area stated:

> I currently reside in Yates County, New York. It has a population of approximately 21,459.... There are about 5 physicians to serve this population, quite unfortunately, several of the physicians refuse to treat Medicaid patients.... Thus, there exists reduced availability and accessibility of health care services for individuals living in this medically underserved area. In addition, the number of individuals without health care providers in this county is staggering. Nurse practitioners would significantly increase the availability and accessibility of health care services (Manfredi 1991).

Summative observations about prescription authority utilized by nurses and information supplied by specialty nursing organizations and State nurses associations suggest that:

(1) Prescriptive privileges provide a mechanism that increases both the scope and effectiveness of nursing care delivery.
2) Most prescriptions written by nurses with such authority are for medications which are not controlled substances.
3) Nurses in advanced practice roles provide important services to the consumer in a variety of community and institutional settings, particularly in underserved urban and rural environments.

REGULATION OF PRESCRIPTION PRIVILEGES

The professions, through social contract, are granted the privilege of and assume the responsibility for self-regulation. Inherent in self-regulation are the concepts of establishing and implementing educational standards; creating, maintaining and enforcing ethical sanctions; the delivery of services to the community; and, in return, relative autonomy over practice. Nursing, while achieving the majority of academic criteria stipulated as requirements for a profession, still struggles with the concept of autonomy. Since the 1930s nursing has been practiced primarily in institutions, legitimizing the employer-employee relationship. Despite the passage and implementation of nurse practice acts which define nursing practice and establish criteria for independent licensure, institutional control or perceptions of the need for physician supervision block progress in acknowledging educational advancement and autonomy related to advancement in education and practice. Contradictions between education and perceived credibility in the professional community surface in the practice arena, and prescription authority emerges as a related issue.

Organized nursing supports and will continue to promote preparation for and implementation of advanced and expanded nursing practice roles as a means of increasing consumer access to health care and broadening consumer options for choosing providers. In addition, such roles strengthen professional opportunities for social contribution and the use of nursing expertise. Since the dispensing and prescribing of drugs, including controlled substances, are central to many nursing roles, drug diversion and drug regulation systems–and changes in them–are of interest and concern.

The Drug Enforcement Administration (DEA) is responsible for the regulation, registration and control of persons who are legitimately engaged in handling and distributing controlled substances. Of the 820,000 practitioners registered with the DEA, approximately 1,500 are registered nurses. In 1990, the Drug Enforcement agency reviewed selected State regulations and ruled that nurses with prescriptive privileges lacked plenary authority for the prescription of controlled substances and are not entitled to hold DEA registration numbers. These efforts apparently derive from initiatives by DEA to strengthen the system to prevent regulation problems. The announcement that DEA would seek a rule change consisting of proposed regulations, "Definition and Exemption of Affiliated Practitioners," was published in the *Federal Register,* February 4, 1991. The stated intent of DEA is to have only parties who, by virtue of the statutory authority vested in their professions, have plenary authority to administer, dispense, and prescribe controlled substances. The announcement evoked strong protest from the American Nurses' Association and specialty nursing groups, especially when DEA announced the intention to suspend DEA numbers of individuals whom they deemed "affiliated practitioners," that is, a nurse whose prescribing authority derives from the authority of the collaborating physician. The designation of the term "affiliated practitioner" constitutes DEA's interpretation of State regulations without consideration of the variety of mechanisms through which prescribing authority is granted. The American Nurses' Association issued the following formal objections.

> (1) The action by DEA does not recognize that case law, regulations and practice have defined the working relationships of collaborating health care professionals as collaborative and equitable working partnerships, not supervisory relationships. The proposed rules treat the role and scope of the nurse practitioner as subordinate to the physician.
> (2) The proposed comments violate the authority reserved by States to regulate, license and control the professional activities of health professionals.
> (3) The proposed regulations will limit the natural evolution of the profession and could reimpose primary liability on physicians involved in protocol and collaborative relationships.
> (4) The arguments made for the rulemaking related to drug diversion concerns are unfounded and cannot be substantiated.
> (5) The proposed rulemaking will limit public access to care. In addition, the association noted some violations of rulemaking protocol.

While State nurses' associations immediately began a review of practice acts and regulations, this action of the Drug Enforcement Administration has broader and more serious implications for the relationships of the professions to regulatory bodies, in particular, Federal regulatory bodies. Of primary concern to the scientific community is the lack of research data to substantiate the need for reducing the numbers of registrations issued. In addition, the interpretation of nurse practice acts by a Federal authority and the overriding of the States' authority to license and regulate health care practitioners encroach upon the rights of the profession to regulate its practice. Other consequences include limiting access to care; in New Hampshire, for example, about 31,000 people would be affected, raising serious ethical problems for practicing nurses and barriers to quality care provision. The American Nurses' Association has recommended that DEA be required to directly provide all prescription numbers and maintain such records issued to all practitioners. Such registration must be available to each practitioner whose State law grants prescribing authority, notwithstanding any designation as plenary or affiliated.

The development of policy to guide the practice of drug regulation has far-reaching effects for the professions and the public. Participation in policy development by representatives of the professions who dispense and monitor the use of prescription drugs, particularly controlled substances, seems a reasonable, if not obvious, course of action. Support by scientific institutes such as NIDA can do much to facilitate a dialog with regulatory bodies and to demand that changes be based on scientific data and existing knowledge of drug and prescribing practices.

Further, there is an immediate need for research on prescribing practices by nurses and their implications for care delivery. At present, little is known about:

(1) Prescribing patterns and classes of drugs prescribed by nurses
(2) The relationship of prescribing practices to therapeutic outcomes and patient/client response
(3) Cost factors which support the value of continuity of care by one nurse provider who offers a full range of services, particularly primary care services
(4) Data on the prevalence of drug diversion by providers licensed to dispense controlled substances.

Nursing welcomes research opportunities which can demonstrate the contributions of nursing interventions and an expanded nursing role to the delivery of quality health care. Prescribing practices need to be studied in the broad nursing context, rather than as isolated functions.

Organized nursing will provide assistance and support the development of State legislation and the refinement of nurse practice acts in order to preserve and attain prescribing privileges for qualified nurses. Achievement of these statutory authorizations for prescribing in one-third of the States bespeaks the importance of such nursing activity to the practitioner and to the public. Representatives of the profession will continue to operationalize the self-regulatory privileges of nursing to advance the profession and provide services appropriate to the growing body of nursing expertise and skillful practice.

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Perspective of the American Pharmaceutical Association

C. Edwin Webb

The letter inviting the participation of the American Pharmaceutical Association (APhA) in this conference noted that there was a current need to revisit the social policy issue of balancing the legitimate clinical use of many types of psychoactive medications against the equally appropriate goal of reducing to a minimum the diversion of such medications for illegitimate use. The over 40,000 members of the American Pharmaceutical Association, the national professional society of pharmacists, are strongly in favor of each of these policy objectives. As pharmacists, we observe on a daily basis in our practices both the tremendous therapeutic value and the potential adverse consequences of the use of such medications. And we share a commitment with our medical colleagues to promote optimal therapeutic outcomes for our patients from the use of medication.

The challenge we face is to identify approaches which achieve both of the objectives stated above simultaneously. Either objective perfectly achieved at the expense of the other will be unlikely to receive broad public or professional support.

APhA believes that systems which focus first and foremost on optimal patient care outcomes have the best chance of reasonably achieving both objectives and will garner the greatest degree of support.

Unfortunately, as we have learned from many of the preceding presentations, there is often inadequate data from which we may derive clear answers to these questions. As a result, we are currently faced with a myriad of approaches, varying substantially in nature and intent, which, one must assume, have not effectively addressed the problems that have prompted the convening of this conference.

The primary diversion control mechanism to receive the attention of the Nation's pharmacists is that of "triplicate" or other "multiple-copy prescription

programs." The APhA House of Delegates adopted a policy in this regard in 1989. That policy states:

> The American Pharmaceutical Association opposes federally mandated multiple-copy prescription order programs.
>
> The American Pharmaceutical Association supports the right of individual States to develop programs to prevent drug abuse and drug diversion.

The view of our organization is that the problem of misuse and diversion of medications with abuse potential is one best addressed at the State level, using "programs" tailored to meet each State's individual problems and needs. It was also clear from the discussion and testimony at the meeting of the House of Delegates that multifaceted approaches, including patient and professional education, are to be preferred over purely administrative and data-gathering systems. APhA believes that this policy is consistent with good patient care and provides appropriate flexibility in an era of rapid change in both pharmacotherapeutics and medication systems management.

In particular, the effective management of prescription medication data–from initiation of the prescription order by the physician through the order processing, regimen review, and consultation activities of the pharmacist to the data management, claims processing, and utilization review activities of payers, is moving rapidly toward total electronic systems. Over 80 percent of the Nation's pharmacies now utilize computer-based information systems for prescription order processing, clinical data review (e.g., duplications, interactions), inventory purchasing, and control and medication records storage and retrieval. Even more importantly, models are rapidly emerging which will provide for the electronic communication of prescription orders between physician and pharmacist. This will allow simultaneous review by both professionals of the prescription data, as well as laboratory and other clinical data, to promote a quality therapeutic outcome while minimizing adverse effects and interactions of medications, In such an interactive professional environment, multiple-copy paper prescription forms represent, at best, an Edsel, if not a Model-T, in a Mercedes-Benz world.

It should be noted that the Drug Enforcement Administration (DEA) is currently seeking legislative and regulatory changes which would facilitate its own movement into the brave new world of electronics. Mechanisms to allow for the electronic ordering and transfer of Schedule II controlled

substances, with the resultant demise of the DEA 222 Order Form, are currently in development within the Agency. APhA is committed to working with DEA to foster this type of progressive activity, and finds an ironic contrast between this portion of DEA's agenda compared to its support for multiple-copy prescription order programs at a national level for pharmacy and medical practitioners.

Other approaches have the potential to better meet *both* of the public policy objectives that are the subject of this conference. The rapidly increasing use of effective drug utilization review (DUR) programs by both public and private entities which provide prescription medication benefits to their clients offers an effective alternative to multiple-copy prescription order programs. While the primary goal of effective DUR programs is to promote high quality patient care as well as more cost-effective drug therapy, such a program may be able to offer a template to achieve many of the desirable public policy features we all seek, while working within a structured patient and practitioner-oriented framework.

This is especially attractive since many DUR programs include education and feedback mechanisms for practitioners regarding prescribing and dispensing practices that are suboptimal. Such an approach, we believe, is critical to success in addressing the issue of diversion. APhA has been a participating member for many years in the AMA's Informal Steering Committee on Prescription Drug Abuse. Through that process, we have come to believe strongly in the value of educational strategies for practitioners to assist them in reducing prescribing and dispensing practices which, knowingly or otherwise, contribute to prescription medication diversion. One of the major failings, in our view, of the majority of multiple-copy prescription order programs currently in operation is a lack of effective intervention strategies which constructively change practitioner behavior.

APhA also remains concerned about the potential for multiple-copy prescription order programs, or other similarly constructed programs, to adversely effect therapeutic choices that practitioners of pharmacy and medicine make. I know that some will dismiss this rather traditional "objection" of the practice community, but it is, I believe, a real issue of concern.

While one may wish that pharmacy and medical practitioners would never allow nonclinical issues to interfere with their clinical decisionmaking, reality and experience suggest otherwise in some cases. In high crime areas, pharmacists regrettably must make a difficult choice between maintaining

appropriate inventories of controlled substances for legitimate patient needs and not stocking such items to reduce the likelihood of robbery and violence in the pharmacy. Such choices are often a "no-win" situation for the pharmacist. And while they may be less dramatic in their impact, programs to eliminate drug diversion often present the same type of "no-win" situation for practitioners.

I would also submit that the jury is still out as to whether the decrease in total use of controlled substances observed with some of the current programs reflects reduced diversion with *no risk* of reduced access to legitimately needed medications by patients. When legitimate therapeutic need is adversely impacted by such programs, their overall public value must, in our view, be seriously questioned.

Obviously, achieving perfection in both of these policy objectives is a difficult, if not impossible, task. APhA believes that both objectives are legitimate and that the intentions of all who participate in this debate are sincere. But APhA also believes that the first priority in this issue must always be to assure appropriate drug therapy for the patients we serve. As health professionals, that must always be our first priority. We will continue to encourage health policymakers to focus on this aspect as well, and to work with our profession to assure that this priority is not lost in a rush to systems which, while they may reduce medication use, neither foster good patient care nor significantly impact controlled substances diversion. To miss the mark on both public policy objectives would indeed be the worst outcome for us all.

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Perspective of the Empire State Medical Association of the National Medical Association

Gerald Deas

I am grateful for the opportunity to share my views with the National Institute on Drug Abuse about how multiple copy prescription programs protect the public health.

I have been listening with interest to the reasons presented-before MDA and elsewhere-against triplicate prescription programs. I have heard representatives of organized medicine object to "trip scrip" on the basis that doctors should not have to worry about regulation, and I have heard political opponents of triplicate prescription say that the program is unnecessary government intrusion.

As a family physician, I have a different-and I think, a majority-view. I practice medicine on the front lines of the struggle to rebuild our communities ravaged by poverty and drugs. In the streets of the inner cities-where "pill mills" and street hustlers prey on our most vulnerable brothers and sisters-the misuse of prescription drugs is just as devastating as the abuse of illicit drugs such as cocaine and heroin.

One silent partner in the tragedy of cocaine addiction is the benzodiazepine class of tranquilizers. People use these drugs to "come down" from a cocaine high-or they abuse them for their tranquilizing effect.

New York State's courageous health commissioner, Dr. David Axelrod, enacted triplicate prescription regulations that led to a dramatic decrease in illicit diversion of these drugs and the availability of these drugs on the street. As Dr. Axelrod battles a crippling stroke (which forced him to resign his post), opponents of triplicate prescription in Albany persist in their attacks on this life saving measure. Much of what is being said against "trip scrip" is inaccurate, misleading, and distorted. Family physicians throughout the State who truly care about the health of their patients and the survival of their communities are not afraid of a little prescription pad. In fact, we welcome anything that protects patients from the terrible toll of drug abuse.

We have all seen too many fine young women and men "zoned out" on pills, nodding through their days, ruining their future. As a family physician at work day after day in communities struggling to survive, I know that abuse of licit drugs such as tranquilizers can be just as devastating as the misuse of illicit drugs like cocaine.

Triplicate prescription regulations in New York have, over 2 years, demonstrated their effectiveness, public health benefits, and value. During this season of close and careful budget watching, Medicaid prescriptions of benzodiazepines have dropped almost 70 percent since 1989 (the year triplicate prescription regulations for these drugs took effect), and the street price of these pills has gone up from 200 to 800 percent.

Despite the propaganda campaign being waged by organized medicine and some industry groups, the truth is that nothing in the regulation prevents the legitimate prescribing of benzodiazepines. There are still approximately 120,000 Medicaid benzodiazepine prescriptions written each quarter-an appropriate level in my view.

The drop in Medicaid prescriptions is due to the impact that triplicate prescription has had on "pill mills." Thanks to this regulation, many of these deadly places have been shut down.

On the streets where I live and work, the scandal of Medicaid "pill mills" is particularly devastating, and this abuse of public health horrifies me as a physician. I know that these so-called pharmacies are doing far more harm than most outsiders can imagine and they are contributing to the demise of entire generations.

I wish that anyone who opposes triplicate prescription could walk with me into the real world where these regulations are saving lives, Many of the voices raised in opposition to these regulations come from proponents and allies of big drug companies who are losing revenue and organized medicine lobbies that just don't like any kind of regulation.

The voices of the people have not been heard. I wish this committee had invited the people I know who have been victimized by prescription drugs. I wish you could hear their cries of pain, as I do, every day.

Our young people cannot advance if they go through life as virtual zombies. They can not do their jobs if they are made sluggish and stupid by drugs readily available on the street.

Drugs rob us of many precious things: our future, our health, and our pride. Whenever I make a house call on my patients, I have been impressed that even in the most humble of homes, I observe one or more old photographs of distant relatives on their walls. These photographs not only reflect dignity in dress but dignity in character as well. These photos reflect pride.

I've collected these photos, along with some verse, in a book called, "If You Can't Remember, Please Don't Forget." In the introduction, I write:

> We must remove the negative forces that exist in our society today that seek to destroy us. We must arm ourselves with dignity and spiritualism. We can't give up!

I know that the professionals at NIDA, and your colleagues elsewhere in the government who are examining this issue, are dedicated to the public health and to serious scholarship. I hope that you will listen carefully to the data presented by the New York State Department of Health about how effective triplicate prescription regulations have been, and that you will remember one thing: What is at stake in this discussion is something very real and very urgent-the health and the future of our parents and grandparents, our children, husbands and wives.

For their sake, we can't give up. They have no powerful lobbies or large budgets to spend. They only have need-and it's our responsibility to help them through sound programs that protect the public health. Triplicate prescription is good medicine.

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Prescribing Practices and Drug Abuse - Perspective of the American Society of Addiction Medicine

Anne Geller

With any drug and with any method of prescription control, the concern of physicians must be for the risks and benefits to our patients. For those physicians practicing addiction medicine, a specific concern is the risks and benefits for that subset of the population particularly vulnerable to the effects of medications which have abuse potential. It is essential that this vulnerable subset be protected from prescribing practices that are hazardous to them, if perhaps innocuous for the majority. Nevertheless, in our zeal to protect the addiction-vulnerable, we should not restrict access to medications in a manner which might harm others, nor should our fear of drug diversion result in our failing to prescribe appropriate medication when needed.

There are two major questions to which we appear to have only partial answers. One is how significant are the problems of prescription drug abuse and diversion? The second is how effective is our current main method of control (triplicate prescription) in reducing either abuse or diversion?

The larger questions, for which we only have hypotheses, are: (1) to what extent do our current prescribing practices contribute to the problem of drug abuse, and (2) how might these practices best be modified to ensure that our patients obtain the greatest benefit from drugs with abuse potential at the least risk?

Patients having problems with prescription medications who arrive for treatment at addiction centers fall into four main categories:

> (1) Those with chronic conditions who have been taking medications as prescribed, but wish to be medication-free and are experiencing difficulty withdrawing
>
> (2) Those with chronic conditions who have escalated the dose in an attempt to control symptoms and whose

physician, family, or themselves want to reduce or discontinue the medication

(3) Those who have discovered the reinforcing effects of the medication in the course of an acute treatment and are now getting multiple prescriptions or buying the drug illegally in order to get high

(4) Those who are abusing prescription drugs obtained legally or illegally as a part of a polydrug abuse pattern

These four groups constitute only a small portion of the universe of patients for whom potentially addicting medications are prescribed, though together they account for 15-20 percent of patients in addiction treatment. The percentage of patients who are abusing only prescription medication is quite small, probably accounting for less than 5 percent in most addiction centers. It is not clear what proportion of patients experience difficulty discontinuing drugs which have been appropriately prescribed and taken. This differs among classes of drugs, and even among a group such as the benzodiazepines, appears to occur more frequently with some compounds, e.g., the triazolo-compounds, than others. The most difficulty occurs at the end of the tapering process (Schweizer et al. 1990). This appears to be an inherent property of the drugs themselves and may be resolved by the development of medications more specifically targeted toward specific symptoms, i.e., noneuphorigenic analgesics and nonsedating anxiolytics.

Appropriate prescribing should take into account the possibility of discontinuation difficulty, but it is unlikely that any administratively applied program wilt affect this population. Inappropriate prescribing includes: using doses that are too high or too tow, continuing a drug too long, prescribing a potentially addictive drug where a nonaddictive drug alternative is available (such as Fiorinal for headaches), prescribing a more hazardous drug such as a barbiturate when a benzodiazepine would be preferable, and prescribing a potentially addictive medication to someone with a history or current indication of alcoholism or drug dependence when another treatment would have a better risk/benefit ratio.

Some of the patients coming into addiction treatment in categories 2, 3, or 4 have been victims of inappropriate prescriptions. It seems unlikely that a program which makes the writing of certain prescriptions more difficult is going to improve the quality of pharmacotherapeutic decisions. In fact, it is

likely to result in an exacerbation of some prescribing problems, such as prescribing doses of analgesics that are too low or too infrequent.

In New York State, one of the consequences of benzodiazepines being placed on triplicate forms has been an increase in the prescribing of more hazardous hypnotics and anxiolytics such as barbiturates, methyprylon, ethchlorvynol, and meprobamate (Weintraub 1990). While overall benzodiazepine prescriptions declined, there is no evidence that this decline was a result of reduced prescribing for the at-risk population or more discriminating medication choices generally.

It would seem that if the goal is to improve physicians' understanding of hypnotics, anxiolytics, stimulants, and analgesics, and their risks, benefits and appropriate dosages, an educational program would be best suited to do this. Achieving an overall reduction in prescriptions is meaningless in this context. In addition to clearly increasing the probability of some types of misguided prescribing practices, a triplicate program also gives a message that the category of medications being thus restricted is extremely hazardous. Benzodiazepines are, in fact, safer than many of the nonrestricted alternatives.

Physiological dependence with protracted withdrawal symptoms is certainly a problem. However, human studies thus far would suggest that benzodiazepines are not more reinforcing than placebo except for a group who may be addiction vulnerable (deWit and Griffiths 1991, Ciraulo et al. 1988). Certainly, benzodiazepines have less abuse potential than the barbiturates they replaced, even though they are most definitely abused by some and overused by others.

To reduce iatrogenically provoked addiction, it is more useful to provide accurate and up-to-date information about these medications and their alternatives and more sophisticated training about addiction than it is to create inappropriate "benzodiazophobia."

Although the American Society of Addiction Medicine has no formal position in this area, and the above remarks are my own, the Society is committed to the general education of physicians regarding addictive diseases and addictive substances and to the dispelling of myths which are so prevalent in this area of medicine.

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Response of the American Academy of Child and Adolescent Psychiatry

Nicholas Rock

INTRODUCTION

Thank you for the invitation to participate in this National Institute on Drug Abuse-sponsored technical review on the evaluation of existing prescription drug diversion systems and their impact upon medical practice and patient care.

The American Academy of Child and Adolescent Psychiatry is a national, professional association of over 4,500 child and adolescent psychiatrists. Its members are physicians who have completed a general psychiatry residency and 2-years' residency training in child and adolescent psychiatry. This medical discipline is concerned with the prevention, diagnosis and treatment of developmental and psychiatric disorders in children, adolescents and their families.

The use of psychotropic medications as a treatment plan option is important to our discipline. This technical review is an excellent opportunity to reinforce the rational and legitimate use of psychotropic medications by qualified physicians. Any frivolous or needless restrictions placed on the prescription of such medications will have damaging results. It is important for many reasons that child and adolescent psychiatrists and their patients and their patients' families are not caught up in efforts to control drug diversion for illicit use.

REASONS FOR RATIONAL DRUG DIVERSION CONTROL SYSTEMS

Practice Parameters

A primary reason to look carefully at the development of new controls is the ongoing preparation of practice parameters by medical specialty associations, including the academy. The academy's Work Group on Quality Issues chose first to develop parameters for the treatment of attention-deficit hyperactivity disorder (ADHD). It was the work group's view that a statement was

needed clearly indicating that medication is often appropriate as part of a thoughtful treatment plan. The work group has recently submitted to the Academy's Council its final draft on practice parameters for conduct disorders, and is working on parameters for schizophrenia, eating disorders, and mood disorders. Each set of practice parameters considers the use of psychotropic medications for acute or chronic therapeutic needs. These medications are predominately within the stimulant, sedative/hypnotic, or antidepressant class. Often they must be prescribed for extended lengths of time when the condition is chronic. It should be emphasized that medications are not to be prescribed in short- or long-term treatment programs without proper medical monitoring.

The use of psychostimulants, particularly methylphenidate (Ritalin), for the treatment of ADHD was carefully considered by the Work Group on Quality Issues for several reasons, not only because of the controversy surrounding it. A statement introducing the parameters indicates that the final decision for each patient must be made by the physician in light of his or her personal knowledge of the patient's illness and life circumstances. For the same reasons, this final decision for using medications and for the length of use and size of the prescription must be made by the physician, not by drug enforcement officials. Patients, their families, and physicians should not be intimidated by reporting requirements that bring suspicion of illegality on anyone involved in prescribing or taking psychotropic medications.

Triplicate Prescription Forms

A second reason for recommending caution in the development of controls for certain medications is the ineffective record set by drug diversion systems such as the triplicate prescription form. This simplistic answer to illegal drug diversion has the State provide physicians with a prescription form which has three copies–one to be kept on file, one to be kept on file at the pharmacy that fills the prescription, and the third is sent to a designated State drug enforcement agency. This type of response has controlled an insignificant amount of illegal drug diversion, yet it has had a significant impact on medical practices and patient care. The Academy has serious concerns about triplicate prescription forms being mandated on a national level. Problems are foreseen with confidentiality, access to care, and increased stigma for patients with mental illness. Treatment of a serious emotional illness which requires medication is difficult for all patients. To distress them further with a prescription system designed to raise more barriers to treatment is unconscionable.

Appropriate treatment requires access to all treatment options, including psychotropic medications. Where States have implemented the triplicate prescription form enforcement system, the decreases in prescribing come from the hassle factor of the system, not from the curtailing of abuse. Patients have had their confidentiality violated when prescription records were confiscated and examined by drug abuse officers. For child and adolescent patients, this can mean a lifetime of insecurity about their health records.

The American Academy of Child and Adolescent Psychiatry joins with other medical specialties and advocacy groups to oppose the imposition of the triplicate prescription form. It has not proven effective, and its effect on the treatment of children and adolescents with serious emotional disorders, especially with chronic disorders, could be to implement a form of harassment that contributes to inadequate treatment or a termination of treatment.

The Academy does not have an official policy regarding the existing drug control systems noted in the draft agenda, but the primary concern of child and adolescent psychiatrists in any method or system is that families and patients are granted the right to treatment without restrictions that add stigma, unnecessarily limit medical decisions regarding prescriptions, and foster further controversy over the use of psychotropic medications.

Mental disorders and drug abuse are both important and serious problems for individuals and for society. The evidence so far has convinced us that hassling physicians' prescription practices will not disrupt drug abuse but will disrupt physicians' ability to treat children and adolescents who suffer from serious mental disorders.

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Impact of Drug Regulations and Diversion Control Systems on Legitimate Narcolepsy Patients

Joseph A. Piscopo

SYMPTOMS AND EPIDEMIOLOGY OF NARCOLEPSY

There are four classical symptoms in the narcoleptic tetrad (Daly and Yoss 1957):

1. Excessive daytime somnolence: inappropriate daytime sleepiness, sleep attacks or sudden urges to sleep, without regard to the amount or the quality of prior nighttime sleep

2. Cataplexy: episodes of partial or general muscular weakness induced by emotions, commonly by laughter, anger, or surprise

3. Hypnagogic hallucinations: vivid, realistic, and sometimes frightening auditory or visual perceptions at sleep onset

4. Sleep paralysis: episodes of temporary inability to move or speak, which occur while falling asleep or while awakening

Narcolepsy is a neurological disorder whose etiology is unknown. It is a lifelong condition that affects both sexes equally. Onset of narcolepsy symptoms commonly occurs in childhood or early adolescence. There seems to be a familial tendency in one-third to one-half of the cases. Narcolepsy is not life-threatening, nor is there evidence of shorter life expectancy. There is no documented case of remission of symptoms (Yoss and Daly 1974).

The prevalence of narcolepsy was estimated at 0.05 percent, or about 125,000 persons, based on a survey in the San Francisco Bay area (Dement et al. 1972), and at 0.067 percent, or about 167,500 persons, based on a survey in the Los Angeles area (Dement et al. 1973). The preliminary data from an unpublished study of the incidence of narcolepsy in the Rochester, Minnesota area over the 30-year period 1950-1979 indicates that the prevalence of narcolepsy may be as high as 0.15 percent, or 375,000 persons, with an estimated incidence of 5 per 100,000, or 12,500 new cases per year (Mayo

Foundation, personal communication, 1990). Based on these estimates, narcolepsy is about as common as Parkinson's disease and more than twice as common as Multiple Sclerosis. The American Narcolepsy Association (ANA) estimates that only 50,000 patients are actually diagnosed and treated for narcolepsy in the United States (ANA personal communication, 1990).

TREATMENT OF NARCOLEPSY SYMPTOMS

There is no known cure or preventive treatment for narcolepsy. The symptoms of daytime sleepiness and sleep attacks are effectively treated with central nervous system stimulants such as methylphenidate (Ritalin), dextroamphetamine (Dexedrine), or pemoline (Cylert). The symptoms of cataplexy, hypnagogic hallucinations, and sleep paralysis are treated with tricyclic anti-depressant medications, such as imipramine (Tofranil) and protriptyline (Vivactil). Research (Mitler et al. 1990) has shown that narcoleptics on 60 mg per day of methylphenidate improved their ability to stay awake to 79.9 percent of the normal control group as compared to only 55.2 percent of normal with no medication. Narcoleptics on 60 mg per day of dextroamphetamine improved to 70.3 percent of normal controls as compared to only 34.8 percent with no medication. Pemoline was found to be of marginal benefit.

While methylphenidate is often the drug of choice for the treatment of narcolepsy, some patients are nonresponsive to that drug. Methamphetamine (Desoxyn) is an alternative stimulant drug for effective treatment of nonresponders to methylphenidate. The use of methamphetamine for narcolepsy was first described by Eaton (1943). The efficacy of methamphetamine for narcolepsy, and its reduced side effects as compared to dextroamphetamine, was again described in great detail by Yoss and Daly (1968, 1974). Yet, methamphetamine is rarely mentioned in the recent literature or in text or reference books about narcolepsy.

In a 1990 survey by the American Narcolepsy Association, 1,067 narcolepsy patients reported using the following drugs and dosage ranges:

49 percent methylphenidate (Ritalin), 5 mg - 400+ mg daily
26 percent dextroamphetamine (Dexedrine), 5 mg - 400+ mg daily
19 percent pemoline (Cylert), 10 mg - 300+ mg daily
5 percent methamphetamine (Desoxyn), 10 mg - 100+ mg daily
1 percent Other amphetamines (Biphetamine), 5 mg - 200+ mg daily

In the same survey, 20 percent of the patients reported difficulty in obtaining a prescription from their physician and 41 percent reported difficulty in getting a prescription filled by their pharmacy (ANA unpublished survey, 1990). Each of the reported drugs is a controlled substance under Schedule II, except for pemoline, which is under Schedule IV. Only methylphenidate and dextroamphetamine are FDA-approved indications for narcolepsy, at dosages from 5 mg to 60 mg per day (Physicians' Desk Reference 1990).

Virtually all research reports on narcolepsy treatment published in the United States since 1975 describe the high risk of tolerance, the dangerous side effects, and the potential for drug abuse and addiction from the use of these stimulant drugs for narcolepsy. Yet, there is no available research, except for uncontrolled studies of only one to three patients, which establishes the scientific basis for such generalizations. In fact, there exists very strong evidence that patients given higher dosages of stimulants on a long-term basis show no decrease in effectiveness and no need for progressive increases in dosages, nor were symptoms of withdrawal, tolerance, dependence, or other abnormalities observed when treatment was discontinued (Honda et al. 1979; Yoss and Daly 1974). A recent study of narcoleptic brains with SPECT found: "It appears that long term, high dose amphetamine use in narcoleptics is not sufficient, in itself, to result in the diminished cerebral perfusion found in the stimulant abusers" (Challakere et al. 1991).

Similarly, there appears to be no scientific basis for the frequent stipulation that "drug holidays" are required for patients on stimulant medications (e.g., two days per week or month without drugs is common). There is also no research confirming that frequent daytime naps are effective as a treatment alternative to stimulants. Patients understand that there is a vast difference between "having one's eyes open" and being fully alert and capable of performance on the job, in school, at home, or driving a car! The American Narcolepsy Association proposes a new standard for determination of treatment effectiveness:

> To be considered effective, treatment of narcolepsy should consist of the minimum drug dosage necessary for the patient to achieve a normal level of alertness throughout the day, without the need for daytime naps or "drug holidays."

EFFECTS OF DRUG REGULATIONS ON NARCOLEPSY PATIENTS

Legitimate narcolepsy patients repeatedly encounter problems obtaining their prescription drugs for narcolepsy, due to a host of costly, impractical, and unreasonable requirements of the various Federal and State controlled substances regulations and the law enforcement policies of the Drug Enforcement Administration (DEA) and the State and local drug agents and officials. In their zeal and pursuit of the national priority to prevent drug abuse, these officials have often behaved as if there were a "war on drugs," rather than a "war on drug abuse." Narcolepsy patients, their physicians, and their pharmacists frequently encounter harassment and intimidation from Federal and State drug agents.

There are frequent "investigations" which require specific proof of the diagnosis of narcolepsy and the current requirement for treatment with controlled drugs, despite the fact that narcolepsy is a lifelong disorder and treatment will continue unchanged for years or decades, and despite the fact that such questions have been previously answered one or more times. Narcoleptics have been referred to as "drug addicts" or "phony" patients. Doctors and pharmacists have been threatened with loss of their licenses. Yet, the drug agents are not even required to have "probable cause" to suspect that narcolepsy patients are either drug abusers or sources for the diversion of drugs for illicit use.

The legitimate use of controlled stimulants for the treatment of narcolepsy is no different from the treatment of cancer pain with opiates, such as morphine. Each is the result of the legal practice of medicine by licensed physicians and pharmacists. Narcolepsy patients and cancer victims are each entitled to obtain the prescribed drugs with no interference, without cause, from drug enforcement agents. They are entitled to due process of law, privacy and confidentiality of their medical condition, and protection against discrimination and harassment by drug agents and officials. Yet, narcolepsy patients have testified before the National Commission on Sleep Disorders Research that these rights have routinely been ignored. They are often treated like criminals or drug addicts. They are required to prove their diagnosis and treatment requirements by having to repeat the very expensive diagnostic tests every couple of years, even though the costs may not be covered by Medicare or private insurance!

Efforts to cope with the Federal and State controlled substances regulations and to deal the drug enforcement officials have been unsuccessful in

alleviating these problems. New and amended Federal legislation is needed to establish and protect the right of legitimate narcolepsy patients to obtain their prescribed medication without discrimination or prejudice, and without unnecessary procedures and undue costs. The availability of medications for narcolepsy must be assured by changing the regulations for setting production quotas for stimulant drugs. The existing policies neglect to include the anticipated needs for the production of methamphetamine because the drug has not been formally approved for that indication by the FDA, even though such approval is not necessary for it to be prescribed for narcolepsy by a physician. The existing quota policies also neglect to include the production needs for patients who may require larger dosages of a stimulant drug than is specifically covered by FDA approval, even though such approval is not required for legitimate prescription of a greater dosage. In some cases, the production quotas may preclude the availability of generic equivalent drugs at lower costs to the patients.

New Federal legislation is also needed to institute greater uniformity and consistency between Federal and State drug regulations. The entire process of regulations covering the prescription, dispensing, and use of stimulant drugs for the treatment of narcolepsy should be covered at the Federal level. The enforcement of the regulations would be enhanced as a result of uniformity and consistency. It would also eliminate the many unreasonable requirements, unnecessary procedures and inappropriate limitations at the Federal or State level, each of which results in either a needless burden or an extra cost to legitimate patients.

The Controlled Substances Act (1988) and the regulations of the Drug Enforcement Administration (1990) together constitute the Federal law governing controlled substances (the "Act"). The Uniform Controlled Substances Act (1990) is a "model Act" which has been adopted by many States and is adapted from many of the Federal regulations. Both the Federal and State acts presently prohibit refills of prescriptions for Schedule II drugs. However, the Federal law is silent regarding other aspects of prescriptions, resulting in great disparity between and among the States on matters such as the required date by which a prescription must be filled or become void; the prohibition of mailed prescriptions or mail-order pharmacy services; the requirement for a doctor's visit to obtain a new prescription; the restricted availability of specific drugs or the dosage levels which may be prescribed by a physician; the limitation on the quantity or dosage unit supply of the prescribed drug to a 30-day maximum; and other provisions which vary widely from State to State.

The American Narcolepsy Association recommends that all aspects governing prescription drugs for narcolepsy be federalized to eliminate the burdens and extra costs involved locally. After all, drugs are almost entirely developed, marketed, distributed, and sold in interstate commerce, which is constitutionally protected from interference by the States. For example, in many states a prescription for a controlled stimulant must be filled by a pharmacy within 48 hours of issuance by a physician. That is often impossible, since many pharmacies do not keep such drugs in their inventory because of security requirements. In such cases, the pharmacy must order the specific drug from its distributor, which usually takes 3-7 days, assuming adequate supplies are available. If the distributor's supply is inadequate, resupply from the manufacturer may take 2-6 months, since the production quotas severely limit the inventory available for unanticipated demands (which might result from a program to stimulate new diagnoses of narcolepsy by the ANA, for example). In some States a doctor's visit is required for every prescription written. In others, a prescription can only be written for a 30-day supply or for 30 dosage-units. Many States limit the partial filling of prescriptions or require a new prescription form for the unfilled amount.

Each of these requirements adds a significant burden and unwarranted inconvenience for the narcolepsy patient, his physician, and pharmacist. More importantly, they necessitate more costs be incurred by the patient, which may not be covered by insurance, for unnecessary doctor's visits (up to 12 times a year), and for limiting the quantity to the most uneconomic amount, at the highest unit cost. The recommended changes in the Federal Controlled Substances Act and regulations would reduce these costs and burdens and at the same time, retain their intended purposes related to prevention of drug abuse and diversion. The Federal regulation on refills and the various State regulations are extremely discriminatory against legitimate narcolepsy patients, since narcolepsy is known to be a lifelong disorder with no known cure or preventive treatment, and whose symptoms show only minor variation for decades or for life. Specific proposed amendments to the Controlled Substances Act and regulations are described in the addendum.

A SUMMARY OF ISSUES AFFECTING NARCOLEPSY PATIENTS

1. Availability of drugs for narcolepsy treatment
2. Federal and State regulations of prescriptions
3. Costs and burdens of drug regulations
4. Abuses of the rights of narcolepsy patients

MAJOR CONCERNS OF NARCOLEPSY PATIENTS

1. Is there a war on drugs, or a war on drug abuse?
2. Are narcolepsy patients responsible for illicit diversion?
3. Are abuses of patient rights necessary or justified?
4. Have existing diversion control systems curtailed drug abuse?

GENERAL RECOMMENDATIONS

1. Establish the rights of legitimate patients by amendments to the Federal and State controlled substances acts and regulations (see addendum).
2. Revise the quota regulations in the Federal act to encourage generic alternatives at lower cost, to permit multi-year quotas for economical production, and to prevent the occurrence of local shortages (e.g. methylphenidate in 1986 and dextroamphetamine in 1990 (see addendum).
3. Adopt uniform prescription drug regulations at the Federal level, to eliminate State-to-State inconsistencies and States' interference with the availability of medications for legitimate narcolepsy patients (see addendum).

RECOMMENDATIONS TO NIDA

1. Actively inform Federal and State drug enforcement agencies about the legitimate use of controlled stimulant drugs for the treatment of narcolepsy.
2. Allocate funding of research projects to study the present usage and the long-term effects of the use of stimulant drugs for the treatment of narcolepsy.
3. Allocate research funding to establish specific scientific criteria for the objective determination of the safety and efficacy of stimulant drugs for narcolepsy treatment.
4. Identify the existence and the extent of actual drug abuse or drug diversion which results from legitimate narcolepsy patients.

5. Educate and inform the drug enforcement officials, health care providers, and the general public on the findings from the above research programs.
6. Communicate and interact with the F.D.A. About the safety and efficacy findings regarding treatment of narcolepsy with stimulant drugs, with the objective of proposed FDA approval for narcolepsy indications.

ADDENDUM

Proposed Amendments to the Controlled Substances *Act*

Specific provisions must be added or amended to protect the rights of legitimate narcolepsy patients in the following areas:

(1) Generally, the regulations must restate in explicit terms the provisions of sections 801 and 801a of the Act which state:

"Many of the drugs included within this subchapter have a useful and legitimate medical purpose and are necessary to maintain the health and general welfare of the American people" (801(l)), and "nothing in the Convention will interfere with ethical medical practice in this country as determined by the Secretary of Health and Human Services on the basis of a consensus of the views of the American medical and scientific community (801a(3)(C)).

Additional provisions are necessary that prohibit harassment or interference without cause, by DEA agents and other law enforcement officials, with the legitimate practice of medicine by licensed physicians and registered pharmacists who treat narcolepsy patients. Repeated investigations of patients, physicians, and pharmacists shall not be permitted without probable cause that further investigation is related to the suspected diversion of drugs for illicit use or to suspected drug abuse. Indiscriminate reference to narcolepsy patients as drug addicts or phony patients is not acceptable. Further, it must be emphasized strongly that narcolepsy patients are considered to be legitimate users of Schedule II stimulant drugs under accepted medical practice. Their right of due process of law and their rights to privacy and confidentiality of their medical history must be assured and respected by DEA agents and officials. Their diagnosis of narcolepsy must be subject to no greater proof than required for other medical conditions, such as treatment of cancer pain.

(2) The provisions regarding the setting of production quotas for controlled substances used for the treatment of narcolepsy (sections 826 and 1303) must be amended to specifically include, for the DEA determination of production quotas for methylphenidate, dextroamphetamine and methamphetamine; the anticipated increases in demand due to new diagnoses of narcolepsy patients, the anticipated increases in the prescribed dosages of these drugs for the treatment of narcolepsy; the need for production and availability of generic equivalents of these drugs in order to reduce the costs to narcolepsy patients; and the legitimate prescription and anticipated needs for methamphetamine to treat narcolepsy, notwithstanding the fact the FDA has not approved such an indication or the higher dosages typical for narcolepsy treatment. The DEA must be advised that supply shortages of stimulants for legitimate patients with narcolepsy, such as of methylphenidate in 1986 and of dextro-amphetamine in 1990, will not be tolerated in the future.

(3) The provisions regarding the regulation of prescriptions for controlled substances used for the treatment of narcolepsy (sections 829 and 1306) must be expanded to bring about clarity and uniformity between the Federal and State regulations which govern prescriptions of Schedule II stimulant drugs. Section 1306.07(c) must be amended to state that "This section is not intended to impose any limitations on a physician or authorized hospital staff to administer or dispense stimulant drugs to persons with narcolepsy." Sections 829 and 1306.12 should be amended to permit refills of stimulant drugs for up to 6 months from the date of the prescription, for up to a 6-month supply of medication (i.e., two per year with a single prescription). A physician shall be the sole source for exercising prudent judgment as to the daily dosage unit or daily total dosage and the sole source for determination of the quantity of medicine covered by each prescription, within the 6-month maximum with one refill, or a lesser period with more frequent refills (e.g. l-month supply with six refills permitted.

The legislation added to sections 829 and 1306.12 is intended to supersede existing inconsistent State regulations over prescribing practices. The new regulations should specifically permit prescriptions for narcolepsy treatment with Schedule II controlled substances to be filled within a reasonable period after issuance by a physician, such as 7-10 days or sufficient time to permit the pharmacy to obtain the drugs from a distributor after receiving the prescription from the patient or physician. The provisions should specifically state that a physician visit shall not be required more frequently than once per year, except where determined solely by the physician's judgment. The

partial filling of a prescription by a registered pharmacist should be explicitly permitted, with the balance of the prescription permitted to be filled by the pharmacist whenever its inventory permits, without the patient having to obtain a new prescription from the physician. Finally, the prescription must explicitly permit prescriptions to be mailed or delivered to the patient, rather than require a personal pickup or doctor's visit. Many patients live in remote locations or rural areas that are far away from their doctor, who is often a specialist who practices in a wide geographical area. Mail-order pharmacies and the filling of prescriptions by mail or common carrier must also be explicitly permitted, so as to preclude interference by the individual States with interstate commerce and the rights of narcolepsy patients to obtain their medication.

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State Cancer Pain Initiatives

June L. Dahl

Early in the course of this technical review, Dr. Portenoy discussed the problem of unrelieved pain. He pointed out that while some pain is truly refractory to therapy, most pain can be relieved if the drugs and other therapies which are currently available are used appropriately. Pain is common with cancer. Unfortunately, cancer pain is often inadequately treated (Daut and Cleeland 1982). The reasons are many, complex, and deeply rooted in our culture. However, a major factor is that health professionals are reluctant to prescribe adequate doses of opioid analgesics at appropriate time intervals. They are excessively concerned about the side effects of these drugs, about exceeding standard "textbook dosages" and about addiction (Cleeland et al. 1986). Patients and families share these concerns (Levin et al. 1985). Morgan has described our society as opiophobic (Morgan 1989). To make matters worse, often neither those who provide care nor those who receive care are certain what they mean by addiction. Does it imply tolerance? Is it synonymous with physical dependence? Addiction has such a negative connotation in our society that it is critically important to distinguish it from the other terms (Schuster 1989). State cancer pain initiatives urge NIDA to work to clarify the meaning of addiction so that patients who take controlled substances for medical purposes are not erroneously labeled as addicts.

Physical dependence is an anticipated physiological response to chronic opioid therapy. It is manifest by the development of a withdrawal syndrome when opioid analgesics are discontinued or when an opioid antagonist such as naloxone is administered. Tolerance implies the need for increasing doses of an opioid to achieve the desired analgesic effect. Not all cancer pain patients treated chronically with opioid analgesics develop significant levels of tolerance. But that is not the issue. What is critical is that patients who are physically dependent or tolerant *are not addicted.* They do not exhibit compulsive drug seeking behavior; they do not take opioids to get high; they take opioids to get pain relief. The quality of their lives is improved by drug use. The quality of life of those who abuse drugs deteriorates over time. Ironically, cancer patients whose pain is inadequately treated may display bizarre behaviors in their efforts to obtain adequate amounts of analgesics for pain relief–behaviors similar to those seen in individuals who are

psychologically dependent (i.e., addicted). Weissman et al. (1991) have labeled this iatrogenic syndrome "opioid pseudoaddiction," a paradoxical problem resulting from health professionals' unsubstantiated concerns about addiction in cancer patients receiving opioids for pain. Some professionals who are involved in the treatment of drug abusers describe any chronic user of controlled substances as an addict. Those who are concerned about benzodiazepine abuse may do so as well. The symptoms of benzodiazepine withdrawal often resemble those that led patients to seek therapy initially. Does the desire of the patient to reinitiate therapy to treat those symptoms mean that the patient is addicted? Those of us in the cancer pain movement would not rush to make that judgment and urge that the addict label not be applied to individuals who have panic and acute anxiety disorders and therefore require chronic therapy. Let us not let the medical controversies surrounding the appropriate use of the benzodiazepines confuse our understanding of addiction.

State cancer pain initiatives have been created to overcome professional and public fears about the use of opioid analgesics and the multiplicity of other factors that account for the undertreatment of cancer pain: deficiencies in knowledge, inappropriate attitudes, and problems intrinsic to our health care system (Cleeland 1987). Initiatives are voluntary, interdisciplinary organizations of health professionals. Physicians, nurses, pharmacists, social workers, psychologists, and medical educators are working to enhance their colleagues awareness of the cancer pain problem, their ability to assess and treat that pain appropriately, and to make them aware of the important benefits of good pain control. Some are also developing and implementing quality assurance guidelines; others are reaching out to patients and families so they will know that cancer pain can be relieved, that they have the right to demand adequate pain control, and that they need not fear addiction and the side effects of potent analgesic drugs. Twenty-five States now have cancer pain initiatives. Their common goals are to make relief of cancer pain a priority in the health care system in this country and an expectation of all individuals with cancer.

The idea for a State cancer pain initiative originated with the Wisconsin Controlled Substances Board (WCSB), the State's drug regulatory authority. The stimulus was the Compassionate Pain Relief Act, a bill introduced into the Congress in 1984 to make heroin available for the treatment of pain in terminally ill cancer patients. The board initially looked at the proposed legislation from a regulatory perspective because its passage would have required the board to authorize physicians to prescribe and pharmacists to

dispense this Schedule I drug. At the same time, the board recognized the magnitude and severity of the cancer pain problem in the United States. Furthermore, it realized that it might have contributed to the problem. By developing a vigorous program to control prescription drug diversion and abuse in the State (Chi 1983), the board had probably sent strong messages to physicians: that if they prescribed opioids liberally for pain, they might come under regulatory scrutiny. Therefore, the board decided to couple its opposition to the heroin bill with positive action and to develop a program that would bring improvements in the management of cancer pain in a way that heroin's availability could not possibly do.

After almost 2 years of planning, the Wisconsin Cancer Pain Initiative (WCPI) convened a statewide strategy session at which participants developed an action plan which has guided the program ever since (Dahl et al. 1982). The WCPI has developed educational materials for patients and families and for health professionals which can be obtained by writing to the Center (WCPI, 3675 Medical Sciences Center, 1300 University Avenue, Madison, WI 53706). Numerous conferences and workshops have been held for doctors, nurses, and pharmacists. The media have played an important role in bringing public attention to the problem and appropriate solutions. A newsletter keeps participants informed of current issues and upcoming events. The WCPI in cooperation with the WCSB reviewed Federal and State laws and regulations to determine if there were obstacles to the appropriate prescribing of opioids for cancer pain. Neither Federal nor Wisconsin laws prohibit physicians from prescribing large amounts of these drugs for extended periods of time. Nevertheless, physicians fear that they will be investigated by drug regulators if they prescribe these drugs liberally. Indeed, this has occurred in other States (Hill 1989). Furthermore, results from a pilot study of Wisconsin physicians show that they do alter their prescription practices because of the fear of regulatory scrutiny (Weissman et al. 1991). They may reduce drug dosage, or quantity, reduce the number of refills, or choose a drug in a lower schedule. Two Wisconsin regulations were found to be impediments to the adequate prescribing of drugs for patients with cancer pain. A Pharmacy Examining Board (PEB) rule limited the amount of a Schedule II opioid that could be dispensed at one time to 120 dosage units or a 34-day supply (whichever is less). Physicians and pharmacists were confused about this rule; some interpreted a dosage unit to mean a tablet. The increasing use of oral liquid and injectable opioids and flexible dosing schedules had further compounded the problem. Individuals who needed large doses of oral opioid analgesics for cancer pain relief had the added burden of continually arranging for new prescriptions from their physicians.

The PEB eliminated the 120 dosage unit restriction on September 1, 1991; the 34-day supply restriction on prescribing and dispensing remains. A second regulatory impediment was associated with a rule promulgated by the Medical Examining Board (MEB) which severely and justifiably restricted the allowable medical uses of amphetamines. The WCPI and the WCSB worked with the MEB to incorporate specific language into the amphetamine rule which indicates that it is appropriate for physicians to prescribe amphetamines to treat refractory opioid-induced sedation.

State initiatives have come together on two occasions to share perspectives and materials, first in July 1989 and again in February 1991. Drug regulations were a topic of concern at both national meetings. The current emphasis on reducing drug abuse in our society has, at the very least, enhanced the concerns of the public and health professionals about the potential for opioids to be abused. As national concerns about drug abuse have increased, there has been a push for greater control over prescription controlled substances both at the Federal and the State level. Thus, multiple copy prescription programs and accountable prescriptions have been strongly promoted by the DEA and adopted in nine States (Joranson and Dahl 1989; Joranson 1990). There has been a reduction in the prescribing of Schedule II controlled substances in States that have instituted those programs. It has been assumed that this reduction in prescribing is accompanied by a decrease in diversion and abuse of prescription drugs, but there are no data to document this assumption. Furthermore, there are no data to indicate what effect reduction in prescribing rates has on the quality of care of cancer patients in pain. Anecdotal reports from physicians suggest that multiple copy prescription programs have a chilling effect on the prescribing of controlled substances. More recently, electronic data transfer (EDT) systems have been advocated and implemented in Oklahoma and Massachusetts. The effectiveness of those programs in reducing prescription drug abuse is not known nor is it known how they affect practice behaviors.

The participants at the Second National Meeting for State Cancer Pain Initiatives raised many questions about these and other drug diversion control programs:

1. Are they needed?
2. What is their impact on diversion and abuse?
3. What is their impact on patient care?
4. How much will they cost and who will pay?

They also felt there were many positive actions that State initiatives could take. They specifically recommended that initiatives:

1. Work for adoption of the Uniformed Controlled Substances Act, particularly because it specifically recognizes the need to assure the availability of controlled substances for medical use.
2. Work with State drug regulators to inform them of the important medical uses of controlled substances and offer assistance to them in identifying and taking action against violative practitioners.
3. Oppose adoption of additional multiple copy prescription programs or other new diversion control programs until there are adequate studies of the impact of these systems on the abuse and diversion of prescription drugs and on patient care.
4. Support studies of the effects of prescription drug control programs on physician prescribing practices and on the availability of prescription controlled substances to cancer patients.

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Benzodiazepine Dependence-A Treatment Perspective and an Advocacy for Control

Robert D. O'Connor

INTRODUCTION

As a board-certified internist, addictionologist, and cardiologist specializing in the field of addictive diseases for 20 years, I have clinically diagnosed and treated many patients with benzodiazepine addiction, in withdrawal and in recovery.

Ever since the controlled studies demonstrated that diazepam and chlordiazepoxide taken for a month in dosages 2-3 times the maximal recommended daily therapeutic dose results in physical dependency and a clinically significant withdrawal syndrome (Hollister et al. 1961), physical dependence on higher doses of benzodiazepine has been widely recognized. There is also concern now, however, that long-term use of benzodiazepines taken within the usual range of therapeutically prescribed doses can also result in physical dependency (Lader 1983; Smith and Wesson 1983; Winokur et al. 1980).

My own clinical experience in addictive medicine confirms this clinical and research evidence. Many individuals take benzodiazepines in therapeutic doses for months to years and then sharply discontinue them without developing symptoms that are indicative of benzodiazepine withdrawal. Other individuals, however, take similar amounts of benzodiazepines, develop physical dependence, and cannot tolerate the withdrawal symptoms, that are identifiable, predictable, and protracted. It is also known that the metabolism of long-acting benzodiazepines is reduced in the elderly, particularly men, which results in physical dependence at lower dosages than in younger individuals.

Suffice to say that benzodiazepine withdrawal syndrome symptoms wax and wane in cycles separated by 2-10 days and include anxiety, panic symptoms, mood swings, restlessness, insomnia, malaise/fatigue, increase in pulse and blood pressure, impaired memory, short-term concentration, tremor, body aches, headache, nausea, vomiting, retching, sweating. depression, feelings of

depersonalization, paranoid reaction, psychosis, and seizures. Other objective and subjective symptoms and perceptual changes may be manifested and may persist for 2-4 weeks.

CLINICAL DATA

In 1989, New York State passed a benzodiazepine Controlled Substance Law (Triplicate Prescription). The cases presented in this paper are those patients admitted in 1989 and 1990 to Conifer Park, a 225-bed alcohol and drug treatment center in Scotia, New York, with a primary diagnosis of benzodiazepine dependence. Thirty-two cases are presented (1989 census = 2,594 patients and 1990 census = 2,387 patients). The patient statistics and profile are demonstrated with this data.

BENZODIAZEPINE PATIENT STATISTICS (1989-1990)

Percentage of total admissions	0.7 percent
Average length of stay	25.67 days
Average age	42 years
Percentage male	52 percent
Percentage female	48 percent
Race	100 percent white
Discharge Types:	
Routine	64 percent
AMA	24 percent
Medical	12 percent
Average days in withdrawal	11 days
Average days on primary care	6 days
Medical Source:	
Physician	76 percent
Street	12 percent
Both	12 percent
Average Duration of Use	6 years
Types of Benzodiazepines:	
(Percentage of occurrences)	
Valium	58 percent
Xanax	33 percent
Librium	9 percent
Ativan	9 percent
Dalmane	3 percent
Family History Positive	24 percent

Medical Complications:	
Anxiety/panic	12 percent
Seizures	15 percent
Peptic ulcer disease	12 percent
Hypertension	6 percent
Depression	12 percent
Cancers	6 percent
Eating disorders	6 percent
Migraine headaches	6 percent
High blood pressure	12 percent
Gastritis, irritable bowel	15 percent
Urinary tract infection	6 percent
Liver enlargement/cirrhosis	6 percent
Other (asthma, vaginitis, etc.)	6 percent
Lab work positive	64 percent
High cholesterol/triglycerides	21 percent
Withdrawal Symptoms:	
Insomnia	45 percent
Nausea	30 percent
Tremors	58 percent
High blood pressure	24 percent
Headaches	6 percent
Restlessness	24 percent
Mood swings	24 percent
Muscle twitches	12 percent
Reasons for admission:	
"I want to get off of drugs, etc"	18 percent
Interference with work/family	21 percent
Intervention (family/friend)	33 percent

In addition, 14 patients gave a primary history of alcoholism and cross-addiction to benzodiazepines. An additional number of patients were prescribed benzodiazepines for anxiety and grief reaction in the presence of known alcoholism. Other patients received benzodiazepines for lumbosacral disc disease and other low back pathology or were given concomitant prescriptions for opiates (codeine, Percocet, Darvon, etc.). Female patients received opiates, sedatives, and benzodiazepines in combination for migraine

headaches, thereby contributing to and resulting in combined addictions and more difficult diagnoses and complicated protracted withdrawal syndromes,

SUMMARY

This clinical data is presented to emphasize the clinical seriousness of benzodiazepine dependence, its relationship to other addictive diseases, the complicated and protracted nature of its withdrawal syndrome, the various clinical reasons for prescribing benzodiazepines, and the need for physicians in all medical specialties to be alert to the possibility of chemical dependence in their patient population. Those of us prescribing benzodiazepines should have a clinical knowledge of addictive diseases and not complicate the disease process by prescribing benzodiazepines when they arc clearly contraindicated.

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A Public Citizen Health Research Group Perspective on Federal Triplicate Prescription Requirements for Controlled Substance Prescription Drugs

Sidney M. Wolfe

The Public Citizen Health Research Group strongly supports a Federal triplicate prescription requirement, which we believe is needed to curb:

> (1) drug diversion through "pill mills" that indiscriminately prescribe psychoactive drugs
> (2) the inappropriate long-term and/or high-dose use of benzodiazepines
> (3) the prescribing of these drugs to cope with everyday problems for which their use is medically inappropriate

We strongly commend the now 29-month-old New York State triplicate prescription requirement for benzodiazepines as well as the older systems of the eight other States which have multiple prescription programs. These programs represent, in our opinion, the most important recent improvements in the out-of-hospital practice of medicine, in enhancing the quality of physician prescribing, and in saving hundreds of millions of dollars of dangerously wasted money.

Given that the number one drug abuse problem in this country–in terms of the number of people affected and the severity of its total effects–involves legal prescription drugs, the triplicate prescription programs are the most successful effort yet in the war on drugs.

In nine States–New York, California, Texas, Indiana, Hawaii, Michigan, Illinois, Rhode Island and Idaho–laws or regulations are in effect requiring multiple (usually triplicate) prescription forms to be filled out by doctors writing prescriptions for any Schedule II controlled substance, drugs such as morphine, codeine, barbiturates, amphetamines, and other prescription drugs which are usually addicting, otherwise dangerous, and subject to abuse. By pressing a little harder on the prescription blank, the doctor makes two extra

copies of the prescription, enabling not only the pharmacist but the State government and the physician to retain copies as well.

According to officials from the Drug Enforcement Agency (DEA), after these laws had been in effect for several years, there was about a 50 percent decrease in the number of prescriptions written for controlled drugs. For example, in Rhode Island in the 7 years following the new requirement, there was a 56 percent reduction in the number of prescriptions written for Schedule II drugs. In Texas, during the 10 year period following enactment, the reduction was 69 percent.

In four of the multiple prescription states–New York, California, Illinois and Indiana–the State also has the authority to apply the triplicate prescription regulation to drugs in Controlled Substance Act Schedules III or IV as well as to Schedule II drugs. Thus far, only New York State has elected to include all of the benzodiazepines–drugs such as the tranquilizers Valium, Librium, Xanax, Ativan, and Tranxene and sleeping pills such as Dalmane, Halcion and Restoril. But New York first had to successfully weather legal challenges from major drug companies producing these drugs (Roche, Abbott, Wyeth, and Upjohn) and from the drug industry-funded New York State Medical Society before the triplicate prescription requirement for benzodiazepines went into effect on January 1, 1989.

Although most of the remaining remarks apply specifically to benzodiazepines, the principles involved are relevant to legal or illegal misuse or misprescribing of any of the drugs covered by triplicate prescription laws or regulations. As noted, we have had much more experience in more States with triplicate prescription requirements for Schedule II drugs. The record is clear these programs have been quite successful in reducing the illegal use and misprescribing of these drugs. Moreover, there is no credible evidence that either patients or physicians have been prevented from using properly prescribed controlled drugs for appropriate periods of time.

It has never been the position of the Public Citizen Health Research Group that benzodiazepine sleeping pill and tranquilizer drugs should be banned; rather, that they are prescribed more often than is necessary, considering their limited time period of effectiveness and the serious risks they pose. Although these risks may be outweighed by their benefits when properly prescribed, for large numbers who get them by diversion from originally legitimate or illegal channels, or the probably still larger number for whom they are prescribed inappropriately, the risks outweigh the benefits. The

triplicate prescription regulation is intended to protect those people for whom benzodiazepines are not properly prescribed.

WHAT IS THE IMPACT OF OVERPRESCRIBING?

Based on data from published studies done in the United States, we have estimated the toll from the use of benzodiazepine tranquilizers and sleeping pills to be:

- Ten thousand hip fractures in older adults due to falls caused by these drugs.
- Seventy-five thousand older adults with drug-induced or drug worsened mental deterioration (dementia) caused by these drugs.
- As noted below, in 1989 alone, according to a study by the Drug Enforcement Agency, there were 60,148 occasions in U.S. hospital emergency rooms in which these drugs were listed in association with drug-overdose problems.
- A variety of other kinds of serious impairment, including addiction, daytime sedation, confusion, increased risk of an auto accident, slurred speech and, especially in combination with alcohol, death.

A large proportion of these serious injuries and deaths could be prevented if the prescribing of these drugs was done more carefully than is now the case. It would also mean, as strikingly seen in New York, a significant decrease in prescribing.

HAS THE NEW YORK TRIPLICATE PRESCRIPTION REGULATION FOR BENZODIAZEPINES WORKED?

The following data were obtained from the New York State Health Department, the National Prescription Audit (IMS, Inc., Ambler, PA), and the U.S. Drug Enforcement Agency.

Prescriptions for benzodiazepines: U.S. v. New York State

From 1988 to 1989, there was a slight (9.8 percent) nationwide decrease in the number of benzodiazepine prescriptions filled in American retail drug-stores–from 82 to 74 million. However, for the New York State employees, family and retiree health plan called Empire, during the same period there

was a four times larger decrease (37 percent) than that seen nationally. New York Medicaid experienced a 59.3 percent decrease–from 1.56 million prescriptions in 1988 to 630,000 in 1989, more than six times the national decrease. This 930,000 prescription decrease was only slightly offset by an increase of 189,000 in the number of prescriptions written for nonbenzdiazepine tranquilizers and sleeping pills during 1989.

By the end of the first year the regulation went into effect, there was a 40 percent decrease in the percentage of people in New York's state-subsidized elderly drug reimbursement plan, EPIC, who received benzodiazepine prescriptions. The percentage of plan members who got a benzodiazepine prescription decreased from 20.9 percent during the last 3 quarters of 1988 to 12.6 percent by the last quarter of 1989.

The case of clonazepam should be of great interest to those who complain–without evidence–that this kind of program might curtail necessary prescribing of benzodiazepines. Clonazepam is the only drug in the benzodiazepine family that is not a tranquilizer or sleeping pill, but is used instead to treat seizure disorders. Unlike the sharp decreases in the other benzodiazepines, prescriptions for clonazepam, actually rose from 1988 to 1989 in the New York State Medicaid program and the State employees program.

Emergency Room Data for Benzodiazepines: U.S. v. New York State

For the entire country, there was no decrease but in fact a slight increase from 1988 to 1989 in emergency room mentions reported to the Drug Abuse Warning Network (DAWN) system for benzodiazepines. These data are based on surveys of the drugs used by patients who wind up with drug abuse problems in hospital emergency rooms. Nationwide in 1989 there were 60,048 mentions for benzodiazepines, and the number rose slightly to 60,148 in 1989.

In New York State, at least in the metropolitan Buffalo and New York City areas, there was a 39 percent decrease in benzodiazepine emergency room mentions following instigation of the triplicate prescription requirement. From a level of 2,611 mentions in 1988, the number decreased to 1,590 in 1989.

Although there was a slight increase in prescriptions for nonbenzodiazepine tranquilizers and sleeping pills accompanying the much larger decrease in benzodiazepines, there was actually a decrease in DAWN emergency room

mentions for these drugs in New York State–from 506 in 1988 to 457 in 1989. Nationally, the number increased from 12,530 to 13,595.

Other gains cited by the New York State Health Department include:

- A 95 percent reduction in benzodiazepine use by one group of about 3,400 patients suspected of diverting almost 250,000 prescriptions annually into illicit use.
- A 76 percent reduction in prescriptions dispensed by New York pharmacies suspected of being "pill mills."
- An increase in "street" prices of 2 to 5 times for benzodiazepines, indicating street supplies were "drying up."

Cost Saving: New York State

There are many parts to answering the question of cost savings resulting from the new New York State triplicate requirement, but those measured thus far are very compelling. There was a saving of $11.2 million in the Medicaid program alone resulting from diminished State purchases of benzodiazepines. Although about a third of this saving was offset by increases in the cost of other nonbenzodiazepine tranquilizers and sleeping pills, there was still a net saving of $7.4 million in 1 year in this program alone. This does not include additional savings from the State employees and older citizen plans nor those resulting from thousands fewer emergency room visits, decreased hip fractures, memory loss, and other serious adverse effects averted through this revolutionary program. If one includes all citizens of New York State, not just those in State-funded programs, we estimate the savings in reduced purchases of drugs and decreased drug-induced diseases and injuries could well approach $100 million.

These enormous decreases in the prescribing of benzodiazepines, which cannot solely be accounted for by a reduction in illegal prescribing, are consistent with a decrease in the amount of overly-lengthy prescriptions and a decrease in the third category of misprescribing, treating the normal stress of daily living with benzodiazepines.

It is clear that causing doctors to pause momentarily as they write triplicate prescriptions for any of these drugs adds to their awareness that these are medications having significant risks as well as benefits. To the credit of doctors in New York State, the first 6 months of the new regulation indicated a significant statewide decrease in prescribing.

THREE KINDS OF MISPRESCRIBING OF TRANQUILIZERS AND SLEEPING PILLS

There are three categories of benzodiazepine misprescribing which the New York State regulation attempted to cure:

The first is street diversion of drugs originally prescribed by a physician who knows, or should usually know, the drugs are going to be diverted and resold on the street, often for large sums of money. This is often referred to as "illicit use," although the initiator is a licensed physician engaging in unethical, if not illegal, activity. It must be noted that in New York State and the few other States which are seriously engaged in efforts to discipline doctors for practices endangering their patients, a common reason for license revocation or suspension is grossly overprescribing drugs such as benzodiazepines or narcotics. These kinds of prescribing practices, combined with the willing filling of these prescriptions by "friendly" pharmacists, are sometimes referred to as "pill mills."

Unfortunately, unethical doctors or pharmacists prescribing or dispensing benzodiazepines, which are not as rigorously controlled as narcotics, are often not caught until they have prescribed or dispensed enormous quantities which wind up on the street or in circles of benzodiazepine-addicted people. An additional type of illegal activity which diverts benzodiazepines is the forging of prescriptions.

The deterrent effect of a triplicate prescription requirement on those doctors and pharmacists who supply such drugs inappropriately has already been demonstrated in New York State during the period since its new regulation went into effect. A memo from John Eadie, Director of the Division of Public Health Protection, to Health Commissioner Dr. David Axelrod, dated March 1, 1989, documents this. In 21 Bronx and Manhattan pharmacies suspected of being pill mills, there was a marked decrease in the number of benzodiazepine prescriptions filled in 1 week in less than a month after the new regulation went into effect. To quote from the memo, "In the center of the 'Pill Mills,' Manhattan and the Bronx, the decrease was 79 percent, in Queens and Brooklyn, 67 percent, and upstate, where less diversion had been suspected, 39 percent."

Although there has been a dramatic decrease in prescriptions for benzodiazepines closely correlated with the extent to which certain geographic areas

have pill mills, there is no evidence that the legitimate prescribing of these drugs has been adversely affected.

A second category of inappropriate prescribing involves prescriptions written without any intention or much possibility of diversion. These prescriptions are written for such legitimate medical indications as severe anxiety or sleeping disorders. However, due to carelessness on the part of the doctor or an unawareness or unwillingness to adhere to approved labeling, the drug regimen is continued for a period of time far in excess of that for which it is effective.

Using data from national surveys, we estimate that over 3 million adults aged 18 to 79 are being given one or more of these drugs daily for one year or longer. This pattern of prescribing occurs despite the fact that the Food and Drug Administration's approved labeling for these drugs says there is no evidence that any of the tranquilizers work for more than 4 months or that the sleeping pills work for more than 4 weeks.

The third category of misprescribing involves doctors giving patients benzodiazepines for the normal stresses of daily living–situations which merit attention by doctors, family, friends, clergy, and others, but which should not be "treated" by these drugs. For the past few years, the labeling for these drugs has stated that "anxiety or tension associated with the stress of everyday life usually does not require treatment with an anxiolytic" *(Physicians' Desk Reference* 1989). There is no evidence that the large amount of prescribing of benzodiazepines for everyday problems of living has decreased as much as it should since this label change was implemented.

HOW CAN THERE BE ANY RATIONAL REASON FOR OPPOSING SUCH A PROGRAM?

Even the American Medical Association, which strongly opposes laws requiring triplicate prescriptions, admits "diversion of prescription drugs for purposes of abuse is a significant contributor to this nation's drug abuse problem and its attendant morbidity and mortality" (AMA 1989).

Despite admitting the seriousness of the problem, the AMA Board of Trustees adopted (in December 1989) the above report and its recommendation that the AMA:

> Oppose expansion of multiple-copy prescription programs to additional States or classes of drugs because of their documented ineffectiveness in reducing prescription drug abuse and their adverse effect on the availability of prescription medications for therapeutic uses.

The above AMA statement opposing multiple prescription programs is filled with false and misleading information. Its degree of misinformation is similar to that of the failed legal effort by the New York Medical Society and its partners in the prescription drug industry (Roche, Upjohn, Wyeth, and Abbott) to stop the New York State Health Department from requiring triplicate prescriptions for benzodiazepines. (A New York Court ordered that the program could begin in January 1989.)

In summary, the New York State regulation requiring triplicate prescriptions for benzodiazepines has had an important impact in the 2 years since it went into effect. In direct proportion to the decreased use of these drugs, there will be a decrease in preventable adverse effects such as memory loss, falls and hip fractures, addiction, bizarre behavioral problems such as aggression, and other serious problems.

We strongly urge passage of Federal legislation that will allow the entire country to reap the benefits that New York State and, to a lesser extent, the other multiple prescription States have obtained. This will not only save an enormous amount of money, but most importantly, bring an increased measure of health protection to the citizens of this country. Although concern has been expressed by some critics of such measures that medical confidentiality could be abridged, there is no evidence that pharmacists have breached such confidentiality and no reason to believe law enforcement personnel are any more likely to do so.

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Consequences of the 1989 New York State Triplicate Benzodiazepine Prescription Regulations

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INTRODUCTION

Effective January 1, 1989, New York State (NYS) regulations require that all prescriptions for benzodiazepines be written on special triplicate prescription forms. For the past 12 years, triplicate prescriptions have been required by the NYS Department of Health (DOH) for all Schedule II drugs. When benzodiazepines were added to the program, they became the first Schedule IV medications to require triplicate prescriptions.

Triplicate prescription pads are printed by the State and sold to registered practitioners on application. When a physician completes a triplicate blank, he gives two copies to the patient to take to the pharmacist. The physician retains the third copy. The pharmacist keeps one copy and forwards the other to the DOH. From this copy, the following information is entered into a centralized computer: the practitioner's name, the patient's name, age and address, the product and amount prescribed, and the pharmacist's name and address.

Under this program, except for patients with panic and convulsive disorders, prescriptions for benzodiazepines can only be written for a maximum 30-day supply. Refills are not permitted. Patients must receive a new prescription for additional medication. When prescribing for epilepsy and panic disorder, practitioners must specify on the prescription the condition either by name or by a designated code issued by the DOH. Pharmacists are then allowed to fill a prescription written for up to a 3-month supply of medication.

As outlined by the New York State Department of Health, the primary objectives for inclusion of benzodiazepines into the triplicate prescription program were to reduce diversion to illicit use, to reduce inappropriate prescribing, and to educate physicians, pharmacists, and the public about benzodiazepines (NYSDOH 1990). Secondary objectives included tracking individual patients, prescribers, and pharmacists who may be using the

medications and the system inappropriately as well as decreasing medication expenditures for the NYS Medicaid System. The DOH viewed maintenance of legitimate benzodiazepine use as inherent in these objectives. In an address, John Eadie (1988) of the DOH informed the American Medical Association that, in the opinion of the New York State government, benzodiazepines are a major public health danger to the citizens of New York. He noted that the State believes that the high level of abuse, misuse, and iatrogenic injury associated with benzodiazepines require monitoring through the triplicate prescription blank program.

The regulations were not passed without strenuous objections from some interested parties, such as the pharmaceutical industry. Medd (1986) predicted that further regulation of benzodiazepines would result in decreased legitimate use and increased costs to patients, the medical community, and the State. Morgan (1986) argued that long range programs of public education would be more valuable in alleviating benzodiazepine abuse. Studer (1986) was concerned that physician prescribing of less appropriate medications as well as inappropriate patient self medication would evolve as a result of the triplicate regulations. Workers in the field of substance abuse treatment also voiced concern. Khuri (1986) warned of the possibility that benzodiazepine abuse may be further criminalized and driven underground. Steinhart (1986) observed that the regulations may result in synthesis of counterfeit benzodiazepines.

Since the outcome of prescribing regulations cannot be accurately predicted, they are a form of experimentation. We, therefore, saw a need for an independent review of the consequences of the triplicate regulations. To evaluate the effects of the triplicate program, we studied prescribing and expenditures for benzodiazepines, other anxiolytics, and sedative-hypnotics considered by prescribers as potential alternatives to benzodiazepines as well as other psychotherapeutic drugs.

MATERIALS AND METHODS

Table 1 lists all the psychoactive medications that were studied. We assessed patterns of prescribing and expenditures both before and after institution of the regulations. Data for analysis were obtained from three independent sources: IMS America, New York State Medicaid, and Blue Cross/Blue Shield of the Rochester Area.

Table 1

Medications Studied

Benzodiazepines

Alprazolam, Chlordiazepoxide, Clorazepate, Diazepam, Flurazepam, Halazepam, Lorazepam, Oxazepam, Prazepam, Temazepam, Triazolam

Antidepressants

Amitriptyline, Amoxapine, Buproprion,* Desipramine, Doxepin, Fluoxetine, Imipramine, Nortriptyline, Protriptyline, Trimipramine, Trazodone

Antipsychotics

Chlorpromazine, Chlorprothixene, Fluphenazine, Haloperidol, Loxapine, Mesoridazine, Molindone, Perphenazine, Promazine, Thioridazine, Thiothixene, Trifluoperazine

Miscellaneous Anxiolytes, Sedatives, Hypnotics and Antihistamines

Buspirone, Butabarbital,* Chloral Hydrate, Diphenhydramine, Ethchlorvynol,* Ethinamate, l Glutethimide, Hydroxyzine, Mephobarbital, Meprobamate, Methyprylon, Phenobarbital

* Not listed in the New York State Reimbursable Drug List.

IMS America Data Base

The IMS national geographic prescription audit provided data from 1988 through the first quarter of 1990. The national prescription audit utilizes prescription data obtained from a sample of 10,000 pharmacies located within the 48 contiguous States (IMS 1990). From these pharmacies, IMS collects every new and refilled prescription. Centralized computers in several locations around the country enter prescription data from participating system pharmacies on a continuous basis. Projections made within geographic regions are added together to create State and national estimates for the number of prescriptions written and dispensed for each medication. IMS data, therefore, represents estimated total prescriptions for the entire region under consideration and includes all income groups and payment plans.

Data on numbers of prescriptions written and dispensed for all the drugs listed in Table 1 were obtained for New York State. For purposes of comparison, similar data were obtained for three other States, California, North Carolina and New Jersey–as well as for the entire United States.

California was selected because it is similar to New York State in its demographic complexity and population size. However, California has a semirestrictive Medicaid formulary system. Over 450 drugs are listed generically in the formulary but the patient's physician or pharmacist may request authorization from the local Medi-Cal consultant for approval of unlisted drugs. By contrast, New York State has a restrictive formulary system under which payment for medications is limited to those listed in the authorized Medicaid reimbursable drug list (NYSDOH 1990). Unlike New York State, North Carolina has an open formulary system for Medicaid patients. New Jersey was selected because it is geographically contiguous with New York State.

We obtained Medicaid prescribing and expenditure data for 1987 through June 1990 from the Division of Medical Assistance, Department of Social Services of New York State. Data were obtained on all drugs listed in table 1 except those indicated as not reimbursable by New York State Medicaid. The total number of prescriptions written as well as the total Medicaid expenditures for each drug were analyzed.

Medicaid is a State-funded medical assistance program. Beneficiaries are generally lower income or unemployed. The total Medicaid eligible

population of New York State is about 2.2 million persons, of whom approximately 1.3 million receive benefits annually .

The data obtained represent total capture of all prescriptions and reimbursement for the entire New York State Medicaid population.

Blue Cross/Blue Shield of the Rochester Area Data

We obtained Blue Cross/Blue Shield reimbursement data on prescribing for 1987 through 1989. Data were obtained on all medications listed in table 1. The units (e.g., tablets or capsules) dispensed for each medication were evaluated.

Blue Cross/Blue Shield health insurance coverage is paid for by clients and their employers. We obtained data from three treatment rider plans. Under the terms of these plans, the subscriber paid the first $2, $3, or $5 of the prescription cost. Blue Cross/Blue Shield reimbursed the pharmacist for the remainder. Total membership for these plans averaged just over 100,000 per year. Subscribers of BC/BS of the Rochester Area are generally employed, middle income Americans, and their family members who live in six counties of New York State: Monroe, Yates, Seneca, Ontario, Wayne and Livingston.

RESULTS

Benzodiazepine Prescribing

A small decrease in total U.S. benzodiazepine prescribing throughout 1988 was seen in the IMS data. This decrease was also noted in California, New York State, and, to a lesser extent, in New Jersey. In 1989 and early 1990, gradual decreases continued in total U.S. prescriptions as well as in California and North Carolina. However, during the first quarter of 1989, just after the triplicate regulations took effect, IMS recorded a 33 percent decrease in benzodiazepine prescribing in New York State. The trend continued, with total prescriptions falling from 5.3 million in 1988 to 2.96 million in 1989, and in the first quarter of 1990 to 603,000.

New York State Medicaid data also revealed a small decrease in benzodiazepine prescribing before the 1989 regulations. From 1987 to 1988, there was a 4 percent decline in Medicaid benzodiazepine prescriptions. However, after the regulations went into effect, benzodiazepine prescriptions for Medicaid

patients fell by 60 percent–from 1.5 million in 1988 to 600,000 in 1989. The large post regulation decrease in benzodiazepine prescribing has persisted into early 1990 (218,000 for the first 6 months).

Blue Cross/Blue Shield subscribers were already receiving a declining number of benzodiazepines before the regulations went into effect. After institution of triplicate regulations, i.e., from 1988 to 1989, there was a further 30 percent decrease.

Medicaid Expenditure Data

Before the triplicate regulations, Medicaid expenditures for benzodiazepines were decreasing slightly. From 1987 to 1988 expenditures went down 8.3 percent. However, when the regulations went into effect, expenditures decreased by 51.9 percent, from $21.7 million in 1988 to $10.4 million in 1989. During the first 6 months of 1990, there was a 3 percent increase in benzodiazepine expenditures from the 6-month mean of 1989 ($5.4 versus $5.2 million).

Expenditures for alternative sedative hypnotic medications increased 115 percent, from $3.9 million in 1988 to $8.4 million in 1989. This increase has persisted into 1990.

Expenditures for the other nonsedative-hypnotic psychotherapeutic drugs studied remained constant until the second 6 months of 1989, when spending increased 28 percent to $13.4 million from a first 6 month figure of $10.4 million. In the first half of 1990 these expenditures increased a further 16.6 percent, to $15.6 million.

The net effect of these changes on total expenditures for the entire group of psychotherapeutic medications was a decrease of 2.4 percent, from $46.7 million in 1988 to $45.6 million in 1989. However, in the first 6 months of 1990, total expenditures increased 17.6 percent from the 1989 6-month mean of $21.3 million to $25 million.

Alternative Medication Prescribing Data

From the IMS database (table 2) it is evident that prescribing for a number of drugs decreased in the United States (excluding NYS) from 1988 to 1989 compared to increases in New York State, e.g., meprobamate, -9 percent nationally versus + 12.5 percent in New York; methyprylon, -15 percent versus +84 percent; ethchlorvynol, -18 percent versus + 29 percent; butabarbital, -15 percent versus + 31 percent; hydroxyzine, -1.1 percent versus + 15 percent, and chloral hydrate, -0.4 percent versus + 136 percent. Some newer and more expensive potential alternatives, e.g., buspirone and fluoxetine increased both nationally and in New York State, but increased to a greater extent in New York. Increased prescribing of these drugs continued into early 1990. Since percentage increases from a small base may cause distortions, the actual numbers of prescriptions for alternative medications are presented in table 2.

Prescribing of alternatives also increased in the New York State Medicaid data. From 1988 to 1989, meprobamate increased 225 percent, hydroxyzine 26 percent, chloral hydrate 99 percent, and buspirone 126 percent. Fluoxetine prescribing increased by 1,250) percent. Unlike the IMS data, Medicaid also recorded increased diphenhydramine use from 1988 to 1989. Increased prescribing of potential replacement medications has continued into early 1990. Methyprylon, ethchlorvynol, and butabarbital are not reimbursable by New York State Medicaid.

Meprobamate, butabarbital, hydroxyzine, chloral hydrate, buspirone, and fluoxetine utilization also increased in the Blue Cross/Blue Shield population As in the Medicaid data, Blue Cross/Blue Shield also recorded increased prescribing of diphenhydramine.

DISCUSSION

All three data bases indicate that the triplicate regulations have resulted in a marked decrease in benzodiazepine prescribing in New York State. Medicaid expenditures for benzodiazepines have also decreased. However, there was not a corresponding decrease in total expenditures for all sedative and psychotherapeutic drugs studied. Among the possible reasons are increased cost of benzodiazepines, the use of more expensive alternative medications,

Table 2

Alternative Psychotherapeutic Medications Prescribed, 1988 and 1989, in thousands of prescriptions (IMS Data).

	New York State		***Total U.S. minus N.Y.S.***	
Medications:	1988	1989	1988	1989
Meprobamate	122	275	2,005	1,826
Methyprylon	22	41	123	104
Ethchlorvynol	17	22	218	178
Butabarbital	46	60	715	608
Hydroxyzine	530	608	6,829	6,756
Chloral Hydrate	43	102	529	527
Buspirone	154	333	1,782	2,194
Fluoxetine	147	356	2,754	5,778

Note: Decimals have been rounded to the nearest whole number.

such as buspirone and possibly fluoxetine, as well as changes in Medicaid payment practices.

Particularly striking is the large percentage increase in the prescribing of alternative drugs such as meprobamate, ethchlorvynol, methyprylon, chloral hydrate, and butabarbital in New York State. These medications have been almost totally replaced by benzodiazepines in modern medical practice. Our data, thus, do not support the State's contention (NYSDOH 1990) that "substitution of alternative drugs has not been a significant issue." The Medicaid reimbursable list appears, however, to have "protected" beneficiaries from receiving some of the alternative medications.

There are potential weaknesses in each of the data bases. IMS, while comprehensive, uses samples to predict total prescriptions. Thus, the accuracy of the estimates may be questioned. However, IMS has been collecting and generating this type of data for almost 30 years and its data are widely used both by academic researchers and by the pharmaceutical industry. The Blue Cross/Blue Shield population is continuously changing as clients change jobs and employers change health insurance plans. Thus, it includes a select and variable group of middle income New York State residents who may not be representative of typical prescription recipients. There may be some bias in the Medicaid data because not all physicians in New York State see Medicaid patients. However, the concurrence of results from three different data sources cannot be ignored.

The effects that prescribing regulations have on the use of alternative drugs are well recognized. Blackwell (1973) commented on the control of minor tranquilizers and the possibility that it may encourage physicians to revert to using more "potent and dangerous alternate drugs." Attempts at controlling dextropropoxyphene (Shenfield et al. 1980) and antibiotics (Kunin et al. 1973) have resulted in the use of potentially unacceptable alternatives.

Since their introduction in 1961, benzodiazepines have enjoyed an enormous popularity among physicians and patients alike. As noted in the current edition of the standard pharmacology textbook, *The Pharmacologic Basis of Therapeutics,* benzodiazepines have a reputation for a low incidence of abuse and dependence (Rall 1990). The World Health Organization (1982) report on psychotropic substances noted that "very few use benzodiazepines as their primary drug of abuse." In the United States, Ayd (1981) reported that most long term single benzodiazepine users do so for therapeutic purposes. Benzodiazepine abuse does not lead to hard drug abuse although the reverse

seems to occur (Marks 1985). Mortality from overdosage of benzodiazepines done is extremely rare (Marks 1985; Finkle et al. 1972; Prescott 1983).

Rall (1990) summarizes the reasons for the decline of barbiturate prescribing and increased use of benzodiazepines. He notes that barbiturates "lack specificity of effect in the central nervous system, they have a lower therapeutic index than do the benzodiazepines, tolerance occurs more frequently than with benzodiazepines, the liability for abuse is greater and the number of drug interactions is considerable."

Other alternative sedative hypnotics have shown deficiencies as well. Meprobamate is preferred to the benzodiazepines by subjects with a history of drug abuse (Roache and Griffiths 1987; Kaufman et al. 1972). Miller and Gold (1989) make the arresting comment that "there is really no valid therapeutic indication for meprobamate." Habituation, tolerance, physical dependence, and addiction occurs with methyprylon, chloral hydrate, and ethchlorvynol (Rail 1990). Intoxication with these agents is quite similar to barbiturate poisoning. Mortality from barbiturate poisoning has ranged from 2 to 40 percent (Rail 1990). Sudden withdrawal from habitual chloral hydrate use may result in delirium and seizures with a high frequency of death. Chronic users of chloral hydrate may suddenly exhibit acute intoxication (Rall 1990). Death from chloral hydrate may occur as the result of an overdose or, in the presence of hepatic injury, a failure of the detoxification mechanism (Rall 1990). The medications being prescribed in New York State to replace benzodiazepines can thus be seen to have major disadvantages.

The use of alternatives has not fully replaced the decrease in benzodiazepine prescribing. Therefore, there are patients who were previously using benzodiazepines or who would have been prescribed benzodiazepines who are probably not being prescribed any minor tranquilizer. In some cases, this will, of course, be excellent medical practice. In others, however, it may indicate undertreatment of clinically significant insomnia and anxiety.

Some evidence exists that drinking alcohol may be a form of self-medication acting as an alternative to taking prescription tranquilizers, at least for males (Mellinger et al. 1978). There are suggestions of beneficial social effects from the use of tranquilizers both at work (Proctor 1981) and in the circumstances of general life (Marks 1985). It is, therefore, important to consider whether potential outcomes from benzodiazepine regulation are acceptable.

According to a New York State Department of Health publication, the Drug Enforcement Agency (DEA) estimated that emergency room admissions for both benzodiazepine and alternative sedative-hypnotic overdoses have decreased from 1988 to 1989 (NYSDOH 1990). However, data from the New York City Poison Control Center (Maddaloni et al. 1990), indicate that, although benzodiazepine exposures have decreased, total overdoses with all sedative hypnotics have not changed. In addition, the Department of Health reports that DEA estimated an increase of 77.7 percent in meprobamate overdoses from 18 in 1988 to 32 in 1989 (NYSDOH 1990). A potential result of the decreased availability of benzodiazepines remains a significant increase in overdoses from the more toxic alternative sedative hypnotics.

In New York State before the 1989 regulation, only 58 percent of practitioners possessed triplicate prescription pads. This percentage may have increased since the 1989 change (NYSDOH 1990). Physicians may have many reasons for being reluctant to use triplicate prescriptions including theft. In New York City, one report indicated that the street price of a single triplicate pad ranges between $100 and $125 (Rodos 1990). In Texas, the price may be as high as $150 (Troisi et al. 1989). Although there is a prison term plus a $2000 fine for any breach of confidentiality (Brahams 1990), computerized State records of the name of both prescriber and patient, represents, to some, an unacceptable public intrusion into confidential and private domains. Some physicians may also resent filling out more forms. By targeting practitioners, triplicate prescription legislation assumes a significant degree of involvement by the majority of practitioners in drug abuse and drug diversion (Troisi et al. 1989). Some physicians may find this contention both insulting and lacking substantiation.

The triplicate benzodiazepine prescription regulations appear to have fulfilled some of their goals, but not all. In addition, they have generated new problems. The major negative consequence seems to be prescribing less acceptable alternatives, which suggests that State regulations may not be the only answer to prescription medication abuse or misuse. Tight controls of one class of medications may, as has been demonstrated here, cause legitimate transfer to alternative substances. It is important, therefore, to ensure that too rigorous control of low-risk medications does not encourage movement to drugs of higher risk. Marks (1985) emphasized that the medication control actions of legislators may perpetuate the abuse they wish to prevent. Professional and lay education must be considered as alternatives to legislation (Rodos 1990). Wider dissemination of the sensible, well-referenced data and

recommendations of the American Psychiatric Association (APA 1990) would be an excellent start for educational interventions.

Other States are moving toward regulation of benzodiazepine prescribing. The Ohio Medicaid system will now only reimburse for Xanax (Upjohn) prescriptions after obtaining a second, concurring opinion (Brahams 1990). California, Indiana, Illinois, Tennessee, Washington, and Rhode Island are currently contemplating triplicate benzodiazepine prescription regulations. At the Federal level, Congressman Stark (California) has proposed making all benzodiazepines Schedule II drugs.

Unfortunately, the true benefit-to-risk ratio of the regulations in New York State remains both unknown and difficult to estimate. However, the wider public health, patient care, and financial implications of triplicate benzodiazepine prescribing regulations are of concern and require further evaluation before wider dissemination.

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Changes in Prescribing Patterns in Long-Term Care Facilities and Impact on Incidence of Adverse Events

Sergio G. Zullich, Thaddeus H. Grasela, Jill B. Fiedler-Kelly, and Francis M. Gengo

INTRODUCTION

> *It is an art of no small importance to administer medicines properly, but it is a much greater and more difficult art to know when to suspend them.*
>
> *Phillipe Pinel, 1820.*

The triplicate prescription program was established 12 years ago in New York State to control the prescribing of drugs believed to have a high potential for abuse. Under this program, all Schedule II drugs, such as narcotics, barbiturates, and amphetamines, must be prescribed on a New York State Triplicate Prescription form. One copy of this triplicate prescription is forwarded to the Department of Health; the pharmacist and prescribing physician retain the other copies. This program provides a mechanism for monitoring physician prescribing habits and identifying high-volume prescribers of Schedule II medications. New York State Department of Health officials have stated that this program contributed to the reduction of abuse and misuse of Schedule II drugs (NYS 1989).

Benzodiazepines have been used extensively for the treatment of anxiety or insomnia (Bellantuono et al. 1980). It is estimated that 60 million benzodiazepine prescriptions were dispensed in the United States alone in 1986 and these agents have consistently appeared in the list of Top 10 drugs prescribed (Higgins 1989). Although there is general agreement among practitioners regarding the benefit of short-term benzodiazepine therapy, there continues to be controversy regarding the risk of long-term use because of the potential for dependency and addiction (Mellinger et al. 1984; Uhlenhuth et al. 1988). In an effort to minimize inappropriate prescribing of the benzodiazepines, New York State recently passed legislation to regulate the use of

benzodiazepines by requiring that they be prescribed using triplicate prescriptions.

A recent report published by the New York State Department of Health indicated that the number of benzodiazepine prescriptions written in New York State decreased from 80 to 53 percent, depending on the population studied, since the regulation was implemented on January 1, 1989 (NYS 1989, 1990). Conversely, the New York State Department of Health reports that a review of prescription data from Medicaid; the Empire Plan, which provides health care insurance for over 423,000 State and local government employees, retirees, and dependents; and the Elderly Pharmaceutical Insurance Coverage (EPIC) prescription program, a State cost-sharing program that provides prescription drug insurance to more than 70,000 low- and moderate-income individuals aged 65 or older, show a marginal increase in claims for potential benzodiazepine substitute drugs not currently included in the triplicate prescription program. This increase does not appear to offset the decline in the number of benzodiazepine prescriptions, suggesting that there has been either a net decrease in the number of patients receiving sedatives, hypnotics, or anxiolytics or a reduction in the extent of inappropriate benzodiazepine use (NYS 1990).

Reports in the literature have shown that the elderly are one of the largest users of benzodiazepines (Mellinger et al. 1984). One study indicates that up to 26 percent of the benzodiazepine anxiolytics and 40 percent of the benzodiazepine hypnotics were prescribed for the elderly (Beardsley et al. 1989). Studies of psychotropic drug use in nursing homes show that benzodiazepines are used extensively for anxiety and insomnia. It is estimated that one-third of nursing home residents take benzodiazepines regularly for insomnia (Beardsley et al. 1989; Buck 1989; Beers et al. 1989; Ray et al. 1980; James 1985). This implies that the elderly, as a group, may be significantly affected by the recent legislation.

The potential increase in use of benzodiazepine substitutes prompted by the triplicate legislation requires close evaluation because many of the drugs used as alternatives to benzodiazepines would be expected to have a greater risk for toxicity than benzodiazepines. This is especially true in the elderly who are more susceptible to adverse events associated with the use of the alternative psychoactive drugs (Beers and Ouslander 1989; Jones 1985). For example, barbiturates and glutethimide, which might be used as nighttime sleep aids, have a much more narrow therapeutic index and higher risk for respiratory depression than benzodiazepines. Neuroleptics and

antidepressants have been associated with increased risk of falling, hip fractures from falls, and abnormal involuntary movement disorders (Sobel and McCart 1983; Granek et al. 1987; Ray et al. 1987; Ray et al. 1989; Jenike 1983). Antihistamine use has been associated with anticholinergic side effects such as increased agitation, memory impairment, and urinary retention (Blazer et al. 1983). Antihistamines may also cause an increase in viscosity of pulmonary secretions in patients with chronic obstructive pulmonary disease, which might increase the risk of pneumonia. Barbiturates are involved in numerous drug interactions due to changes in hepatic metabolism. They may increase the clearance and decrease serum concentrations of antiarrhythmics, antihypertensives, and antibiotics leading to a decrease in efficacy of these drugs. Barbiturates also have a lower clearance rate in the elderly, which increases the possibility of adverse effects (Beers and Ouslander 1989).

This study was undertaken because observations of the benzodiazepine prescribing patterns in a group of nursing homes in the western New York area after the implementation of the triplicate program suggested that benzodiazepines were being replaced by other psychoactive agents such as antidepressants, antihistamines, barbiturates, neuroleptics, and buspirone. If confirmed, this switching to alternative agents represents an important consequence of the triplicate program because of the risks attendant to these agents. The objectives of this study were, first, to assess the impact of the triplicate prescription legislation on benzodiazepine and "benzodiazepine substitute" prescribing patterns and, second, to determine the clinical consequences of alteration in prescribing patterns in terms of significant adverse events occurring in a nursing home patient population.

METHODS

The records of all nursing home patients who resided in one of ten nursing homes in the western New York State area during the l-year period from July 1, 1988, to June 30, 1989, were reviewed for this study. These ten nursing homes were selected because they were serviced by a single clinical pharmacy consulting service. The medication administration record, medical chart, and medical records for all patients were reviewed retrospectively by one of the authors (SGZ). Data taken from the medication administration record included age, sex, and information regarding regularly scheduled and as-needed psychoactive medications as defined by the New York Quality Assurance System (NYQAS 1988). These agents include antidepressants, neuroleptics, barbiturates, benzodiazepines, antihistamines with central nervous system activity, and sedative/hypnotics. All patients who were prescribed a

benzodiazepine during the time period of interest were subsequently included in the analysis described below.

Patient diagnoses were obtained from the medical chart and coded according to the International Classification of Diseases Code Book (ICD-9-CM) (Commission on Professional and Dospital Activities 1978). The first three diagnoses that included any neurologic or psychiatric disorders were used.

The patient's medical record and the institution incidence reports were reviewed to determine the number of adverse events possibly associated with psychoactive drug therapy. The number of patients who experienced a fall, hip fracture, hospital admission, behavioral outbursts, or any report of psychological, somatic, or perceptual changes from baseline occurring within 1 week of discontinuing a benzodiazepine were recorded. Psychological symptoms included any reported increase in anxiety, agitation, irritability, or lethargy. Somatic symptoms included insomnia, headache, muscle pain, tremors, and seizures. Perceptual symptoms included incoordination, vertigo, paranoia, paresthesia, flu-like symptoms, and visual hallucinations (Noyes et al. 1988; Roy-Byrne and Hommer 1988; Zarr 1989; Kellman 1988). Nursing homes operate under statutory requirements to document all falls, hip fractures, and hospital admissions and the administrative records were reviewed to identify patients who experienced these adverse events. The information regarding the occurrence of behavioral outbursts or reports of psychological, somatic, or perceptual changes were collected by review of medical records and nursing notes. These events were selected as indicators of exacerbation of underlying chronic medical conditions, withdrawal from benzodiazepines, or an adverse event to the replacement agent, if any was used. No attempt was made to discriminate the cause of these events. Patients who exhibited an emotional outburst during the period of 1 week prior to discontinuing benzodiazepines were not included in the analysis. Data collected for the adverse events included date of occurrence, description of the event, and a list of regularly scheduled medications the resident was receiving at the time of the event.

Methods to ensure patient confidentiality were approved by the university investigational review board.

STATISTICAL ANALYSIS

Prescribing patterns and adverse events were recorded for a 6-month period prior to and after the triplicate prescription program went into effect. The

data were analyzed for changes in prescribing patterns on a monthly basis during the study period to evaluate the impact legislation may have had on benzodiazepine prescribing in long-term care facilities.

In order to determine the clinical consequences of the triplicate regulations, a group of patients that had been receiving regularly scheduled benzodiazepine therapy and who were either discontinued from benzodiazepine therapy or switched to an alternative agent after the implementation of the triplicate regulations were identified. For each adverse event studied, the population risk ratio for the patients who were discontinued from benzodiazepines was calculated by dividing the number of patients with the particular adverse event after discontinuing benzodiazepines by the number of patients experiencing the event before discontinuing benzodiazepines (Kleinbaum et al. 1982). The McNemar X^2 test for significance of changes was used to test the hypothesis of no difference between the number of patients having adverse events before and after benzodiazepine therapy was discontinued. Ninety-five percent confidence intervals were constructed for the population risk ratio of each adverse event. Statistical significance was defined as $p< 0.05$.

RESULTS

Patients residing in 10 long-term care facilities (8 private for-profit and 2 public non-profit facilities) from the western New York State area were studied. The total number of skilled nursing beds was 1,017 and the number of health related beds was 170. Out of the total possible nursing home population of 1,187 patients who were residents during the study period, the charts of 809 residents with complete documentation were available for review. In the remaining 378 patients, medical records were either missing or data regarding drug administration were incomplete. There were 583 females (72.1 percent) and 226 males (27.9 percent). The average age of the residents was 81.7 years old (S.D. = 9.7) with a range of 40 to 103 years. The nursing home population for all the facilities were similar in distribution of patients with a diagnosis of Alzheimer's disease (5.2 percent), organic brain syndrome (32.4 percent), dementia (21.6 percent), and percent of patients prescribed benzodiazepines (20.5 percent).

Overall levels of benzodiazepine use did not vary significantly during the period from July 1988 to December 1988. On average, 25 percent of the psychoactive drug orders between July 1988 and December 1988 were for a benzodiazepine. From January 1989 to June 1989, coinciding with the implementation of the triplicate regulations on January 1, 1989,

benzodiazepine use decreased steadily to a low of 10 percent of all psychoactive drug orders. The decline in benzodiazepine use was accompanied by a steady increase in the number of orders for alternative agents including chloral hydrate, diphenhydramine, and phenobarbital as sedative/hypnotics, and haloperidol, buspirone, and phenobarbital as anxiolytics. Overall antipsychotic drug use increased slightly during January and February, but then declined to baseline levels.

In July 1988 there were 171 orders for benzodiazepines, with some patients taking more than one benzodiazepine. The orders included 63 (37 percent) orders for sedative/hypnotics, of which 20 (32 percent) were for flurazepam, 18 (29 percent) for temazepam, and 25 (40 percent) for triazolam. In addition, there were 108 (63 percent) orders for an anxiolytic, of which 22 (20 percent) were for alprazolam, 27 (25 percent) for lorazepam, 45 (42 percent) for diazepam, and 14 (13 percent) for other agents.

A total of 166 patients (20.5 percent) had at least one prescription for a benzodiazepine during the 6-month period before the triplicate prescription program went into effect. Eleven of these patients were discontinued from the drug more than 3 months before the triplicate prescription program was initiated and these patients were excluded from further analysis. Thus, a total of 155 patients were evaluated; 78 (50 percent) of these patients were prescribed a benzodiazepine as an anxiolytic, 53 (34 percent) as a sedative/hypnotic and the remaining 24 (15 percent) received both an anxiolytic and a sedative/hypnotic.

During the 3-month period prior to the implementation of the triplicate prescription program, 65 (42 percent) of the 155 patients were receiving benzodiazepines on an as-needed basis, accounting for 35 percent of the anxiolytic patients and 42 percent of the sedative/hypnotic patients. Sixty-seven percent of the patients prescribed both an anxiolytic and a sedative/hypnotic were taking one or both of the drugs on an as-needed basis. Of the 65 patients receiving the benzodiazepines on an as needed basis, 56 (86 percent) patients received less than 10 percent of their maximum possible dose per month. Of the remaining 9 patients, only one received an average dosing rate for the 3-month period that was greater than 50 percent of the total possible dose. Because of the low usage, patients who received benzodiazepine(s) on an as-needed basis were excluded from the analysis of the population risk ratio for adverse events.

A total of 102 patients received benzodiazepines on a regular basis, 51 (50 percent) of whom were on anxiolytics, 31 (30 percent) on sedative/hypnotics, and 20 (20 percent) on both anxiolytics and sedative/hypnotics. Fourteen patients were prescribed both an anxiolytic and a sedative/hypnotic benzodiazepine on an as-needed and regularly scheduled basis.

Of 155 patients receiving benzodiazepine therapy at the time of implementation of the triplicate program, a total of 108 (70 percent) patients discontinued at least one benzodiazepine, whereas only 47 (30 percent) patients continued their previously prescribed benzodiazepines. Of the patients who discontinued benzodiazepine therapy, 74 (68 percent) patients had their benzodiazepine switched to another psychoactive agent, 24 (22 percent) patients were discontinued from their benzodiazepine and not prescribed an alternative agent, and 10 (9 percent) patients were receiving a combination of two or more benzodiazepines and had at least two different outcomes, e.g., one benzodiazepine was switched to an alternative agent and the other was discontinued entirely.

Sixty patients discontinued benzodiazepine anxiolytic therapy and the commonly prescribed alternatives included haloperidol (21 percent), buspirone (8 percent), and phenobarbital (8 percent). Only 17 of these 60 patients were discontinued from all anxiolytics. The number of patients not prescribed an alternative is greater for those with as-needed dosing than those with chronic, regularly scheduled dosing. Sixty-four patients discontinued benzodiazepine sedative/hypnotic therapy and the most common alternatives for these patients were chloral hydrate (26 percent), diphenhydramine (14 percent), and phenobarbital (12 percent). Only 17 (27 percent) of these 64 patients were discontinued from all sedative/hypnotics. As noted previously, it was more common for a patient receiving benzodiazepines on an as-needed basis to be discontinued from all sedative/hypnotics than for a patient receiving chronic, regularly scheduled benzodiazepine therapy. The 60 patients discontinued from benzodiazepine anxiolytics and the 64 patients discontinued from benzodiazepine sedative/hypnotics represented a total of 124 benzodiazepine prescriptions in 108 patients.

In five patients for whom benzodiazepine therapy was discontinued, an alternative agent was prescribed, and after a short period of time, the original benzodiazepine was prescribed again. Two of these patients were receiving an anxiolytic on an as-needed basis and three were receiving a regularly scheduled sedative/hypnotic.

The benzodiazepine regimen of 8 of the 108 patients discontinued from benzodiazepines was apparently tapered prior to discontinuation of the benzodiazepine. In each case, the patient was changed from a benzodiazepine on a scheduled basis to an as needed basis before discontinuing the drug altogether. The patients remained on the as-needed regimen for various lengths of time, ranging from 2 weeks to 6 months.

There was a total of 15 patients who potentially experienced behavioral, psychological, somatic, or perceptual changes from baseline, representing 14 percent of all patients discontinued from benzodiazepines. Thirteen of these fifteen cases were on regularly scheduled benzodiazepines before discontinuation of therapy. One of the patients receiving a sedative/hypnotic on a regularly scheduled basis was tapered to an as-needed basis for nearly 8 weeks, and the day after switching to ethchlorvynol, experienced this symptom complex. Another patient developed this symptom complex 3 days after switching from regularly scheduled to as-needed anxiolytic therapy and starting phenobarbital.

The population risk ratio for adverse events in the 65 patients who were receiving regularly scheduled benzodiazepine therapy and who were either discontinued from benzodiazepine therapy or switched to an alternative agent after the implementation of the triplicate prescription regulations was 0.63 for falls, 1.38 for hospitalizations, and 1.04 for any adverse event including falls, hip fractures, behavioral outbursts, or hospitalization for any reason. A value greater than 1 indicates an increased risk of adverse event after patients were taken off benzodiazepines. None of the population risk ratios were statistically significantly different from 1. Small sample sizes in the groups of patients experiencing hip fractures and behavioral outbursts did not permit a separate analysis of these events. Thus, hip fractures and behavioral outbursts were combined with falls and hospitalization for any reason to create a combined category. The population risk ratio for this combined category was 1.04 ($p>0.05$). In general, there was no discernible trend in the number of adverse events, except for the occurrence of a cluster of behavioral, psychological, somatic, or perceptual changes observed during the month of January 1989.

DISCUSSION

There are a number of outcomes anticipated with the implementation of a triplicate prescription control program, including a reduction in diversion of benzodiazepines to the illicit market, reduction in the costs of prescription

medication use, and a reduction in the number of adverse events related to inappropriate benzodiazepine use such as falls, emergency room visits, and so forth. In evaluating a program with many possible outcomes, it was necessary to identify an endpoint to measure a single determinant. We chose to measure the impact of the triplicate program on prescribing patterns and patient care in nursing homes for several reasons. First, in a nursing home population, physician concerns about diversion to the illicit market would be insignificant. Second, the adverse event rate in elderly patients is intrinsically higher than in younger patients; thus, we would have the greatest likelihood of detecting a change in the rate of adverse events. Third, nursing homes are required by law to maintain administrative records documenting drug prescribing and a number of clinical outcomes of interest to this study, and fourth, benzodiazepines are widely prescribed in nursing homes.

In previous communications, the New York State Department of Health has claimed that the inclusion of benzodiazepines in the triplicate program successfully reduced the use of benzodiazepines, with only a slight increase in use of alternative agents (NYSDH 1989, 1990). The results of this study suggest that prescribing patterns for benzodiazepines and other CNS drugs in nursing homes in western New York State were significantly affected by the triplicate prescription program, and a somewhat different picture emerges regarding the prescribing of alternative agents. Although benzodiazepine use declined markedly, nearly half of these patients were switched to alternative agents not currently included in the triplicate program. This raises the question of whether the benzodiazepines were initially an inappropriate choice and the alternative agent represents more appropriate prescribing, or whether patients appropriately receiving benzodiazepines were changed to less appropriate medications. The data present herein were collected retrospectively so that an assessment of therapeutic appropriateness and a specific evaluation of efficacy was not possible. However, the prescribing data for insomnia show a clear increase in use of chloral hydrate and diphenhydramine with the decrease in benzodiazepine use. These alternative medications have generally fallen from favor among physicians, in general, for a number of reasons (Gillin 1991). In addition, well-controlled sleep studies have not shown antihistamines to have an effect on nocturnal sleep latency, suggesting that they may be unreliable in inducing nocturnal sleep. Furthermore, agents such as brompheniramine and triprolidine can suppress REM sleep (Nicholson et al. 1989). These data suggest that antihistamines would be less efficacious than benzodiazepines for patients needing a sedative/hypnotic. Although chloral hydrate has been shown to reduce nocturnal sleep latency and increase total sleep time acutely, these effects are not long-lived.

Most studies show a loss of hypnotic efficacy within 5 days (Kales et al. 1970). When one adds limited efficacy to the additional side effects from the anticholinergic actions of antihistamines (Nicholson et al. 1989) or narrow safety range of chloral hydrate (Kales et al. 1970), it is hard to accept that increased utilization of these drugs constitutes more appropriate prescribing.

A similar argument can be made regarding the alternative use of neuroleptics as anxiolytic drugs. These agents have been associated with anticholinergic effects, orthostatic hypotension, lethargy, and extrapyramidal reactions (Ray et al. 1987, 1989; Solomon and Hart 1978; Lader et al. 1980; Lader 1980; Moran et al. 1988). The argument that the triplicate prescription program results in a change toward more appropriate prescribing becomes even more tenuous based on changes observed in drug prescribing to treat anxiety. Moreover, the increased utilization of haloperidol, thioridazine, and other neuroleptics in an aged population seems contradictory with other New York State programs designed to review neuroleptic use in institutionalized patients (NSDOH 1988). These programs have been declared successful due to a decrease in neuroleptic use, but it is difficult to acknowledge the triplicate prescription program for benzodiazepines to be successful if the result has been increased neuroleptic use by institutionalized elderly patients.

It has been suggested that the reduction in benzodiazepine use following their inclusion in the triplicate program has resulted in a cost savings to New York State. This cost savings is attributable in part to reduced falls, hip fractures, and hospital admissions. In the results reported here, the risk of falling, hospitalization for any reason, or all combined events were not significantly altered despite a reduction in benzodiazepine use. The lack of significant reduction in these gross indices despite reduced benzodiazepine use may indicate that the alternative agents also contribute to these risks.

It is important to recognize that the adverse events selected for monitoring were gross indices to assess the clinical impact of the effect of the change in prescribing patterns. The fact is that the study was performed retrospectively, and the lack of availability of detailed clinical records did not permit a study of the more subtle endpoints for efficacy or toxicity of the alternative agents.

Larger population-based studies have demonstrated important differences in risks of adverse events in the elderly related to their psychoactive drug use. Important differences in the risk of adverse events have been noted for long half-life versus short-half-life drugs. In two studies done by Ray et al.

(1987, 1989) it was suggested that long elimination half-life psychotropics may increase the risk of hip fractures. In a case-control study of a population of elderly Medicaid participants, it was noted that hypnotic-anxiolytics with an elimination half-life greater than 24 hours were associated with a greater risk of hip fracture. This included flurazepam, tricyclic antidepressants, haloperidol, and thioridazine (Ray et al. 1987). A nested case-control study of residents of Saskatchewan 65 years and older was done to assess the relative risk of hip fractures in long half-life benzodiazepine versus short half-life drugs. It was observed that individuals receiving long half-life benzodiazepines had a greater risk of hip fracture (Ray et al. 1989).

In the nursing home population examined herein, the majority of patients were receiving short half-life benzodiazepines prior to the initiation of the triplicate prescription program. After enactment of the triplicate legislation, a significant number of patients were switched to long half-life drugs including antidepressants, haloperidol, phenobarbital, and thioridazine. These patients may be at an increased risk of adverse events as suggested by Ray et al. (1987), but we were unable to determine agent-specific population risk ratios because of the small sample size. At the present time, it is unclear whether one can validly compare the safety of drugs based on the half-life of drugs, particularly across classes of drugs. It would be important to specifically evaluate the individual agents typically categorized as short half-life drugs and to specifically compare benzodiazepines versus nonbenzodiazepines.

Our study demonstrated that a significant number of patients were discontinued from regularly scheduled benzodiazepine therapy with no attempt to taper the dose. It is interesting to note that only 15 patients (14 percent) of the 108 patients who stopped benzodiazepine therapy experienced minor symptoms of behavioral, psychological, somatic, or perceptual changes as recorded in the medical record and no patient required hospitalization during the l-week period following discontinuation of benzodiazepine. Fourteen of the fifteen patients received benzodiazepines longer than 3 months and one patient for at least 1 month before discontinuation of therapy. Of the 15 cases of this symptom complex observed during the study period, 9 occurred during the month of January. This is undoubtedly an underestimation of the number of patients who experienced these symptoms because this study relied on the medical record and entries were not always made on a daily basis. This lack of documentation also created difficulties in differentiating the occurrence of symptoms secondary to benzodiazepine withdrawal versus other etiologies, such as exacerbation of underlying chronic disease or adverse

events caused by the replacement drug, if any. It is unlikely that we missed serious events resulting from benzodiazepine withdrawal syndrome, such as seizures, however, because these would have resulted in an incident report or hospitalization. In a review of published studies, it is reported that benzodiazepine withdrawal syndrome can occur in 40 to 100 percent of patients who discontinue therapy abruptly (Roy-Byrne and Hommer 1988; Zarr 1989). These previous findings suggest that minor symptoms of benzodiazepine withdrawal syndrome were not detected or reported in a substantial number of the patients examined in this nursing home population,

It is important to consider a number of potentially significant limitations to this study. A relatively small number of patients representing prescribing patterns of a small number of physicians are included in this report. Thus, our ability to safely extrapolate to other nursing homes in New York State is limited. In addition, this study addresses the importance of triplicate regulations on a subset of patients and does not address the impact of the triplicate regulation on other patient groups. Furthermore, this study makes no attempt to measure the impact of the regulation on the diversion of benzodiazepines to the illicit market or its impact on unethical physicians who abuse prescription writing privileges for profit. New York State has evidence, however, that the triplicate program has had a desired impact in both of these important areas (NYSDH 1989, 1990). Finally, the data was collected retrospectively and a number of difficulties were encountered in obtaining complete records; nearly 32 percent of patients had to be dropped because of incomplete data. This does not negate the finding of a significant increase in utilization of benzodiazepine substitutes. In fact, it may represent an underestimate of the extent to which prescribing patterns have been altered. The impact of the missing data on the interpretation of the adverse event data is unknown, however, and can be substantially affected by the missing data. Thus, our findings with regard to the adverse events must be interpreted with caution.

SUMMARY

The addition of benzodiazepines to the triplicate prescription program in New York State was successful in reducing the use of benzodiazepines in a nursing home population, but the use of alternative agents was substantially increased. The reduction in benzodiazepine use could not be shown to be associated with any reduction in risk of adverse events during a retrospective review. In order to evaluate the impact of a triplicate prescription program on patient care, endpoints of efficacy as well as toxicity must be identified

prior to the implementation of new legislation. It should be incumbent upon those States considering implementation of triplicate legislation to realize that the imposition of these regulations is tantamount to forced enrollment in a clinical trial for the patients affected by the legislation. A mechanism must be available to prospectively assess changes in prescribing patterns and their clinical consequences in order to determine objectively whether the legislative intervention was a success.

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A Research Agenda for Prescription Drug Diversion Control

Constance Horgan, Jeffrey Prottas, Christopher Tompkins, Linda Wastila, and Melissa Bowden

A. Reasons for Further Research

During our review of prescription drug diversion systems (Horgan el al. 1991), several past, ongoing, and proposed studies involving MCPPs or other diversion control systems were identified. Often it was perceived by people involved in diversion control that this issue was being "overstudied." Moreover, many respondents believed that they already knew the answers to evaluation questions being addressed in some or all of the studies. In the light of these observations, what could justify more research on this topic? There are four reasons for considering further research on diversion control systems:

- To specify ongoing diversion control activities
- To consider outcomes from multiple perspectives, including impact on medical practice and patient care, as well as the impact on diversion reduction
- To go beyond anecdotal and impressionistic data
- To explore the nature and role of subjective experiences in affecting prescribing behavior

First, States appear to employ various combinations of approaches to diversion control. Some States apparently do much more than others to curb drug diversion. As a result, program directors and others in the field generally have idiosyncratic experiences. Moreover, prescribing patterns and substance abuse patterns apparently differ considerably among States, making comparisons of program efficacy across States difficult. Thus, it is important to describe the circumstances and interventions relevant to any particular State, including pertinent State laws and regulations.

Second, the perspective taken by people involved in diversion control is often strongly influenced by their professional responsibilities. Law enforcement officials are better able to identify actual and potential benefits of alternative approaches to prescription drug diversion control. Similarly, health

professionals are more often aware of potential effects that diversion control efforts can have on medical practice and patient care. Thus, the perceived costs and benefits of alternative diversion control systems are determined greatly by each observer's vantage point. An objective and comprehensive evaluation should take into account these multiple perspectives.

Third, many people involved in the field make use of anecdotal and impressionistic data to support their conclusions. However, reliable data have not been available to quantify the magnitude of diversion or the effects of diversion control in terms of reduced diversion or changes in medical practice. A lack of formal evaluation results limits available information, and the extent of current knowledge should not be considered sufficient to warrant definite conclusions.

Fourth, it would be worthwhile to investigate in more depth the attitudes of law enforcement and health professionals regarding their perceptions and experiences with alternative diversion control mechanisms. Many of the same voices are heard repeatedly on the subject, but it is not clear the extent to which these views are held by people working in the relevant professions. Moreover, it would be useful to supplement other evaluation measures with attitudinal and subjective indicators for representative population samples in order to enhance interpretation of other findings.

B. Diversion Control Systems: Pluses and Minuses

This study has shown very clearly that prescription drug diversion control involves a number of interrelated issues and several disparate points of view. For an evaluation of the alternative public policy options to be comprehensive, it would have to take into account all of the potential benefits and costs to society attributable to a diversion control program. Policymakers may have different opinions about the relative importance of each type of benefit and cost. However, within relevant resource and data constraints, evaluators must allow for the testing of pertinent hypotheses regarding alternative diversion control programs.

A necessary starting point is to establish what criteria might be included in a formal evaluation. Identifying and measuring all relevant benefits and costs satisfactorily would be difficult. Also, available data may not be sufficient in all cases to adequately account for certain important factors.

1. Positive aspects

a. Reduced diversion

A basic potential benefit of a diversion control system is reduction in the diversion of prescription drugs. This could result from impeding the diversion process, reducing the demand for nonmedical use of prescription drugs, increasing the probability of catching culpable practitioners, stiffening the penalties given to offenders, and so forth.

Reduced diversion implies a whole set of related potential benefits, including reductions in:

- short- and long term health consequences of substance abuse,
- accidents and injuries
- productivity losses
- unnecessary expenditures for drug products, and prescribing and dispensing services.

b. More appropriate use of controlled substances

This potential benefit can take the form of reduced inappropriate drug therapy and increased appropriate drug therapy. Sometimes the difference between drug diversion, which is the focus of law enforcement, and drug therapy, which is in the realm of health professionals, is fundamentally related to standards of care accepted in the medical community. Systematic attention to prescribing and diversion patterns for controlled substances could heighten collective and individual awareness among practitioners regarding the proper use of those drugs. This could have the effect of decreasing instances of overprescribing (e.g., using drug therapy longer than necessary) as well as overcoming tendencies toward underprescribing (e.g., failing to reach optimal therapeutic dosages).

Developing and evaluating prescribing guidelines and increasing the dialogue among practitioners regarding the care of individual patients could foster more optimal prescribing patterns. Although reducing over- and underprescribing are both beneficial to society, their effects on aggregate utilization rates are exactly opposite. This exemplifies the limitations of using aggregate data on prescription rates exclusively or indiscriminately.

2. Negative aspects

a. Implementation and operating costs

Every diversion control system involves the consumption of capital and labor resources. Systems differ in terms of the mix of inputs or the technologies involved, and States (or other governments and institutions) differ in terms of the level of resources allocated to diversion control. The benefits attributed to diversion control in any given geographic area must be weighed against the value of the resources consumed for that purpose.

b. Consequences of underutilization and substitution

In this study, it was learned that some physicians and some patient advocacy groups believe that the quality of care rendered to patients would suffer as a result of certain diversion control mechanisms. This could result from physicians being influenced by cost considerations, inconvenience, or the prospect of scrutiny. Likewise, patients may avoid medically appropriate drug therapies due to certain apprehensions: that their medical conditions would become known; that they would be labeled drug abusers; and that their names would be "in the computer." Any such outcomes associated with inferior treatment, both foregone benefits due to underutilization and higher risks due to questionable substitutions, ideally should be counted as costs to society, which detract from the value of the diversion control system.

c. Improper use of information

A diversion control system may generate, organize, centralize, or otherwise facilitate access to data that threaten the confidentiality of physician-patient relationships. Interviews carried out in this study strongly suggested that confidential and sensitive information was closely protected. However, just as a facet of drug diversion involves dishonest or undisciplined practitioners, so, too, it must be recognized that a small minority of officials with access to data may misuse information obtained by the system, either advertently or inadvertently, or may neglect to adequately protect confidentiality.

C. Areas For Further Study

Several studies, or several distinct components of a larger study, would be necessary in order to provide comprehensive and reliable assessments regarding the major issues delineated in the previous section. In this section, some

analytical approaches and data sources are discussed that could be used to better understand the costs and outcomes associated with diversion control systems. These are not intended to be detailed research proposals, but rather to lay out an agenda for answering the interrelated questions surrounding the use of diversion control systems. Four domains of research are presented: the nature and magnitude of diversion; costs and processes associated with diversion control; reductions in diversion and related outcomes; and effects on medical practice and patient care.

1. ***Nature and magnitude of diversion***

There appear to be disparate views on the nature and magnitude of prescription drug abuse and diversion in this country. Idiosyncratic experiences can lead to distorted perceptions of the problem. Understandably, law enforcement officials who are inundated with diversion cases could view the problem as being immense. Likewise, physicians who practice for years without observing drug abuse or diversion could conclude that diversion is, at most, a small problem.

Notwithstanding the perceptions based on experience, there do not appear to be very good or recent data on the magnitude of diversion. An important starting point for this research needs to be specific definitions of diversion, including operational or observable events that can be used to signify diversion. Toward that end, many assumptions used in the interpretation of data should be tested. For example, observing certain drug products on the street does not necessarily pinpoint their source as diversion (versus illegal importation or manufacture).

In this study, it has been noted that States may differ in terms of the precise definition of diversion, i.e., where the line is drawn between criminal diversion per se and defensible behaviors. However, within the category of criminal diversion, there is a general consensus on its manifestations. These include forgeries, doctor shopping, impaired professionals, and deliberate criminal activities among practitioners. Presumably, definitions of diversion and estimates of its magnitude could be based on one or more of these categories of diversion.

Having specified the nature and operational definitions of diversion, research can proceed to estimate its magnitude. There are several reasons for doing this. First, data regarding the true magnitude of drug diversion will permit more informed decisions about the potential value of diversion control and,

therefore, the extent of public investment that is justified. Second, if the levels of diversion could be broken down according to method (e.g., forgeries, etc.), then the type of diversion control system(s) most appropriate might be clearer. Third, baseline estimates of magnitude can be compared to subsequent estimates to ascertain the effectiveness of diversion control efforts. The comparisons could be used to evaluate the overall effectiveness in controlling diversion versus any tendencies for methods to change. For example, tamper proof prescription forms may greatly reduce forgeries, but overall diversion would not show a commensurate decline if diverters increased their doctor shopping. Similarly, monitoring the magnitude of diversion in comparison sites (e.g., other States) would help to isolate the unique contributions of diversion control systems.

A number of approaches could be taken to give views of the diversion problem from multiple perspectives. The NIDA National Household Survey sample is not large enough to provide reliable estimates of nonmedical use of prescription drugs for any given State, but a similar population survey could be administered to sufficiently large samples of residents in selected areas. This approach offers the unique advantage of being able to explore possible substitution of other substances (e.g., street drugs and alcohol) for prescription drugs. Surveys of physicians and pharmacists could reveal the levels of diversion in their own practices that have caught their attention.

Audits of pharmacy records may be a useful approach as well, where either individual pharmacies or pharmacies in selected geographic areas constitute the sampling unit. Auditing all relevant records in all pharmacies within chosen geographic areas may provide a more comprehensive view, since it will uncover diversion perpetrated in a single pharmacy (e.g., forgeries and illegal safes) as well as diversion perpetrated in multiple pharmacies (e.g., pharmacy and doctor shopping), assuming that scams are likely to concentrate in particular communities for a period of time. Other data sources may prove useful as well. Medicaid fraud units and pharmaceutical units within law enforcement agencies, for example, could provide information regarding which pharmacies, prescribers, and patients have been implicated in diversion activity.

Using data sources such as these would permit pharmacies, prescribers, and patients in the sample to be categorized according to the relative volume of diversion uncovered. In addition, any or all of these units could be aggregated into geographic or market areas, which could also be categorized according to relative amounts of diversion. A likely level of aggregation for

evaluation purposes would be the State, since diversion control systems often are implemented at that level. Any approach of direct measurement may underestimate the actual levels of diversion, because some amount of diversion is likely to go undetected. Information from other States, i.e., those without the particular system under study, could be used to make comparisons in terms of relative diversion levels.

The validity of proxy variables for identifying potential diversion could be assessed as well. Proxy variables such as prescription volume or exceptions reports may not require such extensive data collection efforts, but they provide only indirect measures of diversion. Several systems (such as ARCOS, Medicaid, and MCPPs) can be used to create exceptions reports that presumably identify probable diversion activities. The logic is that entities (pharmacies, etc.) that handle relatively large volumes (e.g., many times the mean for all pharmacies) are more likely to be involved with diversion and are worthy of closer scrutiny. The extent to which relative prescription volume is associated with diversion levels might be tested empirically. The observed relative diversion levels of pharmacies, prescribers, market areas, and possibly individual patients could be compared to their rankings in terms of the exceptions reports. The closer their correspondence, the more valid would seem to be the process of generating exceptions reports based on prescription volume. In addition, the research could be used to select alternative parameters for exceptions reporting that would improve the balance between falsely identifying potential diverters and failing to identify actual diverters.

2. ***Costs and processes associated with diversion control***

A second area of research would focus on the diversion control systems themselves. How are their goals defined? What do they do to control diversion? How much do those efforts cost? In what way are potential negative outcomes minimized?

Evaluation issues such as these would require detailed program-specific information. A case study research approach could provide comprehensive descriptive information about a system. Researchers would conduct interviews and onsite visits for the purpose of documenting relevant aspects of a system and its environment. Moreover, for some analyses (e.g., cost), researchers would need to make other special data collection efforts.

a. Cost assessments

An issue of clear concern is the cost of operating the system. Case studies could provide detailed information related to the differential cost associated with operating the system for diversion control. Differential cost is not always the same as total cost, since some retail drug diversion control methods "piggyback" on other programs. For example, the ARCOS system generates data and provides certain analyses through DADS that are useful for diversion control. However, it is not the total cost of ARCOS that appropriately reflects the differential cost of using these data for retail diversion control. Conceptually, the differential cost is equal to the amount of direct savings that would be realized if a retail diversion control system were discontinued (or reduced or altered, if those were the relevant questions under study).

As part of the cost accounting analysis, it might be pertinent to estimate the relationship between program costs and the volume of activity observed. Classifying costs according to the extent they vary with the volume of effort (e.g., fixed versus variable) would permit estimation of how costs could change with possible modifications in the scope, scale, or method of a system.

Finally, the degree of financial cost or burden of effort on practitioners and patients may have implications for the behavioral responses and perceptions associated with a diversion control system. For example, charging prescribers for multiple-copy prescription forms may be a convenient source of funding but might generate bad feelings and, in and of itself, might reduce the volume of prescriptions for covered drugs. Other types of costs or burdens are associated with various systems, including dispenser compliance with EPOS requirements and pharmacy audits.

b. Process evaluations

Process evaluations describe the activities that are associated with the system. To address issues of confidentiality and potential misuse of information, it would be necessary to describe data collection, storage, access, and retrieval. For that reason, and to better understand the contribution of the program to the prevention, identification, investigation, and prosecution of drug diversion cases, the flow of information and the general inner workings of the system would have to be expounded. Issues to be included in a process evaluation are:

- Agencies and staff that are involved
- Degree of involvement among key individuals and agencies
- Coordination among participants
- Accessibility of data to those needing it
- Timeliness of data accessibility and reporting
- Standards/guidelines used to identify potential diversion

As some of these issues indicate, it is necessary to investigate and document what other diversion control methods are employed in each State under observation. The varied and multipronged approaches taken by States for diversion control necessitate some consideration of the State as the unit of observation rather than a single system. For example, many States are engaged in educational as well as investigatory efforts to reduce diversion. In an evaluation of the outcomes of any particular system, it would be important to acknowledge the rightful contributions of these other activities to outcomes in the State.

3. ***Reductions in diversion and related outcomes***

Answering many types of diversion control system evaluation questions entails isolating the unique circumstances attributable to the diversion system itself. A potentially powerful approach to this is making quantitative measurements of outcomes, and making inferences about what would have occurred if the diversion control system had not been operating. The implementation of a diversion control system constitutes a natural experimental opportunity for researchers. The choice to implement could be related to a number of potential causes and effects. The confidence with which inferences about outcomes can be made depends on the extent to which other factors affecting levels of diversion have been taken into account.

In other words, comparisons must be made between data observed under a diversion control system and data observed under conditions not involving the particular system under study. For example, surveys of pharmacists could be conducted prior to and after implementation of a system in a certain State, if circumstances permitted, to determine whether there was a reduction in forgery attempts. Alternatively, survey samples could be drawn from States with and without the diversion control system under study to compare levels of forgery attempts. It is important to account for factors that could affect differences over time or across areas, including underlying differences in abuse patterns, other ongoing diversion control efforts, chance, etc. The

need for comparison groups and statistical controls results from the interrelationships among naturally occurring events.

In addition, the measures chosen on which to make comparisons must accurately reflect the concept under study. The value of proxy variables such as relatively high retail sales volume of a drug may be shown to be high, through analyses like those described earlier. Otherwise, only relatively direct measures of diversion should be employed. The alternative of assuming that proxy variables primarily reflect diversion levels would not inform policymakers regarding the differential effects of interventions on actual diversion versus acceptable medical practices.

There are other potential benefits to diversion control as well. Some of these measures would require special studies in order to establish their link to nonmedical use of prescription drugs. For example, research could investigate the relationships between nonmedical use of prescription drugs and job performance or vulnerability to accidents or injuries. Such studies are often undertaken in laboratory settings using standardized tasks and extensive monitoring. A second link necessary to infer reductions in these measures is to establish that nonmedical use of prescription drugs occurs in the workplace, before or while driving, etc. Surveys and interviews could probe the circumstances in which drugs are abused as well as the frequency and level of abuse. Similarly, special studies could investigate the effects of prescription drug abuse on the use of other health services, police and criminal justice activities, and other social services.

One of the most obvious and straightforward benefits of reduced diversion is lower costs to third-party payers that reimburse prescribers and dispensers for their products and services. Indeed, some interest in diversion control systems emanates from concern about the added costs to insurers for unnecessary prescription drug consumption related to diversion.

Studies of the effectiveness of systems to control diversion could make use of either time-series or cross-sectional data, or both. Statistical comparisons can be made of diversion levels in pre- and postimplementation periods or between States. A time-series or repeated measures study design would investigate diversion levels before and after the implementation of a control system, hopefully observing outcome measures continuously or at several points in time. Repeated observations may be important in order to safely conclude that observed differences were due to the diversion control system and not due to underlying trends or chance factors.

Many systems currently in operation were implemented many years ago, and creating data files referring to that period may not be possible. For other reasons as well, cross-sectional data referring to geographic locations served by the diversion control system(s) and comparison locations without the system(s) could be used. In this type of design, the sample of observations could refer to different States, permitting the establishment of norms and the inclusion of covariates thought to be related to levels of diversion. Any State(s) with the system under study could be compared to similar States, and differences (net of those related to specified covariates) could be subjected to statistical tests of significance.

Time-series and cross-sectional analyses could be used in other ways to test for reductions in diversion. For example, geographic areas smaller than states (e.g., counties or ZIP codes) could be used to investigate relative increases in diversion levels in areas that border States implementing a diversion control system. As another example, the relative usage rates for individual drugs could be compared pre- and postimplementation, and across areas. Such analyses could test hypotheses that drugs more popular for diversion are observed in lower quantities with a diversion control system, whereas less popular drugs for diversion are observed in the same or higher quantities.

In addition, specific hypotheses could be tested related to patterns of use. For example, the relative skewness in the distributions of drug quantities by patients and by prescribers might provide insight about diversion levels. If a large part of aggregate reductions are associated with a tiny fraction of prescribers or patients, this may be more indicative of diversion control than if quantities were lower for patients and providers across the board. Other comparisons could include the usage rates within a State in settings subject to scrutiny versus other settings (e.g., outpatient versus inpatient prescription rates in MCPP States); or different circumstances (e.g., morphine generally versus morphine for terminally ill patients).

The implementation or demise of a program is essentially a natural experiment, i.e., not arbitrarily manipulated for experimental purposes, as previously mentioned. The recent implementation of EPOS in Oklahoma could provide a valuable opportunity for evaluating the effects of that approach. Other States that may be looking toward adopting EPOS, such as Massachusetts, may also provide timely opportunities for conducting pre- and post analyses.

Adding or deleting drugs that are the focus of diversion control efforts also creates opportunities for studying effects on diversion. A good example is the addition of a class of drugs, namely, benzodiazepines, in the New York MCPP. Other States have added individual drugs or classes of drugs to their MCPPs as well. These provide chances to study the patterns for a select few drugs at a time, whereas program implementation affects a comparatively large number of drugs at one time.

4. ***Effects on medical practice and patient care***

The effects of diversion control systems can be investigated within another domain of research, namely, the more general effects on medical practice and patient care. The questions raised in this aspect of the research revolve around the issue of whether physicians, when faced with similar medical situations, change the levels or mix of therapies ordered for patients when a particular diversion control system is operating. Proponents of diversion control believe that some reductions in prescription rates may result from some prescribers "reexamining" their choice of therapies, but that appropriate prescriptions are not affected. The opposing view is that diversion control systems intentionally or unintentionally cause a "chilling effect" in the medical community, interfering with acceptable medical practice patterns.

Specific hypotheses reflected in this controversy cannot be tested, nor can specific conclusions be drawn regarding the nature of changes in prescribing patterns, without carefully defining valid measures to be used. Consistent with some criticisms of data analysis for diversion control, development of valid measures in this domain requires the clinical context within which prescriptions are written. Thus, the preferred data sources will include relatively detailed records of medical service and prescription drug utilization, such as health insurance claims files. In certain circumstances, even more detail may be useful, such as information taken from medical records, interviews of patients or practitioners, or surveys of prescribers.

The latter may be indispensable for demonstrating that observed changes were intended by prescribers, and do not simply reflect changes in diversion patterns. Even while data collection and regulatory monitoring may affect prescribing patterns, they may also affect diversion patterns. In other words, there may be reductions in both diversion and legitimate use of drugs that are subjected to scrutiny. Similarly, drugs that are not being monitored so carefully may become preferred by both prescribers and diverters. Interpreting the outcomes properly may require that prescribers be asked directly

whether prescriptions for their patients are different because of the regulation.

As with studies of diversion per se, it is necessary to begin with a baseline from which comparisons can be made. The baseline could reflect data prior to implementation of the diversion control system or comparable data from other States. From the baseline or comparison data, several benchmarks can be established. For drug usage, these include the proportion of patients who receive the prescribed medications under study and the overall quantities prescribed. Utilization rates for other types of services, such as physician office visits and days of institutional care, would also be helpful in order to test for possible substitutions for prescription drug therapies.

These measures should be calculated on homogeneous clinical subgroups so that hypotheses about differential effects for differing clinical circumstances can be evaluated. The homogeneity of subgroups will depend on the richness of the data base available. Diagnoses, types, and amounts of health services received (including inpatient services), and the specialties of physicians seen would be useful criteria for defining subgroups and are likely to be available from claims data. To be thorough, researchers may wish to confirm that the patterns of care associated with the subgroup definitions are comparable between the analysis and comparison data. For example, patients could change their preferences among different types of specialists at the same time that prescribing patterns were changing.

For illustration, consider the following hypotheses. Patients identified in Medicaid claims records who have been treated for chronic pain due to a slipped disc will have a lower probability of being prescribed the Schedule II drug hydromorphone (Dilaudid) or will have lower amounts of hydromorphone prescribed when an MCPP is operating in those patients' State of residence. Conversely, higher proportions of those patients will be prescribed alternative or substitute drugs such as the Schedule IV drug pentazocine (Talwin Nx), which is assumed here not to be covered under the MCPP. Also, under the MCPP, those patients will have higher rates of physician visits and will tend to see more physicians over the observation period.

One stage in an analysis would be to select data for the subgroup under study and to determine the patterns relevant to the hypotheses that patients were being underserved or inappropriately treated as a result of the regulations. Statistical comparisons of the data before and after implementation of the system, or between areas with the system and areas without the system,

would indicate whether there was empirical support for the hypotheses. However, those findings would also be consistent with competing hypotheses, such as diversion being channeled to lower schedule drugs or physicians making improvements in care by choosing drugs with lower risks.

Other data sources may be required to firmly demonstrate the relative merits of the competing hypotheses. Ultimately, such decisions may have to be made on a case-by-case basis, suggesting that relatively small samples of cases should be investigated thoroughly. An alternative approach that could assist in interpreting the data would be to survey physicians regarding their attitudes and behaviors in response to the diversion control system. That information could be used to document the nature of the incentives brought about by the system, as perceived by prescribers, and the likely effects of those incentives in terms of modified prescribing patterns.

D. Summary and Priorities of Research Agenda

There are several reasons for conducting further research in the area of prescription drug diversion control systems. Thus far, there has been little research to quantify the potential positive and negative outcomes of diversion control or in many cases to differentiate among them. Successful diversion control would be expected to reduce unnecessary costs associated with non-medical use of controlled substances. The effects of diversion control on medical practice patterns generally are rather unclear.

Starting and operating a drug diversion control system consumes government resources. Choosing an optimal size and type of system in any given State is obviously an important matter.

To a great extent, settling debates about the pros and cons of diversion control systems would require something beyond aggregate, proxy variables such as volume of drug sold. Researchers need to separately specify dependent variables that accurately convey the concepts of diversion (such as number of forged prescriptions) and acceptable medical practice (such as prescription rates for patients with specified health conditions). Baseline and followup data, or cross-sectional data involving several States, can be used to draw inferences regarding differences in diversion or medical practice patterns associated with the existence of a diversion control system. Assuming that data limitations will exist for evaluators, in many cases empirical findings can be used to support or refute hypotheses regarding reductions in diversion

or effects on medical practice patterns. From those results, indirect evidence can be brought to bear on the relative merits of competing hypotheses.

This paper has provided a comprehensive discussion of components of a research agenda for prescription drug diversion control. This forms a basis for the following recommendations for three research priorities.

First, estimates of the nature and magnitude of diversion need to be improved. This is a difficult undertaking because there are data only on what gets detected and reported; however, several different sources of information could contribute to better estimates, albeit underestimates, of diversion activities. This would involve piecing together existing secondary data from many different sources, including Federal, State, and local levels. Types of data that might be useful include State crime lab reports, Medicaid data, non-suicide DAWN emergency room mentions, and DEA data on various activities related to diversion. The estimates generated in this manner may be quite rough; however, it would be a first step toward quantifying the magnitude of diversion activities. The process of piecing together data would also allow an assessment of the gaps in our knowledge regarding certain aspects of diversion and additional data collection activities might be recommended in order to improve estimates for the future.

Second, a comprehensive assessment of the EPOS system should be undertaken in Oklahoma and the soon-to-be-operational Massachusetts program. Reasons for selecting EPOS as a research priority are twofold: (1) the timing is such that a natural experimental opportunity exists and pre- and postimplementation analyses are possible, and (2) the electronic data transfer aspect of EPOS is, a new innovation for diversion control systems that appears to have appeal from an efficiency standpoint and has potential for being replicated elsewhere.

It is important that an assessment of EPOS be comprehensive and address all four research domains discussed above. These research domains include: (1) the nature and magnitude of diversion in each State, (2) the costs and processes associated with diversion control efforts in the State, (3) reduction in diversion and related outcomes, and (4) effects on medical practice and patient care. An assessment of the nature and magnitude of diversion would allow the development of better estimates, perhaps through primary data collection, which might eventually serve as a model for improved data collection on magnitude at a national level. The costs and processes are important to determine how these programs affect the balance between the

competing goals of maximizing diversion prevention and identification and minimizing changes in legitimate and appropriate prescribing. An additional advantage of taking a comprehensive approach to an evaluation of EPOS is that the State becomes the unit of analysis, thus State laws and regulations can be put into perspective.

Third, it would be useful to have an evaluation of two MCPPs and two similar comparison States. It probably is not possible at this point in time to design a pre- and postevaluation strategy for the MCPP States, unless another State institutes such a program in the near future. However, it is important that the four domains described above be evaluated in a similar fashion to the EPOS. It would then be possible to attempt to make comparisons across six indepth and comprehensive case studies of prescription drug control systems: two EPOS programs, two MCPPs, and two control States.

Because of the lack of knowledge about the extent of diversion, and the dual impact of prescription drug diversion control programs on both diversion activities and medical practice, it is essential that a research agenda be comprehensive across the four domains discussed. The focus should be on carefully selecting the States for evaluation and then developing common measures so that all four research domains may be addressed expediently and simultaneously.

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The Impact of Prescription Drug Control Systems on Medical Practice and Patient Care-A Summary of Research Recommendations

Dorynne Czechowicz

INTRODUCTION

Early in 1990, the Office of National Drug Control Policy (ONDCP) asked the Department of Health and Human Services (DHHS) for its position on multiple copy prescription programs to assist in developing the Administration's position on this issue. Following a series of meetings between ONDCP, DHHS, the Department of Justice, and the Drug Enforcement Administration, as well as with congressional representatives, the Office of National Drug Control Policy asked the National Institute on Drug Abuse staff to evaluate the impact of prescription drug diversion control systems on medical practice and patient care. In response to this request, MDA funded Brandeis University to undertake a review of available data on prescription drug regulatory programs and to address needed research. The conclusions and research recommendations from the Brandeis University study are summarized in two papers included in this monograph (Horgan et al. 1991*a*, 1991*b*). Then in May 1991, MDA sponsored an open technical review meeting to obtain the views of many experts, researchers, medical practitioners and other health professionals, professional associations, rep-resentatives from several State and Federal agencies, and advocacy groups on the current state of our knowledge regarding the therapeutic usefulness of psychoactive prescription drugs; the nature, extent and consequences of prescription drug abuse; the relative magnitude of different sources of diversion; the advantages and limitations of existing diversion control systems; the im-pact of diversion control systems on medical practice and patient care and areas needing additional research.

On October 3 and 4, 1991, MDA convened a research advisory panel to further define and expand on additional studies needed to determine the impact of prescription drug regulatory mechanisms on medical practice and patient care.

From the NIDA technical review, the NIDA-funded Brandeis study, and the Research Advisory Panel meeting, some preliminary evidence emerged that treatment of patients with chronic and recurrent illnesses may be adversely affected by health professionals' fears of drug abuse and addiction when prescribing abusable drugs for chronic use and by concerns over drug regulatory mechanisms. This sometimes results in undermedication of these illnesses. While there is a need to prevent prescription drug abuse and diversion, it must be balanced against the need to have psychoactive medications available for legitimate medical and psychotherapeutic indications.

Although there is an abundance of anecdotal evidence suggesting some prescription drug diversion control programs have an adverse impact on patient care, there are no systematic patient-based clinical research studies. To effectively evaluate changes in prescribing patterns and the impact of comprehensive prescription drug regulatory mechanisms on patient care, research is needed incorporating patient medical care data and prescription drug utilization. Patient and practitioner surveys are also necessary to determine how attitudes, knowledge, and prescribing behavior vary in response to diversion control systems.

AREAS FOR FUTURE RESEARCH

The following research agenda areas emerged from the discussion of research priorities in the recent NIDA-sponsored technical review meetings:

- Studies to determine the impact of prescription drug regulatory mechanisms on medical practice and patient care.

- Studies of the nature and magnitude of prescription drug diversion from both licit and illicit sources, the cost and processes involved in diversion control, reductions in diversion, and related outcomes resulting from regulatory changes.

- Cost/benefit studies to determine how prescription drug regulatory programs affect the balance between the competing goals of preventing diversion of psychoactive prescription drugs while minimizing their impact on legitimate medical care and appropriate prescribing.

- Studies of the development and testing of an epidemiological surveillance system model for pharmaceutical drug diversion that utilize Federal and State data bases having potential for replication in other States.

- Research on the criteria or standards to be used in case identification, and the evaluation of cases requiring further review in any prescription drug diversion control system (encompasses practice parameters and peer review).

- Population-based clinical research studies to determine the impact of diversion control mechanisms on medical practice and patient care particularly prospective clinical outcome studies that incorporate prescriber and patient level data from records of medical services, prescription drug utilization data from health insurance claim tiles, and patient and practitioner interviews. Population-based clinical studies are needed that take into account patients' histories, diagnoses, treatment, and the clinical appropriateness or inappropriateness of changes in prescribing practice.

- Studies of physicians, pharmacists, nurses, and patients to determine the impact of comprehensive prescription drug regulatory mechanisms on health care practices, prescribing behaviors, medication dispensing, and patient care. Studies of factors influencing prescribing decisions are needed to develop effective education programs.

- Clinical studies of patients taking legitimately prescribed psychoactive medications for chronic and recurrent medical and psychiatric illnesses to determine risk factors associated with drug abuse and addiction (in contrast to dependence).

- Studies to develop better screening and assessment instruments to assess the risk of addiction in primary care populations being treated for chronic medical and psychiatric illness.

- Studies to determine whether some patient populations may be under- or overmedicated or have difficulty obtaining adequate treatment with controlled substances as a result of

prescription drug control programs. Models and instruments have been developed to measure patients' satisfaction, their quality of life, and their functional status.

- Additional emphasis must be placed on including minorities and women of all ages in studies of diseases, disorders, and conditions that affect them specifically.

- Clinical studies of drug-abusing populations in and out of treatment and in various treatment settings (e.g., primary care, emergency rooms) to determine the nature, extent, patterns of use, the sources of abused prescription drugs (including "doctor shopping"), and the consequences of prescription drug use and misuse, abuse and diversion.

- Research on innovative skills-based, educational approaches for physician education in appropriate prescribing of drugs with abuse liability and to heighten professional awareness of patients likely to abuse psychoactive drugs.

- Research on interventions to change prescribing behaviors that range from individual approaches to computer-generated strategies. Further study of the effects of these interventions on prescribing behaviors and patient outcomes is needed.

Since some States are currently planning to implement an electronic data transfer system for monitoring Schedule II prescription drugs, this is an opportunity to conduct naturalistic experiments allowing longitudinal prospective studies, with pre- and postimplementation evaluation of the drug regulatory control program. The electronic data transfer aspect of EPOS is also a new innovation for diversion control systems. Preliminary analysis suggests this approach may be less labor intensive and less expensive than less automated approaches. An assessment of prescription drug control systems should be comprehensive and include the following research areas:

- the nature and magnitude of diversion
- the cost and processes involved in diversion control
- reduction in diversion and related outcomes
- effects on medical practice and patient care

Studies of the nature and magnitude of diversion should develop better estimates through primary data collection that might serve as a model for improved data collection at the national level. Cost/benefit studies are necessary to determine how these programs affect the balance between the competing goals of diversion prevention while minimizing impact on legitimate medical care and appropriate prescribing of psychoactive medications.

Additional research questions and recommendations will undoubtedly emerge as public policies designed to control drug abuse evolve in an era of heightened emphasis on health care cost containment, managed care, and new regulatory approaches to monitoring prescribing practices.

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