MEDICATION ADHERENCE IN CHILDREN AND ADOLESCENTS WITH MAJOR DEPRESSIVE DISORDER

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to
my parents

MEDICATION ADHERENCE IN CHILDREN AND ADOLESCENTS WITH MAJOR DEPRESSIVE DISORDER

by

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DISSERTATION

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MEDICATION ADHERENCE IN CHILDREN AND ADOLESCENTS WITH MAJOR DEPRESSIVE DISORDER

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Major Depressive Disorder (MDD) is a serious psychiatric disorder in children and adolescents where antidepressant adherence remains an important issue. The present study uses electronic monitoring (Medication Event Monitoring System, APREX, Fremont, California [MEMS® caps]) to compare various methods of measuring adherence. Subjects who met the Diagnostic and Statistical Manual of Mental Disorders' (DSM-IV) criteria for MDD participated in a

randomized controlled trial involving fluoxetine. A subset of patients had their medication adherence monitored for up to 12 weeks using MEMS caps, blood levels, self-report, medication diaries, physicians' estimates, and pill counts. Throughout the 12-week process, patients also completed a number of questionnaires assessing treatment expectancy, side effects, family functioning, school functioning, cognitive beliefs, depressive symptoms, and the identity of the individual(s) dispensing medication.

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LIST OF ABBREVIATIONS

HBM: Health Belief Model

MEMS: Medication Event Monitor System

MDD: Major Depressive Disorder

SSRIs: Selective Serotonin Reuptake Inhibitors

CBT: Cognitive Behavioral Therapy

DSM-IV: Diagnostic and Statistical Manual of Mental Disorders

K-SADS-PL: Kiddie Schedule for Affective Disorders and Schizophrenia for School- Aged Children – Present and Lifetime Versions

NIMH: National Institute of Mental Health

R & R: Relapse and Remission

RP: Relapse Prevention

CDRS-R: Children's Depression Rating Scale – Revised

CGI – S: Clinical Global Improvement Scale - Severity

CGI – I: Clinical Global Improvement Scale – Improvement

CGAS: Children's Global Assessment Scale

FGAS: Family Global Assessment Scale

SFI – II: Self-Report Family Inventory – Second Edition

TADS: Treatment for Adolescents with Depression Study

CMCD: Children's Medical Center of Dallas

UTSW: University of Texas Southwestern Medical Center

FDA: Federal Drug Administration

SAE: Serious Adverse Events

RCT: Randomized Controlled Trial

OCD: Obsessive Compulsive Disorder

ADHD: Attention Deficit Hyperactivity Disorder

ACR: Adequate Clinical Response.

QIDS-C: Quick Inventory of Depressive Symptomatology-Children's Version

CHAPTER I

INTRODUCTION

Statement of the Problem

Depression is a common psychiatric disorder that affects up to 2% of children and 6% of adolescents (Emslie, Rush, Weinberg, Rintelmann & Roffwarg, 1990). This prevalence rate is especially significant given the risks associated with being diagnosed with early-onset MDD. Specifically, studies have shown that depression often leads to school impairment (Asarnow, Carlson, & Guthrie, 1987), legal problems (Kandel & Davies, 1986), suicidality (Brent, 1988; Garrison, 1991; Lewinsohn, Hops, Roberts, Seeley, & Andrews, 1993; Shaffer et al., 1996), recurrent depression, (Bardone, 1998; Harrington, Fudge, Rutter, Pickles, & Hill, 1990), homicidal ideation (Deykin, Buka, & Zeena, 1992), family discord (Sheeber & Sorensen, 1998), substance abuse (Rohde et al., 1991), low self-esteem (Beck, 1987; Garber & Hilsman, 1992), and early parenthood (Brent et al., 1997). However, when depressed patients are referred to mental health professionals, as many as half of the patients do not complete the referral (Katon et al., 1995). Fortunately, for those that do seek treatment, there have been three pharmacologically-based studies that have proven the efficacy of fluoxetine in early-onset MDD (Emslie et al., 1997; 2002; Treatment for Adolescents with Depression Study, [TADS], 2004).

Despite the proven efficacy of certain antidepressant medications, there has been much publicized debate about the safety of antidepressants in youth (Cheung, Emslie, & Mayes, 2005). This safety debate resulted in the Federal Drug Administration (FDA) issuing a black box warning describing an increased risk of worsening of depression and suicidality for all current and future antidepressants used in those under the age of 18 (Cheung et al., 2005). The FDA's decision was based on adverse events reported across clinical trials of antidepressants in youth. However, adherence was not objectively measured in any of these trials (Cheung et al., 2005). It is impossible to know, then, whether the patients' increased suicidality was a function of the medication or a function of nonadherence, which can lead to a relapse in depression symptoms (i.e. suicidality).

Adherence is defined as the "extent to which a person's behavior coincides with medical advice" (Haynes, Taylor & Sackett, 1979). There is a high percentage of nonadherence associated with antidepressants (Osterberg & Blaschke, 2005). In a systematic review by Cramer and Rosenheck (1998), the mean rate of medication adherence among those with depression was 65% (range 58-90 %). The disparity between the highest and lowest estimates can be attributed to the methodology used in different studies (Cramer et al., 1989). Furthermore, adherence seems to decline over time, as half of the patients with

major depression will not be taking antidepressant drugs three months after they started their treatment (Vergouwen, VanHout & Bakker, 2002). Additionally, adherence in children and adolescents is estimated to be even lower than that of adults (Fotheringham & Sawyer, 1995). In addition to the aforementioned relationship between nonadherence and increased suicidal ideation, nonadherence is also associated with numerous other clinical problems, including: exacerbation of illness (Osterberg & Blaschke, 2005; DiMatteo, Lepper & Croghan, 2000; Budd, Hughes & Smith, 1996), incorrect diagnoses (DiMatteo, Lepper & Croghan, 2000), rebound side effects (Urquhart, 1997), an increase in caretaker stress (Budd, Hughes & Smith, 1996), delayed recovery (Osterberg & Blaschke, 2005; Fotheringham & Sawyer, 1995), wasted financial resources in health services (Fotheringham & Sawyer, 1995; Osterberg & Blaschke, 2005), suicidal ideation (Goldston et al., 1997), patient and physician frustration (DiMatteo, Lepper & Croghan, 2000), inappropriate changes in treatment regimen (Fotheringham & Sawyer, 1995), unnecessary hospitalizations (Riekert & Drotar, 2002), and equivocal efficacy in clinical drug trails (Urquhart, 1997). Due to the serious consequences of nonadherence, patient adherence to medication treatment has recently been identified as a "critical mediator between physician's medical expertise and patient outcomes" (Kravitz, Hays & Sherbourne, 1993). Patient outcomes are important, and in a recent review, it was noted that, "patients with

psychiatric illness have the greatest potential for benefiting from adherence" (Osterberg & Blaschke, 2005).

While a myriad of hypotheses has been generated to explain nonadherence, in general, little research has been devoted to documenting adherence in children and adolescents (Jay, Litt, & Durant, 1984). Additionally, many of the recent studies have failed to consistently identify factors that are correlated with nonadherence (Cromer & Tarnowski, 1989). One of the considerable problems in reliably asserting which factors correlate with adherence has been the lack of reliability in documenting a patient's adherence (Adams & Scott, 2000). Medication diaries, self-report measures, pill counts, physicians' estimates, and pharmacy records have all been found to overestimate actual adherence (Osterberg & Blaschke, 2005). However, the recent advent of a new tool, electronic monitoring, has fast become the gold standard in measuring adherence (Urquhart, 1997). With this advanced technology, a new wave of research looking at medication adherence in youths can be initiated and operationalized.

This advancement is timely, as a recent review called for "more fundamental and applied research to improve our understanding of the causes of nonadherence and to develop interventions to help patients maximally benefit from their medications" (Haynes, McKibbon, & Kanami, 1996). The World Health Organization (WHO) has also responded to the need for further

information about medication adherence, as it has published an evidence-based guide for clinicians, health care managers, and policymakers to improve strategies of medication adherence (Sabate, 2003). With both the identification of medication nonadherence as a major health problem and the advent of electronic monitoring, the possibility of deconstructing and understanding medication adherence in youth with depression can be initiated. Following are the major aims of this study.

Aims of the Present Study

The lack of research in this particular area necessitates further study on identifiable characteristics of nonadherence. The present study will 1) examine the characteristics of nonadherence that are found in children and adolescents with MDD. 2) Examine the relationship between various methods of measuring nonadherence (electronic monitoring, self-reports, pill counts, medication diaries, blood levels, and physicians' estimates). 3) Examine whether the average rate of adherence changes over time, during the 12-week open-label trial of fluoxetine. 4) Examine the correlation between medication adherence and treatment outcomes. 5) Determine the mean rate of medication adherence in children and adolescents with MDD. It is hoped that the results of this study will offer valuable information to the clinicians who treat this population.

CHAPTER II

LITERATURE REVIEW

Depression in Children and Adolescents

Major Depressive Disorder in children and adolescents is a serious psychiatric disorder with prevalence rates in children ranging between 0.4% and 2.5% and between 0.4% and 8.3% in adolescents (Birmaher, Ryan, Williamson, Brent, & Kaufman, 1996; Lewinsohn, Rohde, & Seeley, 1993). Multiple studies have shown that 40-70% of depressed children and adolescents have comorbid psychiatric disorders, with at least 20-50% having two or more diagnoses (Birmaher, Ryan, Williamson, Brent, & Kaufman, 1996). MDD in children occurs around the same rate in girls and boys, although the adolescent rate is 2:1 (female to male), which parallels the rate reported in adults (Birmaher, Ryan, Williamson, Brent, & Kaufman, 1996). It is estimated that by 18 years of age, 20-25% of adolescents will have experienced an episode of affective illness, (Lewinsohn, Rohde & Seeley, 1993) which is similar to the adult prevalence rate. Studies of depressive disorders among adults have indicated that the most frequent age of onset of depression is adolescence (Christie et al., 1989).

Children with depression have a fourfold risk of adult MDD (Harrington, Fudge, Rutter, Pickles, & Hill, 1990). Approximately 70% of children with MDD experience another depressive episode within five years (Kovacs, Feinberg,

Crouse-Novak, Paulauskas, Finkelstein, 1984). While this recurrence rate is comparable to adult rates, it is much more severe because the pattern of recurrence begins much earlier in the individual and family life cycle when onset occurs in youth. Thus, the results are more devastating (Kovacs, 1996).

Studies have highlighted the multitude of risk factors associated with early-onset MDD. These factors impact all areas of a person's life. Specifically, studies have shown that depression often leads to school impairment (Asarnow, et al., 1987), legal problems (Kandel & Davies, 1986), recurrent depression, (Bardone, 1998; Harrington, et al., 1990), homicidal ideation (Deykin, et al., 1992), family discord (Sheeber & Sorensen, 1998), substance abuse (Rohde et al., 1991), low self-esteem (Beck, 1987; Garber & Hilsman, 1992), and early parenthood (Brent et al., 1997). One of the most dire risk factors associated with early-onset MDD is increased suicidality (Brent, 1988; Garrison, 1991; Lewinsohn, et al., 1993; Shaffer et al., 1996).

Suicide remains the third leading cause of death in adolescents (National Center for Health Statistics, 2001). Approximately 19% of teenagers (aged 15-19) in the general population think about suicide and nearly 9% of teenagers make an actual suicide attempt (MMWR, 2000). These rates are even higher in patients receiving some type of care for depression. Studies find that 35-50% of these youths have made, or will make, a suicide attempt (Cheung et al., 2005). Similarly, Lewinsohn et al. (1996) found that depression is the most common

diagnostic condition associated with a suicide attempt, with 40-80% of adolescent attempters meeting diagnostic criteria for depression at the time of the attempt. In fact, depressive disorders are the leading cause of morbidity and mortality in the pediatric age group (Fleming & Offord, 1990). When an individual patient makes a suicide attempt during the course of treatment, it is simply not possible to know if the event was related to the medication or if it was a part of the illness itself, especially if adherence is not measured.

Overall, treatment costs for depression, in excess of $12 billion in 1990, have led to the continued focus of effective depression treatment (Greenberg, Stiglin, Finkelstein, Berndt, 1993). Several large-scale studies have documented that pharmacological treatment is effective in reducing the severity of depression in adolescents (Cheung, et al., 2005). In the landmark randomized controlled trial of fluoxetine versus placebo, Emslie, et al. (1997) was the first to demonstrate the efficacy of fluoxetine in the treatment of pediatric depression in a large double-blind placebo-controlled trial. In this study, 56% of those treated with fluoxetine improved with respect to their depressive symptoms, compared to 33% who improved on placebo, ($p = 0.02$). Recent studies have replicated Emslie's initial findings supporting the efficacy of the fluoxetine in pediatric depression. In a multi-site random-controlled trial, Emslie et al. (2002) found 52.3% of those treated with fluoxetine improved with respect to their depression, as compared to 36.8% who improved on placebo ($p = 0.028$). Most recently, the TADS study

(2004) found 61% improved with fluoxetine as compared with 35% who improved on placebo.

In 2004, Whittington et al. conducted a review of all available published and unpublished data regarding safety and efficacy of selective serotonin reuptake inhibitors (SSRIs) for depression in children and adolescents. He concluded that fluoxetine is a safe and efficacious treatment for depression in youth. Additionally, a recent review article (Cheung, et al., 2005) detailed the adverse events that occurred in both the 1997 and 2002 randomized controlled trials (RCT) of fluoxetine in children and adolescents with MDD.

In the 1997 study (Emslie et al.), two subjects (4.2%) on placebo and five subjects (10.4%) on fluoxetine discontinued the study due to adverse events. In the placebo group, one subject developed mania and one had a suicide-related event. Three of the fluoxetine subjects developed manic symptoms, one developed a rash, and one had a suicide-related event. In the 2002 study (Emslie et al.), nine subjects (8.2%) on placebo and five subjects (4.6%) on fluoxetine discontinued the study due to adverse events. In the placebo group, one each discontinued for rash, abdominal pain, alopecia, anxiety, dizziness, headache, kidney infection, aggressive behavior, and self-mutilation. Three of placebo subjects who discontinued were also considered serious adverse events because the event required hospitalization (kidney infection, aggressive behavior, and self-

mutilation). In the fluoxetine group, one each discontinued for rash, agitation, constipation, hyperkinesias, and a manic reaction.

In both studies, the rates of discontinuation were not statistically different between the active treatment group and the placebo group. Again, medication adherence was not measured in either of these studies, thus it is impossible to differentiate whether the subjects who experienced adverse events on fluoxetine were actually taking fluoxetine. Therefore, it is possible that these adverse events were due to medication nonadherence and thus similar in nature to adverse events experienced by subjects on placebo. Thus, the absolute safety of fluoxetine is still in question, although fluoxetine is still considered to have an acceptable risk-benefit ratio (Cheung, et al., 2005; Brent, et al., unpublished).

While the safety and efficacy of fluoxetine has been established, only a small percentage of the general population seeks treatment for depression. Many of the risk factors associated with early-onset depression (suicidality, recurrent depression, homicidal ideation, family discord, and low-self esteem) are also some of the very same factors that are hypothesized to contribute to decreased medication adherence. For example, considerable research suggests that support from a patient's family and social network is of great importance in helping with a patient's continued adherence with medical treatment (DiMatteo, 1994). Unfortunately, depression is often accompanied by considerable social isolation

and withdrawal from the very individuals who would be essential in providing emotional support and assistance.

Additionally, many of the symptoms associated with mood disorders, such as impaired cognitive focus, decreased energy, and lessened motivation also correlate with a patient's unwillingness and inability to follow through with treatment (DiMatteo et al., 2000). For example, reductions in a patient's cognitive functioning would impair their ability to remember to follow through with treatment recommendations. Another hallmark symptom of depression is hopelessness, which affects a patient's ability to be optimistic that their current action will affect their long-term future. If patients are not invested in their future, their motivation to get better and comply with medication treatment is likely to suffer (DiMatteo et al., 2000). Yet, it seems that long-term regimen adherence is related to motivational factors (Dishman, 1982).

In the same vein, suicidal thoughts were strongly associated with serious nonadherence, as 63.6% of teenagers who reported suicidal thoughts within the past year were not adherent to their medical regimen (Goldston et al., 1997). Additionally, having a current psychiatric disorder was the strongest correlate of both suicidal ideation and nonadherence with medical treatment (Goldston et al., 1997). Thus, the pattern of self-destruction is propagated, as both suicidal ideation and nonadherence are ultimately harmful. Additionally, if adolescents are noncompliant and do not take their medication, there is an increased

likelihood that they have an opportunity to stockpile their medication, which is potentially dangerous if they are at risk for overdosing.

Medication Adherence

Adherence is defined as "the extent to which a person's behavior coincides with medical advice" (Haynes et al., 1979). The word "adherence" is preferred by many health care providers because "compliance" suggests that the patient is passively following the doctor's orders, and that the treatment plan is not based on a therapeutic alliance or contract established between the patient and physician (Osterberg & Blaschke, 2005). Many previous studies have treated adherence as a dichotomous variable, rather than as a phenomenon with multiple dimensions. Treating adherence as a dichotomous variable is dangerous. Labeling a patient as "nonadherent" versus "adherent" just because they do not consume every pill at the desired time can stigmatize their future relationship with their health care provider (Osterberg & Blaschke, 2005). It also vastly oversimplifies the matter.

In reality, adherence to treatment recommendations is a dynamic and complex phenomenon. Medication adherence should be viewed along a continuum from 0 % to more than 100%, since patients sometimes take more than the prescribed amount of medication (Osterberg & Blaschke, 2005). However, rarely is 100% adherence obtained (Bachman, Stephens, Richey, & Hook, 1999).

Adherence can be total, partial, or erratic (Cramer, 1995). A patient may adhere to one part of the treatment recommendations, but not to another (Orme & Binik, 1989; Fotheringham & Sawyer, 1995). Patients may take one medication and not another. They may initially adhere and then discontinue. It is not a simple "yes" patients take their medications or "no" they do not; both the pattern and rate of missed doses is important. Rudd et al. (1989) showed that treatment adherence is a variable behavior. His study showed marked inter- and intra- subject variability in adherence to medication on a week-to-week basis.

Partial adherence encompasses a wide range of adherence behaviors, ranging from taking too little medication to provide benefit, to taking less than 100% of what was prescribed, but enough medication to provide some efficacy. Inadequate partial compliers have demonstrated an understanding of their medical diagnosis, the need for treatment, and an intention to comply, by filling the prescription and taking some of the medication. Nonetheless, most patients who reach this stage of their treatment plan do not achieve full adherence with the prescribed regimen (Cramer, 1995). Throughout the literature, certain aspects of partial adherence have been operationalized and defined.

Specifically, dose frequency adherence is the number of doses taken daily; whereas, dose interval adherence is the number of hours between doses (Cramer, 1995). "Toothbrush" or "white coat" adherence is the phenomena in which patients increased their adherence several days prior to a medical appointment

(Feinstein, 1990). A "drug holiday" is defined as three or more days' interruption in dosing (Urquhart & Chevally, 1988). Adherence can further be classified on the basis of whether the missed dose is intentional or unintentional. Litt and Cuskey (1980) showed five different patterns of nonadherence: 1) when a patient completely fails to take any medications 2) when a patient takes their medications albeit improperly 3) when a patient misses a dose 4) when a patient increases or reduces the dose or daily number of doses 5) when a patient takes their medications but for the wrong purpose or they take outdated or discontinued drugs.

Despite all of these aspects of partial adherence, the main way adherence is calculated in research studies is to express the percentage of the doses taken divided by the total number of doses (Dunbar, 1983); thus, the timing of doses has historically not been utilized. Yet, electronic monitoring has shown that both delays and omissions are the predominant medication error by patients (Osterberg & Blaschke, 2005). Six patterns have emerged among patients being treated for chronic illnesses who continue to take their medication: 1/6 patients have perfect adherence, 1/6 take nearly all of their doses but with some timing irregularity, 1/6 miss an occasional single day's dose and have some timing inconsistency, 1/6 take drug holidays three to four times a year with occasional omissions of doses, and 1/6 take few or no doses while giving the impression of good adherence (Urquhart, 2002). Thus, a "V"-shaped curve is typical of long-term regimens of

asymptomatic conditions, since dosing the day or two prior to scheduled visits is usually correct (Litt & Cuskey, 1980). In Urquhart's study (2002), drug holidays increased from 18% the first month of therapy to over 50% after six months.

Average adherence rates are typically higher among patients with acute conditions, as compared with those with chronic conditions (Osterberg & Blaschke, 2005). In addition to the split in adherence rates between acute and chronic conditions, there are also differences in adherence between physical and psychiatric diagnoses. Psychiatric diagnoses are associated with even further decreased medication adherence than non-psychiatric illnesses (Haynes, 1976). Compared with nondepressed patients, the odds are three times greater that depressed patients will be noncompliant with medication treatment recommendations (DiMatteo et al., 2000).

The average rates of adherence in clinical trials can be remarkably high, owing to the self-selection bias of patients who are motivated to be involved in research and because of the attention they receive. Yet, even clinical trials report average adherence rates of only 43-78% among patients receiving treatment for chronic conditions, like depression (Cramer, Rosenheck, Krik, Krol, & Krystal, 2003). Adherence should be monitored during the conduct of a trial in order to safeguard the power of the study. Adherence data is also helpful in the interpretation of trial results, to avoid both erroneous conclusions and to enrich the value of the data (Stichele, 1991). Indeed, a recent review stated that

"collecting adherence data from subjects is now considered an essential part of clinical trials" (Osterberg & Blaschke, 2005).

If adherence goes unmeasured, it can significantly alter the results of clinical drug trials in the form of Type I and Type II errors. High levels of nonadherence in a clinical trial increases the risk of a "Type II" error, which is when researchers find no significant difference in drug action between the substances compared, when there is a real difference. Differential adherence with experimental regimens can lead to a "Type I" error, which is when a researcher reaches the false conclusion that a less effective treatment is superior to a more potent one, if, for whatever reason there is less adherence with the more potent treatment (Stichele, 1991).

Electronic monitoring reveals that a surprisingly large fraction of clinically-judged nonresponsiveness is actually nonadherence (Stichele, 1991). It has been found that participants in clinical drug trials who do not follow medication regimens or placebo regimens have poorer prognosis than subjects in the respective groups who do follow instructions (Horwitz & Horwitz, 1993). But what is quantitatively considered "adequate adherence?" There is no consensual standard for what constitutes adequate adherence. Some trials consider rates of greater than 80% to be acceptable, whereas others consider rates of greater than 95% to be mandatory for adequate adherence (Osterberg & Blaschke, 2005). However, it seems that 95% adherence rates are mostly used as a cutoff for

studies involving AIDS. Thus, 80% adherence will be considered adequate adherence in this study.

Antidepressant adherence has been documented to decay over time, with the greatest rates of discontinuation during the first month of treatment (King, Hover, Brand, & Ghazivddin, 1997). Specifically, Lingam and Scott (2002) studied adult antidepressant adherence and found that patient's discontinuation of their medications was a function of time. Specifically, 16% discontinued their medications within the first week, 41% within the second week, 59% within the third week, and 68% within the fourth week. In another study, Hotopf et al. (1997) found 30% adults stopped taking antidepressants within the first month of treatment and 45-60% stopped by three months of treatment.

Over 200 variables have been examined in studies of medication nonadherence under the assumption that nonadherent patients possess a unique set of characteristics that differentiates them from adherent patients (Dolder, Lacro, & Dunn, 2002). The overwhelming number of complex factors that comprise adherence may preclude generalization of findings from one study population to the next (Cromer & Tarnowski, 1989), especially considering the different methodologies used; the lack of clearly operationalized variables; and the significant interactions between mediating behavioral, psychological, environmental, structural, and physical variables (Adams & Scott, 2000).

One view that attempts to simplify the factors affecting nonadherence is the Health Belief Model (HBM). Health beliefs are simply defined as factors that prompt people to engage in certain behaviors because they influence the interpretation of information and experiences that guide behavior (Adams & Scott, 2000). The HBM assumes that certain psychological beliefs plus a "cue to action" contribute to the likelihood of a patient's adherence. A "cue to action" can be either internal (i.e. discovery of a disease) or external (i.e. postcard notification of a doctor's appointment), and triggers the mobilization of health beliefs and subsequent action (Cromer & Tarnowski, 1989).

The specific psychological beliefs that the HBM asserts to be of importance are: the perceived susceptibility of a disease; the subjective estimation of its severity; the estimation of the prescribed regimen's effectiveness in reducing future vulnerability; and the perceived physical, psychological, and financial costs of adherence to the regimen (barriers of adherence) (Adams and Scott, 2000; Becker & Maimon, 1975). Thus, the model indicates that adherence is more likely to occur if the perceived threat of illness (susceptibility and severity) is high and the perceived benefits of treatment exceed the barriers (Adams and Scott, 2000). However, this relationship is not exactly clear, as one study found that perceived severity of illness is a double-edged sword, as low levels of severity inhibit nonadherence, although high levels of severity also tend to immobilize preventative health behavior (Jay et al., 1984). Previous studies

have found that the HBM accounts for 0-20% of the variance in adherence behavior (Adams and Scott, 2000). Despite variability in study designs, consistent positive correlations have been demonstrated between selected health beliefs and adherence, thus underscoring the robustness of the model (Cromer & Tarnowski, 1989).

However, the HBM also has weaknesses. As alluded to in the previously mentioned Cromer and Tarnowski (1989) statement, the robustness of the model has been demonstrated with selected health beliefs. Studies utilizing the HBM as a whole have produced a mixed pattern of findings. However, adherence is typically predicted by various combinations of individual health beliefs, rather than by the precise interaction of variables specified by the model (Horne & Weinman, 1998). The HBM also tends to neglect the possibility that nonadherence can be unintentional (Jay, Litt, & Durant, 1984). An additional assumption of this cognitive model is that a patient acts solely on a rational basis, which is usually untrue (Jay et al., 1984). Patients are often ambivalent, forgetful, careless, or deny their illness (Cramer et al., 1989). Thus, knowledge, attitudes, and behaviors are not necessarily causally linked, as posited by the theory. Finally, its constructs are not adequately operationalized, so different authors have conceptualized the HBM in markedly different ways (Champion, 1984). These methodological differences make it difficult to compare research studies with one another.

Consequences of Nonadherence

Nonadherence is associated with several adverse consequences. For example, if a doctor is unaware of a patient's nonadherence, they may increase a patient's dose or add several other types of medication to the patient's current drug regimen because they think the patient is not responding to the original medication or dose. Therefore, a patient's nonadherence can ultimately lead to an inappropriate change in the treatment regimen (Fotheringham & Sawyer, 1995). Or, the doctor may change the patient's medication altogether if they change a patient's diagnosis based on the patient's initial nonresponsiveness (DiMatteo et a., 2000). Thus, the patient's nonadherence could cause the symptom picture to not be adequately managed by the doctor, which could result in unnecessary hospitalizations, diagnostic tests, and a drain of financial resources (Fotheringham & Sawyer, 1995; Riekert & Drotar, 2002). The physician's actions could also lead to increased medication complications or worsened side effects, which could contribute to a patient's further decline in adherence (Riekert & Drotar, 2002).

Along the same principle, if a person takes a drug holiday and skips three days of medication in a row, they are more likely to experience rebound side effects (Urquhart, 1997), unnecessary levels of symptomatology (Budd et al., 1996), delayed recovery, and symptom relapse (DiMatteo et al., 2000). All of these consequences will increase their likelihood of continued poor adherence (Urquhart, 1997). The bottom-line is that poor adherence, in and of itself may

contribute to a further decline in adherence. Overall, nonadherence leads to patient, parent, and physician frustration in treating children and adolescents (DiMatteo et al., 2000). Of all the medication-related hospital admissions in the country, 33-69% are due to poor medication adherence with a resultant cost of approximately 100 billion dollars a year (Osterberg & Blaschke, 2005).

Factors affecting Nonadherence

Indicators of poor adherence to a medication regimen are a useful resource for physicians to help identify patients who are most in need of interventions to improve adherence. However, over 200 variables have been examined in studies on medication nonadherence, although these have been classified and organized under broad categories (Dolder et al., 2003). Some studies organize the variables as being patient-related, medication-related, or environment-related. Logan (2003) classified them in the following subgroups: 1) disease regimen factors (duration/course of illness, symptom severity, complexity of regimen, efficacy of regimen, side effects of regimen). 2) Patient factors (developmental characteristics, level of autonomy). 3) Interpersonal or attributional tendencies (depressive style, psychological coping strategies, self-efficacy). 4) Peer/family influence (stigma of disease, perceived need for secrecy, family cohesion/conflict, parental support, shared responsibility for regimes). 5) Patient's relationship with the medical team.

Within these categories, several variables have consistently been discussed in the literature as the main variables influencing adherence. These include: treatment expectancy, medication-regimen barriers, doctor-patient interaction variables, demographic variables, cognitive factors, family factors, and psychosocial variables. The evidence is equivocal as to which of these factors is most important and the data does not predict which individual from within an "at-risk" group will become noncompliant (Adams & Scott, 2000). However, the literature surrounding these variables is discussed below.

Treatment Expectancy

As the HBM asserts, one of the main variables that is likely to determine adherence is the patient's perception of the benefit of treatment. If a patient thinks that it is unlikely a medication or treatment will work, then there is little chance that they will follow through and take their medication regularly. On the other hand, compliers are more likely to perceive medication as having a broad range of benefits (Budd et al., 1996). Across cultures, confidence in treatment has been shown to be an important determinant of recovery from somatic and psychiatric ailments (Williams et al., 1998).

However, it is not just a patient's beliefs about medication, in general, that are important, but adherence behaviors have been shown to be strongly related to personal views about specific prescribed medications (Horne & Weinman, 1999).

Also, a patient's initial expectations and attitudes about treatment were the variables most strongly correlated with adherence assessed two months after discharge (Williams et al., 1998). Horne & Weinman (1999) found that medication beliefs were more powerful predictors of reported adherence than the clinical and sociodemographic factors, accounting for at least 19% of the explained variance in adherence. In yet another study, Bush and Iannotti (1988, 1990) found that adolescents' perceptions of the benefit of medication and the severity of their illness were the most important aspects related to adherence.

A patient's willingness to believe that their prescribed treatment will have a positive effect may be related to their perception of the severity of their condition and their previous experience with antidepressant medication. Indeed, Budd et al. (1996) found that patients' perceived severity of symptoms was associated with greater medication adherence. Additionally, in one study, most patients (68%) viewed depression as having negative consequences, but only 39% endorsed depression as a serious condition (Brown et al., 2001). These individuals did not believe that their symptoms could be improved with treatment (Brown et al., 2001). Adams and Scott (2000) found that perceived benefit of the treatment and perceived severity of illness, together accounted for 43% of variance in adherence with adults. Patients who had received prior mental health treatment perceived depressive symptoms as being more chronic in nature and having a greater negative impact on their functioning (Brown et al., 2001).

One of the difficulties in working with children and adolescents is that there is a triadic nature to the doctor-patient relationship that must be managed (Fotheringham & Sawyer, 1995). On one side, there is the child and parents' adherence to doctor's orders. Then, there is the child's adherence to the parents' directions. There are yet to be conclusive studies discerning which attitude is more important in determining adherence, that of the parent or that of the youth. Although, one study described that parental discomfort about pharmacotherapy is a main factor in nonadherence (Williams, Hollis, & Benoit, 1998). The reality is that it is probably not always the child's opinion that is most important or the parents' opinion that is always most important, but it is whichever one dispensing the medication that is most important. This is especially important given the wide diversity of ages in which children become solely responsible for managing their own medication regimens, although the average age at which children first take medication independently is 9.14 years (Bush & Iannotti, 1985). That means some very young children are made to be responsible for their medication regimen even when they lack the necessary developmental skills (Fotheringham & Sawyer, 1995).

Thus, children and adolescent's views about medication should be considered. When a group of adolescents were asked if they needed medication for their mental health problem, between 50-58% of the three diagnostic groups (bipolar disorder, unipolar depression, and schizophrenia) said "no" (Scott, Lore,

& Owen, 1992). Data obtained from hospitalized adolescents with psychiatric conditions suggest that attitudes and beliefs antithetical to medication adherence are common with this subpopulation (Williams et al., 1998).

Sixty one percent of 115 variously diagnosed adolescents reported a lack of positive expectancy and biases against taking medication as part of their treatment plan (Williams et al., 1998). When a group of incarcerated females were asked question, "Do you think a medication of some kind could help improve mood, learning, or behavior problems you have been having?" 43% said "no", 47% said "yes" and 10% said that they were unsure. However, people with previous medication treatment were more likely to say "yes" (Williams et al., 1998). Given the studies outlining the efficacy of fluoxetine in pediatric depression, all of these studies describing adolescents' decreased treatment expectations are discouraging.

Medication Regimen Barriers

Another variable related to adherence posited by the HBM are "barriers to adherence." Janz and Becker (1984) found that "barriers to adherence" were the most powerful predictor of adherent behavior and Logan (2003) showed that the perceived burden of the regimen is a major risk factor. Such barriers include the side effects of medications, the number of doses per day, the number of medications per day, the duration of medication regimens, and the costs of the

medications (Jay et al., 1984; Osterberg & Blaschke, 2005). Many of the barriers to adherence are under the patient's control, so attention to them is a necessary and important step in improving adherence (Osterberg & Blaschke, 2005).

One of the most discussed medication barriers is whether certain side effects prohibit the use of certain medications. Side effects can be rated in severity as mild, moderate, or severe. Evidence regarding the impact of side effects has been equivocal. Traditionally, it was believed that even mild side effects had significant impact on medication adherence (Cromer & Tarnowski, 1989). However, recent data indicates that side effects are related to nonadherence, but to a lesser extent than initially believed. For example, a recent depression study indicated that many of the patients in the sample (89 of 130, or 68%) reported side effects that they associated with the antidepressant medication. Almost half of these (43 patients, or 48%) reported that the side effects were "quite" or "extremely" bothersome. Surprisingly, neither the overall report of side effect nor the report of very bothersome side effects was associated with reported adherence (Sirey et al., 2001). However, a recent review cited that new antidepressant drugs generally have fewer side effects than do older medications, and, consequently, their use results in reduced rates of discontinuation, indicating that side effects are contributors to medication adherence (Osterberg & Blashcke, 2005). Adams and Scott (2000) indicated that the fear of side effects or adverse events is more predictive of nonadherence than

the actual experience of side effects. Thus, a final understanding of the relationship between side effects and medication adherence is yet to be fully determined.

Another medication barrier is the number of doses taken daily. Studies looking at this factor have been equivocal, as Horne & Weinman (1998) found no relationship. However, a large systematic review of 76 trials in which MEMS caps were used, found that there is an inverse relationship between the number of daily doses and adherence (Claxton, 2001). Specifically, using electronic monitoring, adherence rates averaged 76% during 3428 days observed. 87% of the once daily, 81% of the twice daily, 77% of the thrice daily, and 39% of the 4-times daily dosages were taken as prescribed (Cramer et al., 1989).

In looking at the impact of length of medication regimens, Sackett and Snow (1979) showed that adherence is greater in short-term regimens than in the long-term. Overall, simple dosing helps to maximize adherence. Finally, financial obstacles may prevent families from adhering to treatment protocols. It is an unfortunate part of the United States' system of healthcare that individuals without health insurance frequently receive episodic care with little or no follow-up. Even when noninsured patients do receive regular health care, they may still be unable to afford medication over a prolonged period of time (Divertie, 2002).

Doctor-Patient Interaction Barriers

Broadly, health care systems create barriers to adherence by limiting access to health care, using a restricted formulary, switching to a different formulary, and having prohibitively high costs for drugs, co-payments, or both (Osterberg & Blaschke, 2005). But, on a more personal level, another variable that is important in a patient's desire to adhere with their treatment plan is the relationship that they have with their physician. Physicians contribute to patients' poor adherence by prescribing complex regimens, failing to explain the benefits and side effects of a medication adequately, not giving consideration to the patient's lifestyle or cost of medication, and having a poor therapeutic relationship with their patients (Osterberg & Blaschke, 2005).

The knowledge and skills of primary care physicians regarding treatment and their ability to establish rapport, assess patient attitudes and beliefs, and negotiate physician-patient differences in medication beliefs and expectations influence adherence to treatment recommendations (Katon et al., 1995). Patients who perceive their doctors to be friendly and attentive are more likely to be adherent (Fotheringham & Sawyer, 1995). Additionally, if a patient does not trust their doctor's assessment, diagnosis, prognosis, and treatment plan, then it is less likely that they will be adherent (Cramer, 1995). In fact, studies have shown that the mother's belief in the accuracy of the diagnosis and their perceptions that the child was "easily susceptible to disease," resulted in improved adherence

(Cramer, 1995). Mothers who expected to learn the causation and the nature of their child's illness and failed to do so were less likely to be satisfied than any other group of patients (Francis, Korsch, & Morris, 1969).

Thus, adherence to treatment appears to be high when both practitioner and patient have common representations of the illness, they agree upon treatment procedures, and they share criteria for outcome appraisals. Nonadherence is common when these discrepancies arise (Leventhal, Leventhal, & Diefenfach, 1992). Additionally, practical aspects of the patient-physician interaction have been shown to be important. For example, long waiting times at office or clinic visits are strong deterrents for continuing treatment (Jay et al., 1984). When the doctor-patient encounter is brief, and characterized by impersonality, patient adherence is reduced (Fotheringham & Sawyer, 1995).

Treating children, adolescents, and their families requires flexibility and responsiveness to individual problems. It is also complicated by the triadic nature of the doctor-parent-child relationship. Doctors need to educate both the parents and the patients about the necessity of medication adherence and to address any concerns the patient or family might have. For example, when a doctor prescribes medication, they determine the number of doses per day to provide for a nearly steady-state drug concentration. However, when a patient takes doses too close together or too far apart, these considerations are lost. Taking doses too close in time could increase adverse effects, whereas taking doses too far apart could

diminish the efficacy if drug concentrations fall below a threshold needed for the individual patient (Cramer, 1995). Both of these scenarios could subsequently decrease adherence, thus these principles are important to impart upon the patient. Jay et al. (1984) found that the amount of physician instruction was associated with the accuracy of the patients' perceptions of what the physician expected, which in turn was related to adherence with medical advice.

Family Barriers

Family dysfunction (conflict, hostility, negative affect, low cohesion) is associated with depressive illness (Downey & Cayne, 1990; Fleming & Offord, 1990; Gillham et al., 2000; Garber & Flynn, 2001; Tamplin & Goodyer, 2001). However, it is unclear whether the family functions poorer as a reaction to the depressed member, or whether the patient's depression is a result of the family dysfunction (DiMatteo et al., 2000). It has been established that early-onset major depression is highly familial, and has a strong genetic component. However, environmental factors, such as disrupted parent-child attachments and poor parent-child bonding may mediate the impact of parental depression on children's symptoms (Weissman et al., unpublished). The possibility of increased dysfunction in the families of children and adolescents with MDD has major ramifications for the likelihood of continued adherence.

Specifically, five of six studies showed greater adherence among patients whose families were supportive (Litt & Cuskey, 1980). The social support of parents and siblings have been found to indirectly influence patient adherence by enabling patients to overcome barriers to adherence such as psychological strain or environmental stressors (Fotheringham & Sawyer, 1995). However, families, in which one of the members of the parental dyad is depressed, might not have the emotional resources to provide support to their depressed children. Thus, adherence might suffer.

If the family is a source of stress and not a source of support, then this may overwhelm the child further (Fotheringham & Sawyer, 1995). Studies have shown that depressed children describe their families as less cohesive and supportive, and less able to communicate effectively (Barrerra & Garrison-Jones, 1992; Cole & McPherson, 1993). Moreover, in observational studies of families with preadolescent children, parents of depressed children displayed less positive, rewarding, and supportive behaviors than did parents in comparison families (Cole & Rehm, 1986; Messer & Gross, 1995). Dysfunctional interactions and poor communication significantly related to nonadherence have been consistent findings in several studies that evaluated families of adolescents (Cromer & Tarnowski, 1989). This data questions whether depressed families are able to consistently help a youth take their medications in a proactive, organized, and nonpunitive manner. Another possible barrier to medication adherence is if the

patient's family is opposed to the medication regimen. Bush and Hardon (1990) found that medication use, family beliefs, and health-related practices are instilled in children by school age and influence their readiness to take prescribed medication. Thus, if a patient's family is negative and unsupportive about medication treatment early in their life, the patient may carry this belief for years to come, and may be less compliant as an adolescent or adult.

Additionally, medication adherence in youths is complicated because adherence depends not only on the adherence of the patient, but that of the parent, and other family members. While adolescents are more knowledgeable about their disease than younger children, mothers are the most knowledgeable group. The team of mother (or parent) and child working together may be the most effective for disease management than the youngster working alone (LaGreca, 1990). If this combined teamwork is not in place, errors in medication adherence may occur. Specifically, if children self-administer their medications independently, caregivers may be unaware of episodes of nonadherence and may be misled by children reluctant to acknowledge decreased use (Riekert & Rand, 2002).

Even if the patient has a supportive, caring, and cooperative family, the individual characteristics of the patient may interfere with the family's assets. For example, if the patient is an adolescent, then they are involved in the developmental stage of establishing their autonomy (Jay et al., 1984). This may

mean that they insist on dispensing their own medication and reject the help and support of their family; thus the allocation of dispensing medication may remain unclear (Fotheringham & Sawyer, 1995). This is especially relevant in families with a depressed member, as previously cited studies indicate that communication is often impaired (LaGreca, 1990). On one hand, adolescents may not have consistently reliable supervision of their treatment (Divertie, 2002), but on the other hand, forcing the dependency of an adolescent would likely be a chronic source of conflict for an adolescent with depression (Cromer & Tarnowski, 1989).

Psychosocial Barriers

A patient's peers can have an effect on their adherence, especially if they are concerned about "fitting in" with their friends. Certainly, for most, "fitting in" and being one of the "cool kids" does not include taking antidepressant medication, as the mentally ill are still one of the most stigmatized groups (Link et al., 2001). A patient's level of self-esteem is important during adolescence, but if depressed adolescents compare themselves against their 'normal' peers, the comparison may produce feelings of defectiveness and low-self esteem, which is contraindicated with adherence (Scott et al., 1992). Perceived stigma is the belief that most people will devalue and discriminate against individuals who use mental health services and/or have a mental illness (Sirey et al., 2001). The Surgeon General's report on mental health highlighted stigma as a powerful obstacle to

seeking care (Sirey et al., 2001). On a macro level, Jorm and Korten (1997) found that the public more often perceives psychiatric medication as harmful rather than helpful. Sirey et al. (2001) found that perceived stigma was sufficient for people to discontinue their psychiatric treatment, as subjects want to avoid the stigma, both publicly and personally, of taking medication.

This is even a more sensitive topic for children and adolescents because of their current developmental stage. In early adolescence, the process of identity formation causes them to be concerned with physical appearance and fitting in with their peer group (Divertie, 2002). Being ill and receiving medical care can imply a need for more supervision, dependence, and difference from others in a peer group, which is undesirable in adolescence. In one study, most adolescents (56%) felt that they needed to hide their conditions from peers to avoid negative appraisals and stigmatization (Williams et al., 1998). Indeed, most pediatric patients had not told their friends because they were fearful of being teased and fearful of being thought of as "crazy." Feelings of social isolation often accompany adherence difficulties (Scott et al., 1992). If children and adolescents choose to discontinue their medications, then their depressive symptoms, including withdrawal, social isolation, and anhedonia, are likely to lead to further endorsement of interpersonal problems and increased feelings of depression.

Demographic Influences

Many demographic variables (age, gender, and race) have been studied previously in the adherence literature, and they have not been consistently associated with certain levels of adherence (Haynes, et al., 1979; Jay et al., 1984; Litt & Cuskey, 1980). However, some data indicates that adolescents are less adherent than young children and adults (Cromer & Tarnowski, 1989).

There are several developmental issues pertinent to adolescents that relate significantly to their ability and willingness to comply with medical advice. One of the most important developmental differences between adolescents and adults is their level of cognitive ability (Cromer & Tarnowski, 1989). According to Piagetian theory, the final stage of cognitive development is termed formal operations, which represents a transition from thinking at a concrete level to an ability to solve problems logically and abstractly (Ginsburg & Opper, 1979). The age of acquisition of formal thinking differs from teenager to teenager; thus, a normal adolescent may lack to the ability to foresee the long-term consequences of their health behavior (Cromer & Tarnowski, 1989).

Another developmental task of adolescence is affective individuation and separation from the family (Cromer & Tarnowski, 1989). As stated by Lidz (1983), 14- to 15-year-old children "cannot continue to regard themselves as children dependent upon their parents and must begin to feel capable of directing their own lives." As teenagers get older, they gradually assume more control over

all aspects of their life, culminating in their emergence into the world as a mature adult.

Cognitive Factors

Cognitive development affects the adolescents' capacity for medication adherence and their motivation for treatment adherence due to the interaction with 1) memory 2) perception of time 3) understanding of abstract concept such as causality and consequences (Williams et al., 1998). Thus, complex cognitive processes are required to understand the varied presentation of depression symptoms, the multiple causes of depression, and the factors that contribute to the severity of the symptoms. Illness cognitions have five distinct components: identity, cause, timeline, consequences, and perceived controllability. Even when patients do recognize that they have depression, they may not understand the seriousness of the disorder, its clinical course, its impact on functioning, and its amenability to treatment. For example, although some adolescents are capable of abstract reasoning, they tend to focus on the here and now (Muscari, 1998) and not on long-term consequences.

Because an adolescents' level of cognitive development is hard to assess, there are few studies documenting it (Cromer & Tarnowski, 1989). However, of the studies that do exist, one of the major trends in medication adherence in children and adolescents is that once they have a remission of symptoms, then

they think that they are well, and they discontinue treatment prematurely (Emslie, personal communication). Generally, adolescents do not tend to believe they are well until they have stopped medications.

People have beliefs about medications in general as well as beliefs about specific medications prescribed. However, certain medication beliefs appear to be common across several illnesses and cultural groups. Williams et al. (1998) studied attitudes about psychiatric medications among incarcerated female adolescents. Specific concerns about medication included, "Medicine is hard to swallow, tastes bad (44.4%)," "Medicines are a crutch; people should solve problems on their own (33.2%)," "Medicines might change my personality and not let me be myself (30.8%)," "I don't want others to know about my medicine—I might get teased," "Medications might cost too much for my family," "The medication might make me feel sick or hurt me (52.8%)."

Direct Measuring of Medication Adherence vs. Indirect Measures

Several approaches to measuring adherence have been used. They include physician estimate, self-reports, electronic monitoring, pharmacy records of medication-dispensing patterns, pill counts, medication diaries, and drug levels. The methods available for measuring adherence can be broken down into direct methods of measurement (drug levels) and indirect methods of measurement (physician estimate, self-report, pharmacy records, pill counts, electronic

monitoring, and medication diaries). The general conclusion is that each of these assessment methods has potentially serious limitations in validity and reliability (Riekert & Rand, 2002).

Direct Measures

Blood Levels

The quantitative analysis of blood to determine the levels of a drug's metabolite is an example of a direct and objective method of measuring adherence (Jay et al., 1984). However, this adherence measure is limited by the individual differences in rates of metabolism. It is also limited by the necessity to perform a blood stick, which is a painful, time-consuming, costly practice (to both the patient and the health care provider) (Jay et al., 1984). One other limitation is that rapidly cleared drugs achieve drug serum concentrations near target levels after several doses. Appropriate administration for a few days before a scheduled blood test could result in drug concentrations that are reasonably close to target. Thus, "spot concentrations" can reflect medication taking over very short intervals and may not be representative over longer periods of time (Cramer, 1995). Thus, serum concentrations are most helpful with drugs that are taken chronologically, have a long half-life, and reach a steady state level in blood (Cramer et al., 1989). With drugs such as these, measuring levels is a good and commonly used means of assessing adherence.

Several articles in both adults (Jannuzzi et al., 2002) and children (Wilens et al., 2002) have noted the between-subject variability in patients' steady states. Wilens (2002) was the first prospective trial to evaluate fluoxetine and norfluoxetine levels in children and adolescents with MDD and obsessive-compulsive disorder (OCD). He found that the mean steady state fluctuated from 28-312 ng/mL, with mean steady-state fluoxetine levels being 127 ng/mL and mean steady-state norfluoxetine levels being 151 ng/ML. However, Wilens (2002) had no measure of adherence in his study, to ensure that patients were actually taking their medication.

Indirect Measures

Physician Estimate

One indirect method of medication adherence is physician estimates. Physician's estimates were initially thought to be reliable because doctors have experience with a wide range of patients, so they might be able to make meaningful distinctions in adherence behaviors among patients (LaGreca, 1990). While it would be logical to assume that experienced physicians might become adept at estimating adherence among their own patients, studies have shown this not to be true. Whether it is because physicians need to believe that the patient follows their advice and accepts their authority or simply because they have a low index of suspicion, the physicians' estimates of the patient's adherence cannot be

relied upon as an accurate measure in most clinical situations (Jay et al., 1984). The ability of physicians to recognize nonadherence is historically poor, as they tend to overestimate adherence (Jay et al., 1984).

In one study by Davis (1966), medical students were found to be better than attending physicians in identifying patient nonadherence. In another study, the correlation between actual adherence and physician's estimates was 0.48 indicating that physician's judgment was better than chance, but low in accuracy. Physicians' estimates did not improve as they gained familiarity with patients (Roth & Caron, 1978). Doctors overestimated their patient's adherence by 50% whereas patients overshot it by 100% (Roth & Caron, 1978). Part of the reason doctors are bad at estimating adherence is the assumption that if patients are keeping their appointments, then they are compliant with their medications (Feinstein, 1990). However, patients can continue to keep appointments even though they are not taking medications.

Pill Counts

Pill counts are one of the most commonly used methods to track adherence. It requires the patient return the medication bottle at the time of the appointment, so that the remaining pills may be counted and discrepancies between the number remaining and the number prescribed documented (Jay et al., 1984). Although the simplicity and empiric nature of this method are attractive to

many investigators, pill counts are problematic because patients can switch medications between bottles and they can discard pills before visits in order to appear more compliant and "please the doctor" (Jay et al., 1984; Osterberg & Blaschke, 2005). "Dumping" is defined as intentionally discarding medication to look more compliant (Riekert & Rand, 2002). For these reason, pill counts should not be assumed to be a good measure of adherence. In addition, this method provides no information on other aspects of taking medications, such as dose timing and drug holidays (Osterberg & Blaschke, 2005).

Other problems associated with pill counts include the pharmacist's or research assistant's error in initially filling the prescription and the patient's forgetting to bring medication to the visit (Litt & Cuskey, 1980; Jay et al., 1984). If a pill count is used, adherence is reported as the number of pills removed/number of pills prescribed x 100% (Litt & Cuskey, 1980). Adherence via pill count overestimated adherence by 10% compared to urine analysis (Litt & Cuskey, 1980). The correlation between electronic monitoring and pill counts range from 0.17 to 0.52 (Riekert & Rand, 2002).

Medication Diaries

Medication diaries are forms that both patients and parents can fill out at home, which document a patient's adherence, day-by-day. Medication diaries also have space for parties to state why certain doses were omitted. The identity

of the person collecting the medication diaries makes a difference, because if doctors are collecting them, then patients tend to tell doctors what they think the doctor wants to hear; not the truth. However, people tend to be more truthful when questioned by a medical student or research assistant, who is not directly involved in the therapeutic relationship. This is because the patient does not fear the repercussions of their nonadherence (Cramer et al., 1989). With medication diaries, patients who admit to poor adherence also appear to be nonadherent based on more objective measures (LaGreca, 1990).

Self Report

One of the simplest and most practical ways of assessing adherence is to ask the patient if they are taking the medication as prescribed. If this is done in a nonthreatening, nonjudgmental manner, about half of the noncompliant patients will admit to missing at least some of their doses (Jay et al., 1984). It can be reassuring to the patient when the physician tells them, "I know it must be difficult to take all of your medications regularly. How often do you miss taking them?" This approach makes the patient feel comfortable in telling the truth and facilitates the identification of poor adherence (Osterberg & Blaschke, 2005). While a patient who admits to poor adherence is generally being candid (LaGreca, 1990), even patients who confess that they are not taking some of their medications will overestimate the extent of their adherence by at least 20%, on

average (Haynes, 1982). Thus, self-report measures can be susceptible to misrepresentation and tend to result in the health care provider's overestimating the patient's adherence (Riekert & Rand, 2002). Stephenson et al. (1993) confirms that the sensitivity of self-report is less reliable, as self-report overestimates adherence by 17%. Additionally, self-reports only identify 25% to 50% of the noncompliant subjects (Stichele, 1990).

Asking patients about their adherence is a start, but it should be supplemented with family/caregiver reports and objective measures of adherence. Multiple methods should be used when possible, especially combinations of subjective and objective measures of adherence. Assessing secondary outcomes, such as functioning and quality of life are also crucial measures that must continue to be examined in order to gain a better understanding of an intervention's effects (Dolder et al., 2003). When patients are being questioned about their medication use, they should also be asked about side effects, whether they know why they are taking medications, and the medications' benefits, since these questions can often expose poor adherence (Osterberg & Blaschke, 2005).

Electronic Monitoring

Electronic monitoring is another indirect, albeit objective way to measure adherence. Electronic monitoring provides the most accurate and valuable data on adherence in difficult clinical situations and in the setting of clinical trials and

adherence research. It has advanced our knowledge of medication-taking behavior; (Osterberg & Blaschke, 2005) thus, it has fast become the gold standard (Cramer et al., 1989). Rather than providing weekly or monthly averages, these devices provide precise and detailed insight into patients' adherence behavior (Osterberg & Blaschke, 2005). For example, electronic monitoring results reveals poorer adherence rates than by any other measurement strategy, with an average recorded adherence below 70%. When dosing intervals are accounted for, adherence is even lower, around 30-60% (Riekert & Rand, 2002). However, MEMS caps are still considered an indirect adherence measure, as they do not document conclusively whether the patient actually ingested the correct drug or dosage (Riekert & Rand, 2002). Specifically, patients may open the container and not take the medication, take the wrong amount, invalidate the data by placing the medication into another container, or take multiple doses out of the container at the same time (Osterberg & Blaschke, 2005).

The strengths of electronic monitoring are that it provides more complete longitudinal information than other methods (physician estimates, self-reports, medication diaries, pill counts, blood levels), and it does not rely on a patient's memory. Electronic monitoring can explain and define differences in outcomes between subsets of patients (Riekert & Rand, 2002). MEMS caps allow doctors better understanding of whether a medication, or dose, has failed because of a lack of efficacy or failure of the patient to take the medication as prescribed

(Cramer, 1995). Furthermore, MEMS caps have not been tested before in depressed adolescents, so there is a robust opportunity to contribute to physician's understanding of adherence in pediatric depression.

However, there are also several disadvantages of using MEMS caps, the first of which is the cost. MEMS caps are not covered by insurance, so the devices are not in regular use (Osterberg & Blaschke, 2005). Other disadvantages of MEMS caps include the reality that they can be inaccurate, as an opening of the cap does not always mean someone ingested the pill. However, it is unlikely that volunteer patients would take the time to regularly open the bottle at set intervals but not consume the medication (Riekert & Rand, 2002). Another limitation is the MEMS caps inherent interference with existing adherence routines, like popular pillboxes with compartments for daily dosage. Or, participants may have medications in different places (home, school), and may be difficult to monitor all locations (Riekert & Rand, 2002). Researchers must also inform patients that they will be monitoring subjects' adherence, and it is not fully understood what the effects of this behavior are (Riekert & Rand, 2002). There is also a relative frequency of missing data with the MEMs cap (0-24%) due to device malfunction, unreturned devices, and participants using other medication devices, take devices apart, or damaging devices (Riekert & Rand, 2002).

CHAPTER III

METHODS

Subjects

From 2004-2006, subjects were recruited from clinical referrals and newspaper and radio advertisements to the general child and adolescent outpatient clinic and pediatric psychopharmacology services at Children's Medical Center of Dallas (CMCD). All subjects were either enrolled in the NIMH Relapse and Remission (R & R) in Children and Adolescents with MDD study (Emslie, principle investigator, 2000) or the Relapse Prevention (RP) study (Kennard, principle investigator, 2005). R&R is a randomized controlled trial investigating the course of illness in children and adolescents with nonpsychotic depression when fluoxetine is continued or discontinued after 12 weeks of open label treatment. The RP study is a randomized controlled trial investigating the efficacy of medication management alone or fluoxetine plus cognitive behavioral therapy (CBT) to prevent relapse after a 12-week acute phase, open trial of fluoxetine in children and adolescents with MDD. Treatment was preceded by a 2-week (3-visit) diagnostic evaluation to verify eligibility for enrollment. Enrollment required DSM-IV diagnoses of MDD based on the K-SADS-PL, a CDRS-R score $\geq$ 40, and a CGI-S score $\geq$ 4.

Additionally, a subset of R & R patients and RP patients had their medication adherence tracked for 12 weeks using electronic monitoring, blood levels, physicians' estimates, self-report, pill counts, and medication diaries.

Informed Consent

Approval was obtained from the University Institutional Review Board (IRB) and written informed consent was obtained from all subjects. Specifically, the consent form was read, discussed, and a research assistant was available to answer questions. The patient and their guardian then signed the consent form before any study procedures were initiated. Participants were free to withdraw from the study at any time. The patient and their guardian also signed the HIPAA Authorization for Use and Disclosure of Protected Health Information form prior to the initiation of the study. The patient's guardian received a copy of the consent form and the HIPAA Authorization form.

The "Dear Parent" Letter (dated September 29, 2004) regarding the FDA meetings on September 13-14, 2004 on the use of antidepressants in children and adolescents was given to the patient and their guardian at their first visit. The family was informed that they could contact Dr. Graham Emslie if they had any additional questions regarding the FDA Advisory Committee findings or recommendations. The family was also told that they would become informed as new information became available.

Inclusion Criteria

For the R & R study, outpatients must have been 7-18 years of age and still attending school. For the RP study, outpatients must have been 11-18 years of age and still attending school. Thus, older adolescents who had left school were not included, as school functioning was a major assessment area in this age group and an item on the severity scale (CDRS-R). The patient must have had a primary diagnosis of non-psychotic major depressive disorder (single or recurrent) for at least four weeks as defined by DSM-IV with a CGI $\geq$ 4 for depression and CDRS $\geq$ 40. The patient must have been in good general medical health and of normal intelligence, i.e. IQ > 80 based on the WISC-III, if concerns about intellectual capabilities were evident on clinical assessment.

Exclusion Criteria

For both R & R and RP studies, subjects were excluded if they had any lifetime history of a psychotic disorder, including psychotic depression. Other diagnoses that excluded a patient from participating were bipolar I or II disorder, alcohol or substance abuse or dependence within the past six months, and a lifetime history of anorexia nervosa or bulimia. Other groups which were also excluded were pregnant or lactating females, sexually active females not using medically acceptable means of contraception (IUD, birth control pills or barrier devices), those with chronic medical illness requiring regular medication, those on

medication(s) with psychotrophic effects (anticonvulsants, steroids, etc), patients with first degree relatives with Bipolar I disorder, or subjects with severe suicidal ideation or a previous history of serious suicide attempt. Subjects were excluded if they had failed on a previously adequate treatment of fluoxetine (defined as at least 20mg/day for 4 weeks). While MDD must have been the primary cause for dysfunction, other concurrent disorders (anxiety, attention deficit hyperactivity disorder [ADHD], or conduct disorder) were not excluded. Subjects with ADHD who were stable on a stimulant or Strattera (as rated by a clinician) were eligible for the study.

Inclusion of Women, Minorities, and Children

Based on the 2000 census, the population of Dallas County is approximately 2.2 million people, with the following ethnic group breakdown: 0.6% American Indian, 4.4% Asian, 20.8% African American, 29.9% Hispanic, and 30.7% Caucasian, with a male to female ratio of 49.9% to 50.1% (http://www.nctcog.org/ris/census/sf1.asp?Geo=County &Area=113). Thus, males and females were recruited in equal proportions. The ethnic distribution of the participants in the study strived to represent that of Dallas County. No ethnic group was excluded. This study included youth from 7 to 18 years of age. This age group meets the NIMH definition of a child.

Procedures

Diagnostic Evaluation

Patients referred to either the R & R or RP studies were screened by telephone for possible inclusion in the study using a standard screening form. Appropriate subjects were scheduled for an initial diagnostic interview. After informed consent was obtained from the parent(s) and assent from the patient, research personnel trained in conducting clinical evaluations interviewed the parents and patient separately. The same interviewer interviewed the child and parent using the K-SADS-PL, so that the course of illness and a consensus diagnosis could be generated, based on the information obtained from the interviewer. The severity of depressive symptoms was also assessed using the CDRS-R and CGI-S. The interviewer also obtained a general family psychiatric history from the parent(s).

Following the initial diagnostic interview, subjects were scheduled for a repeat diagnostic interview, which an experienced, trained clinician (psychologist or psychiatrist) conducted five to ten days later. In that interview, the subjects and parents were interviewed separately using the K-SADS-PL, covering all criteria symptoms on the depression and mania items of the K-SAD-PL, as well as any comorbid disorders that were present (either full diagnosis or subthreshold symptoms) at the initial visit. Information about course of illness was also confirmed during the interview. The severity of depressive symptoms was

assessed using the depression items of the semi-structured interview, the Clinical Global Improvement Ratings (CGI) and the Childhood Depression Rating Scale–Revised (CDRS–R). During both diagnostic visits, the severity of depressive symptoms was also assessed using the Children's Global Assessment Scale (CGAS), the Child's Family Global Assessment Scale (FGAS), and the Quick Inventory of Depressive Symptomatology-Clinician rated (QIDS-C) (Rush et al., 2003).

During the screening phase the child also had a physical examination and blood test to check their general health status. A urine drug screen was also done at that time. Females of childbearing age were given a urine pregnancy test. Subjects who met all inclusion criteria and did not meet any exclusion criteria were scheduled for a baseline visit. At baseline, the psychiatrist assessed the patient. This same psychiatrist followed the patient and their family, whenever possible, throughout the acute phase of treatment, to ensure consistency of care. If the patient met criteria for MDD on the K-SADS-PL and had a CDRS-R $\geq$ 40, then they began active medication treatment. If subjects were unable to come in for visits within these scheduled windows, they were not excluded. However, a note to file was written for each case where the schedule was not kept.

Consensus Evaluation

The diagnostic information of a patient was reviewed in a consensus diagnostic conference chaired by Dr. Emslie, to minimize discrepancies between the two separate diagnostic evaluations. All subjects received a consensus staffing following the two evaluation visits. At this meeting, all inclusion and exclusion criteria, rating scales, current and lifetime diagnoses, and course of illness were discussed among all psychiatrists and research staff to determine consensus diagnoses and plan of action. Additionally, all subjects were also discussed briefly (regarding response and any concerns) at each weekly meeting.

Active Treatment

Child and adolescent outpatients who met the inclusion and exclusion criteria and completed a two-week, three visit diagnostic evaluation were treated openly during acute phase treatment with fluoxetine for 12 weeks by Dr. Graham Emslie and his research staff. Participants started at 10 mg for the first week and were then increased to 20 mg. In order to allow the treatment response to be maximized, after six weeks of treatment, the dose could be increased to 40 mg if the child was showing insufficient response. During the 12 weeks of active treatment, Children's Depression Rating Scales (CDRS-R), Clinical Global Improvement Scales (SGI-Severity), and Clinical Improvement Scales (CGI-Improvement) were completed based on child and parent interviews. Additional

self-report measures were also obtained at this time, including family measures, school measures, and treatment expectancy measures. Demographic variables (gender, age, and race) were also collected. Blood tests were done at week 6 and week 12 to determine fluoxetine and norfluoxetine blood levels.

Fluoxetine blood samples were collected in serum red top vacuum collection tubes. Fluoxetine/norfluoxetine was extracted from serum using a solid-liquid, followed by liquid-liquid extraction. In a third extraction, fluoxetine/norfluoxetine was back-extracted from the organic phase into a small volume of acidified aqueous solution, and an aliquot of the aqueous phase was analyzed by high-pressure liquid chromatography. The extraction and injection steps have been entirely automated by the use of the Gilson ASPEC Specimen Processing System. The detection limit for fluoxetine or norfluoxetine was 20 ng/mL (Nichols et al., 1992).

Additionally, the subset of patients in active treatment who had their medication adherence closely tracked were given a special pill container that had a microprocessor in the cap (MEMS caps), that recorded the date, time, and duration of each container opening. The MEMS caps in this study had no cuing mechanisms and their appearance was similar to any other medication bottle. These participants were given the following instructions about the cap, “the medication bottles given to you are important because they keep track of the doses of medication your child receives. For this reason, there are some

instructions to help all of us stay on the same page: open the package only when it is time to take the medication. Remove the dose. Close the package immediately. Take medication right away. Remember to record taking medication on medication report forms. Both parent and child should fill in their own forms. Do not remove the medication and put it in another package, or your record will be incomplete. Bring the medication bottle with cap and medication report forms to every visit."

While controversial, the decision to inform patients was done from a practical standpoint, as patients needed to bring their MEMS caps to every visit, to have the bottle read. Additionally, disclosure was necessary, as they were barred from using other medication containers and pillboxes.

Once medication was prescribed, patients came in for eight subsequent visits (Visit 1, 2, 3, 4, 6, 8, 10, 12). Each week, the patient saw the psychiatrist and a research assistant, who performed independent pill counts to assess the number of pills remaining in contrast to the number of pills prescribed. Patients were also asked who administered the medications ("parent or patient"). Both patients and parents were asked to keep separate medication diaries to detail the number of missed doses and the reason for the omission. Families were reminded to bring in their medication diaries at each visit. Parents and patients were also asked to circle on a piece of paper, whether they "did not take any medications, took less than half, took half, took most, or took all of their medications." At the

end of the acute phase of treatment in the R&R study, each psychiatrist was asked to rate whether they believed patients were adherent or nonadherent, and their reasoning for their belief. They were also asked to rate whether the patient experienced any side effects from the medication, and whether they believed the patients were clinical 'responders' or 'nonresponders.'

Patients with problems with adherence in the acute phase of treatment were likely to have problems in the continuation phase of treatment. However, establishing stringent criteria for dropping subjects who were nonadherent during the acute phase would lead to a non-representative sample. Thus, it was determined that subjects would be discontinued if they were deemed to be non-compliant (< 70% of pills taken) on two consecutive visits or a total of three visits during the course of the acute phase of treatment. Noncompliance in this instance was determined using pill count data. Participants were also withdrawn from the study if they required additional medications/treatments not allowed in the protocol (medications other than stimulant medication or any specific psychotherapy beyond supportive management provided through the trial).

At week 12, the child was evaluated by the doctor and by an independent evaluator. Clinician-rated outcome measures were based on the scores obtained by the treating physician. The primary outcome measures were the CDRS-R and the CGI-Improvement score. Based on these scores, participants were either classified as a "responder" or "non-responder." Responders were further divided

into “remitters” or “adequate clinical responders” (ACR). Remission was prospectively defined as a CDRS-R raw score of 28 or less and a CGI-Improvement score of 1 or 2. ACR was defined as a decrease of at least 50% in the CDRS-R raw score adjusted for minimum score of 17 and a CGI-Improvement score of 1 or 2.

Diagnostic Measures

While a multitude of self-report measures were obtained as part of the R&R and RP studies, only the measures relevant to the current study will be detailed.

The Schedule for Affective Disorders and Schizophrenia for School-aged Children - Present and Lifetime Versions (K-SADS-PL)

The K-SADS-PL (Kaufman et al., 1997) is a semi-structured interview designed to determine present episode and lifetime history of psychiatric illnesses, according to DSM-IV criteria. Probes and objective criteria are provided to rate individual symptoms of various disorders. The K-SADS-PL allows for a rating to be scored for both the worst part of the episode and for the past week. The scale uses a zero to three-point rating scale to rank the severity of a symptom. A score of zero indicates the symptom is not present, and a score of three means the patient “meets criteria.” To address differential diagnoses, the K-SADS-PL

includes five supplements for affective disorders; psychotic disorders; anxiety disorders; behavioral disorders; and substance abuse, eating, and tic disorders. The data is synthesized using the interviewer's best clinical judgment to generate DSM-IV Axis I child psychiatric diagnoses.

The K-SADS-PL is administered first to the child and then to the parent(s), and both parties may be re-interviewed to solve any discrepancies. In this study, the KSADS will be used to obtain diagnostic information as it pertains to eligibility. Inter-rater reliability is 1.0 for depressive disorders and test-retest reliability for MDD and other affective disorders was 0.77-1.00 (Klein, 1993). Convergent and discriminate validity have been established as well.

Children's Depression Rating Scale-Revised (CDRS-R)

The CDRS-R (Poznanski et al., 1984) is a 17-item clinician-rated instrument that assesses the presence of depressive symptoms during the past two weeks in youth. It is a semi-structured interview that can be administered to children, adolescents, parents, teachers, and caseworkers in approximately 30 minutes. Seventeen symptom areas are assessed by the scale, the last three of which are evaluated using the child's nonverbal characteristics. While it was originally developed to assess depression in children aged 6-12, the CDRS-R has also demonstrated strong psychometric properties, including concurrent and predictive validity, in studies with adolescents (Emslie et al., 1997).

Each item is rated on a 1 to 5 or 1 to 7 point scale, with a "1" describing the absence of the given symptom. The CDRS-R yields a total score from 17 to 113, with a score of $\geq$ 40 considered to be compatible with a diagnosis of depression. Poznanski et al., (1984) conducted reliability and validity studies in a hospitalized pediatric population, a child psychiatric inpatient population, three outpatient child psychiatry clinics, and in an elementary school. The inter-rater reliability yielded a correlation coefficient of 0.86 (n=53). The CDRS-R was found to be a reliable measure of the severity of depression with sound internal consistency, which was able to discriminate depressed from non-depressed children and was insensitive to the age of the child interviewed. High inter-rater reliability, with four raters and 25 subjects, was evidenced by a product-moment correlation of 0.92. The CDRS-R has been used successfully in psychopharmacology studies for some time and allows for ready comparison to be made across studies. For the fluoxetine trial, the CDRS-R had good inter-rater reliability (intra class correlation was 0.95) and correlated highly with global ratings of improvement (Emslie et al., 1997).

Clinical Global Improvement Scale (CGI)

The CGI (National Institute of Mental Health, 1970) will be used at each visit to assess overall clinical severity (CGI-S) and improvement (CGI-I). Each subscale is rated on a 1 to 7 point scale, with 1 describing less pathology. At

intake, only severity can be rated. In subsequent assessments, both severity and improvement will be rated. This is a standard scale for psychopharmacological research, and a CGI improvement of 1 (very much) or 2 (much) improved is considered to be an acceptable response to acute treatment as is a clinical severity rating of less than or equal to 3 (mildly ill). The intra class correlation for CGI improvement as a continuous variable in the above study was 0.93.

Quick Inventory of Depressive Symptomatology, Children's Version (QIDS-C)

The QIDS-C (Rush et al., 1996) is a measure modified from the 30-item Inventory for Depressive Symptoms-Clinician rated (IDS-C). It measures specific signs and symptoms of depression.

Children's Global Assessment Scale (CGAS)

The C-GAS (Shaffer et al., 1983) provides a rating of adaptive functioning. The subject is rated by a single number, equal to the most impaired level of general functioning over the specified time period. The CGAS is scored on 1-100 continuum, with a low score indicating greater dysfunction. Specifically, on the CGAS, a score of 100 is best, a score of 0 is worst, and a score of 60 or less is definitely impaired (Bird et al, 1987). The CGAS is

included in this study because it provides a measure of the overall level of functioning, not limited to impairment from depression.

Child's Family Global Assessment Scale (FGAS)

The FGAS (Mrazek, unpublished, 1992) rates the child's family's most impaired level of general functioning in the past year. There are four areas of functioning to be considered when rating: social functioning of parents as related to economic and social goals; marital/parental teamwork; parent understanding and provision for the developmental needs of the child; and the integrity and stability of family relationships. The FGAS scores range from 1-100, with a low score indicating a greater level of dysfunction. A recent study reports that children and adolescents with low family global functioning are less likely to recover (Emslie et al., 1998).

Self-Report Family Inventory (SFI-II)

The SFI-II (Hampson, Beavers & Hulgus, 1989) is a 36-item self-report instrument designed to evaluate each family member's perception of the family's health/competence, conflict, cohesion, directive leadership, and emotional expressiveness. The health/competence subscale includes nineteen content items involving family affect, parental coalitions, problem-solving abilities, autonomy and individuality, optimistic versus pessimistic views, and acceptance of family

members. The conflict subscale includes twelve content items dealing with overt versus covert conflict, including arguing, blaming, fighting openly, acceptance of responsibility, unresolved conflict, and negative feeling tone. The cohesion subscale includes five content items involving family togetherness, satisfaction received from the family versus outside, and spending time together. The leadership subscale includes three content items involving parental leadership, directiveness, and the degree of rigidity of control. Lastly, the expressiveness subscale includes six content items dealing with verbal and nonverbal expressions of warmth, caring, and closeness (Hampson and Beavers, 1989).

The SFI-II is designed to be completed by family members 11 years of age or older. All items except the last two are answered on a Likert-type scale with 1 being, "Yes fits our family very well," a score of 3 being, "Some: Fits our family some," and a score of 5 being "Does not fit our family." Internal consistency has been assessed at between 0.84-0.88 (Cronbach's alpha). Test-retest reliability coefficients (for 30 to 90 days) ranged from 0.84-0.87 for family health/competence, 0.50-0.59 for conflict, 0.50-0.70 for cohesion, 0.79 to 0.89 for expressiveness, and 0.41-0.49 for directive leadership. The SFI has demonstrated adequate concurrent validity through high correlations with other family self-report instruments. The SFI health/competence scale correlated $r = 0.87$ with the general functioning factor of the McMaster Family Assessment Device (Miller et

al., 1985). SFI cohesion correlates r = -0.82 with the cohesion scale from the FACES III (Olsen et al., 1985).

Treatment Expectancy Questionnaire

The Treatment Expectancy Questionnaire is a 4-item self-report questionnaire that was created to use with the R&R study. It is given to both the patient and their guardian. The four questions include, "how appropriate do you think treatment is," "do you think the treatment will reduce your problems," "would you recommend the treatment to someone else," and "how much improvement do you think will occur by the end of treatment." Patients rate these questions by selecting the appropriate answer from a choice of options.

Adherence Measures

Blood Levels

In this study, the major drug that will be evaluated using blood levels is fluoxetine and its first-order metabolite (Wilens et al., 2002). A drug's half-life is defined as the amount of time it takes to clear 50% of the medication. Fluoxetine is unique in that it has a significantly longer half-life than other antidepressants (Burke et al., 2000). Specifically, the elimination half-life for fluoxetine is two to three days, while the half-life for norfluoxetine is 7-16 days. Four to five times

the half-life is when you achieve steady state; however, adherence variability can lead to trouble reaching steady state.

In this study, the mean steady state for fluoxetine is predicted at 250 ng/mL. The mean state of fluoxetine will reflect adherence to the medications, while subtherapeutic levels (<150 ng/mL) will reflect poor adherence or suboptimal dose strengths. Blood levels will be taken at weeks 6 and 12.

Physician Estimate

In the R&R study, physicians were polled at the end of the acute phase of treatment (after 12 weeks) in the R&R study to see whether they believed a patient was adherent or nonadherent, and why or why not.

Pill Counts

In this study, research assistants perform pill counts at every visit during the acute phase by measuring the number of pills dispensed versus the number of pills returned. The pill counts are a way for research assistants to track a patient's adherence, as patients are discontinued from the study if they have adherence rates lower than 70% on two consecutive visits or a total of three visits.

Medication Diaries

In this study, both patients and parents were asked to keep separate medication diaries logging the number of pills dispensed daily, the number of omissions, and the reason for omission. Parents and patients were reminded at every visit to complete and return these diaries.

Self Report

In this study, both parents and patients were given a handout in which they were asked to describe their medication adherence. Specifically, they noted who dispensed the medication, and then they circled whether they "did not take any medications, took less than half, took half, took most, or took all of their medications."

Electronic Monitoring

In this study, MEMS 6 Track Caps were used to observe the pill-taking habits of individual patients. The MEMS system includes standard-looking pill bottles that are fitted with a cap that contains a microprocessor, which records the date, time, and duration of each container opening. Each bottle opening and closing is recorded as a presumptive dose (Cramer, 1995). Data is retrieved by connecting the bottle to a microcomputer communication port. Information is provided as listings of the date and time of individual bottle openings and

closings, the duration of opening, and the hours since the previous dose. Calendar plots show the number of doses taken each day, the mean, and standard deviation of overall adherence for individual patients (Cramer, 1995). For the purpose of this study, patients could not be considered greater than 100% compliant; therefore, taking an extra pill the next day to make up for a missed does was not counted towards a patient's total percent adherence. Patients were reminded to bring their MEMS caps to each research appointment, so the cap could be read.

Data Management

The data will be computerized and managed using Microsoft ACCESS as part of the large affective disorders study database at the University of Texas Southwestern Medical Center (UTSW). This is an established ongoing database as part of the affective disorders child/adolescent research group managed by Dr. Carroll Hughes. Throughout the study, quality control procedures, like double-entry, are in place to assure accurate and complete data at the end of the study. All data are checked against the original documents.

Full protection of confidentiality of research participants is implemented. All patient research charts maintained by the study will be kept locked at all times unless directly supervised by study personnel and filed by patient numbers. Study personnel will be on call at all times to release research data in the event of an

emergency. Subject identification numbers are used that do not reveal the identity of subjects (e.g. no use of birth dates, initials, social security numbers, names, etc.) Only those involved in the data management will have the ability to make changes in the database, under the close supervision of Dr. Carroll Hughes.

Primary Hypotheses

1. *Examine the characteristics of nonadherence that are found in children and adolescents with MDD. This study will specifically examine the relationship between medication adherence and variables such as: a) patients'/parents' treatment expectancy, b) number of side effects, c) parents'/patients' perceptions of family health competence, and d) the age of the patient.*

Treatment expectancy has consistently been found to be an important component of adherence. Patients who believe medication therapy is unnecessary for their illness are more frequently noncompliant (Scott, Lore, & Owen, 1992). Most investigations have simply examined parents' understanding, parents' satisfaction or parents' reports of adherence with pediatric treatment regimens, and have not included an examination of the views of the child. Approaches that ignore the involvement of children are particularly inappropriate with older children and adolescents, who are likely to take more responsibility for their adherence (Fotheringham & Sawyer, 1995). In this study, both the patients' and

the parents' treatment expectations will be polled. Due to the dearth of data in the literature, there is inconclusive data about which person's attitude is more important in determining adherence, although one study described that parental discomfort about pharmacotherapy is a main factor in nonadherence (Williams, Hollis, & Benoit, 1998).

1ai. At the beginning of the study, parents predict treatment on a continuum of 'appropriate' (1) to 'not appropriate' (4) and they predict treatment response on a continuum of 'successful' (1) to 'not successful' (4). Lower sum scores will be inversely correlated with higher adherence rates, as measured with electronic monitoring.

1aii. It is hypothesized that the treatment expectations of the parent will be more correlated with adherence than the treatment expectations of the patient.

Evidence is also inconclusive about the significance of side effects and nonadherence. Side effects can be categorized as either adverse events or SAEs. A recent depression study indicated that many of the patients in the sample (89 of 130, or 68%) reported side effects that they associated with the antidepressant medication. Almost half of these (43 patients, or 48%) reported that the side

effects were “quite” or “extremely” bothersome. Surprisingly, neither the overall report of side effect nor the report of very bothersome side effects was associated with adherence (Sirey et al., 2001).

1b. In this study, it is hypothesized that the presence of side effects will be inversely related to overall antidepressant adherence.

The literature involving family support and adherence has overwhelmingly underscored a link between the two variables. Litt & Cuskey (1980) noted that five of six studies showed greater adherence among patients whose families were supportive. In this study, families will be rated by both patients and parents using the Self-Report Family Inventory (SFI-II). This instrument has a subscale that specifically measures family health competence.

1ci. It is hypothesized that the baseline scores on the SFI-2 parent version (health competence subscale) will be directly, inversely correlated to mean rates of adherence (lower scores = more health).

1cii. Using the SFI-II, it is hypothesized that the parents’ ratings of health competence will be more correlated with adherence than the health competence ratings of the patient.

In several studies, adolescents have been found to be less adherent than younger children (Fotheringham & Sawyer, 1995). It is hypothesized that this is in large part due to the fact that parents are no longer solely responsible for dispensing medication. Adolescents are involved in a developmental stage in which they are struggling for greater autonomy and challenging the authority of their parents. Thus, there is often confusion over the allocation of responsibility for medicine taking (Fotheringham & Sawyer, 1995). Additionally, adolescents often have their own individual reasons for resisting medications (rebellion, stigma, denial, etc).

1d. Younger age will be inversely correlated with higher rates of adherence, as it is hypothesized that younger children will have their medication adherence dispensed by their parents, which may be a more reliable method than adolescents dispensing medications themselves.

2. *Examine the relationship between various methods of measuring nonadherence (electronic monitoring, self-reports, pill counts, medication diaries, blood levels, and physicians' estimates).*

Self-report tends to underestimate the true extent of nonadherence by approximately 20% (Horne & Weinman, 1999). Additionally, medication diaries tend to overestimate adherence. In one study utilizing electronic monitoring, researchers found an average of 1.1 (SD = 1.5) missing diary entries when there was a MEMS opening recorded. In contrast, there was an average of 3.4 (SD = 6.0) diary entries recorded without a MEMS opening (Riekart & Rand, 2002). Pill counts have also been found to overestimate adherence, as one study found that they failed to identify 87% of patients who were low compliers as documented by tracer levels (Cramer et al., 1989). Finally, in looking at physicians' estimates, it has been found that doctors overestimated their patient's adherence by 50% (Roth & Caron, 1978).

2a. Thus, it is hypothesized that electronic monitoring will show significantly higher rates of nonadherence than will pill counts, medication diaries, self-reports, and physicians' estimates; but will be more positively correlated with blood levels than the other methods.

3. *Examine whether the average rate of adherence changes over time, during the 12-week open-label trial of fluoxetine.*

In the literature, studies have shown that in chronic conditions, like depression, adherence is not static and unvarying, as adherence rates may change considerably over time for the same youngster and family (LaGreca, 1990).

3a. Similarly, it is hypothesized that the average rate of adherence will decline over the 12-week acute phase of open-label fluoxetine treatment.

4. *Examine the correlation between medication adherence and treatment outcomes.*

This relationship is complicated because it is not hypothesized to be linear in nature. Simply speaking, adequate medication adherence is associated with improved health outcomes. Antidepressant medications have been shown to be efficacious after four to six weeks of continuous usage. However, in the pediatric literature, it has also been found that adherence with medication, even for acute conditions, falls off dramatically soon after the patient has symptomatically improved (Jay et al., 1984). Additionally, Budd, Hughes, and Smith (1996) found that one of the common reasons sufferers give for refusing medication is the belief that they are no longer ill.

4a. In this study, the focus is on the first 12 weeks of acute treatment with fluoxetine. Thus, it is hypothesized that adequate medication adherence (greater than 80% using MEMS data) will result in a greater decrease in depressive symptoms by week 12, as measured by CDRS-R scores.

5. A secondary, exploratory aim of the study is to: *Determine the mean rate of medication adherence in a sample of children and adolescents with MDD.*

While there are no statistics specifically involving the average adherence rate in children and adolescents with depression, the closest approximation came in a recent review article which cited, "rates of adherence to medication regimens among children with chronic diseases are similar to those among adults with chronic diseases, averaging about 50%" (Osterberg & Blaschke, 2005). However, other studies have clearly documented that youths have lower levels of adherence than adults (Fotheringham & Sawyer, 1995); and adolescents have lower rates of adherence than children (Litt & Cuskey, 1980). On the other hand, this study does select for patients who are highly motivated to come in weekly for the first six weeks and every other week for the last four sessions. As a result, they receive more attention than the average outpatient and are subsequently reinforced for good medical practices. Thus, the rates of adherence in this study may be overestimated (LaGreca, 1990).

These two aspects of the study potentially balance each other out (the low levels of adherence expected given the population of the study versus the higher levels of adherence expected, given the self-selection bias and rewarding nature of the study).

5a. Thus, it is hypothesized that the mean rate of adherence in this study will be similar to other published rates of adherence, which is approximately 50%.

Statistical Analyses

1a. *Examine the characteristics of nonadherence that are found in children and adolescents with MDD. This study will specifically examine the relationship between medication adherence and variables such as: a) patients'/ parents' treatment expectancy b) number of side effects c) parents'/patients' perception of family health competence, and d) the age of the patient.*

The following four potential predictors of adherence will be assessed: parents' treatment expectancy, parents' perception of family functioning, number of side effects, and the age of the individual(s) dispensing medication. Adherence will be measured by the proportion of compliant days, using electronic monitoring, during the 12-week acute treatment phase. A multiple linear

regression analysis will be done on all available patients (n=31). Standardized regression coefficients will be used, as the units of measurement for these predictors differ. Part and partial correlations will be used to assess the relative effects of individual predictors.

2a. *It is hypothesized that electronic monitoring will show significantly higher rates of nonadherence than will pill counts, medication diaries, self-reports, and physicians' estimates; but will be more positively correlated with blood levels than the other methods.*

The non-parametric correlation, Kendall's tau, will be used to compute the pairwise correlations between percent of days the pill bottle is opened as determined by the MEMS caps, pill counts, medication diaries, blood levels, self-rated medication adherence (ordinal), and observer rated medication adherence (i.e. physicians' estimates) (ordinal).

3a. *It is hypothesized that the average rate of adherence will decline over the 12-week acute phase of open-label fluoxetine treatment.*

Because electronic monitoring is considered the method closest to a gold standard for measurement of adherence, the primary outcome variable will be

obtained from electronic monitoring data. A bivariate linear regression analysis will be performed to investigate this question. The within-subjects factor is time with 8 levels (Visit 1, 2, 3, 4, 6, 8, 10, 12) and the dependent variable is the MEMS cap adherence percentages for each subject.

4a. *It is hypothesized that adequate medication adherence (greater than 80% using MEMS data) will result in a greater decrease in depressive symptoms by week 12, as measured by the CDRS-R scores.*

A two-way analysis of variance (ANOVA) will be conducted to answer this question. Subjects will be divided into two groups: one group will be "compliers" and another group will be considered "noncompliers." This distinction will be made using MEMS caps data ("compliers" $\geq$ 80% adherence; "noncompliers" < 80% adherence). Another factor will be time, which will have two levels (Week 0 (baseline visit) and week 12). The dependent variable will be total scores on CDRS-R.

5a. *It is hypothesized that the mean rate of adherence in this study will be similar to other published rates of adherence, which is approximately 50%.*

Because electronic monitoring is considered the method closest to a gold standard for measurement of adherence, the primary outcome variable will be obtained from electronic monitoring data. Specifically, the adherence rate is calculated as: (the number of days on which the patient was compliant with respect to dose/number of days observed) x 100%.

CHAPTER IV

RESULTS

This study monitored the adherence of patients who were enrolled in two separate large-scale, NIMH-funded studies: "Childhood Depression: Remission and Relapse" and "Relapse Prevention."

Descriptive Statistics

Table 1 provides a summary of demographic and illness variables, such as current episode number, current episode duration (weeks), current episode age of onset, and length of illness (months) for these two distinct groups (R&R and RP). Altogether, the sample consisted of 31 patients and their families. Table 2 provides a summary of all subjects and subsequent adherence measures. Table 3 further describes the illness characteristics for the entire sample. Table 4 enumerates the comorbid diagnoses of the participants, while Table 5 delineates family (mother, father, sibling) psychiatric history. Table 6 provides a frequency analysis for maternal depression ratings on the QIDS-SR. Table 7 provides the schedule of assessments for the R&R study, and Table 8 provides the schedule of assessments for the RP study. Tables 9 through 11 provide descriptive data (number, mean, minimum, maximum, and standard deviation) for all of the continuous variables.

The sample consisted of 31 children and adolescents. There were more females (n=17, 54.8%) than males (n=14, 45.2%) in the total sample. As shown in Table 1, the majority of patients were Caucasian (n=23, 74.2%), followed by African American (n=4, 12.9%), Hispanic (n=3, 9.7%), and Asian (n=1, 3.2%). Participants ranged in age from 7-17, with a mean of 12.77 years (SD=2.9). The mean baseline CDRS-R score was 56.39 (SD=10.13), suggesting moderate depression.

Characteristics of the primary diagnoses of MDD were also examined (see Table 3). Most participants met criteria for MDD, Single Episode (n = 18, 58.06%). Of those who met criteria for MDD, Recurrent (n = 13, 41.94%), 11 were in their second episode, one was in a third episode, and one was in a fourth episode. These children and adolescents had a mean age at onset of the illness of 12.23 years. The mean length of the current episode was 23.78 weeks.

In addition to assessing for MDD, participants were systematically evaluated for all comorbid DSM-IV disorders. Only 6 (19.35%) subjects had no comorbid illnesses. Of the 25 (80.65%) participants with cormorbid disorders, 14 (45.16%) had one comorbid diagnosis, 8 (25.81%) had two comorbid diagnoses, and 3 (9.68%) had three comorbid diagnoses. See Table 4 for the frequency of specific disorders. With regard to family psychiatric history, there were 25 (80.65%) families with a positive history of mental illness in the mother, father, or

sibling. There were 6 (19.35%) families with no history of mental illness. See Table 5 for the frequency of specific disorders.

When maternal depression was looked at objectively using the QIDS-SR, a majority of mothers reported mild, moderate, or severe depression at the beginning of the study. Specifically, 13 (41.9%) mothers reported mild depressive symptomatology, 8 (25.8%) reported moderate symptomatology, and 3 (9.7%) reported severe symptomatology. See Table 6 for the frequency of scores.

Of the 31 subjects who entered the acute treatment phase, 11 (35.5%) were "acute drops" and did not complete the 12 weeks of treatment. Four withdrew consent (two due to need for additional/concomitant treatment, one for inconvenient/time involvement, and one 'other'). Five were withdrawn due to inadequate treatment response, one was lost to follow-up, and one was withdrawn due to noncompliance.

One-sample t tests were conducted on the SFI-2 scores to compare the sample to the normative data on this instrument (see Table 12). With the SFI-2, MDD child/adolescent and parent means for the Health Competence subscale were significantly less healthy than the "healthiest" family group at baseline. At exit, the MDD child/adolescent and parent means for the health competence subscale were less healthy than the "healthiest" family group, but not statistically significantly. At baseline and exit, the parent means for the health competence subscale were significantly healthier than the "least healthy" group. At baseline,

the child/adolescent means were healthier than the “least healthy” but not significantly, although they were significantly healthier than the “least healthy” group at exit.

Demographic characteristics were examined to determine if there were any significant differences between those children and adolescents in the R&R and RP study. There was no significant gender or level of depression differences between the two groups, which was examined using the Mann-Whitney nonparametric analysis. There was a significant difference in age, which is to be expected, as there were different inclusion criteria for the two studies. The R&R study looked at depression in children and adolescents (age 7-17), while the RP study only included adolescents (age 11-18). However, this difference should not interfere with subsequent analyses. Additionally, there were ethnicity differences between the two groups, as determined by the nonparametric Kruskal-Wallis test.

This study was initiated in 2005. Since that time, only one family has refused to use the MEMS cap because it interfered with their medication dispensing routine (using a pillbox). Of the 32 MEMS caps used, two have had technical problems, which prevented researchers from electronically reading the caps, leading to missing data.

Inferential Statistics

Hypothesis 1. *Examine the characteristics of nonadherence that are found in children and adolescents with MDD. This study will specifically examine the relationship between medication adherence and variables such as: a) patients'/parents' treatment expectancy, b) number of side effects, c) parents'/patients' perceptions of health competence, d) the age of the patient.*

A multiple regression analysis was conducted to evaluate how well these variables (age, health competence, side effects, and treatment expectancy) together predicted adherence in children and adolescents with depression. The predictors were age, parent treatment expectancy, parent health competence, and presence of side effects, while the criterion variable was mean percent adherence (MEMS). This model was not found to predict adherence to a significant degree ($R^2 = .162$, $F(4, 23) = 1.111$, $p < .376$) and results are presented in Table 13.

1ai. *At the beginning of the study, parents predict treatment on a continuum of appropriate (1) to not appropriate (4) and they predict treatment response on a continuum of successful (1) to not successful (4). Lower sum scores will be inversely correlated with higher adherence rates, as measured with electronic monitoring.*

Nonparametric correlations (Kendall's tau-b) were made between percent adherence (MEMS) and the parent ratings of treatment expectancy (sum scores). Using the Bonferonni approach to control for Type I error across the ten correlations, a p value of less than .005 (.05 / 10) = .005 was required for significance. No significant correlations were found and results are presented in Table 14. Part and partial correlations were unable to be examined due to the type of analysis used (nonparametric correlations).

Since the initial analysis only looked at the treatment expectancy sum score, a further analysis was conducted to determine whether any of the specific questions on the Treatment Expectancy Questionnaire were correlated with adherence. Again, nonparametric correlations (Kendall's tau-b) were made between percent adherence (MEMS) and the individual components of the treatment expectancy questionnaire for parents and patients. Using the Bonferonni approach to control for Type I error across the nine correlations, a p value of less than .006 (.05 / 9) = .006 was required for significance. No significant correlations were found and results are presented in Table 15.

To further examine the treatment expectancy questionnaire, an item-to-total correlation (Kendall's tau-b) was run both for the parent report and the patient report. For the parent report, the first three questions of the Treatment Expectancy Questionnaire were significantly correlated to the total score, with only the last question, "by the end of treatment, how much improvement will

occur?" not being significantly correlated (see Table 16). For the patient report, the last three items were significantly correlated to the total score, with only the first question, "How appropriate is treatment?" not being significantly correlated (see Table 17).

1aii. *It is hypothesized that the treatment expectations of the parent will be more correlated with adherence than the treatment expectations of the patient.*

Looking at Table 14, a comparison is present between percent adherence (MEMS) and the treatment expectations of the parent and the treatment expectations of the patient. These comparisons are nonparametric correlations (Kendall's tau-b). Neither correlation was significant.

Additionally, it appears that that the patients' treatment expectations were more strongly related to adherence than the parents' treatment expectation, unlike what was hypothesized. Another interesting finding is that the direction of the correlations is different between the parent and the patient report. The hypothesis was that treatment expectancy would be inversely correlated with adherence, as lower scores on the Treatment Expectancy measure are indicative of more optimism. The patients' scores and adherence rates are inversely correlated, as expected. However, the parents' expectations are the opposite of what was

expected—for that sample, more optimistic scores on the Treatment Expectancy measure were correlated with lower adherence rates.

1b. *In this study, it is hypothesized that the presence of side effects will be inversely related to overall antidepressant adherence.*

Nonparametric correlations (Kendall's tau-b) were made between the presence (1) or absence (0) of side effects and percent adherence (MEMS). A significant correlation was not found and results are presented in Table 14. A power analyses was conducted to determine the number of subjects needed to generate a power of 80%. It was found that a sample size of 191 would have been needed. While side effects were not significant in relationship to adherence, it is also evident that the direction of the relationship was the opposite of what was expected.

1ci. *It is hypothesized that the baseline scores on the SFI-2 parent version (health competence subscale) will be directly, inversely correlated to mean rates of adherence (lower scores = more health).*

Nonparametric correlations (Kendall's tau-b) were made between percent adherence (MEMS) and the parent ratings of the SFI-2 health competence

subscale. No significant correlation was found and results are presented in Table 14.

1cii. *Using the SFI-II, it is hypothesized that the parents' ratings of health competence will be more correlated with adherence than the health competence ratings of the patient.*

A nonparametric correlation (Kendall's tau-b) was made between percent adherence (MEMS) and the parents' rating of health competence (SFI-2). A correlation was also made between percent adherence (MEMS) and the patients' rating of health competence (SFI-2). Neither correlation was significant, although unlike what was hypothesized, it appears that the patients' perception of health competence was more strongly related to adherence. Another interesting finding is that the direction of the correlations is different between the parent and the patient report. The hypothesis was that health competence (SFI-2) would be more inversely correlated with adherence, as lower scores on the SFI-2 are indicative of more health. The patients' scores and adherence rates are inversely correlated, as expected. However, the parents' expectations are the opposite—for that sample, less health on the SFI-2 was correlated with higher adherence rates. Results are presented in Table 14.

1d. *Younger age will be inversely correlated with higher rates of adherence, as it is hypothesized that younger children will have their medication adherence dispensed by their parents, which may be a more reliable method than adolescents dispensing medications themselves*.

Nonparametric correlations (Kendall's tau-b) were made between percent adherence (MEMS) and age. The correlation was not significant. A power analyses was conducted to determine the number of subjects needed to generate a power of 80%. It was found that a sample size of 301 would have been needed. Additionally, while the correlation was not significant, it was an inverse relationship, as hypothesized, meaning that younger age was correlated with higher rates of adherence. Results are presented in Table 14.

2. *Examine the relationship between various methods of measuring nonadherence (electronic monitoring, self-reports, pill counts, medication diaries, blood levels, and physicians' estimates). It is hypothesized that electronic monitoring will show significantly higher rates of nonadherence than will pill counts, medication diaries, self-reports, and physicians' estimates; but will be more positively correlated with blood levels than the other methods.*

Nonparametric correlations (Kendall's tau-b) were made between MEMS, parent self-report (1=did not take any medication, 5=took all of medication), patient self-report, pill count, parent medication diary, patient medication diary, blood level visit 6 (total fluoxetine/norfluoxetine levels), and blood level visit 12. Using the Bonferonni approach to control for Type I error across the 16 correlations, a p value of less than .003 (.05 / 16 = .003) was required for significance.

Significant correlations were yielded for MEMS and pill counts ($r = .558$, $p < .000$), MEMS and parent self-report ($r = .614$, $p < .000$); MEMS and patient self report ($r = .525$, $p < .000$); parent self-report and patient self-report ($r=.577$, $p < .000$); pill count and parent self report ($r = .491$, $p <.001$); pill count and parent medication diary ($r = .425$, $p <.003$); and patient medication diary and parent medication diary ($r = .770$, $p < .000$).

Therefore, higher self-report ratings of adherence (patient and parent) were correlated with a higher percent adherence (MEMS). MEMS caps were also positively correlated with pill counts. Pill counts were also correlated with parent self-reports and parent medication diaries. Also, parent and patient measures (self-report and medication diary) were positively correlated with one another. Results are presented in Table 18. Thus, it seems that electronic monitoring was more positively correlated with self-reports and pill counts, not blood levels. The

descriptive statistics in Table 19 illustrates that electronic monitoring shows higher rates of nonadherence than pill counts and medication diaries.

3. Examine whether the average rate of adherence changes over time, during the 12-week open-label trial of fluoxetine. It is hypothesized that the average rate of adherence will decline over the 12-week acute phase of open-label fluoxetine treatment.

A bivariate linear regression analysis was conducted to evaluate the relationship between time (12 week acute phase open-label fluoxetine treatment) and the average rate of adherence (MEMS). The predictor variable was visit number (9 levels: Visit 0, 1, 2, 3, 4, 6, 8, 10, 12) and the dependent variable was percent adherence (MEMS). This model was found to predict adherence to a significant degree (R^2 = .039, F (1, 196) = 7.973, p < .005). Therefore, visit number is mildly related to percent adherence in this sample. Approximately 3% of the variance in adherence is associated with visit number. Results are presented in Table 20. Results can also be seen graphically in Figure 1.

This finding was confirmed with a mixed model analysis, which indicated that there was a statistically significant decrease in mean adherence rates over time, F (1, 50.32) = 9.63, p < .003).

4. Examine the correlation between medication adherence and treatment outcomes. It is hypothesized that adequate medication adherence (greater than 80% using MEMS data) will result in a greater decrease in depressive symptoms by week 12, as measured by the CDRS-R scores.

A two-way analysis of variance (ANOVA) was conducted to compare compliers (≥80% adherence via electronic monitoring) and noncompliers (<80% adherence) on depression measures (CDRS-R) between Visit 0 and Visit 12. The ANOVA indicated a non significant main effect for compliance, $F(3, 49) = .826$, $p < .368$. However, significant main effects were found for visit number, $F(3, 49) = 89.458$, $p < .000$ and for the interaction between visit and compliance, $F(3, 49) = 7.152$, $p < .010$. Therefore, the hypothesis was correct that greater medication adherence would result in a greater decrease of depressive symptoms by week 12 as measured by the CDRS-R scores. Results can be seen in Table 21. Results can also be seen graphically in Figure 2.

Additionally, further exploratory analyses were conducted to determine if scores on various outcome measures differed significantly from Baseline to Exit. Paired sample t-tests were conducted between baseline/exit on the SFI-2 (parent and patient), QIDS-SR, QIDS-C, IDS-P, CGI-S, CGAS, FGAS, and CDRS-R. Using the Bonferonni approach to control for Type I error across the nine correlations, a p value of less than .006 (.05 / 9) = .006 was required for

significance. Mean differences were found for the majority of the outcome measures: SFI-2 health competence, parent version (M = .256, SD = .393, t (25) = 3.327, p < .003); QIDS-C (M = 9.667, SD = .882, t (20) = 10.961, p < .000); IDS-P (M = 20.92, SD = 13.172, t (24) = 7.941, p < .000); CGI-S (M = 2.2, SD = 8.978, t (29) = 10.418, p < .000); CGAS (M = -12.458, SD = 8.978, t (23) = -6.798, p < .000); CDRS-R (M = 27.955, SD = 12.404, t (21) = 10.571, p < .000). It should be noted that lower scores on the SFI-2, CGI-S, QIDS-C, IDS-P, and CDRS-R denote greater levels of health; and, higher scores on the CGAS and FGAS denote greater levels of health. Results can be seen in Table 22.

5. Determine the mean rate of medication adherence in a sample of children and adolescents with MDD. It is hypothesized that the mean rate of adherence in this study will be similar to other published rates of adherence, which is approximately 50%.

A secondary aim of this study was to determine the mean rate of medication adherence in a sample of children and adolescents with MDD. The mean rate for this study, using electronic monitoring as the gold standard was 85.27%, SD = 12.001, range = 41.9% to 100%. Subsequently, mean adherence rates (pill counts) were 91.43%; mean adherence rates (patient medication diary) were 95.13%; mean adherence rates (parent medication diary) were 94.2%, mean

parent self-reports were 4.5 (between “took all” and “took most” of medication), and mean patient self-reports were 4.51.Specifically, the mean adherence rate for the R & R study was 88.16%, and the mean adherence rate for the RP study was 82.18%. Results can be seen in Table 19.

Exploratory Analyses

Paired t-tests were conducted to evaluate whether parent and child reports differed significantly on various measures: the SFI-2 (Baseline); SFI-2 (Exit); Treatment Expectancy questions 1, 2, 3, 4, and sum score; medication diaries; and self-reports. The results, presented in Table 23, indicated that there were no significant differences between these measures. It should be noted that lower scores on the SFI-2 denote greater levels of health, lower scores on the Treatment Expectancy Questionnaire denote greater levels of optimism, and higher scores on self-reports denote greater levels of adherence.

A nonparametric correlation (Kendall’s tau-b) was conducted to compare percent adherence with certain demographic variables (gender and ethnicity). Using the Bonferonni approach to control for Type I error across the three correlations, a p value of less than .02 (.05 / 3) = .02 was required for significance. No significant differences were found and results are presented in Table 24. Specifically, the mean rate of adherence for males was found to be

84.56% (SD = 8.87); the mean rate of adherence for females was found to be 85.85% (SD = 14.33).

Descriptive statistics were utilized to more closely understand the presence of drug holidays in this particular sample of subjects. Table 25 displays that the total number of drug holidays present across 31 subjects was 14, with 12 (38.71%) of the subjects taking at least one drug holiday, which is defined as three or more days' interruption in dosing (Urquhart & Chevally, 1988). The average length of the drug holiday was 8.571 (SD = 4.831), range 3-18. Two drug holidays were present during the first month of treatment, seven drug holidays were present during the second month of treatment, and five drug holidays were present during the third month of treatment. The majority of drug holidays occurred in January (n = 5, 35.71%) and December (n = 3, 21.43%).

Descriptive statistics were also utilized to more closely understand the timing of patients' doses. Results indicate that 22 (70.97%) of patients took their medications predominately in the morning (recommended dosing); whereas, 9 (29.03%) took their medication primarily in the afternoon or evening.

Pearson correlations were made between certain measures of depression (CDRS-R, CGI-S, CGAS, FGAS, QIDS-C, and IDS-P). Using the Bonferonni approach to control for Type 1 error across the 12 correlations, a p-value of less than .004 (.05 / 12) = .004 was required for significance. The results of the correlational analysis are presented in Table 26. It should be noted that high

scores on the CGAS and FGAS are indicative of more health; low scores on the CGI-S, QIDS-C, IDS-P, and CDRS-R are indicative of more health. Significant correlations were found between the CDRS-R and CGI-S ($r = .864$, $p < .000$), CDRS-R and CGAS ($r = -.593$, $p < .000$), and the CDRS-R and QIDS-C ($r = .520$, $p < .003$). Thus, the CDRS-R is significantly correlated with most other measures of depression. Partial correlations adjusting for age, ethnicity, and gender had no clinically meaningful effect on the correlations.

Pearson correlations were made between certain family measures: SFI-2 (parent and patient) and QIDS-SR. Using the Bonferonni approach to control for Type I error across the six correlations, a p value of less than .008 (.05 / 6) = .008 was required for significance. It should be noted that low scores on the SFI-2 and QIDS-SR are indicative of more health. The results of the correlational analysis are presented in Table 27. No significant correlations were found. Partial correlations adjusting for age, gender, and ethnicity had no clinically meaningful effect on the correlations.

CHAPTER V

DISCUSSION

The goal of the present study was to gain a clearer understanding of medication adherence in children and adolescents with depression. Medication adherence has been found to be a critical mediator in patient outcomes (Osterberg & Blaschke, 2005). This study sought to identify specific characteristics of patients and their families that are related to adherence. It also attempted to address a number of methodological limitations of previous studies, such as the reliance on subjective, indirect measures of adherence: pill counts, medication diaries, self-reports, and physicians' estimates.

Data presented here was collected during the acute phases of two NIMH-funded studies: "Childhood Depression: Remission and Relapse" and the "Relapse Prevention" study. R &R is a randomized controlled trial investigating the course of illness in children and adolescents with nonpsychotic depression when fluoxetine is continued or discontinued after 12 weeks of open label treatment. The Relapse Prevention study is a randomized controlled trial investigating the efficacy of medication management alone or fluoxetine plus CBT to prevent relapse after a 12-week acute phase open trial of fluoxetine in children and adolescents with MDD. The present study focused on the acute phase data for 31 child and adolescent participants in the medication trial who also had their medication adherence tracked.

These participants were enrolled in treatment after a comprehensive evaluation, using the K-SADS-PL to verify that they met strict inclusion/exclusion criteria. At study entry, information was collected about the primary diagnosis of MDD; the presence of any comorbid disorders; and self, parent, and clinician-reported family functioning. Participants were then provided 12 weeks of open treatment with fluoxetine, using flexible dosing (10-40 mg) in order to maximize treatment response. During the acute treatment phase, participants were evaluated regularly with measures of depression severity and global improvement (CGI). At the end of treatment, or at early termination, a final CDRS-R and CGI-Severity and Improvement scores were obtained as the primary outcome measure. Family measures were completed throughout the course of treatment. Additionally, 31 patients had their medication adherence tracked for 12 weeks using electronic monitoring, blood levels, physicians' estimates, self-report, pill counts, and medication diaries.

All measures of treatment outcomes for depressive symptoms were quite positive. Overall, participants showed significant improvement in depression severity over the course of treatment. At baseline, the mean clinical Global Severity score was 4.84 (between moderately and moderately ill). By the end of 12 weeks of treatment, the mean CGI-S score was 2.67 (between borderline mentally ill and moderately ill), which was a significant difference, $p < .000$. The mode CGI-S scores at Visit 12 were 1 and 2, together accounting for 71% of the

patients. Additionally, at baseline, the mean CDRS-R score was 56.39. By the end of acute treatment, the mean score was 30.08, which was a significant difference of $p < .000$. Overall, 17 (54.84%) of the participants met full criteria for remission by the end of 12 weeks of treatment. Pertaining to treatment response, "remission" was defined as a CGI Improvement score of 1 or 2 and a CDRS-R score of less than or equal to 28. Three (9.68%) met criteria for adequate clinical response (CGI-I score of 1 or 2 and 50% improvement from baseline on the CDRS-R during the first 12 weeks of treatment), representing an overall response rate of 64.52%. This is consistent with other open trials of fluoxetine (Emslie, 1997, 2002; TADS, 2004). Only 11 (35.48%) of the children and adolescents were classified as nonresponders.

However, there was a difference in response rates between the two separate depression studies (R&R and RP). In the R&R study, 11 (68.75%) of the participants met full criteria for remission, 2 (12.5%) of the participants met criteria for adequate clinical response, and only 3 (18.75%) were classified as nonresponders. Thus, for the subset of R&R patients who had their medication tracked, there was an overall response rate of 81.25%. For the RP study, 6 (40%) of the participants met full criteria for remission, 1 (6.67%) met criteria for adequate clinical response; whereas 8 (53.33%) were classified as nonresponders. The discrepancy in response between these two studies will be discussed further.

Summary of Findings

An aim of this study was to collect initial data determining the mean percentage rate of medication adherence in a sample of children and adolescents recruited for study by CMCD. Research has shown that the mean rate of medication adherence among those with adult depression is 65% (range 58-90%) (Cramer & Rosenheck, 1998). Other figures, cited in the literature include a 43-78% range for adherence rates for those with chronic conditions (like depression) (Cramer, Roshenheck, Kirk, Krol & Krystal, 2003). These seemingly low rates are also remarkable considering they are the adherence rates of patients in clinical drug trials—patients who are motivated to be involved in research and who often receive free medication and ample attention from medical staff. However, there has been no research using objective measures (electronic monitoring) in children and adolescents with depression.

Adherence rates for this study were hypothesized to be similar or lower to those reported for adult studies, 50-65%. However, electronic monitoring data suggested mean adherence rates for children and adolescents with depression to be 85.27%. Subsequently, mean adherence rates (pill counts) were 91.43%; mean adherence rates (patient medication diary) were 95.13%; mean adherence rates (parent medication diary) were 94.2%, mean parent self-reports were 4.5 (between “took all” and “took most” of medication), and mean patient self-reports were 4.51.

It is not initially clear why this study enjoyed higher rates of adherence than other studies cited in the literature. However, several considerations can be made. First, the participants in this study received a great deal of attention from health care providers. Patients were seen weekly for visits -2, -1, -, 1, 2, 3, 4, and every other week for visits 6, 8, 10, and 12. Additionally, adherence was a major theme of these visits as the patient and the physician spoke about it at every visit. Patients were reminded to bring back electronic monitoring devices and medication diaries every week. Furthermore, pill counts were conducted at every visit, medication adherence self-reports (patient and parent) were distributed at every visit, and blood levels were drawn at weeks 6 and 12. Thus, adherence was consistently emphasized and reinforced.

Additionally, in this study patients were informed that the MEMS caps "keep track of the doses of medication your children receive." While not explicitly stating that the caps are monitoring adherence, families may assume or understand that something is being tracked electronically. The decision to inform patients in this study was done for practical reasons, as patients and families needed to bring in their MEMS cap at every visit, and they were barred from using other medication containers and pillboxes. There is some evidence that informing participants of monitoring, without providing them feedback of their results does not change their medication adherence (Matsui et al., 1994). On the other hand, the manufacturers of the MEMS caps do acknowledge that informing

patients that their adherence is being monitored does run the risk of increasing compliance.

Another consideration is the fact that parents were largely responsible for dispensing medication to the patients in 16 (53.33%) families. Parents and patients reportedly were jointly responsible in 5 (16.67%) of families, and children were solely responsible for dispensing medication in 9 (30%) of families. However, the average age of those responsible for taking their own medication was 14.67 years, which is significantly older than 9.14 years (the "average age at which children first take medication independently") cited by Bush & Iannotti (1985) in the literature. Therefore, in this sample, it is possible that adherence is elevated due to the older age of people dispensing the medication.

Finally, another consideration is that in this study, patients were prescribed single-dose medications and their medication was provided free of charge. Previous studies have highlighted the relationship between the number of doses per day and percent adherence. Specifically, Claxton (2001) found an inverse relationship between the number of daily doses and adherence. In this study, while patients were responsible for a long-term medication regimen (12 weeks), the simple dosing and free medication may have helped maximize adherence rates.

Another major aim of this study was to examine the characteristics of nonadherence that are found in children and adolescents. One of the major

limitations in previous studies was the lack of an objective manner in which to monitor adherence. Additionally, the overwhelming number of complex factors that comprise adherence may preclude generalization of findings from one study population to the next (Cromer and Tarnowski, 1989), especially considering the different methodologies used; the lack of clearly operationalized variables, and the significant interactions between mediating behavioral, psychological, environmental, structural, and physical variables (Adams & Scott, 2000). This study was an improvement over previous studies due to the inclusion of electronic monitoring.

However, despite this improvement, no hypothesized variables (presence of side effects, treatment expectancy, family health competence, age) were found to be either significantly correlated with adherence or predictors of adherence. Exploratory analyses were run to see if additional variables (maternal depression, clinical response, completion of acute treatment, gender, or ethnicity) were correlated or predictors of adherence. Again, there were no significant findings. The lack of significant findings further exacerbates on of the major frustrations of adherence research—the difficulty of finding consistent predictors of adherence.

However, in this study, there is a statistical explanation for the inability to find significant predictors of adherence. As has been previously mentioned, the adherence rate in this study was unusually high; therefore there was not a lot of variance in individual patients' adherence rates. Therefore, patients on the other

end of the continuum (poor adherence rates) were either underrepresented or unwittingly excluded due to selection bias. This phenomenon was a major factor in this study's inability to find predictors of adherence.

While the study did utilize electronic monitoring, there were certainly difficulties in clearly operationalizing variables, which also could have contributed to the difficulty in finding predictors of adherence. For example, 'presence of side effects' was a hypothesized predictor of adherence. However, there was uncertainty in how this should be expressed. In both the R &R and RP studies, all adverse events were listed, regardless of whether they were related to the medication or not. Should all adverse events be considered side effects? If not, how should it be determined whether an adverse event was related to medication or not? Should only new events (those different than were present at screening and baseline) be considered as related to the new medication? When the literature was reviewed, there was no consensus on how to reconcile this difficulty. This dilemma highlights the wide disparity among studies' methodologies and the lack of a gold standard when trying to establish clearly operationalized variables (i.e. 'presence of side effects').

Within the correlational data, there were several surprises. While it was hypothesized that parental measures would be more strongly correlated with adherence, it was actually discovered that patient measures (SFI-2, Treatment Expectancy questionnaire) were more strongly correlated with adherence,

although not significantly. Also, within this correlational research was another surprising finding about the parent and patient data. The direction of the correlations was difference than expected for certain measures (SFI-2, Treatment Expectancy-parent). The hypothesis was that treatment expectancy and health competence would be inversely correlated with adherence, as lower scores on the Treatment Expectancy measure and SFI-2 are indicative of more optimism and more health. The patients' scores and adherence rates were inversely related as expected; however, the parents' expectations were the opposite of what was expected. For that sample, more optimistic scores on the Treatment Expectancy measure were correlated with lower adherence rates, although not statistically significantly. Additionally, less healthy scores on the SFI-2 health competence subscale were correlated with higher adherence, although not statistically significantly.

However, it should be kept in mind that paired t-tests comparing parent and child measures (including SFI-2 and Treatment Expectancy) found no statistically significant differences between the mean scores. Therefore, following up on this possible finding (that a patients' attitudes are more strongly linked to adherence than parents' attitudes) with a larger sample size would be an excellent study for future research.

Another surprising directional finding was the positive relationship between the presence of side effects and increased adherence rates, since the

hypothesized relationship was an inverse relationship. While operationalizing this variable was difficult, data on side effects has also been equivocal. The results of the this study actually lend credence to a trend in recent studies which found side effects to either be related to adherence but to a lesser extent than initially believed or not related to adherence at all (Sirey et al., 2001).

Finally, when exploratory analyses were run, it was discovered that scores on maternal depression (QIDS-SR) (where higher scores are associated with less health) were positively related to adherence, although not statistically significantly. The initial hypothesis was an inverse relationship, as it was believed that maternal depression would prevent families from consistently being able to help youth take their medication in a proactive, organized, and nonpunitive manner. However, drawing from the literature involving incarcerated females, people with a prior psychiatric medication history are more likely to believe medication can be helpful in improving mood, learning, and behavior problems. Nineteen mothers of 31 patients had been previously diagnosed and treated for depression and 77.4% indicated mild, moderate, or severe depression on the QIDS-SR at the beginning of this study. While there is no significant correlation between maternal depression and treatment expectancy ($r = .031$, $p < .841$), it may be possible that the mothers' prior experience with depression made them more convicted about the importance of medication adherence and more vigilant about their child's medication adherence.

Another aim of the study was to examine the relationship between various methods of measuring adherence (electronic monitoring, self-reports, pill counts, medication diaries, and blood levels).

Electronic Monitoring

Electronic monitoring was found to be positively correlated with pill counts ($r = .558$, $p = .000$), patient self report ($r = .525$, $p = .000$), and parent self report ($r = .614$, $p = .000$). One of the most surprising findings was the lack of a strong correlation between MEMS and blood levels. However, one of the possible limitations was the high frequency of missing data for blood levels because there were only two data collection points. Many patients who were early terminators missed their Visit 12 blood draw. Also, some patients missed due to their aversion to needles, research coordinator error, or clinic unavailability. Another limitation was the small sample size of this study.

Electronic monitoring was considered the "gold standard" for this study and many subtle medication-taking variables could be scrutinized because of it. For example, in looking at timing of medication doses, 22 (70.97%) patients took their doses predominately in the morning, compared to 9 (29.03%) who took their doses in the afternoon/evening. The recommended dosing is to take fluoxetine in the morning. Therefore, the patients were being nonadherent to the doctor's

recommendations. It is interesting, therefore, that these 9 patients were also significantly less adherent via MEMS (80.71%) than the group average (85.27%).

Electronic monitoring was also used to look at drug holidays. Twelve (38.71%) patients exhibited drug holidays with two patients taking two drug holidays over three months of treatment. The average drug holiday length was 8.57 days, SD = 4.831. Additionally, there were much fewer drug holidays taken during the first month of treatment (n = 2) versus month two (n = 7) and month three (n = 5). This also supports the finding that adherence declines over time. January (5 drug holidays taken) and December (3 drug holidays taken) were the months in which the majority of drug holidays occurred (See Figure 3). Thus, in this sample, the occurrence of drug holidays seemingly corresponds with winter holidays and family vacations.

Pill Counts

While there was a significant relationship between MEMS and pill counts, it is also true that pill counts overestimated adherence by 6.16% compared with electronic monitoring data. Pill counts were also positively correlated with parent medication diaries ($r = .425$, $p = .003$) and parent self-reports ($r = .491$, $p = .001$).

Medication Diaries

There was not a significant correlation found between MEMS and medication diaries, and medication diaries were found to overestimate adherence, which is consistent with the literature. Specifically, parent medication diaries overestimated adherence by 8.93% and patient medication diaries overestimated adherence by 9.86%. Another interesting finding was that no one rated themselves (parent or patient) as less than 85% compliant on medication diaries, even though there were 13 patients who were < 85% compliant using MEMS data. Thus, there appears to be a real reticence for patients and their families to admit nonadherence.

However, one possible mediating factor is the fact that medication diaries were often not returned. Therefore, there was a significant amount of missing data. The return rate of medication diaries often mimicked that of medication adherence—patients often brought back medication diaries at the beginning of the study, but the return rate declined as the studies progressed. Therefore, the medication diaries that would have reflected nonadherence (those later in the study) were often not returned. Finally, a qualitative result of this study was the finding that the number one reason people cited for not taking medication on their medication diary was “forgot.” This supports the assertion that medication nonadherence is often unintentional.

Self-Report

Both parent self-report (r = .614, p = .000) and patient self-report (r = .525, p = .000) were positively correlated with MEMS. Additionally, patient and parent self-reports were correlated with each other (r = .577, p = .000). The moderate correlation indicate that the self-report questionnaires were more effective than medication diaries in gleaning true medication-taking behavior. One of the limitations of this data, however, is the ordinal nature of the data. Also, there were occasionally variable responses to the self-report questionnaires. For instance, in one case, a patient indicated "took all" medication, whereas their mother noted, "took none" of medication.

Physician Estimates

Unfortunately, physician estimates of adherence were only obtained in the R &R study. However, data indicate that out of 16 patients, physicians hypothesized that only one patient was noncompliant. However, this patient's pill count (83.8%) and MEMS data (89.3%) indicated adherence. Physicians failed to identify 4 (25%) other patients whose electronic monitoring data suggested noncompliance (< 80%). Therefore, consistent with the adult literature on medication adherence, physicians overestimated adherence rates in children and adolescents with depression, as electronic monitoring and pill counts did not support their estimates.

Blood Levels

As was mentioned earlier, blood levels were surprisingly not correlated with any other adherence measures. Another methodological limitation to consider with the blood level data is that there were only two data points maximally collected (week 6 and week 12), in contrast to the daily data collected with the MEMS data.

Another aim of the study was to examine whether the average rate of adherence changes over time, during the 12-week open-label trial of fluoxetine. As expected, the adherence rate did decline significantly across the nine visits, although it should be noted that the overall adherence rate was still markedly high.

One possibility associated with this finding is that patients' adherence declined towards the end of the study because patients felt that they were better and no longer need medication. This is a common trend among children and adolescents with depression. The average visit at which patients felt a remission in symptoms (CDRS $\leq$ 28) was 6.45, range = visit 1-14.

The final aim of this study was to examine the correlation between medication adherence and treatment outcomes. Again, as predicted, patients who were considered 'adherent' had lower levels of depressive symptoms (as

measured by the CDRS-R) than nonadherers. This again provides support to previous studies that highlighted the relationship between adherence and patient outcomes.

Methodological Considerations

This study did provide many improvements upon other studies. First, this study was the first to use electronic monitoring in child/adolescent depression research. Second, this study is also the first in which several methods of measuring adherence were used simultaneously. This provided rich data to explore the relationship between different direct and indirect ways of measuring adherence. In addition, a wide array of factors was investigated in addition to child/adolescent depression and adherence, such as maternal depression, family variables, and demographic variables.

However, a major methodological flaw in this study was the small sample size of the subset of patients who had their adherence tracked. This flaw limits the generalizability of positive findings and reduces the power of the experiment. This part of the study was added on after many subjects had already entered the R&R study and was only offered to a subset of RP participants due to time constraints. Additionally, the price of the electronic monitors was more than $100/cap. Therefore, expense also precluded more subjects from being involved in this adherence study. However, it is important for studies to track adherence

objectively on a large-scale to further enhance our knowledge of medication-taking behaviors, especially since this study was inconclusive about predictors of adherence.

As the research was conducted within a university medical setting, these findings may not generalize to other clinical settings (Weisz, Donenberg, Han, & Kauneckis, 1995). However, the liberal inclusion criteria, in terms of acceptable comorbid disorders and use of psychostimulants suggest that the population studied here is probably quite similar to that in other clinical settings. Also, the ethnic characteristics of the group did not match the consensus estimates of Dallas County, even though recruitment strove to represent that of Dallas County. Caucasian youth and families were overrepresented in both the R&R and RP studies. Therefore, the findings of the study may not be generalizeable to other clinical settings.

Another limitation is that many statistical comparisons were conducted, which increases the risk of Type I error. Thus, interpretation of positive results should be considered tentatively pending replication in other studies. In addition, data was collected over a 12-week period with 11 (35.48%) of the participants exiting before the acute phase was completed (12^{th} week). Additionally, there were significant differences in the rates of acute-drops between the R&R study and the RP study. The R&R study had two (12.5%) participants' who did not complete the acute phase of the study; while the RP study had 9 (60%)

participants who were considered acute drops. In the RP study, four participants were transferred to other studies/psychiatrists as they were nonresponders in the study, one needed additional treatment, one was terminated due to visit noncompliance, one was lost to follow-up, one was lost due to personal circumstances, and one was lost because she and her family felt that she had adequately recovered.

While the R&R and RP groups differed significantly in their drop-out rates and response rates, the two groups also differed significantly demographically (age and ethnicity). The age difference was expected, as RP had difference inclusion criteria, limiting its inclusion age to adolescents (age 11-18), while R&R took both children and adolescents (age 7-17). However, these group differences led to an underrepresentation of younger children (<11) in this sample, n = 8 (25.8%). Also, there were ethnic differences between the two groups, although Caucasians were overrepresented in both samples.

While the differences between the two groups increase the external validity and increase the ability to generalize the findings to other populations, the differences in the two groups can also be considered a methodological limitation. Because these two groups differed significantly in many ways, yet were pooled together, there is a possibility that there were certain unique characteristics of adherence within the two groups that were missed. For example, were there more acute drops in RP because of the larger number of adolescents? Is adolescent

depression different from child depression in some unique way that leads to poorer treatment response? Does this also affect adherence? These are necessary follow-up questions to be addressed in future research. The noncompleters were unable to be followed-up with after the completion of the study. Therefore, it is impossible to know if their adherence was qualitatively different from other participants.

A confounding variable that must be noted is the missing data. While sufficient efforts were made to collect all data across the nine visits, there were many situations in which medication diaries were unreturned, blood levels were not drawn, and self-reports were not filled out. Additionally, the MEMS cap malfunctioned in two (6.45%) of participants. For one participant, the cap was unable to be read after Visit 6 for unknown reasons. Another participant acknowledged dropping the monitor on the floor. However, the second participant was issued a second cap, so only 1-2 weeks worth of data were lost.

Clinical Implications and Issues for Future Research

A primary finding of this study is the presence of a significant interaction between compliance and time in relation to CDRS-R scores. Therefore, subjects who had higher adherence rates had lower scores of depression when they finished the acute phase of the study. This finding builds upon other findings in the literature that suggest that participants in clinical drug trials who do not follow

their medication regimens have a poorer prognosis. This finding, therefore, also iterates the importance of further studies investigating adherence, as it has the power to greatly affect patient outcomes. One aspect of adherence that this study was not able to look at due to the small sample size was the relationship between children and adolescents' increased suicidality either as a function of antidepressant use or nonadherence. This is a critical question that warrants further investigation.

Another important finding from this study is the fact that adherence did decline over a 12-week period, in spite of close monitoring. This is an important trend to understand clinically, so that healthcare professionals can educate their patients about the importance of continued adherence and actively try to keep adherence rates elevated in their patients. Another aspect of this finding is the relationship between declining adherence over time and further relapse of depressive symptoms. Research has shown that recurrence of depression in children and adolescents is high. Emslie (1998) found that once recovered from an episode of MDD, 39% of the subjects had a recurrence of depression during the one-year follow-up, with 55% of these occurring within six months. While some of these subjects were still on fluoxetine at the time, adherence was not measured. Therefore, another area of study would be to monitor adherence rates objectively during the continuation phase of a clinical drug trial to compare the relationship between percent adherence and depression relapse.

Another important finding of this study is the strong correlation between MEMS and pill counts and MEMS and self-reports (parent and patient). While pill counts have received a lot of negative attention in the literature for their ability to be easily manipulated by patients, this study showed that they were as sufficient as MEMS caps in measuring adherence. This may be very good news to researchers, as it is initial evidence that adherence can be measured effectively through the use of pill counts or self-reports without researchers having to invest heavily in MEMS caps. Likewise, outpatient psychiatrists would then have some cheap and easy tools in their repertoire for measuring adherence with patients.

However, one aspect of the correlation between MEMS caps and pill counts should be investigated further. In this study, patients were told that their electronic pill bottles were tracking their doses. Thus, patients may have been less likely to manipulate pill counts, as they knew the bottle was already tracking something electronically. Before pill counts are used solely as a measure of adherence, research should be conducted to examine whether pill counts, when used alone indicate higher levels of adherence than when pill counts are used simultaneously with MEMS caps. Another aspect to consider is that this study registered such high rates of adherence, even with the MEMS caps, that there was not a lot of room for pill counts to show significantly higher rates of adherence, which is the trend that is typical of that measure.

One of the main lack of findings from this study is its inability to distill any predictors of adherence. While factors related to adherence have been studied for quite some time, there are still very few core variables shown repetitively to be related to adherence. Further research should be done to elucidate predictors of adherence, since that is a key to developing tools and interventions to increase adherence.

CHAPTER VI

TABLES

Table 1

Subject Variables

	16 R&R Patients					15 RP Patients				
	N	Min	Max	M	SD	N	Min	Max	M	SD
Demographic: Age of child/adolescent*	16	7	15	10.69	2.21	15	12	17	15	1.60
Child/adolescent illness variables:										
Current Episode Number	16	1	3	1.5	0.63	15	1	4	1.53	0.83
Current Episode Duration, wks	16	4	152	21.44	35.49	15	4	64	26.27	20.85
Current Episode Age of onset	16	7	15	10.38	2.28	15	12	17	14.2	1.61
Length of illness, mos	16	2	48	14.38	13.79	15	1	60	15.93	17.5
Gender										
Male			8 (50%)				6 (40%)			
Female			8 (50%)				9 (60%)			
Ethnicity										
Caucasian			11 (68.75%)				12 (80%)			
African American			4 (25%)				0 (0%)			
Hispanic			1 (6.25%)				2 (13.33%)			
Asian			0 (0%)				1 (6.67%)			

*age at initial intake

Table 2

Adherence Summary

Subject	Gender	Age	Race	MEMS %	Pill Ct %	Medication Diaries-Parent	Medication Diaries-Patient	Phy. Est. of Adherence	Dispenses	Fluoxetine Week 6	Fluoxetine Week 12
1	M	10	AA	100	100	100	100	Adherent	Parent	231	263
2	M	13	AA	77.5	97.4	100	100	Adherent	Parent	148	144
3	F	9	C	94.1	92	93.5	92.3	Adherent	Parent		243
4	F	9	C	88.3	90.6	91.2	91.2	Adherent	Parent	417	241
5	M	11	C	83.5	81.5	85.3	85.5	Adherent	Parent	184	197
6	M	15	C	87.9	87	90	91.4	Adherent	Child	226	232
7	M	7	C	79.9	89.4	88.5	88	Adherent	Parent	295	242
8	M	9	AA	89.3	83.8	91.7	92.9	Not adhrnt	Parent		Early Term
9	M	12	AA	67.3	70.2	90.9	93.7	Adherent	Parent/Child	56	601
10	M	10	C	90.9	93.8	92.8	91.4		Parent	358	Early Term
11	F	12	C	89.4	91.4	92.5	92.5	Adherent	Parent/Child	171	118
12	F	12	C	98.5	100	97.2		Adherent		341	
13	F	11	C	98.2	98.2	97.6	98.2	Adherent	Parent	370	327
14	F	14	H	98.8	99.3	99.2	99.2	Adherent	Child	164	338
15	F	8	C	97.4	98.2	98.1	100	Adherent	Parent		
16	F	9	C	69.6	91.5	94.7	97.6	Adherent	Parent/Child		<20
17	M	13	C	95.2	96.7				Child	147	134
18	F	13	H	87.8	86.1	100	97.5		Child	236	
19	M	17	As	81.5	83.2	100	100		Parent		Early Term
20	M	15	H	81.9	92.2	85.7			Child		Early Term
21	F	15	C	92.5	92.9	95.2	95.2		Parent	Early Term	Early Term
22	M	16	C	90	100	100	100		Parent/Child	Early Term	Early Term
23	F	15	C	82.1					Child	128	Early Term
24	M	17	C	87.5	90.7	91.8	89.7		Parent	165	
25	F	15	C	97.3	98.8	93.6	96.5		Parent	270	Early Term
26	F	13	C	78.3	92.5	92.9			Parent		268
27	F	12	C	78.3	86.1				Parent	133	Early Term
28	F	16	C	77.6	80.6	95.2			Child		68
29	F	16	C	89.4	95.8	100	100		Child	303	171
30	M	17	C	71.4		85.7			Parent/Child	100	Early Term
31	F	15	C	41.9					Child	Early Term	Early Term

Table 3

Illness Characteristics

	N (%)
Single vs. Recurrent	
Single Episode	18 (58.06%)
Recurrent	13 (41.94%)
Current Episode Number	
1	18 (58.06%)
2	11 (35.48%)
3	1 (3.23%)
4	1 (3.23%)

Table 4

Frequency of Child/Adolescent Comorbid DSM-IV Diagnoses

DSM-IV Diagnoses	Frequency
Attention Deficit-Hyperactivity Disorder	15
Anxiety Disorders	
Generalized Anxiety Disorder	3
Separation Anxiety Disorder	1
Obsessive Compulsive Disorder	1
Dysthymic Disorder	10
Oppositional Defiant Disorder	5
Enuresis	3
Substance Abuse Disorder	1
Total	39

Note. Total is greater than number of subjects because more than one comorbid diagnosis may be given.

Table 5

Frequency of Mother, Father, and Sibling Psychiatric History

DSM-IV Diagnoses	Mother	Father	Sibling
Depression (dys, sought tx/counseling)	19	7	1
Bipolar I/II	1	0	0
Alcohol or Substance Abuse (last 6 months)	1	2	1
Anxiety Disorder	7	1	2
Attention Deficit-Hyperactivity Disorder	0	1	5
Independent Sleep Disorder	0	1	0
Total	25 Families with a Positive History of Mental Illness in Mother, Father, or Sibling		

Note. Total is greater than number of subjects because more than one comorbid diagnosis may be given.

Table 6

Maternal Depression Ratings on the QIDS-SR

QIDS-SR	Baseline (n)	Exit (n)
No Depression (≤5)	7 (22.6%)	12 (50%)
Mild (6-10)	13 (41.9%)	8 (33.3%)
Moderate (11-15)	8 (25.8%)	2 (8.3%)
Severe (≥16)	3 (9.7%)	2 (8.3%)
Total	N=31	N=24

Note. Seven mothers were missing data at Exit.

Table 7

Schedule of Measures for R&R Study

WEEKS	i	ii	0	1	2	3	4	6	8	10	12
SYMPTOMS/DIAGNOSIS											
Clinician Rated											
K-SADS-PL	X										
K-SADS-affective items	X	X	X								X
CDRS-R	X	X	X	X	X	X	X	X	X	X	X
CGI	X	X	X	X	X	X	X	X	X	X	X
QIDS-C			X								X
BPRS-C		X									
BPRS-9	X		X	X	X	X	X	X	X	X	X
MADRS	X		X	X	X	X	X	X	X	X	X
Self-Reports											
WSAS Short	X	X	X	X	X	X	X	X	X	X	X
MASC	X										X
CST			X								X
PLES	X										X
Hopelessness Scale			X								X
FUNCTIONING											
Clinician Rated											
CGAS	X	X	X					X			X
Parent Reports											
IDS-P	X		X								X
QIDS-SR		X									X
CBCL	X										X
CONSUMER PERSPECTIVE (Parent-Child Reports)											
PQLQ		X									X
Treatment Expectation			X								X
Termination Interview											X
ENVIRONMENTS											
Clinician Rated:											
FGAS	X	X	X								X
FH-RDC	X	X									
Self/Parent Reports:											
SFI-II		X									X
Teacher Reports:											
CBCL	X										X
SYSTEMS											
CASA			X								X

Table 8

Schedule of Measures for RP Study

WEEKS	-2	-1	0	1	2	3	4	6	8	10	12
SYMPTOMS/DIAGNOSIS											
Clinician Rated											
K-SADS-PL	X										
K-SADS-DM		X	X								X
CDRS-R	X	X	X	X	X	X	X	X	X	X	X
CGI	X	X	X	X	X	X	X	X	X	X	X
QIDS-C	X										
SSRS Short	X	X	X	X	X	X	X	X	X	X	X
Self-Reports											
BDI	X	X	X	X	X	X	X	X	X	X	X
CTI	X										X
CCSQ			X								X
MLSS		X									X
LEC	X										
BHS			X								X
Children's Hassles Scale		X									X
SIQ	X		X					X			X
QIDS-SR	X										X
SFI Patient		X									
TEQ			X								X
FUNCTIONING											
Clinician Rated											
CGAS	X	X	X					X			X
FGAS	X	X	X					X			X
Parent-Child Reports											
SFI		X						X			X
Caregiver Strain Questionnaire	X										X
IDS-P	X										X
QIDS-SR	X										X
CONSUMER PERSPECTIVE (Parent-Child Reports)											
Working Alliance Inventory											
Consumer Satisfaction (Parent and Child)											X
Termination Interview											

Table 9

Summary of Dependent Variables at Baseline and Exit

Depression Measures	N	Min	Max	M	SD
CDRS-R - Baseline	31	39	83	56.39	10.13
CDRS-R - Exit	31	18	63	30.08	10.9
IDS-P - Baseline	31	2	61	37.39	14.75
IDS-P - Exit	25	2	37	15.84	9.46
QIDS-C – Baseline	30	8	24	15.33	3.69
QIDS-C - Exit	22	0	23	5.32	4.999
CGAS - Baseline	31	35	65	52.13	7.45
CGAS - Exit	24	45	80	65	10.02
FGAS - Baseline	31	45	85	63.9	9.50
FGAS - Exit	24	50	85	68.13	10.29
CGI-S - Baseline	31	4	7	4.84	0.9
CGI-S - Exit	30	1	6	2.67	1.34
CGI-I - Baseline			Not assessed		
CGI-I - Exit	30	1	5	2.03	1.07
QIDS-SR – Baseline	31	0	24	9.21	5.07
QIDS-SR - Exit	24	0	18	6.25	4.80
SFI-II					
Child/Adolescent Health Competence - Baseline	31	1.42	4.58	2.73	0.89
Child/Adolescent Health Competence - Exit	25	1.26	4.78	2.38	0.92
Parent Health Competence - Baseline	31	1.32	4.42	2.46	0.74
Parent Health Competence - Exit	26	1.26	3.42	2.13	0.62

Table 10

Summary of Clinician-Rated Measures at Baseline and Exit

	Acute Baseline			Acute Exit		
	N	Mean or No. (%)	SD	N	Mean or No. (%)	SD
CDRS-R	31	56.39	10.13	31	30.08	10.9
CGI-S						
1	0	---		30	4 (12.9%)	
2	0	---		30	14 (45.2%)	
3	0	---		30	5 (16.1%)	
4	31	13 (41.9%)		30	4 (12.9%)	
5	31	12 (38.7%)		30	1 (3.2%)	
6	31	4 (12.9%)		30	2 (6.5%)	
7	31	2 (6.5%)		0	---	
CGI-I						
1		Not Assessed		30	11 (35.5%)	
2		Not Assessed		30	11 (35.5%)	
3		Not Assessed		30	5 (16.1%)	
4		Not Assessed		30	2 (6.5%)	
5		Not Assessed		30	1 (3.2%)	
6		Not Assessed		0	---	
CGAS	31	52.13	7.45	24	65	10.02
FGAS	31	63.9	9.5	24	68.13	10.29

Table 11

CDRS-R Percent Change Scores

CDRS-R % Change Scores	N	Min	Max	M	SD
Baseline to Visit 1	28	0	74.36	22.53	17.34
Baseline to Visit 2	24	0	71.79	33.80	20.7
Baseline to Visit 3	27	-11.76	85	46.47	26.44
Baseline to Visit 4	30	-1.47	89.74	53.98	24.59
Baseline to Visit 6	25	7.32	93.33	57.51	26.75
Baseline to Visit 8	26	5.88	97.67	59.77	24.79
Baseline to Visit 10	22	-17.65	97.50	63.97	28.49
Baseline to Visit 12	22	-8.82	96.67	71.2	27.85
Baseline to Exit	31	-8.82	96.67	66.62	26.81

* (Baseline CDRS-R score – Visit CDRS-R score) / (Baseline CDRS-R score – 17) x 100

Table 12

Comparison of MDD Sample to Normative Data for SFI-2

SFI-2		Normative Sample			
	Total Group (N=31)	Healthiest		Least Healthy	
	M (SD)	M	p	M	p
Child					
Health Competence Baseline	2.73 (0.89)	2.06	.000*	3.03	.070
Health Competence Exit	2.38 (0.92)	2.06	.090	3.03	.002*
Parent					
Health Competence Baseline	2.46 (0.74)	1.96	.001*	3.01	.000*
Health Competence Exit	2.13 (0.62)	1.96	.174	3.01	.000*

Note. SFI-2 lower score = more health

*p < .01

Table 13

Multiple Regression Model of Predictors of Adherence

Model	Unstandardized Coeffecients		Standardized Coefficients	T	Sig.
	B	Std. Error	Beta		
Age	-.877	.921	-.209	-.952	.351
Parent Tx Expectancy	-.388	1.641	-.048	-.237	.815
SFI-2 Parent Health Competence	4.706	3.386	.291	1.390	.178
Side Effects	6.591	5.553	.250	1.187	.247

Note: Dependent Variable: Percent Medication Adherence as measured by electronic monitoring (MEMS)

SFI-2 lower score = more health, Treatment Expectancy lower score = more optimism

Table 14

Nonparametric Correlation: Characteristics of Adherence

		n	r	p
MEMS	SFI-2 Health Competence-Parent-Visit 0	31	.078	.540
	SFI-2-Health Competence-Pt-Visit 0	31	-.135	.291
	Age	31	-.163	.217
	Side Effects	31	.197	.193
	Tx Expectancy Parent	28	.039	.788
	Tx Expectancy Patient	30	-.108	.425
	QIDS-C Visit 0	30	.010	.942
	Clinical Response	31	.104	.477
	Acute Completers	31	.128	.397

Note. Using the Bonferroni approach to control for Type I error across the 10 correlations, a p value of less than .005 (.05 / 10) = .005 was required for significance.

SFI-2 lower score = more health, Treatment Expectancy Questionnaire lower score = more optimism

Table 15

Nonparametric Correlations: Treatment Expectancy and Adherence

		n	r	p
MEMS	Parent Tx Ex #1	28	.156	.313
	Parent Tx Ex #2	28	.010	.947
	Parent Tx Ex #3	28	-.077	.632
	Parent Tx Ex #4	28	-.108	.484
	Patient Tx Ex #1	30	-.228	.126
	Patient Tx Ex #2	30	-.057	.697
	Patient Tx Ex #3	30	.149	.327
	Patient Tx Ex #4	30	-.162	.258

Note: Note. Using the Bonferroni approach to control for Type I error across the 9 correlations, a p value of less than .006 (.05 / 9) = .006 was required for significance.

Treatment Expectancy #1 asks, “How appropriate is treatment?

Treatment Expectancy #2 asks, “How successfully will treatment reduce your child/adolescent’s problem?

Treatment Expectancy #3 asks, “Would you recommend treatment to others with the same problem?”

Treatment Expectancy #4 asks, “By the end of treatment, how much improvement will occur?”

Table 16

Parent-Reported Treatment Expectancy and Item-to-Total Correlation Coefficients

	Item-to-Total Correlation	Sig.
How appropriate is treatment?	.550	.001*
How successfully will treatment reduce your child's problems?	.779	.000*
Would you recommend treatment to others with the same problem?	.490	.005*
By the end of treatment, how much improvement will occur?	.392	.019

Note. Using the Bonferroni approach to control for Type I error across the 5 correlations, a p value of less than .01 (.05 / 5) = .01 was required for significance.

* $p < .01$

Table 17

Patient-Reported Treatment Expectancy and Item-to-Total Correlation Coefficients

	Item-to-Total Correlation	Sig.
How appropriate is treatment?	.345	.028
How successfully will treatment reduce your problems?	.748	.000*
Would you recommend treatment to others with the same problem?	.503	.002*
By the end of treatment, how much improvement will occur?	.750	.000*

Note. Using the Bonferroni approach to control for Type I error across the 5 correlations, a p value of less than .01 (.05 / 5) = .01 was required for significance.

*p < .01

Table 18

Adherence Measures Correlated

r (p)	MEMS	Parent Self Report	Patient Self Report	Pill Count	Parent Med Dx	Patient Med Dx	Blood Level 6	Blood Level 12	Dispenser
MEMS									
Parent Self Report	.614 (p=.000)*								
Patient Self Report	.525 (p=.000)*	.577 (p=.000)*							
Pill Count	.558 (p=.000)*	.491 (p=.001)*	.310 (p=.027)						
Parent Med Dx	.319 (p=.022)	.336 (p=.021)	.258 (p=.077)	.425 (p=.003)*					
Patient Med Dx	.261 (p=.098)	.370 (p=.022)	.150 (p=.356)	.424 (p=.007)	.770 (p=.000)*				
Blood Level 6	.417 (p=.010)	.166 (p=.338)	.341 (p=.045)	.204 (p=.240)	.105 (p=.561)	-.087 (p=.654)			
Blood Level 12	.226 (p=.224)	.104 (p=.584)	.170 (p=.366)	.183 (p=.322)	.000 (p=.1.000)	.039 (p=.854)	.121 (p=.583)		

Note. Using the Bonferroni approach to control for Type I error across the 16 correlations, a p value of less than .003 (.05 / 16) = .003 was required for significance.
*p < .003

Table 19

Descriptive Statistics for Adherence Measures

	N	Min	Max	M	SD
Percent Adherence (MEMS)	31	41.9	100	85.268	12.001
Self Report Parent	30	3.83	5	4.501	.395
Self Report Patient	29	3.8	5	4.51	.329
Percent Adherence (Pill Count)	28	70.2	100	91.425	7.188
Percent Adherence (Parent Medication Diary)	27	85.3	100	94.196	4.715
Percent Adherence (Patient Medication Diary)	22	85.5	100	95.127	4.473
Blood Level 6	19	1	2	1.316	.448
Blood Level 12	16	1	2	1.313	.479
Dispenser	30	1	3	1.867	.681

Table 20

Bivariate Linear Regression: Adherence Across Time

Model	Unstandardized Coeffecients		Standardized Coefficients	T	Sig.
	B	Std. Error	Beta		
Time	-.956	.338	-.198	-2.824	.005*

Note: Dependent Variable: Percent Medication Adherence as measured by electronic monitoring (MEMS)

* $p < .01$

Table 21

Two-Way ANOVA: Compliers and Noncompliers on the CDRS at Visit 0 & 12

Measure	Complier N=36 M (SD)	Noncomplier N=17 M (SD)	Statistic	p
CDRS Visit-0	57.77 (10.506)	52.89 (8.824)		
CDRS Visit-12	24.21 (4.209)	34.13 (12.403)		
Compliance			F (3,49) = .826	.368
Visit			F (3,49)=89.458	.000*
Compliance*Visit			F(3,49)=7.152	.010*

* $p < .01$

* N = number of patients included in the analysis at Visit 0 and Visit 12. Nine patients were missing CDRS data at visit 12 due to early terminations.

Table 22

Baseline and Exit Outcome Measures: Paired t-tests

	Mean	SD	Std. Error of Mean	t	df	Sig
SFI-Health Competence-parent	.256	.393	.077	3.327	25	.003*
SFI-Health Competence-patient	.334	.724	.145	2.306	24	.030
QIDS-SR	1.958	4.667	.953	2.056	23	.051
QIDS-C	9.667	4.041	.882	10.961	20	.000*
IDS-P	20.92	13.172	2.634	7.941	24	.000*
CGI-S	2.2	1.157	.211	10.418	29	.000*
CGAS	-12.458	8.978	1.833	-6.798	23	.000*
FGAS	-4.208	8.617	1.759	-2.392	23	.025
CDRS-R	27.955	12.404	2.645	10.571	21	.000*

Note. Using the Bonferroni approach to control for Type I error across the 9 correlations, a p value of less than .006 (.05 / 9) = .006 was required for significance.

SFI-2, QIDS-SR, QIDS-C, IDS-P, CGI-S, CDRS-R lower score = more health; CGAS & FGAS higher score = more health

*p < .006

Table 23

Parent and Child Measures: Paired t-tests

	Mean	SD	Std. Error of Mean	t	df	Sig
SFI-2 Baseline	-.269	.886	.159	-1.691	30	.101
SFI-2 Exit	-.286	.733	.147	-1.953	24	.063
Treatment Expectancy #1	-.250	.844	.160	-1.567	27	.129
Treatment Expectancy #2	.357	2.453	.464	.770	27	.448
Treatment Expectancy #3	.321	2.178	.412	.781	27	.442
Treatment Expectancy #4	.321	2.342	.443	.726	27	.474
Treatment Expectancy Sum	-.481	2.276	.438	-1.099	26	.282
Medication Diaries	-.282	1.458	.311	-.907	21	.375
Self Report #3	.009	.281	.052	.165	28	.870

Note: Note. Using the Bonferroni approach to control for Type I error across the 9 correlations, a p value of less than .006 (.05 / 9) = .006 was required for significance.

Treatment Expectancy #1 asks, “How appropriate is treatment?

Treatment Expectancy #2 asks, “How successfully will treatment reduce your child/adolescent’s problem?

Treatment Expectancy #3 asks, “Would you recommend treatment to others with the same problem?”

Treatment Expectancy #4 asks, “By the end of treatment, how much improvement will occur?”

Self Report #3 asks, “did not take any medications, took less than half, took half, took most, or took all of their medications.”

SFI-2 lower score = more health, Treatment Expectancy Questionnaire lower score = more optimism, Self-Report higher score = more adherence.

Table 24

Nonparametric Correlation: MEMS and Demographic Variables

		r	p
MEMS	Gender	.145	.341
	Ethnicity	.049	.738

Note: Using the Bonferonni approach to control for Type I error across the 3 correlations, a p-value of less than .02 (.05 / 3) = .02 was required for significance.

Table 25

Analysis of Drug Holidays

	N (%)	Min	Max	M	SD
Drug Holiday length (days)	---	3	18	8.571	4.831
Number of subjects positive for drug holidays	12 (38.71%)	---	---	---	---
Total number of drug holidays across subjects	14	---	---	---	---

Note: A “drug holiday” is defined as three or more days’ interruption in dosing

Table 26
Baseline Depression Measures Correlated

r (p)	CGI-S	CGAS	FGAS	QIDS-C	IDS-P	CDRS
CGI-S						
CGAS	-.485 (p=.006)*					
FGAS	.232 (p=.208)	.237 (p=.198)				
QIDS-C	.437 (p=.016)	-.353 (p=.056)	.140 (p=.460)			
IDS-P	.194 (p=.297)	-.243 (p=.188)	-.116 (p=534)	.458 (p=.011)		
CDRS	.864 (p=.000)*	-.593 (p=.000)*	.153 (p=.412)	.520 (p=.003)*	.305 (p=.095)	

Note. Using the Bonferroni approach to control for Type I error across the 12 correlations, a p value of less than .004 (.05 / 12) = .004 was required for significance.

* $p < .01$

CGAS & FGAS higher score = more health; CGI-S, QIDS-C, IDS-P, & CDRS-R lower score = more health

Table 27

Baseline Family Measures Correlated

r (p)	QIDS-SR	SFI-Health Competence-Parent	SFI-Health Competence-Patient
QIDS-SR			
SFI-Health Competence-Parent	.255 (p=.166)		
SFI-Health Competence-Patient	.266 (p=.148)	.420 (p=.019)*	

Note. Using the Bonferroni approach to control for Type I error across the 2 correlations, a p value of less than .025 (.05 / 2) = .025 was required for significance.

*p < .025

SFI-2, QIDS-SR lower score = more health

CHAPTER VII

FIGURES

Figure 1

Adherence Across Time

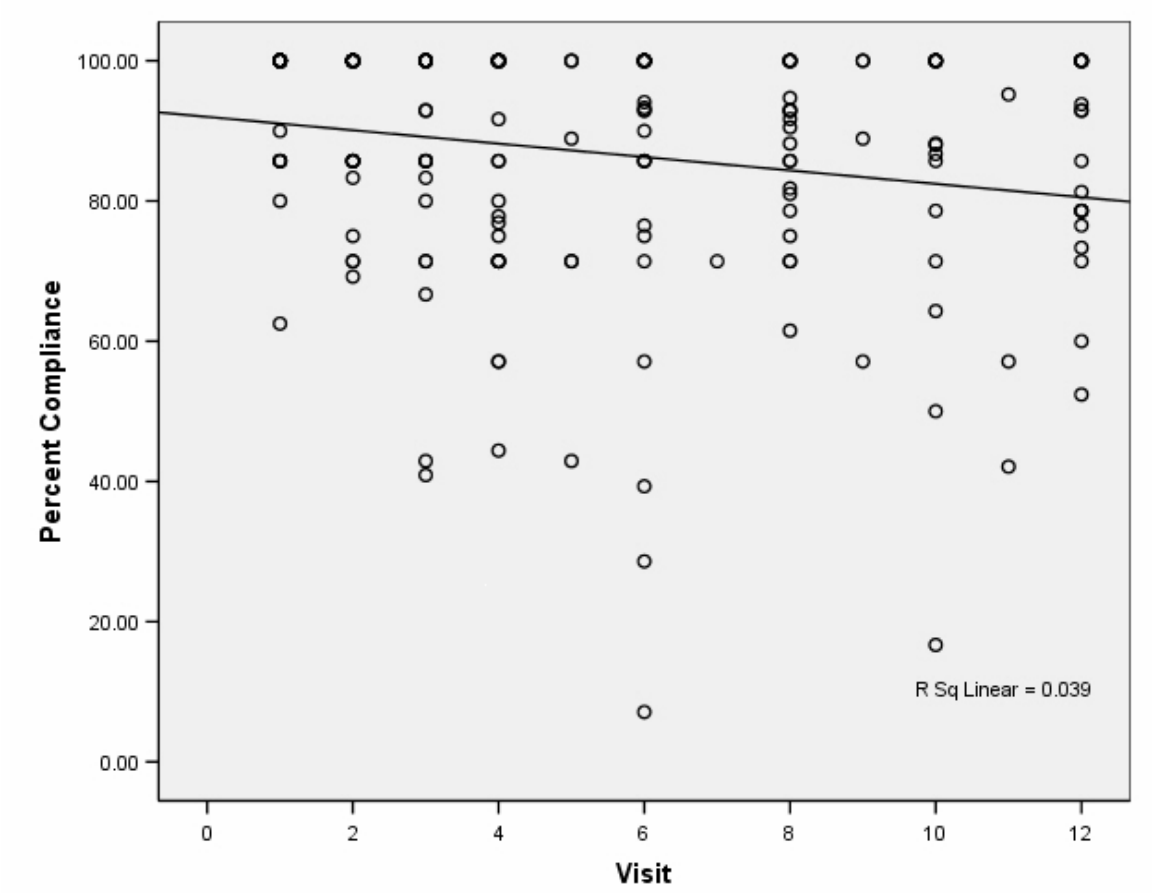


Figure 2

Depression Outcome as a Function of Time and Adherence

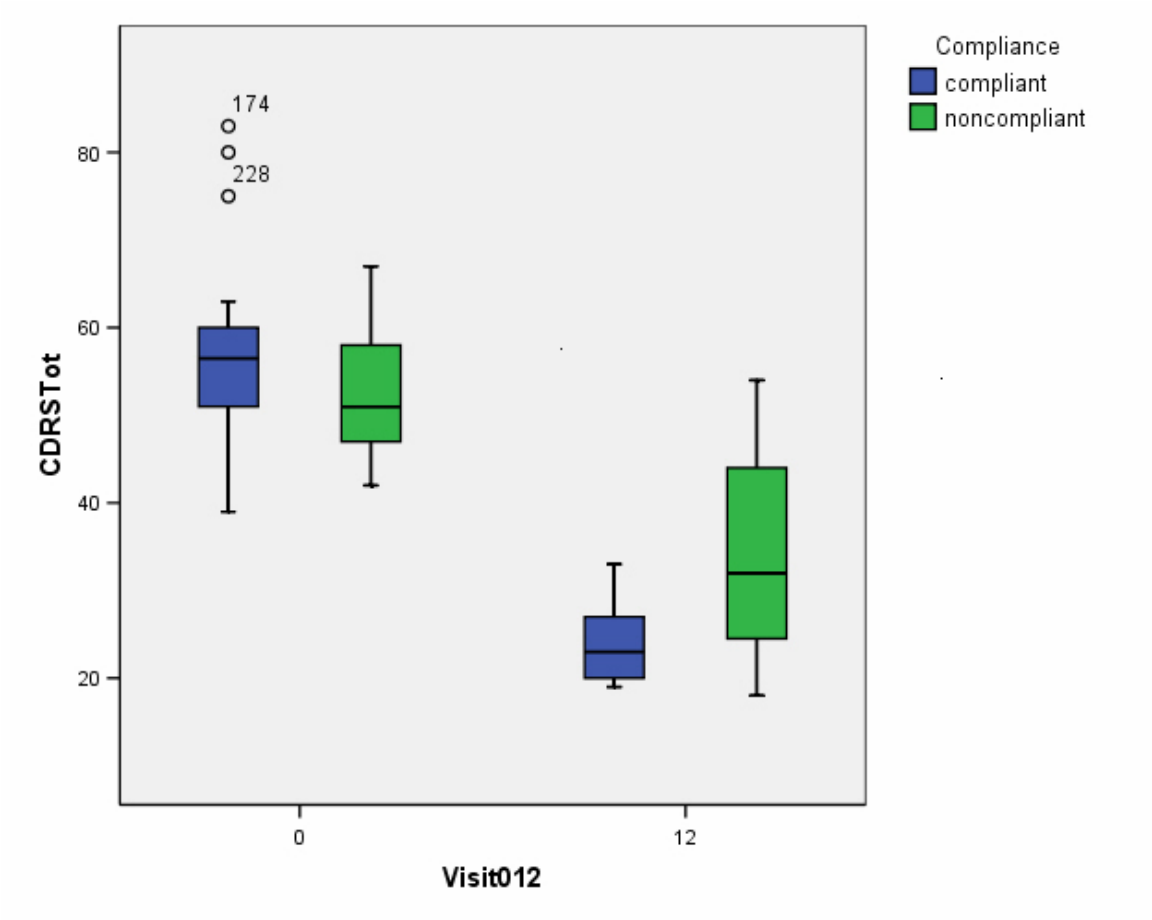
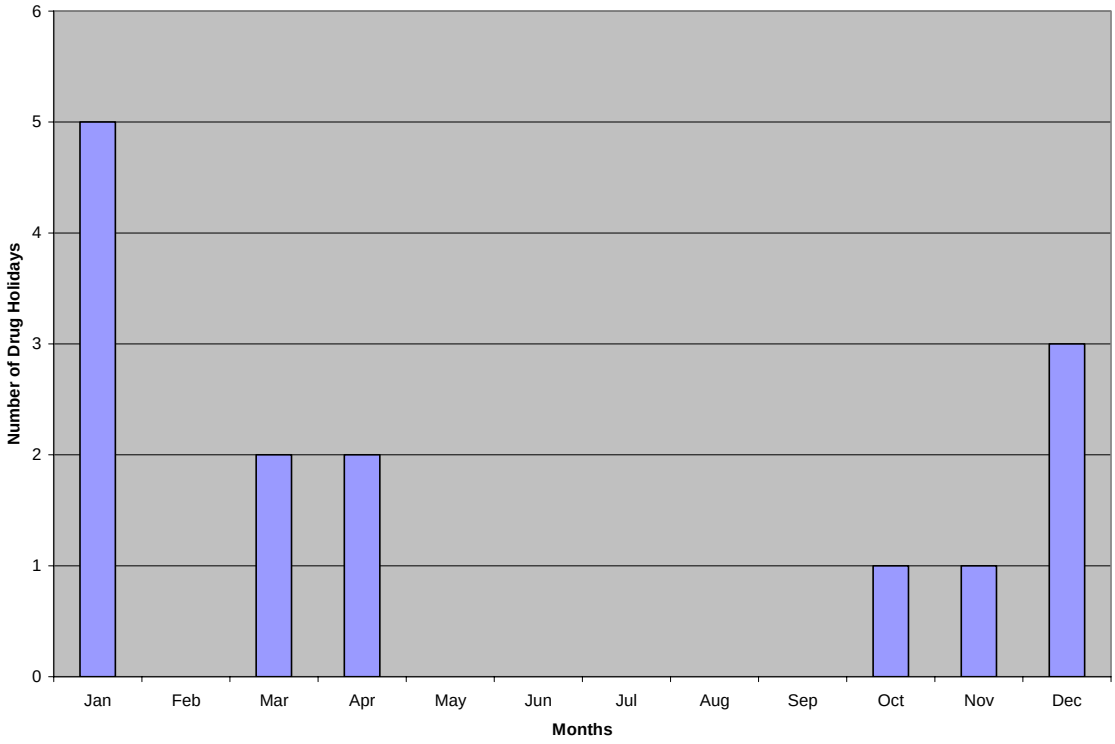


Figure 3.

Occurrence of Drug Holidays across the Calendar Year



CHAPTER VIII

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VITAE

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