Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	February 27, ~~2008~~ Correct Date: February 27, 2009
To:	Sharon Hertz, MD, Deputy Director Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP) Ayanna Augustus, PhD, Regulatory Project Manager, DAARP
Through:	Rita Ouellet-Hellstrom, PhD, MPH, Team Leader, Acting Director Tarek Hammad, MD, PhD, MSc, MS, Team Leader, Associate Director of Epidemiology Division of Epidemiology
From:	Fatmatta Kuyateh, MD, MS Andrew Mosholder, MD, MPH Catherine Dormitzer, PhD, MPH Division of Epidemiology
Subject:	Review of Propoxyphene/Combinations Products Safety Issues and DAWN Data Analysis
Drug Name(s):	Propoxyphene, Darvocet, Darvocet-N
Application Type/Number:	NDA NO. 10-997, 16-862, 17-122
Applicant/sponsor:	Xanodyne
OSE RCM #:	2008-1517

This document contains proprietary drug use data obtained by FDA under contract and confidential information obtained by agreement with the UK MHRA. The drug use data/information cannot be released to the public/non-FDA personnel without contractor approval obtained through the FDA/CDER Office of Surveillance and Epidemiology.

EXECUTIVE SUMMARY

This document describes a review conducted within the Office of Surveillance and Epidemiology Division of Epidemiology. The review consists of three parts:

1. A literature review of propoxyphene-associated deaths in the United States, and the risk of hip fracture associated with propoxyphene use.
2. A review of propoxyphene safety data from the United Kingdom, where the drug has undergone phased withdrawal.
3. Analysis of Drug Abuse Warning Network (DAWN) and drug use data on the numbers of emergency department visits for propoxyphene/combination products and comparator drugs codeine/combination products and tramadol.

This review was conducted as an addendum to a literature review on the association between propoxyphene/combination products and cardiotoxicity[i]. The cardiotoxicity review was in response to a request from the Division of Analgesics, Anasthetics, and Rheumatology Products (DAARP). A Citizen's Petition (CP) in 2006 requested FDA begin a phased withdrawal of all propoxyphene-containing products based on its low margin of safety[ii] particularly in the elderly population and its potential risk of cardiovascular effects with overdosage. An Advisory Committee Meeting was held in January 2009 to address the efficacy and safety issues presented by the CP. The division became aware of new safety data after this AC meeting, and it was decided that an expanded review was needed to further address the safety of propoxyphene/combination products.

This expanded review resulted in following conclusions:

- In the United States, propoxyphene-related deaths are mostly a result of suicides. Accidental deaths occur due to drug abuse, over-medication, and interaction with alcohol.
- The use of propoxyphene/combination products is associated with increased risk of hip fracture in patients 65 years and older. The risk is twice as high than that observed in similar patients who do not use analgesics. The risk of hip fracture with use of propoxyphene/combination products was found to be similar to that observed with use of other opioids.
- A study of overdose mortality in Scotland found that propoxyphene-acetaminophen (APAP) carries a significantly higher risk of death from overdose compared to the other two opioids studied, codeine-APAP, and dihydrocodeine-APAP.
- There is no evidence that a shift towards other undesirable products followed the decline in use of propoxyphene-APAP in the United Kingdom.
- The United Kingdom study findings provide evidence to support the withdrawal of propoxyphene/combination products from the market.

---

[i] The cardiotoxicity review findings did not show a clinically significant association between propoxyphene and cardiotoxicity.

[ii] Other safety issues raised in citizen's petition include inappropriate use by the elderly, drug ineffective, implicated in suicide, dependence, and abuse.

- In the Drug Abuse Warning Network (DAWN) database, when comparing propoxyphene/combination products with codeine/combination products and tramadol, differences in the risk of emergency department (ED) visit were not remarkable.

The DEPI reviewers agree that a restricted distribution system might have permitted use of the compound by a select group of patients with a tolerable risk-benefit balance. However, the Division of Risk Management (DRISK) has indicated that propoxyphene is not appropriate for a restricted distribution plan. [iii] Accordingly, the reviewers favor accepting the recommendation from the Advisory Committee, which voted 14-12 for withdrawing the drug. Of course, this would have to be done with the appropriate guidance to physicians to discourage a shift towards less desirable alternatives.

If the drug is to remain on the market, in addition to the recommendation in DEPI's previous review on cardiotoxicity in the elderly, the reviewers agree that propoxyphene labels should be strengthened to highlight the increased risk of hip fracture in the elderly who are prescribed propoxyphene/combination products.

[iii] Memo from Dr. Mary Willy, DRISK, 2-23-09

TABLE OF CONTENTS

1 INTRODUCTION

The objective of this review is to examine the evidence from the literature on deaths and adverse reactions associated with propoxyphene-containing products beyond cardiotoxicity, and to examine propoxyphene-related emergency department visits in the context of drug utilization. The review consists of three parts:

1. A literature review of propoxyphene-associated deaths in the United States, and the risk of hip fracture associated with propoxyphene use.
2. A review of propoxyphene safety data from the United Kingdom, where it has recently undergone a phased withdrawal.
3. Analysis of Drug Abuse Warning Network (DAWN) and drug use data on the numbers of emergency department visits for propoxyphene-APAP and comparator drugs codeine-APAP and tramadol.

Propoxyphene is a weak opioid analgesic, which has been used for management of pain since the 1950's. Propoxyphene Hydrochloride and Propoxyphene Napsylate were approved in 1957 and 1971 respectively for the relief of mild to moderate pain and have since also been approved as combination products with acetaminophen and aspirin with or without caffeine. Multiple generic products are currently available in the U.S. The recommended dose for therapeutic use is 65mg Propoxyphene Hydrochloride or its equivalent of 100mg Propoxyphene Napsylate every 4 hours not to exceed 390mg/day or 600mg/day respectively. Propoxyphene is marketed as a single agent product and in combination with acetaminophen (APAP), caffeine, or caffeine and aspirin. From this point forward the term *propoxyphene* refers to all propoxyphene/combination products unless otherwise specified.

Propoxyphene labeling warnings call attention to the risk of suicide with use of the drug, and highlight the contribution of drug addiction, suicide risk factors, alcohol, and drug misuse to such risk. The boxed warning highlights the potential for accidental death if excessive amounts of the drug are ingested. In addition, the drug label also warns of drug dependence and impairment of mental and physical abilities. The precautions listed include central nervous system depressant effects drug interactions and possible decreased rate of metabolism in the elderly. Mention is made of several adverse reactions, most commonly dizziness, sedation, nausea, and vomiting. Other adverse reactions include constipation, abdominal pain, skin rashes, lightheadedness, headache, weakness, euphoria, dysphoria, hallucinations, and minor visual disturbances, renal papillary necrosis, liver dysfunction, and subacute painful myopathy.

A Citizen's Petition (CP) was submitted to FDA on February 28, 2006 requesting the phased market withdrawal of propoxyphene and all propoxyphene-containing products based on claims of increased risk of cardiotoxicity, particularly in the elderly and this matter was taken to a joint Advisory Committee held in January 2009. The Division of Epidemiology (DEPI) within the Office of Surveillance and Epidemiology (OSE) had conducted a literature review in November 2008 which focused on the cardiotoxic effects of propoxyphene. In follow-up to the Advisory Committee discussion, DEPI, based on additional information received, decided to conduct an expanded review to further address safety issues of propoxyphene beyond those presented in the CP.

In this review, methods and results of the literature on deaths and hip fractures are presented first, followed by the analysis of the United Kingdom data and emergency room visits using the DAWN data.

2 LITERATURE REVIEW OF DEATHS AND HIP FRACTURES RELATED TO PROPOXYPHENE

2.1 METHODS AND MATERIALS

Studies published between 1960 and 2009 about propoxyphene were identified through a search of PubMed. The search was conducted using propoxyphene terms and adverse event terms describing death, suicide, or hip fracture. Additional publications were identified from searching the cited bibliography of articles identified by PubMed. The term "elderly" was added to the previous search terms in order to identify a subset of publications focusing on safety issues in the elderly. Publications were screened for the following criteria:

- Human observational studies
- Exposure to propoxyphene product
- Outcome of death or adverse event
- Studies performed in the United States (for mortality studies)
- English version of publication available

2.2 RESULTS

2.2.1 Suicide and Accidental Deaths Related to Propoxyphene Use

The literature search strategy identified a total of 165 articles for initial review. Four studies were done in the United States and met all criteria. [1-4] The studies were all surveys of Medical Examiner and Coroner sites looking at propoxyphene-related deaths. The largest study by Finkle surveyed medical examiner and coroner sites in 26 counties across the United States for a period of 11 years from 1972 to 1983. [1] Finkle identified 3679 propoxyphene-related deaths. Forty-five percent of the cases were suicidal; 24.9% accidental; the rest were due to undetermined or other causes. Deaths for which propoxyphene was the sole agent accounted for 10% of all suicides. Mixed-drug cases (including alcohol-related cases) accounted for more than sixty-six percent.

The other three studies were smaller, regional studies. Poklis et al. surveyed medical examiner offices across St. Louis County and the city of St. Louis from 1977 to 1979 for deaths directly and indirectly caused by drugs. The researchers identified 20 propoxyphene-related cases.[22] Three of the 20 cases (15%) were single-agent cases. Amongst all drug-related deaths in that period, propoxyphene was the sixth most common drug listed. Most deaths[iv] were suicide deaths.

Garriott et al. surveyed Dallas County Medical Examiner system for all drug-related deaths over a period of nine years from 1971to 1980.[3] The researchers identified 152 propoxyphene-related deaths, of which 55 (36%) were primarily associated with propoxyphene. Eighty to 90% of the deaths were a result of suicide. Based on the knowledge that propoxyphene's metabolite, norpropoxyphene, builds up in blood and tissue with long term use, the authors determined that the high levels of propoxyphene and norpropoxyphene found in some of their accidental cases suggested that the death occurred following repeated ingestion of relatively high doses of propoxyphene for pain control[v]. These cases were also found to have a clear history of painful medical conditions and large quantity prescriptions for analgesics.

[iv] The authors did not specify the number of deaths that were suicide or accidental.

[v] The authors did not quantify the numer of accidental deaths.

The fourth medical examiner system survey by Wetli et al. examined all fatal propoxyphene-related overdoses in Miami, Dade County[4]. They identified a total of 85 cases of propoxyphene-related deaths; eighty-one were drug overdose cases. A majority of the cases were suicides (76.5%). The rest were accidental. In this study, the accidental deaths were determined to occur due to recreational drug abuse, dosage abuse, polydrug abuse, or propoxyphene-alcohol interaction.

In addition to the above, the Florida Department of Law Enforcement has an initiative to enumerate drug-related deaths occurring each year in the state of Florida, and this data system includes statistics on propoxyphene-related deaths. For each death considered possibly drug-related, Florida medical examiners are requested to designate drugs found at autopsy as either causal or present. These statewide statistics are then compiled annually. According to the 2007 Medical Examiners Commission Drug Report,[5] there were 8,260 drug-related deaths in Florida in 2007, most involving more than one drug. Three hundred and forty one (4%) were propoxyphene-related deaths. Propoxyphene was considered causal in 85 of the deaths. Fifty-three percent of propoxyphene-related deaths were accidental, and 23% were suicide cases. Propoxyphene was found in combination with other drugs in 267 (78.3%) deaths.

2.2.2 Hip Fracture Related to Propoxyphene Use

The literature search identified 12 publications describing propoxyphene-related hip fractures in elderly patients. Four of those studies met our criteria (Appendix - Table A1).[5-8]

In one prospective cohort study of Medicare beneficiaries Kamal-Bahl et al., observed a more than 2-fold increase in risk of hip fracture among patients using propoxyphene compared to patients who used no analgesics [Hazards Ratio[vi] (95%CI) = 2.05 (1.87, 2.25)] This risk was similar to that observed for other opioid use compared to no analgesic use [HR (95%CI) = 2.28 (2.13, 2.45)]. There was no difference, however, when non-opioid analgesic use was compared to no analgesic use [HR (95%CI) = 0.99 (0.92, 1.06)].[6] Upon stratifying users by high or low dose of propoxyphene, the researchers observed a dose-dependent association [HR (95%CI) = 2.05 (1.85, 2.29) and 1.45 (1.26, 1.67) respectively].

Another prospective cohort study by Guo et al. was done in patients aged 75 years and older and had similar findings.[7] Propoxyphene users had twice the risk of hip fractures compared to opioid non-users [Relative Risk (95%CI) = 2.01 (1.19, 3.4)]. Shorr et al. conducted a case control study of patients 65 years and older.[8] Shorr et al. observed that the relative risk[vii] of hip fractures among new users of propoxyphene compared to non-users was significantly higher than the relative risk seen when established users were compared to non-users [Relative Risk (95%CI) = 2.2(1.7, 2.8) and 1.3(1.0, 1.6) respectively; $p < 0.05$].

Kamal - Bahl et al. also conducted a national cross-sectional study in 1998 of Medicare beneficiaries and observed that Medicare beneficiaries with osteoporosis were more likely to use propoxyphene than those without [Odds Ratio (95%CI) = 1.48 (1.2, 1.8)].[9] Likewise, patients with history of hip fracture were more likely than those without such history to use propoxyphene [OR (95%CI) = 1.45 (1.1, 1.9)].

[vi] Time-dependent Cox regressional models used to calculate hazards ratio.

[vii] Relative risks were estimated from the unconditional logistic regression odds ratios using Generalized Linear Interactive Model (GLIM) software.

2.3 DISCUSSION

2.3.1 Propoxyphene-Related Deaths

The majority of deaths reported in these studies were suicides. However, a proportion of accidental deaths were due to overmedication in patients with chronic medical conditions, who were more likely to be elderly. This is important because elderly cases are less likely to make it to the medical examiners table, suggesting that drug-related deaths, including accidental deaths, in the geriatric population could be underreported. This limitation applies to the Florida Medical Examiner data as well.

The methods used for choosing medical examiner and coroner sites to be surveyed are not revealed and there is no way of knowing if the process was systematically biased, for instance towards areas with populations at higher risk for suicide to begin with. Another flaw in the design of these surveys is that the method by which a medical examiner or a coroner determines the cause and manner of death is unknown. There may be some methodological differences between sites as well as inconsistencies within sites. Three of the surveys that were much smaller and focused on small regions provide some insight into the nature of the problem in the United States. However, the results are not projected nationally, raising a question about its generalizability to the entire population.

2.3.2 Hip Fractures

Use of propoxyphene and other opioids increase the risk of hip fracture by up to 220%. New propoxyphene users were at higher risk than established users who had a 30% increased risk of hip fracture. The elderly, who are more likely to have pre-existing risk factors for hip fracture, were more likely to become new propoxyphene users.

A potential for bias in the hip fracture studies stems from the fact that the diagnosis of hip fracture was based on ICD codes without chart reviews, introducing potential for misclassification. Prescription data was used to classify patients into drug use groups based on the assumption that the patient took the medication as prescribed, leading to potential misclassification. Nonetheless, these two sources of bias might lead to an underestimation of risk.

Finally, Guo et al. and Shorr et al. did not control for some key potential confounders that likely affect the risk of hip fracture. However in their prospective cohort study Kamal-Bahl et al. controlled for some of those confounders including osteoporosis, vision, benzodiazepines, psychotropic drugs, and thiazide diuretics, rendering their findings less likely to be affected by residual confounding.

3 REVIEW OF PROPOXYPHENE SAFETY DATA FROM THE UNITED KINGDOM

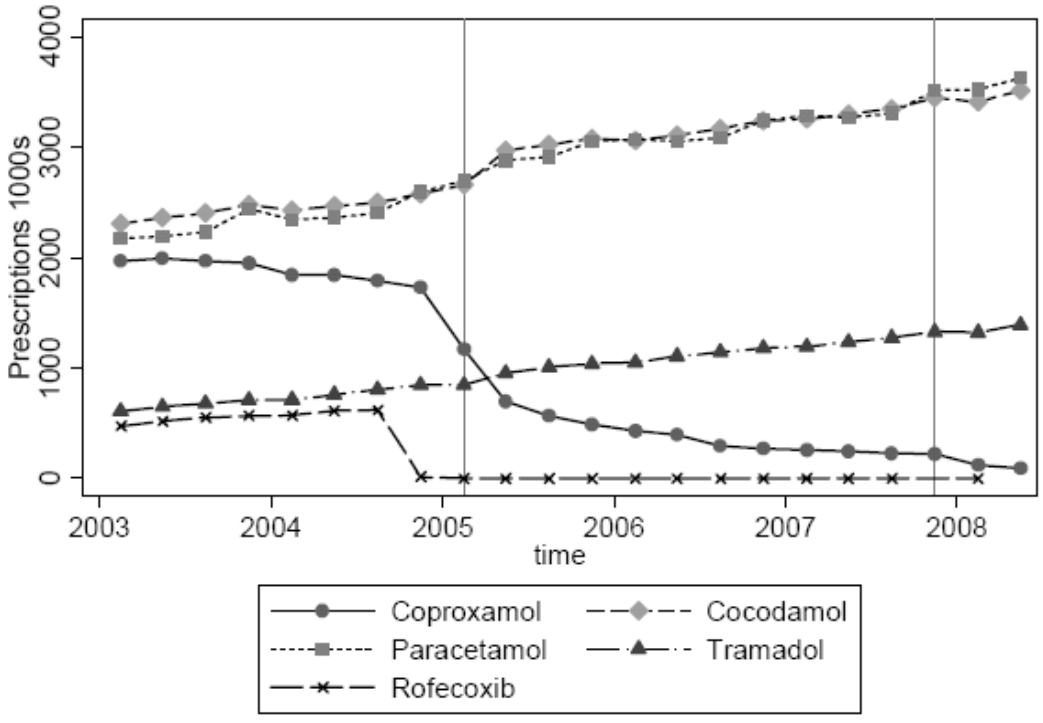
3.1 2009 REPORT FROM MEDICINES AND HEALTHCARE PRODUCTS REGULATORY AGENCY

This report was emailed to Dr. Gerald Dal Pan by Dr. Thomas Leigh of the Medicines and Healthcare products Regulatory Agency (MHRA) on January 10, 2009, in follow up to the January 30th Advisory Committee meeting on propoxyphene. The authorship is anonymous. The purpose of the MHRA report was to assess trends in analgesic use in connection with the 2005 phased withdrawal from the UK market of co-proxamol, the term used for the propoxyphene-APAP combination drug product in the UK. (In 2005, propoxyphene was not available in the UK as a single entity drug product.) Data on prescription volume were available from the UK

National Health Service Prescription Cost Analysis database. Data on current users of propoxyphene were obtained from IMS Mediplus. Please note that propoxyphene-APAP was never available in the UK without a prescription,[10] contrary to the information provided by the sponsor at the Advisory Committee meeting.

Because of concerns that propoxyphene added little analgesic efficacy to the propoxyphene-APAP combination product, yet is potentially lethal in relatively small overdosages or in combination with ethanol, the UK undertook a phased withdrawal of propoxyphene-APAP from the market beginning in February 2005. As of that time, no new patients were to be started on propoxyphene-APAP. Since January 2008, patients have received propoxyphene-APAP on an "unlicensed" or "named patient" basis only.

The results presented in the report showed a decline in propoxyphene-APAP prescriptions, accompanied by a slight increase in prescriptions for tramadol, APAP, and cocodamol (codeine-APAP). The following figure, reproduced from the MHRA report, depicts these trends by quarter in England. Propoxyphene-APAP prescriptions in England declined from a total of 7.2 million in 2004 to 960,000 in 2007.



Prescription Pricing Authority 2008. Prescription of selected analgesics in England 2003-2008

Figure 4 Prescription trends in selected analgesics before, during and after the withdrawal of co proxamol

One limitation of this analysis is that approximately ¼ of total paracetamol (APAP) dispensing is by prescription in England; however, non-prescription sales were also trending upward during this time period (data not shown). Another limitation was that Internet sales data were not captured.

The report also provided demographic data on the current users of propoxyphene-APAP in the UK, from the IMS Medi-Plus general practitioners consultation database. This IMS database is obtained from a panel of 500 general practitioners in the UK, covering 3 million patients.[11] The following table, reproduced from the report, summarizes these data.

Table 1 Current usage of co-proxamol (UK), 1 October 2007 – 30 September 2008. Source: IMS Medi-Plus general practitioners' consultation database. Prevalence (CI 95%)

	Female			*Male*	
Age band	Estimated numbers	Prevalence per 100,000		Estimated numbers	Prevalence per 100,000
<40	2,912	19 (14; 25)		1,120	7 (5; 11)
40-49	6,664	150 (124; 179)		2,520	54 (39;71)
50-59	11,984	332 (282; 370)		5,880	159 (126; 186)
60-69	22,568	715 (606; 737)		12,880	411 (327; 424)
70-79	32,088	1454 (1105; 1302)		13,832	722 (483; 618)
80-89	21,112	1387 (1250; 1534)		7,448	802 (672; 951)
90+	4,536	1113 (884; 1384)		1,232	872 (546; 1320)
Total	101,864	335 (320; 351)		44,912	152 (142; 163)

For the twelve month period ending September 30, 2008, there were approximately 150,000 propoxyphene-APAP users, of which 69% were female and 55% were aged 70 years and older. On a population basis, the prevalence of propoxyphene-APAP use during that twelve month period was greatest among females aged 70-79 years, among whom it was over 1%. The prevalence of use among males increased consistently with age.

Reviewer's comments: This analysis reflects the withdrawal from the market of rofecoxib in 2004, followed by sharp declines in prescribing of propoxyphene-APAP (starting in 2005), with relatively stable rates of increases in prescribing for the other analgesic drugs studied. Currently, users of propoxyphene-APAP under its limited availability are mostly female, and older in age.

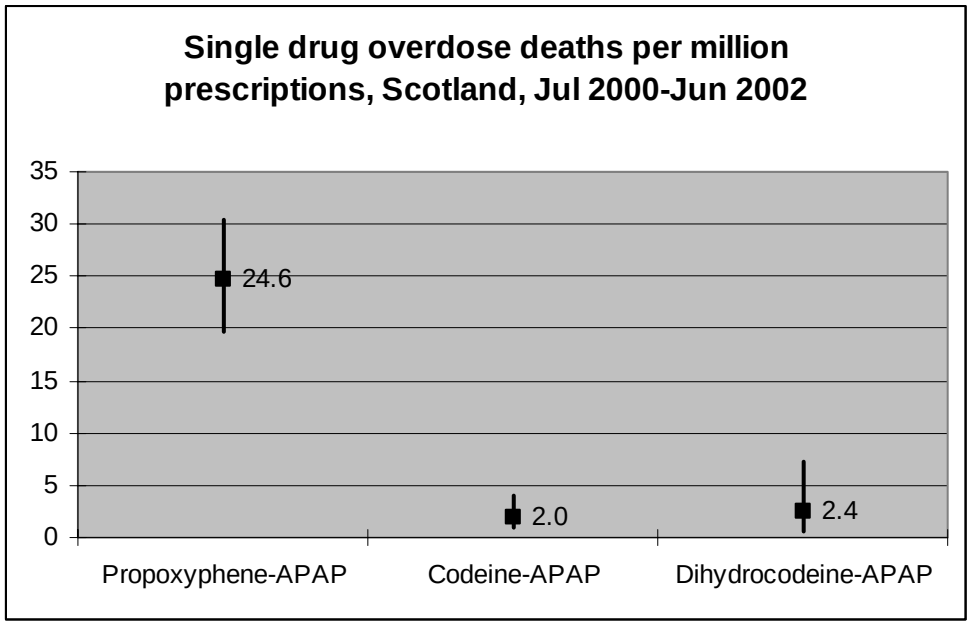
3.2 OVERDOSE MORTALITY DATA FROM SCOTLAND[12]

The purpose of this study was to compare overdosages and poisoning deaths for propoxyphene-APAP to those for codeine-APAP and dihydrocodeine-APAP. Prescription data was obtained from the Scottish Executive Health Department's Information and Statistics Division. Data on poisoning deaths were obtained from the General Register Office of Scotland (GROS). Additional information on the methods for assessing drug-related deaths can be found on the web site for the General Register Office of Scotland.[13] For all deaths reported in Scotland that are suspected of being drug-related, including deaths involving drug dependency, a special information form is completed by a forensic pathologist, with details about the drug or drugs involved (including ethanol). Additionally, staff from GROS perform follow-up to obtain additional information on deaths potentially involving drugs, when the reported details are unclear.

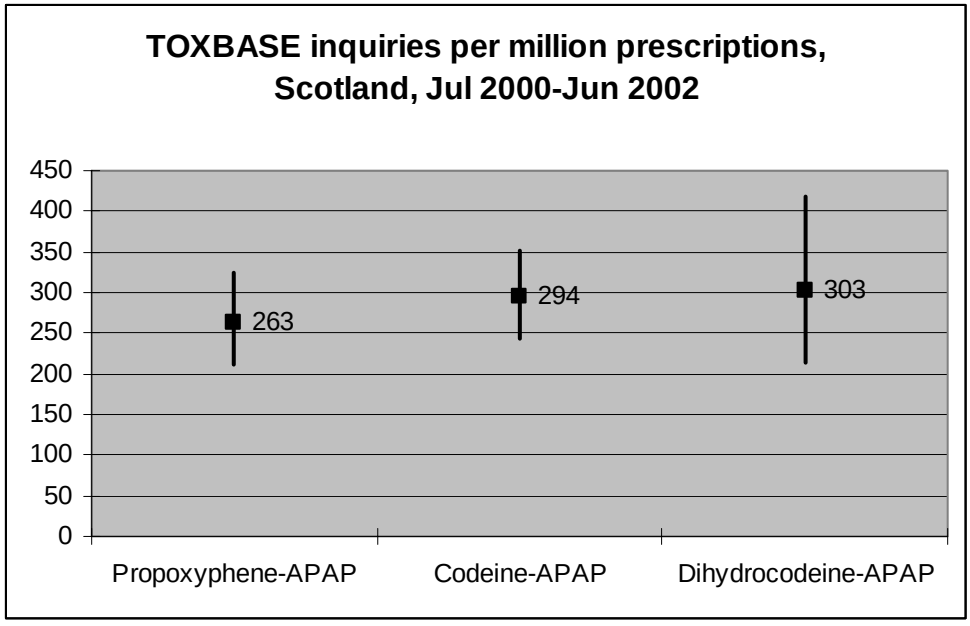
The National Poisons Information Service provided data on the number of inquiries received regarding clinical management of poisonings with the aforementioned drug products. The authors also analyzed hospital discharges related to overdosage for the locality of Edinburgh. A Poisson distribution was used for the analysis and provided 95% confidence intervals for events per million prescriptions. Data were for the two-year period July 2000-June 2002.

The following graph displays overdose deaths per million prescriptions in Scotland for the period of the study, with corresponding 95% confidence limits. For propoxyphene-APAP, there were 3.5 million prescriptions and 85 single-agent overdose deaths, compared to 3.9 million prescriptions with 8 such deaths for codeine-APAP, and 1.2 million prescriptions with 3 deaths for

dihydrocodeine-APAP. Per amount prescribed, propoxyphene-APAP was associated with roughly ten times the number of overdose deaths versus the comparator opioids.



The next figure depicts the number of TOXBASE inquiries received regarding overdosages of the specified drug, per million prescriptions, for the same period of time (with 95% confidence intervals).



Telephone inquiries to the National Poisons Information Service were much less frequent than Internet inquiries to TOXBASE presented above, but inquiries also occurred at the same frequency per million prescriptions for all three drugs (data not shown). Finally, Edinburgh hospital discharges involving the three drugs occurred at a similar proportion per million prescriptions (data not shown).

The authors concluded that propoxyphene-APAP, per amount prescribed, was no more likely to generate inquiries to the National Poisons Information Service than the comparator opioids, but was ten times as likely to produce a fatal overdose. Thus, patients prescribed propoxyphene-APAP did not appear to be more likely to overdose than patients prescribed the other two opioids, but were ten times as likely to die from an overdose. The authors concluded that these data reflect an excess risk of fatality from propoxyphene-APAP overdose relative to overdosage with the other two opioids studied.

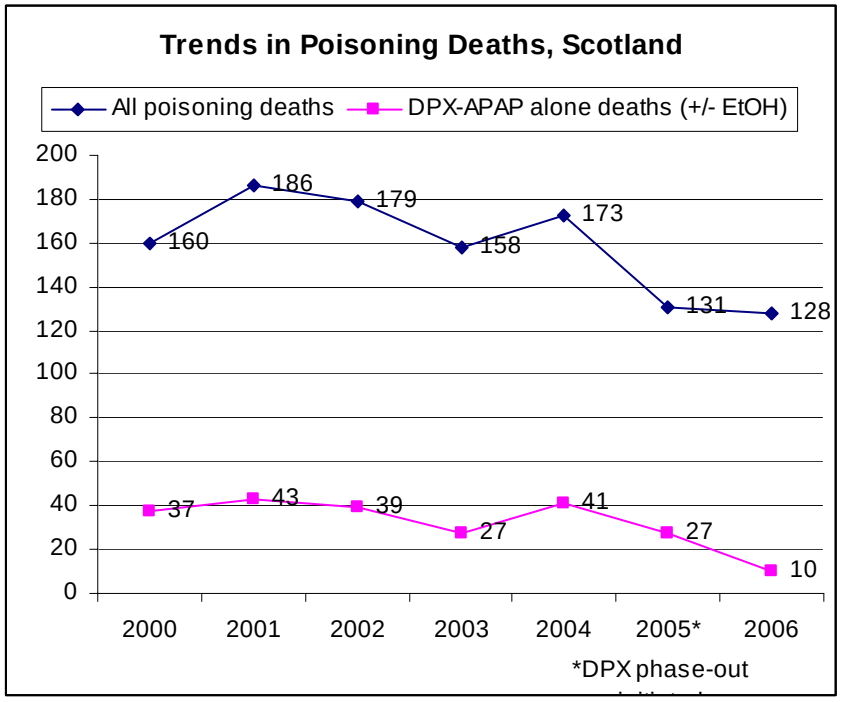
Reviewer comments: The authors note that the majority of fatal propoxyphene-APAP overdose cases never reach medical care; however, this may well be true of fatal overdoses in general.[14] *Ideally, one would be able to enumerate all overdoses that occur in the population with a drug of interest, and also be able to enumerate how many of these were fatal. However, existing health information systems are not that complete. Accordingly, the authors of this study used inquiries to poisoning information resources as a proxy for the relative number of overdosages that occurred with the study drugs, and found a large discrepancy between the number of fatal overdoses with propoxyphene and the number of poisoning inquiries, after adjusting for prescription volume.*

I agree with the author's interpretation that the most likely explanation for the pattern seen in these data is that propoxyphene carries a significantly higher risk of death from overdose compared to the other two opioids.

3.3 TRENDS IN FATAL OVERDOSAGES FOLLOWING WITHDRAWAL OF PROPOXYPHENE-APAP IN SCOTLAND[15]

The data from this observational study show trends in poisoning deaths in Scotland from before and after the withdrawal of propoxyphene-APAP. The purpose was to discern possible effects of the withdrawal on overdose mortality. The authors obtained data on poisoning deaths involving single agents from the General Register Office (described above), including propoxyphene-APAP and other analgesics for comparison. Deaths involving propoxyphene-APAP plus ethanol were included, but deaths involving additional drugs were not. Deaths were categorized according to in hospital versus out-of-hospital. Prescription volume data were obtained from the Scottish Executive Health Department. The time period of the study was 2000-2006, while the phased withdrawal of propoxyphene-APAP was initiated in 2005. Statistical comparisons were made with Fisher's exact test and Student's t-test.

The author's results are depicted graphically in the following figure.



For the years 2000-2004, prior to withdrawal, there was an average of 37 single-agent poisoning deaths per year due to propoxyphene-APAP in Scotland. In 2006, there were 10 such deaths, a statistically significant difference from the mean for 2000-2004. In addition, total annual poisoning deaths declined from a mean of 171 for the years 2000-2004 to a mean of 130 for the years 2005 – 2006, also a statistically significant change, although the authors point out that the decrease in 2005 was steeper than the decrease in propoxyphene-APAP deaths. Both in-hospital and out-of-hospital propoxyphene-APAP deaths decreased, although the majority (roughly 80%) remained out-of-hospital. The authors noted a shift in the age distribution among fatal propoxyphene-APAP poisoning cases towards older age bands in 2006 (data not shown).

On a quarterly basis, total prescriptions in Scotland for propoxyphene-APAP from July 2003-December 2004 averaged 301,000; by the first quarter of 2007 prescriptions declined to 36,000. The authors noted a corresponding increase in prescribing for APAP and codeine-APAP.

The following figure, reproduced from the article, depicts the trends in fatal poisonings with specific analgesics.

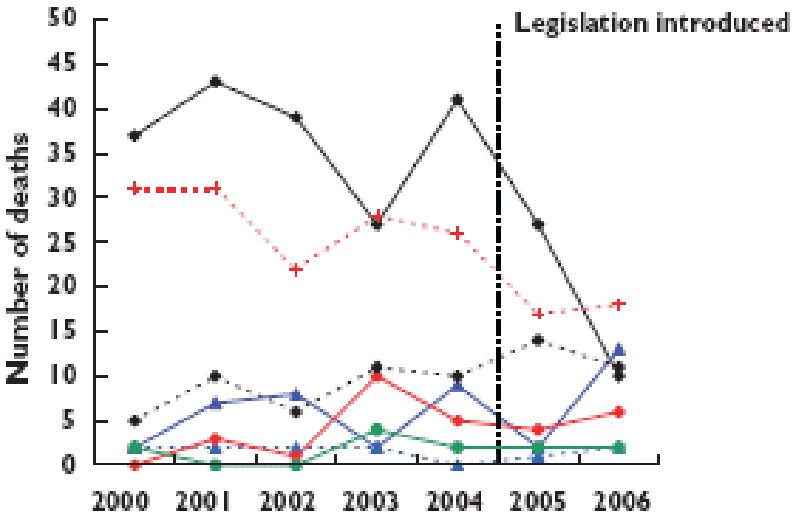


Figure 1

Scottish mortality figures from poisoning with commonly prescribed analgesics. Coproxamol, (—●—); co-codamol, (—▲—); codydramol, (··▲··); tramadol, (—●—); dihydrocodeine, (··◆··); codeine, (—●—); paracetamol, (··+··)

The authors concluded that the withdrawal of propoxyphene-APAP had yielded a reduction in poisoning deaths from propoxyphene, without a compensatory increase in poisoning deaths from other analgesics. Projecting these data from Scotland to the entire UK yields an estimated reduction in poisoning deaths of 300 per year. The authors note one important limitation is that they had a relatively short period of observation following the propoxyphene-APAP withdrawal.

Reviewer's comments: This is essentially an ecological analysis and thus shares the limitations of all such analyses, in that there could be other factors not accounted for that influenced the trends observed. In addition, there are obvious differences between the health care systems of Scotland and the U.S., plus propoxyphene-APAP was more widely used in the UK than it is currently in the U.S. With these caveats in mind, these data would not support the hypothesis that withdrawal of propoxyphene could shift use towards less safe analgesics.

4 DRUG ABUSE WARNING NETWORK ANALYSIS

4.1 EMERGENCY ROOM VISITS

Emergency room visits associated with propoxyphene were examined to determine if use of this drug resulted in high numbers of individuals needing urgent medical attention. Comparator drugs, codeine and tramadol were included in this analysis. These drugs were selected because they are opiate analgesics that are similarly scheduled under the Controlled Substances Act. Because the number of emergency room visits may be the result of greater drug utilization, i.e. greater drug exposure, drug utilization data were incorporated into this analysis.

This analysis utilizes data obtained from the Drug Abuse Warning Network (DAWN) on the numbers of emergency room visits as well as data on drug utilization obtained from SDI Vector One®.

4.2 DRUG ABUSE WARNING NETWORK (DAWN)

The DAWN, administered by the Substance Abuse and Mental Health Services Administration (SAMHSA), is an active public health surveillance system that examines drug abuse related emergency room visits and drug abuse related deaths. DAWN monitors drug-related visits to hospital emergency departments (ED) and provides data on patients treated in hospital emergency departments. Drug-related ED visits are found by retrospective review of medical records in a national sample of hospitals. Hospitals eligible for DAWN include non-Federal, short-term, general hospitals that operate 24-hour emergency departments.

National estimates of drug related ED visits were obtained for propoxyphene and comparator drugs codeine and tramadol for the years 2004 – 2007.

4.3 SDI: VECTOR ONE®

To take drug utilization into context of the amount of ED visits, estimates of drug utilization were obtained using SDI Vector One®: National (VONA) which is a national-level projected prescription and patient-centric tracking service. The number of dispensed prescriptions is obtained from a sample of approximately 59,000 pharmacies throughout the U.S. accounting for nearly all retail pharmacies and representing nearly half of retail prescriptions dispensed nationwide.

For this analysis, to compute a ratio of ED visits per 10,000 prescriptions by year for propoxyphene and comparator drugs, codeine and tramadol; the numbers of ED visits using DAWN data were divided by the number of total prescriptions available in VONA and multiplied by 10,000.

Table 4.1 summarizes the findings of this analysis. More details are provided in Table A2 of the Appendix. Overall, there were approximately 8 ED visits per 10,000 prescriptions for propoxyphene, 15 ED visits for codeine and 10 ED visits for Tramadol.

Table 4.1 Number of ED Visits per 10,000 Prescriptions for Propoxyphene, and comparator drugs Codeine and Tramadol by age groups for the years 2005 to 2007

	ED Visits per 10,000 Prescriptions								
	Propoxyphene			Codeine			Tramadol		
Age Group	2005	2006	2007	2005	2006	2007	2005	2006	2007
18-24	31.0	22.7	19.8	31.3	25.5	25.7	33.7	39.0	42.0
25-34	17.7	16.3	23.9	20.0	18.4	25.3	19.7	14.2	24.7
35-44	12.0	11.2	12.3	18.2	17.7	15.2	9.6	13.1	14.3
45-54	5.4	7.6	10.5	8.0	11.2	11.9	4.3	6.0	9.0
55-64	3.4	4.6	4.4	5.1	7.9	7.4	4.0	3.4	5.6
65-74	5.0	3.4	2.9	8.3	8.4	10.5	3.0	7.4	5.7
75+	6.1	8.8	5.6	11.3	17.1	23.0	6.6	8.9	12.2
Total	**7.7**	**8.2**	**8.5**	**13.0**	**14.1**	**15.5**	**7.6**	**9.1**	**11.7**

Source: SDI: Vector One ® National, Extracted 2/09 and Office of Applied Studies, SAMHSA, Drug Abuse Warning Network

4.4 DISCUSSION

It is important to note the following limitations of this analysis. The estimates provided are not true ratios or rates. Each dataset (DAWN and SDI VONA) has different sampling methodologies, different populations and different methods for calculating point estimates and respective confidence intervals. Furthermore, these data are not linked, in that, for each dataset, data is collected independently. The individuals who went to the emergency room may not, necessarily have had prescriptions for the drugs associated with the ED visit. Therefore, the observations are ecological associations only.

Another important limitation of the DAWN data is that it represents patients that were able to make it to the emergency room. Any differential in the risk of death that occurs prior to the ED visit will not be captured using DAWN ED data.

5 OVERALL CONCLUSIONS

The overall conclusions of this three-part review on the safety of propoxyphene-containing products include the following:

Literature Review of Propoxyphene-Related Deaths and Hip Fractures

- The literature review findings show that propoxyhene-related deaths in the United States are more likely to be cases of suicide. Accidental deaths more likely occurred with drug abuse, over-medication, and interaction with alcohol.

- There is evidence to suggest an increased risk of hip fracture among older patients who use propoxyphene compared to patients who use other non-opioid analgesics, or no analgesics. This risk is similar to other opioids tested.

Review of Propoxyphene Safety Data from the United Kingdom

- A study of overdose mortality in Scotland found that propoxyphene-APAP carries a significantly higher risk of death from overdose compared to the other two opioids studied, codeine-APAP, and dihydrocodeine-APAP.
- There is no evidence that a shift towards other undesirable products followed the decline in use of propoxyphene-APAP in the United Kingdom.
- The United Kingdom study findings provide evidence to support the withdrawal of propoxyphene products from the market.

Analysis of DAWN Data

- When comparing propoxyphene with codeine and tramadol, differences in the risk of ED visit were not remarkable. Similar ratios of ED visits per 10,000 prescriptions were found for all three drugs.
- Although small variations were seen across years and drugs, the differences were small.
- For all three drugs, young adults (18 to 44 years) are at higher risk of having an ED visit. Among the elderly (75+ years), those on codeine are more likely to have an ED visit.
- Any differntial in the risk of death that occurs prior to the ED visit will not be captured using DAWN ED data.

6 RECOMMENDATIONS

The DEPI reviewers agree that a restricted distribution system might have permitted use of the compound by a select group of patients with a tolerable risk-benefit balance. However, the Division of Risk Management (DRISK) has indicated that propoxyphene is not appropriate for a restricted distribution plan.[16] Accordingly,the reviewers favor accepting the recommendation from the Advisory Committee, which voted 14-12 for withdrawing the drug. Of course, this would have to be done with the appropriate guidance to physicians to discourage a shift towards less desirable alternatives.

If the drug is to remain on the market,in addition to the recommendation in DEPI's previous review on cardiotoxicity in the elderly, the reviewers agree that propoxyphene labels should be strengthened to highlight the increased risk of hip fracture in the elderly who are prescribed propoxyphene.

7 REFERENCES

[1] Finkle BS. Self-poisoning with dextropropoxyphene and dextropropoxyphene compounds: the USA experience. Hum Toxicol. 1984 Aug;3 Suppl:115S-134S.

[2] Poklis A, Gantner GE. Drug deaths in St. Louis City and County: a brief survey, 1977-1979. Clin Toxicol. 1981 Feb;18(2):141-7.

[3] Garriott JC, DiMaio VJ, Petty CS. Death by poisoning: a ten-year survey of Dallas County. J Forensic Sci. 1982 Oct;27(4):868-79.

[4] Wetli CV, Bednarczyk LR. Deaths related to propoxyphene overdose: a ten-year assessment. South Med J. 1980 Sep;73(9):1205-9.

[5] Florida Department of Law Enforcement. Drugs Identified in Deceased Persons by Florida Medical Examiners. 2007 Report. Available at www.fdle.state.fl.us/CJST/MEC/Publications/2007%20Drug%20Report.pdf. Date accessed: February 27, 2009.

[6] Kamal-Bahl SJ, Stuart BC, Beers MH. Propoxyphene use and risk for hip fractures in older adults. Am J Geriatr Pharmacother. 2006 Sep;4(3):219-26.

[7] Guo Z, Wills P, Viitanen M, Fastbom J, Winblad B. Cognitive impairment, drug use, and the risk of hip fracture in persons over 75 years old: a community-based prospective study. Am J Epidemiol. 1998 Nov 1;148(9):887-92.

[8] Shorr RI, Griffin MR, Daugherty JR, Ray WA. Opioid analgesics and the risk of hip fracture in the elderly: codeine and propoxyphene. J Gerontol. 1992 Jul;47(4):M111-5.

[9] Kamal-Bahl SJ, Doshi JA, Stuart BC, Briesacher BA. Propoxyphene use by community-dwelling and institutionalized elderly Medicare beneficiaries. J Am Geriatr Soc. 2003 Aug;51(8):1099-104.

[10] Dr. Euan Sandilands, National Poison Information Service Edinburgh, Personal Communication. February 19, 2009.

[11] MEDIPLUS Patient Populations. http://www.ims-global.com/disease_analyzer/patient_and_features.htm. Date accessed: February, 27,2009.

[12] Afshari R, Good AM, Maxwell SRJ, and Bateman DN. Co-proxamol overdose is associated with a 10-fold excess mortality compared with other paracetamol combination analgesics. Br J Clin Pharmacol 2005; 60: 444–447.

[13] General Register Office for Scotland. Drug-related Deaths in Scotland. http://www.gro-scotland.gov.uk/statistics/publications-and-data/drug-related-deaths/index.html. Date accessed: February 27, 2009.

[14] Blanc PD, Kearney TE, and Olson KR. Underreporting of fatal cases to a regional poison control center.

West J Med 1995;162:505-509.

[15] Sandilands EA and Bateman DN. Co-proxamol withdrawal has reduced suicide from drugs in Scotland. Br J Clin Pharmacol 2008;66:290-293.

[16] Memo from Dr. Mary E Willy, Division of Risk Management. February 23, 2009.

APPENDIX

Appendix 1 Table A1. Summary Table: Association between Propoxyphene Use and Hip Fracture

Reference	Study Design	Age	Study Variables	Results
Kamal-Bahl et al. 2006	Prospective Cohort Jan 1999 to Dec 2000 MarketScan Medicare Supplemental Coordination of Benefits database (Claims Data) n= 362,503	65 and older	Exposure: opioid use, high dose or low dose PPX (>=260mg or <260mg propoxyphene hydrochloride or napsylate equivalent per day) Outcome: hip fracture	**2 fold increase risk of hip fracture.** PPX use compared to no analgesic use: HR = 2.05 (95% CI = 1.87 -2.25) Other opioid use compared to no analgesic use: HR = 2.28 (95% CI = 2.13 -2.45) Non-opioid analgesic use compared to no analgesic use: HR = 0.99 (95% CI = 0.92 -1.06) **Dose-dependent association.** Low-dose: HR = 1.45; 95% CI = 1.26 -1.67 High-dose: HR = 2.05; 95% CI = 1.85 -2.29
Kamal-Bahl et al. 2003	Cross Sectional 1998 Medicare Current Beneficiary Survey (national sample) n = 10950 (34.8 million weighted)	65 and older	Propoxyphene use, risk factors for hip fracture (osteoporosis, history of hip fracture)	PPX and Hx of osteoporosis: OR = 1.48; 95% CI = 1.2 -1.8 PPX and History of hip fracture: OR = 1.45; 95%CI = 1.1 -1.9
Guo et al. 1997	Prospective cohort in a community-based Swedish population. n = 1608	75 and older (mean age 82)	Exposure: cognitive function, drug use Outcome: hip fracture	PPX use compared to opioid non-use: RR = 2.01; 95% CI 1.19 – 3.40
Shorr et al. 1992	Case Control using automated prescription data and hospitalization data in Saskatchewan Province, Canada. 1977 to 1985. non-users n (cases) = 4500 n (controls) = 24041	65 and older	Cases: ≥ 65 with first hospitalization having a discharge diagnosis of fracture of the proximal femur Control: population controls match by birth year, sex, and hospitalization date Exposure: codeine, propoxyphene	Opioid analgesic use compared to no analgesic use; PPX: RR = 1.6 (95% CI = 1.2 -2.2) Codeine: RR = 1.6 (95%CI = 1.3 -1.9) New use compared to no analgesic use ($p < 0.05$); PPX and codeine: RR = 2.2 (95%CI = 1.7 -2.8) Continuing use compared to no analgesic use; PPX and codeine: RR = 1.3 (95% CI = 1.0 – 1.6)

PPX=propoxyphene, HR = hazards ratio, CI = confidence interval, OR = odds ratio, RR = relative risk

Appendix 2 Table A2: National Estimates of ED Visits Reported in DAWN and Number of ED Visits per 10,000 Prescriptions for Propoxyphene, and comparator drugs Codeine and Tramadol

DAWN National Estimates

	Propoxyphene				Codeine				Tramadol			
	2004	**2005**	**2006**	**2007**	**2004**	**2005**	**2006**	**2007**	**2004**	**2005**	**2006**	**2007**
age group												
18-24	2,036	2,455	1,771	1,466	3,070	3,615	2,831	2,848	666	1,921	2,515	3,057
25-34	2,898	3,115	2,857	4,033	4,438	3,787	3,324	4,573	1,971	3,344	2,791	5,518
35-44	2,670	3,564	3,200	3,262	3,738	4,562	4,078	3,497	2,826	3,060	4,524	5,240
45-54	2,213	2,427	3,299	4,350	1,917	2,660	3,526	3,750	1,846	1,906	2,962	4,857
55-64	1,441	1,481	2,003	1,894	1,572	1,313	1,979	1,859	782	1,431	1,364	2,576
65-74	1,128	1,960	1,277	1,078	1,052	1,379	1,351	1,694	...	728	2,029	1,795
75+	1,718	3,225	4,320	2,701	1,613	1,950	2,731	3,676	980	1,936	2,855	4,346
Total	**14,104**	**18,227**	**18,727**	**18,784**	**17,400**	**19,266**	**19,820**	**21,897**	**9,071**	**14,326**	**19,040**	**27,389**

Drug Utilization Estimates

	Propoxyphene				Codeine				Tramadol			
	2004	**2005**	**2006**	**2007**	**2004**	**2005**	**2006**	**2007**	**2004**	**2005**	**2006**	**2007**
18-24	882,713	792,754	781,360	739,138	1,264,705	1,154,163	1,108,182	1,108,182	523,798	569,615	644,739	728,227
25-34	1,971,530	1,759,841	1,750,405	1,690,666	2,132,651	1,896,328	1,808,646	1,808,646	1,587,989	1,693,520	1,959,881	2,230,620
35-44	3,336,509	2,979,208	2,865,702	2,647,812	2,860,560	2,507,794	2,300,309	2,300,309	3,030,072	3,181,217	3,451,663	3,669,694
45-54	4,729,936	4,468,159	4,361,871	4,153,230	3,570,535	3,318,502	3,147,554	3,147,554	4,022,152	4,449,436	4,917,685	5,420,635
55-64	4,420,068	4,371,654	4,343,512	4,297,820	2,596,471	2,572,311	2,518,209	2,518,209	3,078,941	3,548,988	4,018,643	4,561,412
65-74	3,897,769	3,921,739	3,743,987	3,705,698	1,659,249	1,661,808	1,616,877	1,616,877	2,033,742	2,395,975	2,747,562	3,158,151
Age 75+	5,203,286	5,254,674	4,901,320	4,787,510	1,677,981	1,722,929	1,596,174	1,596,174	2,464,763	2,947,068	3,201,802	3,553,287
Total	24,441,811	23,548,029	22,748,157	22,021,874	15,762,152	14,833,835	14,095,951	14,095,951	16,741,457	18,785,819	20,941,975	23,322,026

ED Visits per 10,000 Prescriptions

	Propoxyphene				Codeine				Tramadol			
	2004	**2005**	**2006**	**2007**	**2004**	**2005**	**2006**	**2007**	**2004**	**2005**	**2006**	**2007**
18-24	23.1	31.0	22.7	19.8	24.3	31.3	25.5	25.7	12.7	33.7	39.0	42.0
25-34	14.7	17.7	16.3	23.9	20.8	20.0	18.4	25.3	12.4	19.7	14.2	24.7
35-44	8.0	12.0	11.2	12.3	13.1	18.2	17.7	15.2	9.3	9.6	13.1	14.3
45-54	4.7	5.4	7.6	10.5	5.4	8.0	11.2	11.9	4.6	4.3	6.0	9.0
55-64	3.3	3.4	4.6	4.4	6.1	5.1	7.9	7.4	2.5	4.0	3.4	5.6
65-74	2.9	5.0	3.4	2.9	6.3	8.3	8.4	10.5	...	3.0	7.4	5.7
75+	3.3	6.1	8.8	5.6	9.6	11.3	17.1	23.0	4.0	6.6	8.9	12.2
Total	5.8	7.7	8.2	8.5	11.0	13.0	14.1	15.5	5.4	7.6	9.1	11.7

Source: SDI: Vector One ® National, Extracted 2/09 and Office of Applied Studies, SAMHSA, Drug Abuse Warning Network

---

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Fatmatta Kuyateh
2/27/2009 04:08:28 PM
MEDICAL OFFICER

Rita Ouellet-Hellstrom
3/1/2009 04:58:13 PM
DRUG SAFETY OFFICE REVIEWER
Signed for Solomon Iyasu