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RFA Meeting:

Testing Interventions to Improve Adherence to Pharmacological Treatment Regimens

AGENDA

RFA Meeting:

Testing Interventions to Improve Adherence to Pharmacological Treatment Regimens

OCTOBER 9, 2003

8:00 am	**Continental Breakfast**
8:30 am	**Welcome and Introductions, Overview of RFA Meeting Aims, Announcements** Ron Abeles, OBSSR
	Significant Findings and Issues *(15 minute presentations & 10 minutes of questions/discussion)* Moderator: Ron Abeles
9:00 am	**Improving Adherence to Pharmacological Treatment In Patients With CHD** Ira S. Ockene, MD, University of Massachusetts Medical School
9:25 am	**Improving Medication Adherence in Comorbid Conditions** Jacqueline Dunbar-Jacob, PhD, RN, FAAN, University of Pittsburgh, School of Medicine
9:50 am	**Improving Adherence for Dyslipidemia and Anticoagulation** Peter Rudd, MD, Stanford University
10:15 am	**Increasing Treatment Adherence Through Social Engagement** Larry Davidson, PhD, Yale University School of Medicine
10:40 am	**Refreshment Pause**
11:00 am	**Medication Adherence and Outcomes in Schizophrenia** Dawn I. Velligan, PhD, University of Texas Health Science Center at San Antonio
11:25 am	**Tuberculosis Adherence Partnership Alliance Study (TAPAS)** Paul W. Colson, PhD, MSW , Charles P. Felton National Tuberculosis Center at Harlem Hospital
11:50 am	**Improving Drug Use for Elderly Heart Failure Patients** Michael D. Murray, PharmD, MPH, Purdue University, Regenstrief Institute

RFA Meeting:

Testing Interventions to Improve Adherence
to Pharmacological Treatment Regimens

12:15 pm **Lunch (on your own)**

1:30 pm **Issues in Research on Adherence**
Howard Leventhal, Rutgers University

2:30 pm **Discussion Session I: Recruitment and Retention of Participants and Sites**
Moderator: Suzanne Heurtin-Roberts, NCI

Screening and selection of participants (patients)
Hard to recruit populations
Selection and recruitment of professionals (intervention sites)

3:45 pm **Refreshment Pause**

4:00 pm **Discussion Session 2: Defining & Assessing Adherence: Pros and Cons**
Moderator: Susan Czajkowski, NHLBI

Adherence and/or self-care
Electronic devises
Physiological indicators
Multiple morbidity
Other outcome measures and measurement issues
Variation in validity and reliability across populations
Variation across health conditions

5:15 pm **Adjourn**

7:00 pm **Dinner (on your own)**

RFA Meeting:

Testing Interventions to Improve Adherence
to Pharmacological Treatment Regimens

OCTOBER 10, 2003

8:00 am **Continental Breakfast**

8:30 am **Discussion Session 3: Delivery and Administration of the Intervention**
Moderator: Timothy Cuerdon, NIMH

Treatment fidelity
Other threats to validity
Midcourse corrections
HIPPA and privacy issues

10:00 am **Refreshment Pause**

10:20 am **Issues and Recommendations**
Moderator: Howard Leventhal, Rutgers, The University of New Jersey

What do we wish we had known before starting this project?
What lesson would we offer to others entering the field?
What promising strategies, techniques, and perspective can we recommend?
What are the barriers to progress in understanding adherence?
What influences the implementation of successful interventions?

12:00 pm **Meeting Wrap-up, Future Activities**
Moderator: Ron Abeles, OBSSR

What should NIH do next to foster research and training in this area?

Adjournment

Tuberculosis Adherence Partnership Alliance Study (TAPAS)

Paul W. Colson, PhD, MSW

Charles P. Felton National Tuberculosis Center at Harlem Hospital

Subject Matter
TAPAS is a randomized clinical trial utilizing the Precaution Adoption Process Model (PAPM) as a basis for a peer support intervention to promote adherence to treatment of latent tuberculosis infection (LTBI).

What are the issues or concerns addressed?
A resurgence in tuberculosis (TB) was noted in the 1990s in the United States. Since 1992, TB control efforts such as directly observed therapy (DOT) for ensuring TB treatment completion have resulted in the gradual decrease in TB case rates in the United States. Despite this decline, the TB case rate in Harlem to 60.6/100,000 in 1998, this rate is still over nine times the US rate (6.8 cases/100,000) and over twice the NYC rate (21.3 cases/100,000). Another important strategy for control of TB is its prevention in patients with latent TB infection. However, treatment of LTBI has been associated with limited completion rates. Socioeconomic factors within the Harlem community and the asymptomatic nature of LTBI pose major challenges in achieving the national TB control target of 80% LTBI treatment completion.

Harlem, a predominantly African-American community with a rapidly increasing foreign-born population, faces diverse socio-economic challenges such as weak social support, poverty, drug and alcohol use, homelessness, and HIV infection. Paucity of information regarding LTBI, cultural beliefs, and inadequate health care provide further obstacles to treatment for LTBI. Risk factors such as these result in a substantial threat for failure to initiate or complete treatment for LTBI and subsequent progression from LTBI to TB disease in this community.

Patients with LTBI are completely asymptomatic, are often unaware or doubtful of having this infection, are not aware of the availability of effective preventive treatment, have unrealistic optimism and fail to appreciate the threat of TB disease. In addition, they often do not appreciate the efficacy of LTBI treatment, and may overestimate the potential adverse events associated with medications used for this purpose. They may also have many competing priorities in their lives and fragile support networks. Finally, they may not have role models in their own lives or environment for adopting this precautionary behavior.

TAPAS attempts to address these issues by utilizing a peer-based strategy that utilizes peer counselors who have successfully completed LTBI treatment in order to promote LTBI treatment and adherence among study participants. Peers share similar backgrounds and characteristics with the participants and are therefore able to bridge the gap between health care provider and patient, and offer multi-faceted support for completion of treatment. This strategy is being compared to current clinical practices used in treatment of LTBI.

What are the research questions and/or hypotheses?
Primary hypothesis: We hypothesize that participants assigned to the peer-based experimental intervention will achieve higher rates of completion of LTBI treatment than those assigned to current clinical practice (CCP), based on completion criteria established by the CDC.

Secondary hypotheses: We hypothesize that (a) the peer-based experimental intervention will be more cost effective than current clinical practice; and that (b) specific socio-demographic and attitudinal factors will be associated with adherence.

What are the theoretical or conceptual orientations guiding your research?

The study utilizes key behavior change models that are especially suited to the treatment of LTBI, the Health Belief Model and the Precautionary Adoption Process Model (PAPM). The Health Belief Model fits the framework of LTBI well, given its focus on susceptibility (infection with TB germ), severity of disease (risk of development of TB disease), perceived benefits (prevention of TB disease, preservation of health, prevention of spread to the community), perceived barriers (side effects from medications, confidentiality concerns) and self-efficacy. The PAPM provides an appropriate staging pattern of the candidates for LTBI treatment that will facilitate the delivery of a stage-specific intervention and the assessment of their progress during the intervention. The PAPM identifies 7 critical stages of adopting health behaviors, 1) "Unaware," 2)"Unengaged," 3)"Deciding," 4) "Declined to Adopt," 5) "Decided to Adopt," 6) "Initiated," and 7)"Completed."

"Unaware" is the first PAPM stage in which people simply have no information about a given health risk. In the second they have information but have not applied it to their own lives and are still "unengaged" in the sense that they perceive no risk to their own health. In the "deciding" stage people have a heightened perception of the risks and severity of a health condition and are contemplating the benefits that appropriate action might bring. At the same time, people are evaluating what they perceive to be the barriers to undertaking such action. This evaluation process leads to one of two following stages. The "declined" stage represents a perception that barriers and risks are greater than the expected benefits of a health behavior. Upon processing new information or reformulating their perceptions, people may shift from declined to the alternative stage, "decided". In this stage, when the benefits of a new health action are salient, cues to action can be powerful aids to overcome perceived risks and tangible barriers to the action. In the next stage, when people have "initiated" the behavior, such barriers may actually increase, and patients will benefit from instrumental support to resolve, or cope with, them and fit their health regimen into their daily lives. In the final stage, "completion", patients take stock of their accomplishments, either maintaining a behavior when appropriate, or by assessing the direct and tangential benefits of the adopted behavior.

Project goals

The specific goals of TAPAS are the following:

- To assess the impact of a peer-based intervention based on the PAPM model on adherence with treatment for LTBI. Adherence will be measured by participant self-report, computer touch screen methodology, electronic monitoring devices and assessments by provider and peers.

- To identify patient demographic, social and behavioral characteristics that are associated with adherence in this inner-city population.

- To assess the impact of specific components of the intervention on treatment adherence.

- To assess the cost effectiveness of the experimental intervention.

Research Design

The study is a randomized clinical trial in which candidates for LTBI treatment are randomized to the TAPAS experimental intervention versus Harlem Hospital current clinical practice (CCP). The latter is consistent with usual care provided for LTBI at other centers and clinics. The randomization of the participants is stratified at baseline by PAPM stage.

The experimental intervention is based on Health Belief and the Precaution Adoption Process Models, enriched with social support concepts and is delivered by peers who support clients to adhere to and complete LTBI treatment.

Questionnaires that evaluate adherence and other key demographic, social and behavioral characteristics are administered at baseline and monthly intervals until treatment completion. The primary outcome of the study is completion of prescribed therapy on time.

Participants and sampling methods

A total of 200 participants will be enrolled into the study. Participants are recruited from the Harlem Hospital TB Clinic and include patients who have been recommended/prescribed treatment for LTBI. The inclusion criteria used to determine participant eligibility is as follows:

Inclusion Criteria

- Recommended for initiation of a self-administered drug regimen for treatment of LTBI
- Age of 18 years or older
- Able and willing to sign consent form

Exclusion Criteria

- Ineligible for treatment for LTBI as per clinical guidelines
- Receiving Directly Observed Preventive Therapy (DOPT)
- Evidence of active TB disease

Experimental or observational plan

A baseline interview is completed within one week of participants being prescribed/recommended a CDC approved treatment for LTBI. Participants are then randomly assigned to one of two groups: intervention (peer-based) and control (CCP). In both groups, participants are followed by their own health care provider and receive the medications prescribed by their provider.

Each participant in peer-based group is assigned a peer who works one-on-one with the participant to provide social and adherence support. Peers make weekly contact with their assigned patients on the phone or by face-to-face encounters. The study health educator concentrates primarily on intervention clients in Stages I to 4, assessing stage specific barriers to adherence and tailoring appropriate targeted interventions to specific issues associated with each stage. The ultimate goal of the intervention is to advance participants from one stage to the next with the aim of achieving treatment completion.

Participants in CCP group receive current clinical practice of LTBI treatment. Activities utilized to ensure adherence in the CCP include patient education, frequent follow-up visits, incentives to cover transportation costs, and prescription refills. At monthly follow-up visits, providers and other Clinic staff review medications for all patients, dosages, specific instructions and potential adverse effects, along with discussing adherence. Social services are also available through the assigned caseworker in the TB Clinic.

Intervention

The PAPM model recognizes that adoption of a particular precautionary behavior, in this case adherence to LTBI treatment, involve seven distinct stages of perceptual, cognitive and behavioral change. Interventions that are tailored to clients' specific stage will therefore be more successful in achieving the desired behavior. The participants' readiness for behavioral change is assessed with the PAPM staging questionnaire at baseline and at monthly intervals thereafter. Based on this classification, participants are treated with the appropriate protocol for that stage.

The intervention consists of two phases: 1) a cognitive/perceptual phase which focuses on guiding participants toward making the decision to undergo LTBI treatment. This phase incorporates individuals in Stages 1, 2, 3, and 4; and 2) a behavioral phase which focuses on helping participants be adherent to LTBI treatment. This phase includes individuals in Stages 5, 6, and 7. The first phase emphasizes the use of such constructs from the Health Belief Model (HBM) as susceptibility, severity, perceived benefits, and perceived barriers. Additionally, the development of self-efficacy is emphasized and informational and instrumental forms of social support are offered. In the second phase, greater attention is given to HBM constructs such as cues to action and self-efficacy, along with emotional and appraisal forms of social support.

The intervention is delivered by 5 peer workers, 3 men and 2 women, and a health educator. Peers are individuals who themselves have completed LTBI treatment, are from the Harlem community, have good communication skills, and are committed to controlling TB. They provide support to adhere and complete treatment by discussing their personal experiences with LTBI treatment, emphasizing the positive outcomes they have experienced by confronting the situation and commencing treatment. They also offer emotional support by fostering an atmosphere of trust.

Key independent, mediating/moderating, and dependent variables

- *The key independent variables* are 1)Peer support provided to all experimental clients and 2)Health Educator Intervention provided to all experimental clients especially those in PAPM Stages 1 through Stage 4.

- *The dependent variable* is completion of LTBI treatment as prescribed in terms of recommended number of doses within the recommended time span.

- *The mediating/moderating variables* are demographic, clinical and social characteristics; knowledge of and attitudes toward TB, LTBI and LTBI treatment; perceived benefits and barriers to taking treatment; substance use; self-efficacy; and social support; depression; social desirability; health utilization and PAPM stage.

How measured/operationalized

The study is *operationalized* by assessing participant adherence at each monthly follow-up assessment until treatment completion. *Adherence is measured* by 3-day self-reported adherence, Medication Event Monitoring System (MEMS), computer assisted touchscreen questionnaires, peer and provider assessment of participant adherence and clinic visit adherence. The mediating variables are measured monthly at follow-up assessments by interviewer. The effect of the mediating variables and the intervention on adherence and treatment completion will be determined upon study completion. Other measurements conducted at baseline and follow-up include assessment of PAPM Stage, perception of benefits and barriers to LTBI treatment, self-efficacy, substance use (Addicition Severity Index), social supports and social networks, knowledge and attitudes about TB treatment, quality of life (SF-12), social desirability (Marlowe-Crowne Social Desirability Scale), depression, (CES-D) health utilization and participant assessment of the intervention and the clinic.

Results

A total of 118 participants have been enrolled since May 2002, 68.6% are men, 47.5% African American, 30.5% African, 9.3% Latino. Mean age is 39+12.6 years and the median is 36 years with 12.4 mean years of schooling. More than half of the participants are unemployed (56.8%) and foreign born (53.4%), with 38.1% having a history of homelessness and 16.9% are currently homeless. By PAPM stage, 6.8% are Stage 1 "Unaware", 10.2% Stage 2 "Unengaged", 11.9% Stage 3 "Deciding", 2.5% Stage 4 "Declined", 62.7% Stage 5 "Decided" and 5.9% Stage 6 "Initiated". The study is ongoing.

Increasing Treatment Adherence Through Social Engagement

Larry Davidson, PhD

Department of Psychiatry,
Yale University School of Medicine

Subject Matter

The study evaluates the effectiveness of two complementary approaches to increasing adherence among adults with co-occurring substance use and psychiatric disorders. The first approach uses a psychoeducational, skills training model that has been effective in increasing medication adherence in patients with psychosis or substance use separately. The second approach augments skills training with a social engagement model based on input from dually diagnosed patients, including those of African American and Latino origin. Utilizing this form of participatory involvement, the study is based on the premise that increasing medication adherence among dually diagnosed patients requires attention to their social situation and day-to-day lives in order to first engage them in treatment and decrease their substance use.

What are the issues or concerns you are addressing?

Poor adherence to medication and ready access to, and frequent use of, alcohol and illicit drugs have become two of the most troubling of the unintended consequences of deinstitutionalization. These two unanticipated factors emerging from the return of people with psychotic disorders to the community have combined to produce a new cohort of dually diagnosed patients who demonstrate a "revolving door" cycle of recurrent, brief inpatient and detox admissions followed by a return to drug use and an inability to maintain community tenure. Primarily young and in urban areas, these patients also are more likely to be from ethnic minority communities and to be disaffiliated from mental health and addiction ser-vices. Despite the development of new medications and effective community-based treatments, including interventions targeted specifically to increase adherence and prevent relapse, poor clinical and functional outcomes and a high rate of readmissions continue to occur for these patients and to account for a disproportionate share of the limited resources allocated for sub-stance abuse treatment and mental health care.

Research Design

The study uses a randomized, controlled design involving approximately 250 adults with co-occurring psychotic and substance use disorders recruited during an index hospi-talization. Participants are randomly assigned to one of three conditions consisting of standard outpatient care plus 1) transportation vouchers; 2) transportation vouchers and a skills training intervention; or 3) skills training plus participation in a social engagement program, called the "Engage" program. Process measures are monitored to ensure fidelity of the interventions to manualized curricula. Effectiveness is being assessed through interviews at baseline, 12 weeks, and 9 months post discharge on measures of adherence, clinical and functional status, substance use, and rate and duration of inpatient and detox admissions. Changes in social support, self-efficacy, and degree of collaboration and cultural sensitivity in outpatient treatment relationships are being assessed to test the theoretical model informing the study.

What are your goals in this project?

First, to evaluate the effectiveness of psychoeducational, skills training both with and without the augmentation of a social engagement program in increasing medication and outpatient treatment adherence in the first 12 weeks and 9 months following index hospitalization for adults with co-occurring psychiatric and substance use disorders in a public sector, urban setting. Secondary outcomes hypothesized to be mediated by adherence include an increase in functioning and decreases in psychiatric symptoms, substance abuse, and rate and duration of inpatient and detox admissions.

Second, to test a theoretical model of adherence that stipulates relationships between demo-graphic and diag-nostic characteristics, clinical and functional status, social support, self-efficacy, and degree of collaboration and cultural sensitivity present in outpatient treatment relationships between patients and their providers in mediating medication and outpatient treatment adherence among an urban population of adults with co-occurring psychiatric and substance use disorders.

What are the research questions or hypotheses?
Primary

Hypothesis I: Medication non-adherence will be 50% lower in the social engagement condition, and 25% lower in the medication adherence skills training condition, as compared to standard care.

Hypothesis II: Attendance at scheduled appointments will be 20% higher in the social engage-ment condition, and 10% higher in the skills training condition, as compared to standard care.

Secondary

Hypothesis I: Functioning will improve as evidenced by a 20% increase on the M-GAF and a 20% decrease in severity on the ASI in the social engagement condition, and by a 10% increase on the M-GAF and a 10% decrease on ASI for the skills training condition, as compared to standard care.

Hypothesis II: Symptoms will be reduced as evidenced by the PANSS syndromes and total score by 20% in the social engagement condition, and 10% in the skills train-ing condition, as compared to standard care.

Hypothesis III: Substance use will decrease by 50% as evi-denced by negative urine toxicology results in the social engagement condition, and 25% in the skills training condition, as compared to standard care.

Hypothesis IV: Utilization of acute inpatient and detoxifi-cation services will decrease as evidenced by 40% fewer admission and days in treatment in the social engagement condition, and 20% in the skills training condition, as compared to standard care.

What are the theoretical or conceptual orientations guiding your research?
This study was based on pilot work with the target population utilizing a participatory, qualitative method of involving people with co-occurring disorders in identifying their barriers to adherence and recovery and in designing interventions to address these barriers. As a result, the study design has been based on a theoretical model that stipulates a lack of responsive care, demoralization, and social isolation as primary barriers to adherence and recovery, and that offers a social engagement program to augment care to address these barriers.

Participants and sampling methods
Participants will include a total of approximately 250 adults, age 18 and older, who are diagnosed with co-occurring psychotic and substance use disorders. Psychotic disorders will be defined as schizophrenia, schizoaffective disorder, and affective disorders with psychotic features as determined by DSM-IV criteria. Substance abuse and dependence similarly will be deter-mined by DSM-IV diagnostic criteria, in both cases through use of the Structured Clinical Interview for the DSM. Participants are recruited during an index hospi-talization and are randomized into one of the three experimental groups.

How measured/operationalized?
The following measures are being administered at base-line, three month and nine month intervals to assess the following constructs:

Substance Use
Addiction Severity Index (ASI)

Psychotic Symptoms
Positive and Negative Syndrome Scale (PANSS)

Functioning
Global Assessment of Functioning Scale (GAF)

Social Support
Personal Network Interview (PNI)
& Social Functioning Scale (SFS)

Demoralization
Center for Epidemiological Studies Depression Scale (CES-D)
& Depressive Experiences Questionnaire (DEQ)

Responsiveness of Care
Collaboration and Cultural Competence Scale (CCCS)
& Therapeutic Alliance with Clinician Scale (TAC)

Influences on Adherence
Rating of Medication Influences Scale (ROMI)

In addition, clients are administered a Rate and Duration Scale assessing attendance at outpatient appointments, as well as inpatient and detox admissions. Participants who take their medications independently are being given Medication Event Monitoring System (MEMS) units, that are special caps which attach to standard medication vials and which record the date and time of each bottle opening. Data is downloaded to a computer using software that displays the list of dose time, or dose intervals, and calendar plots.

Key independent, mediating/moderating/and dependent variables
The key independent variable is the intervention type, including the skills training program with or without concurrent participation in the social engagement program. Dependent variables are medication adherence and attendance at outpatient treatment appointments. Secondary dependent variables are global functioning, positive and negative symptoms of psychosis, rates of substance use, and rate and duration of inpatient and detox admissions.

The mediating/moderating variables for adherence are hypothesized to be social support, self-efficacy, and collaboration and cultural sensitivity in outpatient treatment relationships.

Experimental or Observational Plan
See above for timeline and details related to the collection of quantitative data. In addition to the administration of formal measures, ethnographic interviews are being conducted on participants who have either especially benefited from the skills training and Engage program or who have chosen not to participate in an effort to better understand the individual factors that inform participation and adherence.

How will "adherence" in particular be measured?
Adherence is being measured via results of urine toxicologies, the rate and duration of attendance at outpatient treatment appointments, and the rate of medication compliance as indicated by clinicians' assessments and MEMS data.

Key preliminary results
To date 117 participants have been enrolled, randomized into the three experimental arms of the study, and been administered the testing batteries at baseline, 3 month and 9 month intervals. Formal quantitative analysis has not been completed, as data entry is on-going. However, study participants randomized to the third arm—skills training plus participation in the social engagement program—have demonstrated greater participation in the study, as indicated by greater attendance in study appointments and groups, and higher rates of completion of study interviews. Participants randomized to the second arm—standard care plus skills training—have shown greater levels of attrition than those in the third arm.

Improving Medication Adherence in Comorbid Conditions

Jacqueline Dunbar-Jacob, PhD, RN, FAAN

University of Pittsburgh,
School of Nursing

Subject Matter
Examine the impact of a telephone delivered counseling intervention among poor adherers on treatment adherence and selected clinical outcomes and examine temporal variation in adherence among good adherers who are being treated with oral medications for Type 2 Diabetes comorbid with either hypertension, hyperlipidemia or both.

What are the issues or concerns you are addressing?
The aim of the study is to evaluate an intervention developed within a problem-solving framework, in a sample using multiple pharmacological therapies for co-morbid conditions. Secondarily, we propose to explore the cost-effectiveness of improving adherence with this intervention.

What are the research questions and/or hypotheses?
Our *primary aims* are to: (1) evaluate the effect of a problem solving based adherence intervention on adherence to medication taking, singly and in combination, at the end of intervention (t^1) and after a six month follow-up period (t^3), in a sample of 198 persons with two or more comorbid conditions (type 2 diabetes and either hypertension, hyperlipidemia or both) who are poorly adherent (<80%) to one or more of three prescribed drug regimens, compared to usual care; (2) evaluate the effect of a maintenance intervention, added to the adherence intervention for a six month follow up period, on adherence to medication taking singly and in combination at the end of six month follow up (t^3), compared to adherence intervention with no additional maintenance intervention; (3) evaluate the effect of adherence improvement to pharmacological regimen on clinical outcomes at the end of a six month intervention (t^2) and after a further six month follow-up period (t^3) in a population of persons with two or more co-morbid conditions, specifically addressing hemoglobin A1c, blood pressure, total cholesterol level and LDL cholesterol, cognitive function, instrumental activities of daily living (IADLs), and quality of life; (4) examine the impact of comorbid conditions, complexity of the treatment regimen, functional ability including both physical and cognitive function, sociodemographic characteristics, and selected psychosocial factors as moderators of adherence to one and to multiple pharmacological regimen; and, (5) examine the degree of stability of adherence over one year among persons identified as good (≥ 80%) adherers to multiple pharmacological regimen and determine what, if any, factors are associated with stable long term adherence, including such factors as the complexity of the treatment regimen, functional ability, including both physical and cognitive function, sociodemographic characteristics, and selected psychosocial factors.

Secondarily, (6) we propose to explore the short-term cost-effectiveness of intervening with poor adherers to pharmacological regimen among persons with type 2 diabetes and either hyperlipidemia or hypertension or both.

We hypothesize that 1) poor adherers receiving intervention (t^2) will have higher adherence, quality of life, IADLs, and cognitive function, as well as lower HbA_1C, total cholesterol, LDL cholesterol and blood pressure, than those in usual care at the end of intervention (t^2); 2) individuals receiving maintenance intervention will be more likely to sustain adherence, quality of life, IADLs, cognitive function, HbA_1C, total cholesterol, LDL cholesterol, and blood pressure at the end of the six-month follow-up (t^3). We would further predict that the total number of comorbid conditions, total number of drugs prescribed, total frequency of daily medication taking, functional ability, cognitive capability, mood, tangible support, symptom distress, anxiety, problem solving capability, and perception of treatment efficacy are associated with levels of adherence.

What are the theoretical or conceptual orientations guiding your research?
Intervention will be based upon principles of problem solving (D'Zurilla & Goldfried, 1971; D'Zurilla, 1988; Kanfer & busenmeyer, 1982; Platt, Prout & Metzger, 1987). Problem solving is a major model within the broader cognitive-behavioral model of intervention (Dobson & Block, 1988). Problem solfing is seen as a process of developing coping strategies for problems in everyday living where problems are defined as life situations requiring a response where an effective response may not be available (D'Zurilla, 1988). Problem solving counseling has been used in a number of arenas, e.g. depression (Lewinsohn & Gotlib, 1995), family therapy (Reid, Rotering & Fortune, 1989), alcoholism (Bennun, 1985), as well as oncology (Nezu, Nezu, Houts, Friedman, & Faddis, 1999), unexplained physical symptoms (Wilenson & Mynors-Wallis, 1994) and emergencies (Salkovskis & Storer, 1989). The interventions have been tested in primary care (Mynors-Wallis, Davies, Gray, Barbour & Gath, 1997; Wilkenson & Mynors-Wallis, 1994; Gath & Catalan, 1986) and have been delivered by nurses (Mynors-Wallis, et al., 1997).

Intervention in problem solving therapy is designed to train individuals in procedures that promote independence in the management of day to day problems as well as generalization (Dobson & Block, 1988). Such an intervention would seem ideally suited to managing day to day adherence problems where the nature of the interfering problems are multiple and may vary from situation to situation for the patient. Important features of intervention include increasing sensitivity to the problem, focusing on positive problem solving, maximizing effort and persistence, collection of relevant data, solution generation and selection, and evaluation of the effectiveness of the chosen solution (D'Zurilla, 1988)

What are your goals in this project?
To recruit 396 participants having Type 2 diabetes concurrent with either hypertension or hyperlipidemia. Of these, 198 will be poor adherers over 30 days of screening and 198 will be good adherers at screening. We will administer 12 sessions of intervention to 132 of the poor adherers and administer 5 maintenance interventions to 66 of these treated poor adherers.

Research Design
This study will utilize a randomized, controlled design to examine the effects of a problem solving based, multicomponent, intervention, delivered by telephone, and usual care on adherence to multiple medications among patients with comorbidities.

Participants and sampling methods
Subjects. A total of 198 patients with adherence $< 80\%$ will be randomized to either usual care (UC) (N=66) or to the intervention arm (N=132). The 132 intervention patients would be further randomized, blocked on initial group assignment, and level of adherence at end of treatment, into maintenance intervention (AIM) or observation only (AID) with 66 patients in each group. The usual care group will continue to be monitored. An additional 198 consenting patients with adherence $\geq 80\%$ to the three medications for the target conditions would be followed for a 12 month period to observe the natural course of adherence over time as well as to identify predictors of good adherence.

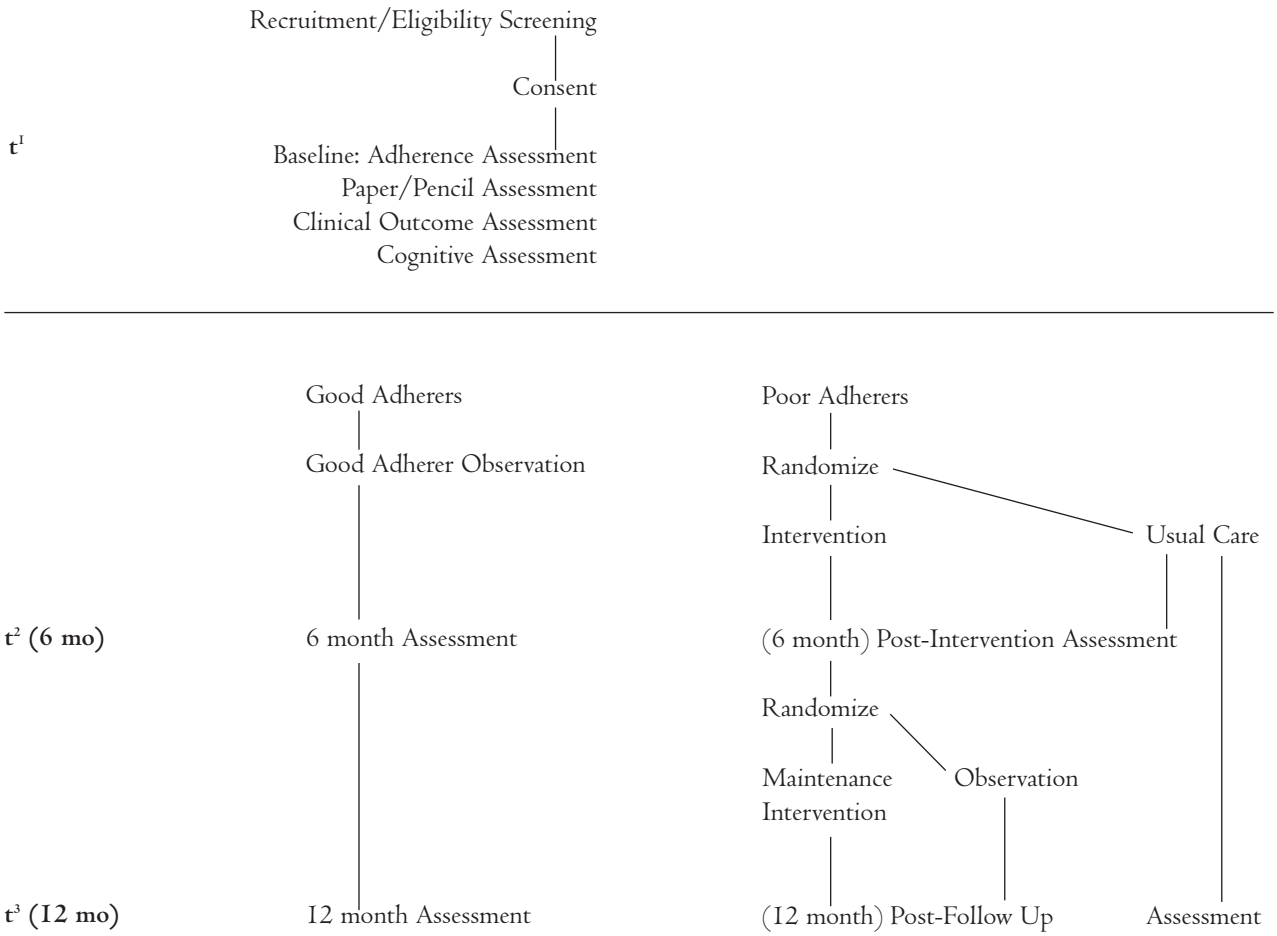
Participants will be recruited from various primary care, endocrine, and other specialty physician practices. In addition, participants are recruited through the community by way of health fairs, pharmacy notices, websites, and news advertisements. We will also be instituting a mass mailing through a marketing agency.

Eligibility criteria. Patients must have a physician confirmed diagnosis of type 2 diabetes with either hypertension or hyperlipidemia or both. They must have had type 2 diabetes for at least one year duration and be a continuing patient in the practice, that is, as evidenced by a one year history in the practice site. Patients must be at least 40 years of age or older. They must be prescribed at least one oral medication for each of the required two or three.

Exclusion criteria. Patients will be excluded if they are unable to read and write English, and if they do not have a telephone, cannot use a telephone, or are not willing to give out the telephone number. Patients will be excluded if they do not manage their own medications. If patients appear confused, a mini-mental status examination (Folstein, Folstein & McHugh, 1975) will be administered and patients who make two or more errors, will be excluded. In addition, subjects who are participating in other educational or counseling trials that may confound or be confounded by this trial will be excluded.

Experimental or observational plan

Figure 1. Overview of Research Plan



Key independent, mediating/moderating, and dependent variables

Assessments for this proposed project will be carried out at three time periods for subjects in all arms of the study and will be identical for each group, that is the intervention groups and the observational/usual care groups, including the good adherer observational group. Data collection will occur at baseline (t^1) prior to randomization, at the end of the six month intervention period (t^2) and at the end of the six month follow-up/maintenance period (t^3). Four types of data will be collected: 1) adherence; 2) clinical outcomes; 3) potential moderators; and 4) cost-effectiveness data. The primary endpoint will be adherence at the post treatment assessment.

How Measured/Operationalized

Measures of pharmacological adherence

Electronic Monitor. We have elected to use for the primary measurement of adherence an electronic event monitor. The monitor represents a significant advance in the assessment of medication adherence and represents the technological cutting edge of such assessment. Specifically, we will use the eDEM, electronic Drug Exposure Monitor, which is made by AARDEX Ltd. This monitor consists of a cap that is fitted with a microprocessor which records the date and time that the cap is removed from a standard 30, 40, or 60 dram medication vial. The duration of time the cap is off the vial is also recorded. The monitor has sufficient memory to record and store the dates and times of 2000 doses.

Measures of clinical outcomes

At baseline, post treatment and post maintenance we will obtain lipid profiles (total cholesterol, hdl and ldl), glycosylated hemoglobin, blood glucose, insulin levels, and blood pressure.

Quality of life outcome

Quality of life: General measure. Medical Outcomes Study Short Form-36 (MOS SF-36)

Quality of life: Disease-specific measure. Diabetes Quality of Life Measure (DQOL) (Jacobson et al., 1995)

Measures of Moderator Variables

- *Depression.* Beck Depression Inventory-II (BDI-II)
- *Anxiety.* The Spielberger State-Trait Anxiety
- *Problem Solving Skills.*
- *Neuropsychological Assessment Battery.* Each subject will complete a battery of cognitive measures designed to take approximately 2 hours at baseline and post maintenance (12 months).
- *Symptom Distress.* Symptom Distress Scale (SDS)
- *Functional Status.* Jette Functional Status Inventory FSI.
- *Perceived Treatment Efficacy.* Perceived Therapeutic Efficacy Scale.
- *Social Support.* Interpersonal Support Evaluation List
- *Project Specific Questionnaire.* Participants will be given a project specific questionnaire to collect regimen and disease data. Information will be elicited on medications taken, estimated numbers of missed doses for a one-month and one-week period, reasons for missed doses, the typical daily medication routine, costs of treatment, and the occurrence of physical symptoms that may be common side effects of the drugs used for type 2 diabetes, hypertension, and hyperlipidemia
- *Co-morbidity.* Modification of the Charlson Co-Morbidity Index (Charlson et al., 1987)

In particular, how is "adherence" measured?
Based on the results of our preliminary analyses, electronically monitored adherence data (see Measures of pharmacological adherence above) will be summarized at baseline (t^1), post-treatment (t^2), and post-maintenance (t^3). Our past work has indicated that daily adherence summarized to take into account the time interval between administrations over a two-week period yields a fairly stable estimate of the subject's average daily adherence that is sensitive to deviations in the timing of administrations. Initially, adherence will be analyzed considering the combination of medications being monitored, followed by analyses performed considering each regimen individually, in an effort to help control for inflation of the type I error rate. The repeated measures approaches previously described will be used for these analyses. In particular, planned comparisons will be conducted to test for differences in change in adherence between usual care group and adherence intervention group at the end of the adherence intervention (t^2) and after a six-month follow-up period (t^3). When evaluating the effects of the maintenance intervention, differences in the change in adherence between maintenance intervention group and the adherence intervention group with no additional maintenance intervention at the end of six month follow-up (t^3) will be tested by formulating contrasts as previously described. When testing these specific comparisons, the level of significance will be set at .05 (one-tailed).

Key (Preliminary) Results
No preliminary results are available. Due to a combination of a delayed funding start, IRB (HIPPA) changes, and organizational policy changes we are in the early stages of recruitment. An update will be given at the time of the meeting.

Improving Drug Use for Elderly Heart Failure Patients

Michael D. Murray, PharmD, MPH

Purdue University
Regenstrief Institute

Subject Matter (A.1)
Medications improve the function and health-related quality of life (HRQL) of patients with chronic heart failure (CHF), and reduce morbidity, mortality, and the costs of patient care. Randomized controlled trials have documented the benefits of multiple medications in older adults with CHF. Despite the well-documented efficacy of these medications, patients may not receive prescriptions for these drugs from their physicians, they may not tolerate the drugs when prescribed, or they may not adhere to a complicated regimen. Poor adherence is especially likely to occur when patients must chronically self-administer five or more drugs, a situation that could easily occur in patients with CHF who must also regularly take medications for other comorbidities such as hypertension. Clearly, any putative benefits of these medications would not apply to patients at suboptimal adherence. The purposes of this project are to develop and test a pharmacy-based medication use system aimed at improving patient medication adherence and health outcomes, and identify risk factors associated with the clinical deterioration of CHF.

Aims (A.2)
The study aims are to:

- design a multi-leveled, pharmacy-based program to improve medication adherence by using tailored strategies such as patient education, reminders, and special medication packaging,
- conduct a randomized controlled trial in which 366 elderly patients with CHF will be randomly assigned to usual care or to intervention by a specially trained and equipped pharmacist,
- determine the cost-effectiveness of the study intervention, and
- identify the determinants of clinical deterioration of heart failure.

Hypotheses (A.3)
We are testing two *primary* hypotheses:

- Medication adherence will be greater in the intervention group, which will, in turn, improve HRQL.
- Acute exacerbations of CHF will be fewer in the intervention group.

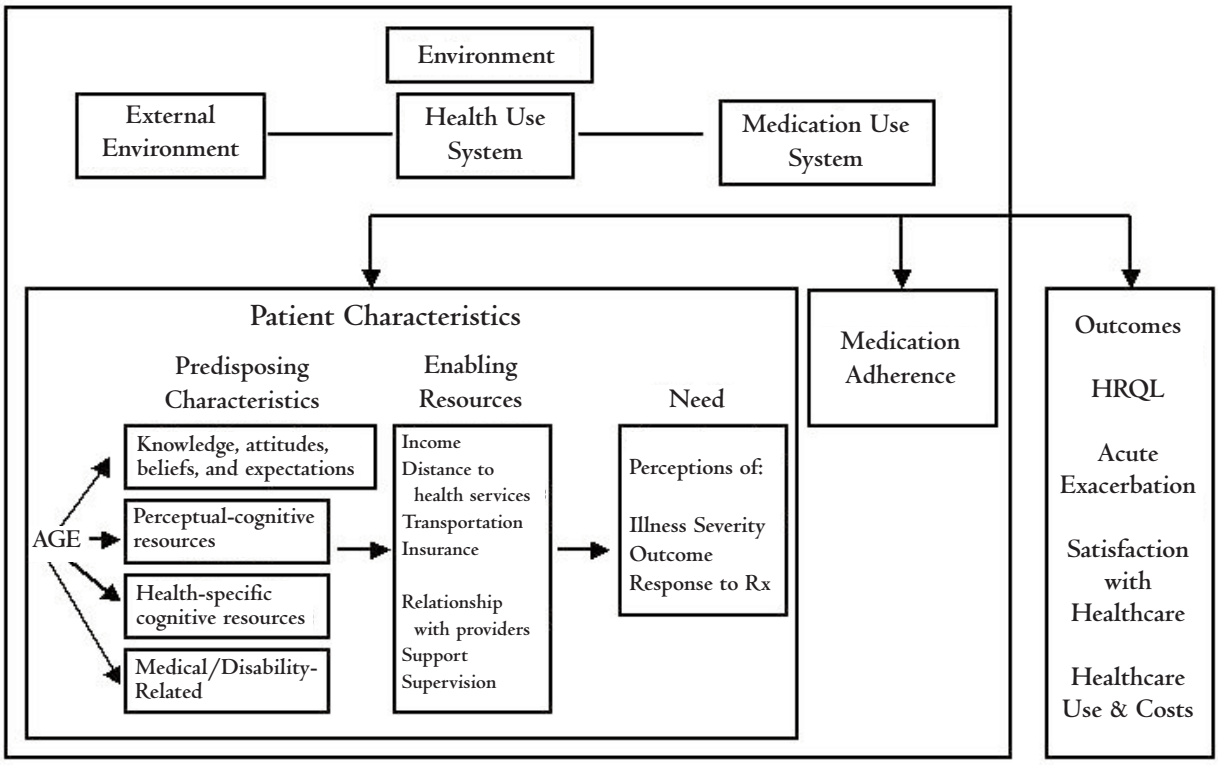
We are testing three *secondary* hypotheses:

- Patient satisfaction with healthcare will be greater in the intervention group.
- Urgent and emergent visits to the emergency department and hospital admissions will be lower in the intervention group
- Health care costs will be lower in the intervention group.

Theoretical/conceptual Orientations (A.4)
Cognitive and behavioral factors contribute to low medication adherence in older adults. Cognitive resources are lower in older adults resulting in forgetfulness and problems in comprehension, which are exacerbated by low health literacy. Patients have retrospective memory failure that results in forgetting what they have been told about their medications and whether they took a pill. Prospective memory failure results in forgetting to take the medication. Behavioral devices are available to assist older people with these cognitive deficits in order to help them remember their medications. Such devices include cues to remember to take a medication and recall that a dose has been taken. But, many older adults have not been trained to use these behavioral devices because no one has taken the time to show them. Lack of monitoring of medication use and limited communication among patients, physicians, and pharmacists compound the problem. The intervention will address these barriers by improving comprehension and communication of instruction with the use of explicit pharmacist consultation, patient-specific organization of information with handouts designed according to theories of cognitive aging and instruction design, large-print instructions, simple language, and icon-based education materials that link to the medication being used by the patient. All of these improvements address the cognitive declines associated with aging to educate patients *how* to adhere and *why* it is important to do so.

Our focus is on the relationship among environmental factors, patient characteristics, and medication adherence as a process that ultimately affects patient outcomes. No one existing model fit our study plan. Therefore, we developed a framework that integrates several existing models. First, because adherence to medications is a self-care healthcare utilization process that is affected by many social and behavioral factors, we adapted the behavioral healthcare utilization model described by Phillips (Figure). This model relates environmental and population characteristics to health behavior including personal health choices e.g. medication adherence. Second, a conceptual model of medication adherence constructed by Park and Jones was instrumental in determining the dimensions of our adaptations to the Phillips model.

Figure. Conceptual model of factors affecting medication adherence and patient outcomes.



Project Goals (A.5)
Our goals are to determine:

- whether our pharmacy-based intervention is effective and cost-effective
- the relationships among the predisposing characteristics, enabling resources, and needs
- how adherence is affected by the predisposing characteristics, enabling resources, and needs
- the relationship among self reported adherence, prescription refill adherence, and electronic adherence
- the factors, including adherence, that predict HRQL, exacerbation, satisfaction, and healthcare utilization and costs

Research Design (A.6)
This is a 4-year randomized controlled trial to evaluate a multi-leveled pharmaceutical care program that is designed to improve medication adherence using tailored strategies such as patient education and special medication packaging implemented by a specially trained and equipped pharmacist. Patients with CHF (N=314) have been assigned to intervention (n=122) and usual care (n=192) and each participant is followed for 12 months. The larger usual care group provides us with sufficient statistical power to identify the determinants of clinical deterioration of CHF.

Patients assigned to the intervention group receive 9 months of active intervention and a 3-month post-intervention follow-up. Intervention patients are provided verbal education, use of icon-based written patient handouts, icon-labeled medication containers, monitoring of drug therapy, and improved communication among patients, the pharmacist, and patients' physicians. Outcomes include HRQL, acute exacerbation, and cost. Patients assigned to the usual care group will receive no intervention by the study pharmacist.

Participants and Sampling Methods (A.7)
The study site is Wishard Health Services, a county tax-supported urban teaching medical center located at the Indiana University Medical Center (Indianapolis), which includes a 350-bed hospital, 65 outpatient clinics, and the busiest emergency department in Indiana. It serves predominantly inner-city patients. The Primary Care Center (PCC), located adjacent to Wishard Hospital, is the setting for this study. Subjects for this study have been recruited by ResNet, which is the research network within Indiana University Medical Group-Primary Care (IUMG-PC). It is the only method by which IUMG-PC allows its primary care patients to be recruited into research projects.

Variables (A.8)
Dependent: Medication adherence, HRQL, exacerbation of CHF (hospital admissions and emergency department visits), satisfaction with pharmacy and medical care, healthcare utilization and costs.

Covariates (Independent/Mediating/Moderating):* Age, gender, race, education, marital status, supervision, income satisfaction, vision, health literacy, listening abilities, cognitive abilities, New York Heart Association classification, ejection fraction (from echocardiography), brain natriuretic peptide and other hormones relevant to heart failure, medication regimen complexity, symptom burden, depression and other relevant comorbidities, distance traveled for care and mode of transportation, communication with physician, care expectations, health beliefs, activities of daily living, health insurance type, quality of well-being, religion, social support

** Covariate classification will depend on the analysis used to address a specific question.*

Measurement (A.9)

General Measurement Approach: Blinded research assistants conduct interviews, unblinded pharmacist conducts medication history and evaluation, echocardiography performed by a technician and cardiologist, autacoid and hormone assays are conducted by clinical pharmacology laboratory technicians, refill adherence and healthcare utilization and costs are extracted from the Regenstrief Medical Record System

Adherence Measurements: 1) electronic adherence data derive from MEMS V Trackcap on all medications for CHF, 2) refill adherence data are extracted from the Regenstrief Medical Record System, 3) self-reported adherence data are from blinded research assistant interviews.

Preliminary Results (A.10)

Our original analytic plan does not call for an interim analysis to determine the effect of the pharmacy-based intervention. As such, results heretofore are primarily cross-sectional studies using baseline data to address goals 2 – 5 in *Section A.5* above. Recently, we have begun analysis of our electronic adherence data for control participants with at least six-months of data.

We have recruited 310 participants toward our goal of 314. In this third study year, we have broadened our efforts to recruit subjects and continue to contract with ResNet. Of the 310 participants recruited, as of 5/14/2003, 292 have completed baseline health related quality of life (HRQL) interviews, 282 have completed cognitive testing and pharmacist assessments, 222 have completed their 6 month HQRL and cognitive testing interviews, and 117 have completed the study. Interviewers have conducted 1025 face-to-face interviews and 1923 telephone interviews. A total of 261 echocardiograms have been completed. Study subjects are 63 years of age ± 9 years (SD), 67% are female, and 47% are African-American. The distribution of subjects by the New Heart Association Classification is as follows Level I: 54 (19%), Level II: 125 (44%), Level III: 92 (33%), and Level IV: 11 (4%).

Research projects submitted for publication are listed under *Section A.11* below. The study by Dr. Michelle Chui [1] demonstrated that the timing of patient administration of their diuretic is an important predictor of admissions for heart failure and all cardiovascular causes. We feel that this is the result of erratic administration compounding the problems of an erratically absorbed diuretic (furosemide). Dr. Dan Clark [2] recently analyzed baseline data and reported the association of demographic and pathophysiologic measures, social-cognitive measures, and environmental variables with HRQL as measured by the Kansas City Cardiomyopathy Questionnaire clinical and functional subscales, the Chronic Heart Failure Questionnaire emotional, fatigue, and dyspnea subscales, and patients' overall perceived health. Overall perceived health was associated with age and positive health beliefs. Older patients, males, and African-Americans had higher disease-specific HRQL scores, as did persons reporting positive health beliefs, greater income, social support, and communication with their physician. These cross-sectional data highlight the potential significance of social and behavioral factors in CHF-specific HRQL.

Dr. Dan Morrow determined patient preferences for our written education materials and their ability to comprehend these materials.[3-6] He found a tendency for older adults to prefer our patient-centered instructions to standard pharmacy instructions.[3] However, preferences also depended on patients' medication-related goals. Those preferring the patient-centered instructions focused on ease of understanding the instructions (supported by large font, use of icons, and patient-centered organization), while those preferring the standard pharmacy instructions focused on the amount of information about drug interactions and side effects that were provided by these instructions. In a separate study, Dr. Morrow found improved recall with the patient-centered instructions for new medications. In addition, patients with lower levels of health literacy recalled instructions less accurately. [4]

We assessed the effects of antihypertensive medications on cognitive function in a collaborative project involving a prospective cohort of 1,900 inner city African-American subjects.[7] An important finding was that antihypertensive medications reduced the odds of incident cognitive impairment by 38% (odds ratio 0.68; 95% confidence interval 0.45 to 0.84). The effect of antihypertensive medications on the preservation of cognitive function was particularly apparent among subjects who used their medications continuously.

Dr. Kevin Stroupe describes the relation between medication refill adherence and the patterns and predictors of health care costs and utilization of health services of patients with heart failure.[8] He found that only 53% of patients received appropriate supplies of medications for heart failure. Those patients having under or oversupplies had an increased risk of hospital admission and annual healthcare costs that were 25% greater than patients with appropriate supplies of their medications. Our hope is that our study intervention will improve the use of medications and reduce total healthcare expenditures.

To assist our analysis of utilization data, Dr. Wanzhu Tu developed a new model for over-dispersed healthcare utilization data, such as outpatient visits, emergency department visits, and hospitalizations.[9] Traditionally, healthcare utilization across a patient population is modeled as Poisson counts although extra-Poisson variability in such data is known to violate important model assumptions. Dr. Tu's new modeling approach accommodates the over-dispersion and is able to provide correct estimation and inference for utilization data.

We have been working with our colleagues from the Indiana School of Nursing on studies of the relationships among generic and disease-specific instruments for assessing HRQL[10-12] and health utilities.[13] Several other relevant projects include our work related to improving prescribing and medication use. [14-16] The paper by Dr. Margaret Brunt highlights the problems associated with early release of information via the popular media pertaining to cardiovascular medications.[16] Moreover, we have submitted our study methods for publication.[17]

Finally, we have recently submitted several research abstracts describing the ability of vision, reading, health literacy, and listening skills to predict electronically measured medication adherence measure over 6 to 12 months. Our preliminary findings – in our control (usual care) participants – suggest that health literacy and listening skills are important predictors of adherence. We are currently in the process of ascertaining whether health literacy and listening skills are independent predictors. We are also determining the relationship between cognitive abilities and electronic adherence.

Publications (A.II)

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2. Clark D, Tu W , Weiner M, Murray M. Correlates of Health-Related Quality of Life among Lower-Income, Urban Adults with Congestive Heart Failure. (Submitted)

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9. Tu W , Piegorsch WW. Empirical Bayes Analysis for a Hierarchical Poisson Generalized Linear Model. Journal of Statistical Planning and Inference (in press).

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14. Murray MD, Callahan CM. Improving Medication Use for Older Adults: An Integrated Research Agenda. Annals of Internal Medicine (In press).

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17. Murray MD, Young J, Morrow D, Weiner M, Tu W , Hoke S, Clark D, Stroupe K, Wu J, Deer M, Bruner-England T, Sowinski K, Smith FA, Oldridge N, Gradues-Pizlo I, Murray L, Brater DC, Weinberger M. Improving drug use for elderly heart failure patients. (Submitted)

Pharmacist Intervention To Improve Adherence To Pharmacological Treatment In Patients With CHD

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University of Massachusetts
Medical School

Abstract

The overall goal of this study is to implement and evaluate the effects of a systems-based and pharmacist-mediated program designed to improve adherence to lipid-lowering pharmacologic therapy for patients with known coronary heart disease (CHD) and of their physicians/nurse practitioners (MD/NPs) to the National Cholesterol Education Program Guidelines. The program to be tested will intervene on three levels: the patient, the provider, and the system. In this two-condition randomized clinical trial the Intervention condition will include: (1) a computer-based tracking system designed to facilitate follow-up of patients who were initially seen for a coronary clinical event at the University hospital of UMass Memorial Health-Care, Inc.; and (2) an initial inpatient contact and a series of coordinated follow-up patient telephone counseling sessions carried out by pharmacists using a patient-centered approach to improve adherence. The pharmacists will utilize pharmacy refill records to obtain medication adherence information, and will provide feedback and recommendations to the patients' MD/NPs.

The study population will consist of 800 pts admitted for a clinical CHD event, and recruited from the cardiac catheterization laboratories. Patients will be randomly assigned to a control (usual care) condition (UC) which will consist of patients provided with usual care only, or to the adherence-enhancing Special Intervention condition (SI). The patient is the unit of randomization and analysis. SI will be implemented and coordinated by pharmacists, who will utilize the Lotus Notes-based tracking system that we have developed and used successfully in a number of previous projects.

The primary outcomes which will be evaluated at one year are the following:

1. Percentage of patients with an LDL level <100 mg per dl;

2. Proportion of prescribed lipid-lowering medication taken by patients as measured by a continuous multiple-interval measure of medication availability (CMA) based on pharmacy records (ratio of days supply obtained to total days in the observation period).

Secondary outcomes will include:

1. Percentage of patients on pharmacologic lipid lowering therapy;

2. Proportion of selected non-lipid-lowering prescribed medication taken by patients as measured by CMA; and

3. Percentage of patients with an LDL level <130 mg per dl.

Overview

Lack of compliance to medical therapy has been documented for decades, and in particular pharmacologic therapy for preventive interventions has been repetitively documented to be associated with inadequate adherence in approximately 50 percent of patients. The majority of patients with known CHD either are inadequately treated for hyperlipidemia or, if treated, do not adhere to the regimen. Reasonable estimates based on the literature would suggest that no more than 30 percent achieve an LDL-C goal level of <100 mg/dl. Adherence is a challenge on multiple levels, i.e., the pt, the provider, and the system, as described in the American Heart Association (AHA) special report published in 1997 entitled "The Multilevel Compliance Challenge". Our intervention occurs on all three levels. The primary intervention agent in our study is the pharmacist, who in the intervention group counsels the patient immediately following their cardiac catheterization and also follows up by telephone on at least five occasions over the subsequent year. Feedback is also provided to the patient's primary care provider, and the pharmacist works within a computer-driven system designed to increase the MD/NP's effectiveness and adherence to the NCEP guidelines, and assist pts to identify strategies and develop a plan to enhance adherence to their medication regimens.

The role of the pharmacist in enhancing medication adherence

In recent years, there has been increasing awareness of the role that pharmacists can play in improving medical therapy. Such interest has been heightened by the increased reporting of medication errors, highlighted in the report of the Institute of Medicine entitled "To Err Is Human: Building a Safer Health System". Studies identify medication noncompliance, adverse drug events, and medication errors as factors in patient morbidity and mortality. Rendering pharmaceutical care is now considered to be the mission of pharmacy practice by most national pharmacy organizations, with increased emphasis placed on counseling services and patient-focused care. Thus if pharmacist-delivered services are demonstrated to have a significant effect on the prescription and appropriate use of lipid-lowering medication the use of such services would be generalizable to a large proportion of health-care systems.

In addition to rigorous training in pharmacotherapeutics, pharmacists have the skills to provide effective and accurate patient education and counseling. Asking patients open-ended questions pertinent to their medication regimen is a strategy that is commonly utilized by pharmacists to assess adherence. Such questions include: 1) What did your doctor tell you this medication is for? 2) How did your doctor tell you to take this medication? 3) What did your doctor tell you to expect from this medication? Application of this model for assessing adherence to a prescribed regimen has demonstrated reduction in all-cause mortality and heart failure events in the Pharmacist in Heart Failure Assessment Recommendation and Monitoring (PHARM) study. Provision of pharmaceutical care services also has influenced outcomes of patients on antihypertensive therapy. Pharmacists are respected by physicians, and their recommendations are overwhelmingly likely to be appreciated and accepted by busy MD/NPs. In a study by Leape and colleagues of pharmacist participation on ICU rounds, the rate of preventable medication-ordering adverse drug events decreased by 66% in the pharmacist participation group. The pharmacist made 366 recommendations related to drug ordering, of which 362 (99%) were accepted by physicians.

Although this study is primarily oriented towards adherence to statin therapy, we are also following adherence to two other classes of drugs commonly used in cardiac patients: beta-blockers and ACE inhibitors. Our primary measure of medication adherence involves the use of pharmacy refill records, using the continuous multiple-interval measure of medication availability (CMA). The CMA is the ratio of days supply obtained to total days in the observation period. Other methods of assessing compliance are available, but tend to overestimate medication consumption (pill counts) or are very expensive (electronic monitors). Pharmacy refill records have the additional important advantage of being adaptable to routine clinical care, and the ease of doing this will progressively increase as the technology of developing pharmacy databases and establishing secure communication links continues to rapidly improve over time. Essentially all pharmacies now have data-based record systems, making adherence assessment by this methodology entirely feasible. Patient authorization to access such records is always required, so that patient privacy and confidentiality are safeguarded. In our study we

have obtained refill records from numerous pharmacies, including those of large chains such as CVS and managed care organizations such as Harvard-Pilgrim Health Care, and all have been willing to provide pharmaceutical records if the pt provides appropriate consent.

Theoretical underpinning of the study

The study utilizes the patient-centered counseling model to assist patients with CHD to develop and adhere to a plan for taking lipid-lowering medication. The model for patient-centered counseling reflects principles from the following research-supported theories and models: the Stages of Change Model, the Health Belief Model, Social Cognitive Theory, the Relapse Prevention Model, and Behavioral Self-Management Principles.

What have been the problems we have encountered?

Recruitment. In our planning for this project we assumed that recruitment would not be an issue. The number of patients needed for the study is far exceeded by the number of patients coming through our catheterization laboratories. We have however encountered difficulty in recruiting adequate numbers of women and minority subjects. Because of our interest in the potential effect of gender on adherence, we stipulated that our study population would be 50% female. Although women only compose one third of the patients coming to the cardiac catheterization laboratories, the potential number of female patients seemed sufficient. What we have encountered, however, is that the frequency with which patients coming to catheterization turned out to have normal coronary arteriograms is far higher among the women than among the men, and reduced the number of potential subjects the point where it has been difficult to reach the 50% mark. This has also to some extent influenced our recruitment of minorities, as many of the Hispanic women with chest pain syndromes have not turned out to have coronary disease at catheterization.

Selection bias. The catheterization laboratory is a place of considerable chaos. Many of the patients are ill, and over the course of the grant the conscious sedation policy of the laboratories changed so that most patients now receive significant levels of sedation, making it more difficult to talk to them and recruit tham into the study during the time available following the procedure. Furthermore, patients are sent home as soon as possible, further limiting the time available to interact with them. As a consequence, there is a natural tendency both for the recruitment specialists to seek out and for the physicians and nurses to point them towards those patients who are easiest to recruit, i.e., patients who are younger, more alert, and more cooperative. Obviously, these are also the patients who are likely to be more adherent to and have fewer problems with their medications. I have repetitively reminded our recruitment personnel that those patients who are most desirable for our study are probably those patients they would least like to approach: the elderly, the uncooperative, the suspicious, and the cognitively impaired. I do not yet have data to know for certain that this bias exists, but I strongly suspect that it does, and such a bias would tend to minimize the effects of our intervention.

What has gone well?

1. The interaction between the pharmacists and the patients has gone very well. Patients in the intervention group seem to very much appreciate both the inn-hospital and outpatient contacts, and the rate at which the patients accept the phone calls is very high, remaining at the 85% level even out at the 5th phone call. The pharmacists themselves enjoy the interaction. It is clear that pharmacists want to provide counseling to their patients, and in a world where they frequently find their time very closely monitored in the setting of large pharmacy chains, they appreciate the ability to use their counseling skills and provide patients with the information and assistance they need.

2. Obtaining the pharmacy refill data has in general gone well. There were a number of early glitches. It was important to reassure pharmacies that the patients had signed a specific consent for release of this information (and we send that consent to the pharmacies) and it was also important to assure them that the fax machine to which they would be sending data was secure. We initially attempted to work out a method of sending information by e-mail, but this did not succeed. It became clear that pharmacies were used to working with fax machines but not with e-mail, and they were also much more concerned about the security of e-mail despite the reality that faxes often come into machines located in essentially public areas such as secretarial pools whereas e-mails go into individual computers which are generally password-protected. One small pharmacy wanted to charge us for providing the refill data, but were eventually convinced not to.

Pharmacy refill data certainly has some weaknesses. Patients may obtain medications as samples, they may use medications obtained from spouses or other individuals, they may obtain refills in other states, or, for various reasons including cost-savings, they may take a lower dose then that prescribed (sometimes quite intentional on both the doctors' and the patients' part, e.g., have a prescription written for a dose that is double the desirable level and then cut the pills in half). We have attempted as much as possible to obtain data regarding these practices but primarily depend on the randomized nature of the trial to overcome such difficulties.

The study is just completing recruitment, and follow-up will continue for another year.

Improving Adherence for Dyslipidemia and Anticoagulation

Peter Rudd, MD

Stanford University

Subject Matter

The proposed project seeks to improve the medication adherence and clinical control of ambulatory patients prescribed treatment for two clinical situations:

1. Chronic oral administration of 3-hydroxy-3-methyl-glutaryl coenzyme A reductase inhibitors (statins) for reducing dyslipidemia and thereby cardio-vascular morbidity and mortality, and

2. Chronic oral anticoagulation therapy with warfarin for dysrhythmias, prosthetic heart valves, congestive heart failure, and thromboembolism.

These situations reflect high prevalence, considerable long-term risk, well defined and established therapies, demonstrable benefit exceeding risk from treatment, but disappointing overall impact in real world settings. Improving adherence for these situations should translate into better clinical outcomes and provide lessons useful for other conditions requiring long-term treatment with oral medications without prompts from symptoms.

What are the issues or concerns you are addressing?

The project is a randomized controlled trial that

- applies adherence-enhancing interventions at the levels of patient, physician, and medical care system for the two clinical situations;

- demonstrates that improved levels of medication adherence occur in the INTERVENTION compared to the USUAL CARE groups;

- evaluates the potential for dissemination by replicating into community-based practices the successful interventions from academic clinic settings; and

- assesses the cost-effectiveness of the interventions compared to usual care in both academic and community practice environments.

What are the research questions and/or hypotheses?

The *primary hypothesis* is that the integrated interventions will achieve significantly higher levels of days with correct dosings for these two treatment conditions compared to usual care.

The *secondary hypotheses* are that (1) such enhanced adherence will produce improved levels of clinical control for these conditions, and (2) the interventions, initially developed for academic clinic settings, can successfully make the transition to community-based practice environments and retain use effectiveness, even in more challenging circumstances.

What are the theoretical or conceptual orientations guiding your research?

- The interventions reflect both social cognitive and self-determination theory as well as continuous quality improvement strategies using clinical process guidelines.

- Patients' achievements by levels of adherence and clinical control provide a strategic matrix for feedback that guides actions by the prescribing physician and the project educator.

- Electronic medication monitoring allows dynamic and comprehensive assessment of medication adherence by day as well as by longer interval corresponding to times of clinical visits and evaluation.

- Feedback from such monitoring to both patient and physician as well as physicians' adherence to practice guidelines provides keys to improving overall adherence and outcomes.

What are your goals in this project?
The proposed project seeks to improve the medication adherence and clinical control of ambulatory patients prescribed treatment for two newly diagnosed or pre-existing clinical situations:

1. Chronic oral administration of 3-hydroxy-3-methyl-glutaryl coenzyme A reductase inhibitors (statins) for correcting dyslipidemia and reducing cardiovascular morbidity and mortality;

2. Chronic oral anticoagulation therapy with warfarin for dysrhythmias, prosthetic heart valves, congestive heart failure, and thromboembolism.

We shall achieve these goals in a randomized controlled trial by accomplishing the following:

1. Apply proven adherence-enhancing interventions at three levels: patient, physician, and medical care system for the two clinical conditions

2. Demonstrate improved levels of medication adherence in the INTERVENTION versus the USUAL CARE group

3. Evaluate the potential for dissemination of the methods by replicating the successful interventions from academic clinic settings into community-based practices

4. Evaluate the cost-effectiveness of the interventions compared to usual care in both academic and community practice environments.

Research Design
The project consists of two linked randomized controlled trials of interventions versus usual care, each over 18 months: a *confirmation* phase (Phase I) and a subsequent *dissemination* phase (Phase II). In both phases, our efforts will concentrate on two treatment conditions with well-established therapeutics, reasonable professional consensus, but suboptimal translation of full benefit to patients in real world settings: dyslipidemia for cardiovascular risk reduction and chronic oral anticoagulation for dysrhythmias, congestive heart failure, and thromboembolism prophylaxis.

During **Phase I** (Model Confirmation), the work established the practical details of implementing the adherence-enhancing program in selected academic clinics, both in primary care and medical subspecialties. During **Phase II** (Model Dissemination), we extend the model to community practice settings, seeking to confirm the use-effectiveness in non-academic environments. The model confirmation phase serves as a foundation for dissemination, helping reduce professional resistance and offering convincing "local" data on costs, risks, and benefits.

The core study design is identical for each phase, as summarized in Figure-2. After eligible and consenting subjects enter the study, they complete baseline assessments and undergo randomization to the INTERVENTION group (IG) or USUAL CARE (UC) group.

Figure-2
Study Design for Each Phase and Each Treatment Condition

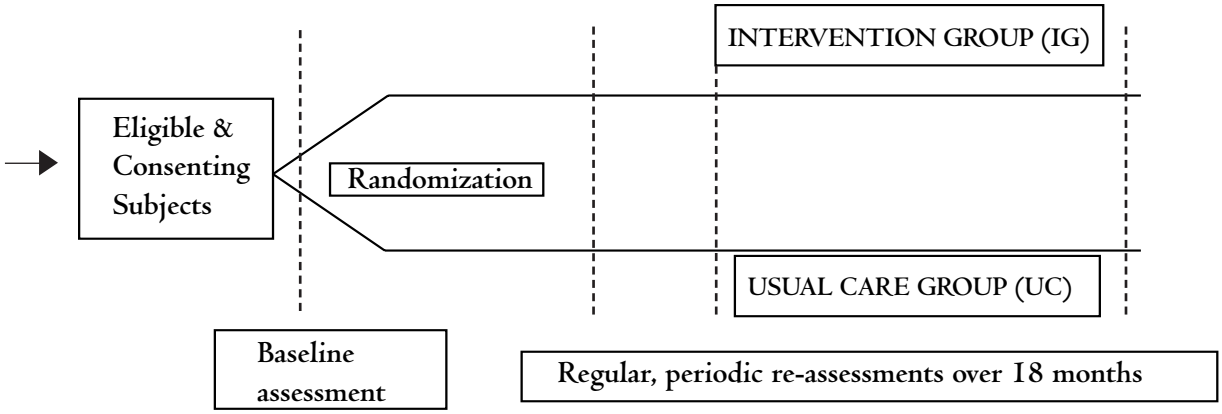
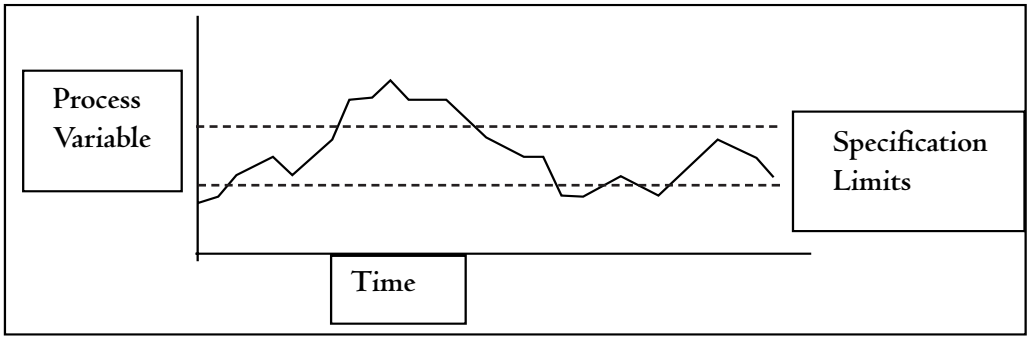


Figure-3

Generic Control Chart for Process Variables Over Time Versus Specification Limits



Participants and sampling methods.
We sought to meet the following *inclusion criteria:* (a) age 21-75, (b) prescribed at least one of the target medications (warfarin *or* lovastatin, pravastatin, fluvastatin, simvastatin, or atorvastatin) for an anticipated duration of 18 months; (c) living or working within 30 minutes drive of the treating facility; (d) fluent in spoken and written English; and (e) willing and able to provide written informed consent to participate.

Similarly, we used the following *exclusion criteria:* (a) inability to open and use electronic medication monitor vials without assistance; (b) unwillingness to participate in any of the stated components as outlined within the informed consent document, including using the eDEM device for dispensing the target medication. No special classes of subjects will or need be involved in either study phase, such as fetuses, pregnant women, children, prisoners, institutionalized individuals, or others who are likely to be vulnerable.

During Phase I (Model Confirmation in academic sites), we recruited the 130 needed subjects from among two primary care clinics (Stanford Medical Group, and Stanford Family Practice) and two subspecialty clinics (Preventive Cardiology and Oral Anticoagulation Clinics).

During Phase II (Model Dissemination), the community based practice sites have populations similar to those found in the Stanford Medical Group with a modest proportion of patients showing indications for lipid-lowering and chronic oral anticoagulation.

Under HIPAA guidelines, we are dependent on physician referral of eligible patients rather than primary recruitment from prescreened databases of suitable candidates.

Experimental or observational plan
Common, baseline assessment of IG and UC groups for sociodemographic, psychosocial, clinical, and utilization data.

Key independent, mediating/moderating, and dependent variables

Independent Variables	Mediating Variables	Dependent Variables
• Sociodemographic • Psychosocial • Clinical • Utilization • Complications • Major life events	• Intervention vs. Usual Care • Self-monitoring • Feedback • Alerts and reminders • Academic detailing intensity	• Days with proper dosing of target medication • Change scores for clinical control (LDL cholesterol; proportion of days with therapeutic INR)

How measured/operationalized
- Patient self-report, self-monitoring diary
- EDEM (Aardex) electronic medication monitor
- Medical record review
- Periodic reports to IG physicians
- 1-on-1 as well as group sessions for academic detailing

In particular, how is "adherence" measured?
- eDEM for medication-taking
- Medical Record notes for physician changes

Key (Preliminary) Results
Phase 1
- Difficult recruitment: prolonged, disproportionate number of high adherers (limited distribution)
- No significant difference from Intervention in rates of adherence
- Extreme complexity from warfarin regimen changes, complicating pill counts and calculated adherence rates

Phase 2
- Difficult recruitment: new HIPAA requirements, focus only on patients failing to achieve clinical goals (LDL reduction per NCEP III guidelines)
- Eliminate warfarin as clinical focus
- Restrict intervention from 12 to 6 months, continue observation for 6 months after intervention

Medication Adherence and Outcomes in Schizophrenia

Dawn I. Velligan, PhD

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Issues Addressed

It is well established that poor adherence to antipsychotic medication can lead to relapse and rehospitalization in schizophrenia patients. Years of study with conventional neuroleptic medications has suggested that as many as 50% of outpatients do not take medication as prescribed. It has been widely assumed that the increasing availability of the atypical antipsychotics with fewer side effects and a broader range of efficacy would improve adherence in schizophrenia. However, preliminary evidence indicates that major obstacles to adherence remain. We are examining rates of adherence to atypical antipsychotic medication, and predictors of adherence. In addition, we are examining treatments to improve adherence. Cognitive Adaptation Training or CAT is a comprehensive manual-driven series of environmental supports (signs, checklists, electronic devices) that cue, sequence, and direct multiple domains of adaptive behavior in the patient's home environment. These supports address multiple areas of functioning. Pharm-CAT treatment is a series of environmental supports that address only medication adherence. These two treatments are compared to treatment as usual (medication follow-up and limited case management in a public outpatient clinic).

Research Questions and Hypotheses

Specific Aim I

We will test the hypothesis that rates of non-adherence to atypical antipsychotics in the first three months following hospital discharge and reasons for non-adherence to these newer medications are similar to those found in published studies with conventional neuroleptics.

Hypothesis 1: We hypothesize that rates of non-adherence to atypical antipsychotics will be between 40 and 60%.

Hypothesis 2: We hypothesize that non-adherence at three months post-discharge will be related to medication side effects, overall level of cognitive dysfunction, negative attitudes toward medication treatment, complexity of the treatment regimen and previous poor adherence with medication.

Specific Aim II

We will test the hypothesis that environmental supports improve treatment adherence and outcomes in schizophrenia patients.

Hypothesis 1: We hypothesize that both Pharm-CAT and CAT will improve adherence to medication treatments, symptomatology and rates of relapse.

Hypothesis 2: We hypothesize that only the comprehensive full-CAT program will improve adaptive functioning.

Hypothesis 3: We hypothesize that without continued treatment, adherence will approach baseline levels within six months.

An additional question is how to measure adherence in schizophrenia patients.

Theoretical or Conceptual Orientations

Reasons for poor adherence to medications include medication side-effects, a lack of information regarding the illness, denial or lack of insight, and simple forgetting. A high percentage of patients who participate in clinical research (i.e., patients who are willing to follow research protocols) demonstrate poor adherence. This suggests that for a large number of outpatients, adherence may be more influenced by a poor ability to comply rather than by refusal to comply. Additional evidence for this notion comes from studies demonstrating that more than 50% of patients forget or misinterpret even simple instructions, and that poor adherence is associated with regimens that are complex and difficult to follow. Moreover, individuals with schizophrenia perform more poorly than age-matched control subjects on a wide range of tests of neurocognitive ability including those that assess attention, memory, and executive functions (the ability to plan and carry-out goal directed activity).

Environmental supports can be used to bypass deficits in cognitive functioning and improve community adaptation. Research has demonstrated that using environmental supports to cue and reinforce taking medications has been found to be among the most effective for individuals with physical illness. In behavioral terms, antecedent control can directly improve medication taking behavior. Supports are established for each functional deficit based upon two dimensions 1) level of impairment in executive functioning and 2) whether the overt behavior of the individual is characterized more by apathy, disinhibition, or a combination of these styles.

Goals in this project

- To examine different methods of measuring adherence to oral antipsychotics.
- To examine rates of adherence and predictors of adherence prospectively in an inception cohort of schizophrenia patients recruited at hospital discharge.
- To test interventions for adherence.

Research Design

Ninety schizophrenia patients are receiving blood draws during a baseline period in which all medication intake is monitored. This will determine plasma concentration of antipsychotic medication during optimal adherence. Subjects will then be followed prospectively for three months to examine medication adherence prior to any intervention. After three-month assessments, subjects will be randomly assigned to one of three treatments: 1) Full-CAT, 2) Pharm-CAT, or 3) treatment as usual. Patients will be treated for nine months and then followed for six months after discontinuation of treatment. Attitudes toward treatment, symptomatology and adaptive functioning will be assessed every three months using semi-structured interviews and both observer-rated and performance-based measures of activities of daily living and community adjustment. Plasma levels and pill counts will be obtained during two unscheduled home visits during each assessment month. Pharmacy records will also be examined.

Participants and Sampling Method

Subjects will be 90 inpatients with schizophrenia identified for participation through chart reviews conducted at the San Antonio State Hospital. Subjects are between the ages of 18 and 60, have a diagnosis of schizophrenia or schizoaffective disorder, are receiving treatment with risperidone, olanzapine, or aripiprazole (amendment in process), and are primarily responsible for taking their own medication. All admissions are screened and all patients meeting preliminary inclusion criteria are approached for participation.

Key variables

Medication Adherence—Each of the following can be viewed as continuous or dichotomous variables.

Blood Plasma Concentration. Blood is drawn three times during a baseline medication monitoring phase during with medication intake is observed, and on two randomly scheduled home visits each three months throughout the study. All samples are obtained prior to the first morning dose. Primary measures of adherence are percent variability in plasma concentration over time (%CV) and mean plasma concentration/dose (Cp/dose) for drug or drug plus active metabolite. Percent variability from baseline levels of adherence is examined by comparing the variability obtained in each pair of follow-up assessments with that obtained during baseline. Greater than 30% variability in consecutive levels and greater than 30% difference in Cp/dose in consecutive draws are considered to be evidence of problem adherence.

Pill counts. Pills are counted and a measure of compliance generated by dividing the number of pills missing from the bottle by the number of pills prescribed during the time period. Taking less than 80% of prescribed doses is considered to be evidence of problem adherence.

Pharmacy records. Electronic records are obtained from prescribing pharmacies at regular intervals to examine mean gap ratio.

Additional measures

Drug attitudes, insight, complexity of pill regimen, symptoms, cognitive function, adaptive function, relapse and rehospitalization, and medication side effects are obtained at three-month intervals.

Preliminary Results *(available on the first 68 patients)*

Baseline Period—None of the subjects who consented to this study completely refused to take medication during the baseline period. However, 4% of subjects (3/68) refused at least one dose. Pill counts at group-homes during the first few months of the study, when group home staff monitored medication intake (n=14 subjects) suggested that less than 60% of doses were administered to residents who were subjects on the study. A total of 10 of these 14 patients missed doses (in all cases multiple doses). This prompted us to have study staff observe all doses even for those patients in residential facilities. In addition to the 10 residential care subjects who missed doses, seven other subjects were not home or did not answer the door to take medications during at least one medication visit. Therefore, 25% (17/68) of subjects had all ready missed medication doses during the 10-day to two-week period following hospital discharge.

Clinical Observations—Observations during our first home visit suggested that discharge instructions were routinely misunderstood. In many cases, due to short lengths of stay, these individuals had been discharged from the hospital while still experiencing high levels of psychotic symptoms. It is unlikely that they were able to attend to and remember the instructions delivered by the hospital treatment team. We found several subjects were planning to take both the recently prescribed antipsychotic and the antipsychotic that was prescribed prior to their index hospitalization, not understanding that one medication was intended to replace the other. We found different medications mixed together in the same bottle. When questioned, subjects could not accurately identify the pills.

We also found evidence for non-adherence or partial adherence which predated the index hospital admission and the subjects' participation in the current study. We found between 2 and 22 bottles of antipsychotic medications which had not been taken. The amount of unused medications found in only this small sample of patients is suggestive of the potentially large amount of health-care dollars wasted on non-adherence.

Multiple problems with living environment and daily routines were identified as barriers to treatment adherence. Several individuals kept medications in locations that made it unlikely that they would be able to take all doses prescribed (e.g., in their car, or at the home of a relative). Many subjects were asleep at multiple dosing times, and without our staff waking them during the baseline period, would likely have missed over 50% of their doses. Subjects' lives were often chaotic and unstructured. Several slept at the homes of different relatives each night of the week. Many did not eat regular meals or follow a regular hygiene routine that could be linked with medication taking.

Even subjects who resided in group-homes missed multiple doses of medication without our supervision. If subjects were not present at medication distribution times, or failed to appear at the distribution desk, residential care staff was rarely able to follow-up to see that medications were taken at a later time.

Follow-up period—3 months post discharge—in the period between baseline and 3 month assessment, 25% (17/68) of these patients were readmitted to hospital and 12% (8/68) went to jail or became homeless. Based upon pre-established criteria for each assessment method, subjects were divided into adherent and non-adherent groups. For each method, criteria were chosen such that subjects taking at least 80% of their prescribed dose were considered adherent. Based upon pill counts, only 40% of patients were adherent. In fact, only 9% of patients took all doses prescribed in the 3 month period. In contrast, 55% of subjects reported that they were perfectly adherent, taking all doses prescribed. Analysis of blood level data suggests that only 27% of patients were adequately adherent during the three month period.

Problems Identified—Methods of assessing adherence do not agree. Kappa's ranged from .17 to .25. There are many reasons for this lack of agreement. Blood levels are especially influenced by behavior in the days immediately preceding the draw, where as pill counts are influenced by behavior over a longer interval. None of these methods assesses the amount of medication actually getting into the subject. They are at best proxy measures of adherence.

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RFA Meeting:

Testing Interventions to Improve Adherence
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INFO

RFA Meeting:

Testing Interventions to Improve Adherence to Pharmacological Treatment Regimens

Hotel and Transportation Information

The meeting is held at the Bethesda Marriott:

Bethesda Marriott
5151 Pooks Hill Road
Bethesda, MD 20814
Phone: (301) 897-9400 or (800) 228-9290
Fax: (301) 897-4156
http://www.marriotthotels.com

The closest airports are:

Reagan National
(703) 417-8000
http://www.metwashairports.com/national

Washington Dulles
(703) 572-2700
http://www.metwashairports.com/dulles

Baltimore Washington International
(800) 435-9294
http://www.bwiairport.com

Taxi

Reagan National to Bethesda Marriott ~ $35
Dulles Airport to Bethesda Marriott ~ $50
Baltimore Washington International
to Bethesda Marriott ~ $60

Metro
http://www.wmata.com

From Reagan National Airport, a cost-effective way to get to Bethesda is by using the metrorail system. From the airport station, take the Yellow Line towards Mt. Vernon Square. You will get off at the Gallery Place/Chinatown stop and transfer towards Shady Grove. Get off at the Bethesda stop and take a taxi to the hotel. The taxi should cost approximately $5.

The Super Shuttle

http://www.supershuttle.com
(800) Blue-Van (258-3826)

Useful Sites

Bethesda Area Attractions
http://www.bethesda.org