Residual Symptoms in Pediatric Depression after Acute Pharmacological Treatment

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DEDICATION

This thesis would not have been possible without the support, encouragement, and assistance of many people. First I would like to thank my chairperson, Dr. Betsy Kennard for all of your guidance, support and interest in the subject of residual symptoms. I have enjoyed my time working with you and have had a good model of what a successful career and family life can be like.

I would like to thank the rest of my committee Dr. Carroll Hughes, Dr. Graham Emslie, and Taryn Mayes. This project could not have made it to this point without each of you helping with your vast knowledge in child and adolescent psychology. Jeanne Rintelmann I appreciate all of you help in creating my data base more than you know, your assistance made the process much smoother for me. Dr. Sunita Stewart I could not have gotten through my logistic regression without your help, you truly prevented a nervous break down.

I would like to thank all of my classmates and friends that have listened to countless anxiety attacks, and nervous breakdowns. Each one of you helped me in your own way to

refocus, and take a much needed time out. Specifically my dear friend Aleiva you helped so much by just being a friend even when you could not understand the motivation for putting myself under this kind of stress you still helped me see the light at the end of the tunnel.

Finally I would like to thank my family…Mom and Dad, I would not be where I am or going on to a Ph.D. program without your love and support over a life time. Thank you for supporting me emotionally, academically, and financially. Dad, thank you for all of your editing and technical advice. I could not have done it without you. Mom, thank you so much for dealing with the frustrated frantic phone calls and keeping me going. I could not have made it through the last two years without your stress reducing interventions.

Morgan Sowell, 2006

Residual Symptoms in Pediatric Depression after Acute Pharmacological Treatment

By

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THESIS

Presented to the Faculty of the Graduate School of Biomedical Sciences

The University of Texas Southwestern Medical Center at Dallas

In Partial Fulfillment of the Requirements

For the Degree of

MASTER OF SCIENCE

The University of Texas Southwestern Medical Center at Dallas

Dallas, Texas

August, 2006

RESIDUAL SYMPTOMS IN PEDICATRIC DEPRESSION AFTER ACUTE PHARMACOLOGICAL TREAMENT

Publication No. _____

Morgan Michelle Sowell, B.A.

The University of Texas Southwestern Medical Center at Dallas, 2006

Supervising Professor: Betsy Kennard, Psy. D.

Children and adolescents with major depressive disorder (MDD) are at an increased risk for school failure, school drop out, and suicidality. Childhood onset of MDD has been linked to an increased likelihood of relapse of MDD in child and adolescent research. Adult studies have found that residual symptoms increase the risk of relapse, and shorten the time to onset of relapse. This study sought to confirm the presence of residual symptoms in children and adolescents after successful treatment with antidepressant medication. An additional objective was to identify predictors of remission in those who have an adequate response to treatment. The participants (N=315) are from a combined data set of two

separate studies conducted by Graham J. Emslie investigating the efficacy of fluoxetine 20 mg/day for 8 weeks in children and adolescents with non-psychotic depression. Evaluating the patients using the more stringent criteria of remission in responders, showed that 64% of fluoxetine treated patients, and 56% of placebo treated patients successfully achieved remission. In this subgroup of responders, dysthymic disorder and CDRS-R total baseline score were found to be predictive of responders who remit.

Residual symptoms were found to be present in both the fluoxetine and placebo treatment group responders in high frequency. Finally, using the CDRS-R individual item scores of ≥3, fourteen different types of residual symptoms where found for the 86 fluoxetine responders, and eleven different types of residual symptoms were found for the 57 placebo responders.

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CHAPTER ONE
Introduction

Remission (absence of symptoms post treatment) is the gold standard in the treatment of depressive illness, but in the majority of clinical treatment trials researchers use response (much or very much clinical improvement) as the treatment outcome goal. Low levels of remission after acute care and high numbers of residual symptoms in adult treatment studies of depression is predictive of poor long term treatment outcomes. In children and adolescents the investigation of the presence of residual symptoms at the end of acute treatment, and their impact on long term outcome is a worthy area of research.

Depression in children and adolescents is a serious problem occurring in approximately 2% of children and 4% to 8% of adolescents (American Academy of Child and Adolescent Psychiatry [AACAP], 1998). Children and adolescents with major depressive disorder (MDD) are at an increased risk for school failure and drop out, and adolescents with MDD are at increased risk of suicidality. Gould et al. (1998) found that having a diagnosis of MDD increases the likelihood of the occurrence of suicide attempts from 3.3% to 22%. Findings like these have prompted research in the area of child and adolescent depression, but the number of well controlled clinical trials lags behind the research performed in the adult population.

Studies have found that the major risk factors for MDD relapse or recurrence are presence of subthreshold depressive symptoms, history of at least 2-3 prior depressive episodes, chronic depression (episode more than 2 years), family history of mood disorders, comorbidities of anxiety or substance abuse, and an early onset in childhood or adolescent's or late onset (age >60 years) (Lin, et al 1998; Nierenberg, Petersen & Alpert, 2003).

Lewinsohn, Allen, Seeley & Gotlib (1999) reported that adolescents with a history of MDD had an increased risk of recurrence when there were elevated levels of dysphoria and dysfunctional thinking at baseline. In an evaluation of clinical outcome after short-term psychotherapy for adolescents with MDD, of patients that recovered 33 (38%) of 86 patients experienced 1-2 recurrences during follow up. Among those participants the median time to recurrence was 4.2 months (Birmaher et al., 2000).

There are very few reports of remission rates and residual symptoms after acute phase treatment in children and adolescents. Recently, results have been published from the Treatment for Adolescents with Depression Study (TADS, 2004), a National Institute of Mental Health (NIMH) sponsored multisite controlled clinical trial of pharmacotherapy (i.e., Fluoxetine (FLX)), cognitive behavioral therapy (CBT), their combination (COMB), or placebo (PBO) in 439 adolescents with major depressive disorder (TADS Team, 2004). Based on the criteria of CGI-I scores of "much" or "very much" improved (1 or 2), COMB (71%) was the most effective treatment, followed by FLX alone (60.6%), CBT alone (43.2%) and PBO (34.8%) (TADS Team, 2004). Utilizing these response criteria, both COMB and FLX were statistically more effective than PBO, but CBT was not. With the end-of-treatment Children's Depression Rating Scale – Revised (CDRS-R) dichotomized as ≤ 28 (remitted) vs. >28 (not remitted), the rate of remitted subjects at end of treatment (regardless of type of treatment) was 102 out of 439, or 23% (Kennard, et al., in press). Responders, defined as a CGI-I score of 1 or 2 in the intent to treat sample was 229/439, or 52% (TADS Team, 2004). In terms of remission rates by treatment group, 37% in COMB were remitted (CDRS-R ≤ 28), which was greater than the FLX (23%; p=.02), CBT (16%; p=.0004) or

PBO (17%; p=.0009; Kennard, et al., in press). Across randomized, controlled trials (RCT) of antidepressants, while up to 50-65% of subjects achieve response to treatment, only about one third are remitted at end of treatment (Emslie et al., 1997, 2002; Kennard et al., in press). In a 12 week open treatment study of fluoxetine in children and adolescents 110/168 (65%) remitted at 12 weeks (Tao et al., 2005). Remission was defined as a CDRS-R score of ≤ 28. Of those that remitted 71% were children and 60% were adolescents.

In adult studies of the treatment of depression a high frequency of residual symptoms are noted even after adequate treatment for MDD. Recent research has found that the treatment of residual symptoms after acute phase treatment may reduce risk of relapse in adults. Specifically, cognitive behavioral therapy in the continuation phase of treatment has been shown to be effective in reducing the risk of relapse (Fava, Rafanelli, Grandi, Canestrari, & Morphy, 1998; Teasdale, Scott, Moore, Hayhurst, Pope, & Paykel, 2001).

CHAPTER TWO
Review of the Literature

DEFINITIONS OF RESPONSE AND REMISSION IN DEPRESSION RESEARCH

In clinical treatment trials the primary outcome measure of the efficacy of the treatment is usually response. Response is generally defined as a lessening of depressive symptoms (e.g. 50% drop on a clinician rating scale) or an improvement score on a clinician rating scale (e.g. Clinical Global Impression-Improvement score, CGI-I=1, very much improved, or 2, much improved) (Nierenberg et al., 1999; Nierenberg & DeCecco, 2001).

Frank et al., (1991) investigated the inconsistencies across studies in the use of remission, recovery, relapse and recurrence and proposed universal operational definitions. Frank (1991) proposed cut off scores for asymptomatic status in adult studies which include: less than or equal to 2 symptoms present on the Schedule for Affective Disorders and Schizophrenia; less than or equal to 7 on the 17-Item Hamilton Rating Scale for Depression; and less than or equal to 8 on the 21-Item Beck Depression Inventory. Paykel (1998) defined partial response as HAM-D score of 8-18, and found this group had mild to moderate residual symptoms. Other studies use a percentage of decrease in scores from baseline to end of acute treatment to define response. Nierenberg et al., (2003) found a 50% reduction from base line to end of treatment on a depression rating scale (HAM-D). Studies have found that those who respond to treatment for depression, many continue to have residual symptoms (Fava & Kaji, 1994; Nierenberg et al., 1999).

In child psychiatry research, the CDRS-R has been used to define remission in clinical trials (CDRS-R total score less than or equal to 28 at final week of treatment). In addition the CDRS-R individual items have been used to identify residual symptoms (CDRS-

R individual item score greater than or equal to 3); (Tao, Mayes, Hughes, Rintelmann, & Emslie, 2005). Kennard et al. (in press) similarly used a threshold cut off score of 3 on the K-SADS depression items to define residual symptoms.

Defining Residual Symptoms

The term residual symptom has only been used over the past 15 to 20 yrs and as a result, it has not been operationally defined in a consistent manner across studies. Fava (1999) defined residual symptoms as "the persistence of symptoms and signs despite apparent remission or recovery from depression." Menza, Marin, & Opper (2003) provided a more elaborate definition, "residual symptoms are generally thought of as core depressive symptoms that have not resolved with treatment." Judd et al. (1998) uses an alternative term of "residual subthreshold depressive symptoms" defined as "minimal depressive symptoms beneath the diagnostic threshold for minor dysthymic or MDD." Judd et al. (1998) also cites residual subthreshold depressive symptoms with increase rates of episode relapse.

Despite different definitions these studies hold in common that residual symptoms are symptoms that remain after treatment and, typically are few enough in number to be just under the diagnostic threshold established by the Diagnostic Statistical Manual-IV (DSM-IV) as meeting criteria for MDD.

Residual Symptoms of Depression in Adult Population

Multiple studies in adults have identified residual symptoms as a causal agent in the relapse process (Nierenberg, et al., 1999; Judd, et al., 1998; Paykel, Ramana, Cooper, Hayhurst, Kerr, & Barocka, 1995). These studies have also found that residual symptoms occur not only in patients with partial response but also in patients who meet the studies

criteria for response or remission of the depression. In adult studies of depression, the most frequently identified residual symptoms are irritability (Fava, Grandi, Canestrari, & Molnar, 1990), impairment in cognitive functioning (Paykel & Weissman, 1973), fatigue (Fava, Grandi, Zielezny, Canestrari, & Morphy, 1994; Nierenberg et al., 1999), sexual symptoms (Paykel, 1998), anxiety (Fava et al., 1990; Fava & Kaji, 1994; Paykel et al., 1995), social maladjustment (Fava, Fabbri, & Nicoletta, 2002), and sleep disturbances (Nierenberg et al., 1999; Paykel et al., 1995).

Nierenberg et al., (1999) investigated residual symptoms after treatment with fluoxetine in treatment responders (N=108). In this study a Hamilton Rating Scale for Depression (HAM-D) cut off score of 7 or lower was used to define remission. Despite the use of a low HAM-D score (7 as opposed to 8) as a measure of remission, only 19 (17.6%) of those with a final HAM-D score of 7 or lower were free of symptoms. While 28 (25.9%) had 1 symptoms, 25 (23.2%) had 2 symptoms, 20 (18.5%) had 3 symptoms, and 16 (14.8%) had 4 to 6 symptoms. Researchers in the above cited studies of specific symptoms have proposed many contributing factors to the presence of residual symptoms. Fava & Kellner (1991) suggested that prodromal symptoms may have a pathophysiological role in major depression and that some residual symptoms may progress to become prodromal symptoms of relapse. Others view them as a result of rollback phenomenon or the unmasking of a comorbid disorder. In the roll back phenomenon "as the illness remits, it progressively recapitulates, even though in reverse order, many of the stages and symptoms that were seen during the time it developed" (Fava et al., 2002). It is important to take into consideration any comorbid disorder that was not properly diagnosed or did not remit during MDD treatment,

because it may be mislabeled as residual symptoms of depression resulting in incomplete treatment. There is also a risk of premorbid personality traits being confused with prodromal and residual symptoms. To avoid this last misinterpretation, many researchers recommend including only symptoms with a clearly defined onset.

Treatment of Depression in Children, and Adolescents with Selective Serotonin Reuptake Inhibitors

Many individuals will experience their first episodes of depression during their adolescent years. Puberty marks a substantial rise in the overall prevalence of depression and is associated with a shift in the sex ratio, with the preponderance of initial onset occurs in females (Emslie et al., 1997). Research suggests that the earlier the onset of MDD, the more likely it is to have a recurrence. Many adults that suffer with depression most likely first experienced it as a child or adolescent, and with further longitudinal studies in depression and residual symptoms it may be possible to understand how early intervention can impact depressive cycles throughout the life span.

Currently antidepressant medication is widely prescribed to children for treatment of depression primarily using the data from adult studies. For the first-line acute treatment of MDD in children and adolescents, the AACAP recommends psychotherapy, treatment with a selective serotonin reuptake inhibitor (SSRI), or both combined, dependent upon the patient's severity of MDD and circumstances. SSRIs are recommended because of their relative safety, low lethality on overdoes, and ease of administration (AACAP, 1998).

In children and adolescents, the optimal length of treatment using medication has not been established. It has however been found that the use of fluoxetine shows promise as a

safe effective medication for children and adolescents. In a naturalistic follow-up of children and adolescents who had participated in a trial of acute fluoxetine treatment, Emslie et al. (1998) found that almost 40% of patients who had recovered from MDD experienced recurrence with in one year. In comparison a 2-year follow-up study of adolescents treated with short-term psychotherapy for MDD, Birmaher et al. (2000) found that 30% of patients experienced relapse or recurrence, with a median time to recurrence of 4.2 months. Suggesting that there may be a faster relapse rate for therapy alone treatment.

In the first reported clinical study evaluating the benefit of long-term treatment for children and adolescents with a history of MDD (Emslie et al., 2004), it was found that in the population evaluated that "long-term therapy with fluoxetine is efficacious and well tolerated." This study focused on the last 32 week relapse-prevention phase of a 51 week trial of fluoxetine versus placebo. The data indicated that fluoxetine 20 to 60 mg/day was well tolerated and could significantly delay relapse of MDD symptoms in children and adolescents. Relapse was defined as a CDRS-R score of >40 with a 2-week history of worsening of depressive symptoms. The estimated percentage of patients meeting criteria for relapse was 21% of the fluoxetine treatment group, and 47% of the fluoxetine/placebo substitution group. Time to relapse was significantly longer in the fluoxetine group (203.0 days, SE = 13.0) than the fluoxetine/placebo substitution group (37.2 days, SE = 2.1; $p = .032$). It was found that relapse primarily occurred within the first 8 weeks after placebo substitution.

Depressed children and adolescents once recovered have a high rate of relapse and recurrence of depression, with nearly 50% experiencing another episode of depression by the

time they are adults (Lewinsohn, Rohde, Klein, & Seeley, 1999). In the last year researchers have begun to look at the role residual symptoms play in relapse of MDD in children and adolescents. In an open label 12-week trial of fluoxetine in children and adolescents, Tao et al. (2005) identified impaired school performance, sleep problems, irritability, and low self-esteem as more frequent residual symptoms among remitters. In analysis of the TADS database Kennard et al. (in press) found that at the end of acute treatment, 50% of responders still had one or more residual symptom based on the K-SADS-P. Only 78 of 439 subjects (18%), treated for 12 weeks, were symptoms free. The most common residual symptoms for responders who failed to remit were sleep disturbance, mood, fatigue, and concentration. Follow-up data has not been published on either study.

Purpose of the Current Study

This study proposes to investigate the presence of residual symptoms of depression in children and adolescents who participated in a RCT of fluoxetine 20mg/day. The second purpose of this study is to identify baseline predictor variables of remission. In light of the relationship between residual symptoms after acute treatment and poor long term outcomes in adults, research into residual symptoms in children and adolescents after acute treatment is an important area for investigation.

Questions of the Current Study and Hypothesis

Question I: What are the remission rates in fluoxetine and placebo responders?

Hypothesis I: It is hypothesized that remission rates will be higher in fluoxetine responders than in placebo responders.

Question II A: What is the frequency of residual symptoms in fluoxetine and placebo responders?

Hypothesis II A: Placebo responders will experience more residual symptoms than fluoxetine responders.

Question II B: What are the types of residual symptoms in fluoxetine and placebo responders?

Hypothesis II B: It is hypothesized that placebo responders will experience more mood related symptoms (i.e. mood, irritability, and low self esteem) than fluoxetine responders who will have more sleep disturbances.

Question III A: Can baseline variables predict remission at the end of treatment in patients with MDD?

Hypothesis III A: It is hypothesized that analysis of the 315 patients that treatment group, younger age, gender, no prior episode, shorter duration of depression, and lower baseline CDRS-R total score can predict patients who will respond and remit.

Question III B: Within patients who respond to 8 weeks of treatment (fluoxetine or placebo), can baseline variables predict full remission?

Hypothesis III B: It is hypothesized that analysis of the 146 treatment responders that younger age, gender, no prior episode, shorter duration of depression, no comorbid diagnosis,

and lower baseline CDRS-R total score can predict remission in both fluoxetine and placebo responders.

CHAPTER THREE
Methodology

PARTICIPANTS

The participants are from a combined data set of two separate studies conducted by Graham J. Emslie M.D. investigating the efficacy of fluoxetine 20 mg/day for 8 weeks in children and adolescents with non-psychotic depression. Both studies were double-blind, randomized, placebo-controlled trials and are briefly described below. Table 1 and Figures 1 and 2 display clinical and demographic characteristics of the treatment groups. Figure 3 tracks the number of participants that exited the study each week.

Emslie et al. (1997) conducted at UT Southwestern Medical Center at Dallas consists of 96 participants ages 7-18 who were self-referred or referred by other practitioner to the mood disorders program, and who met DSM-III-R criteria for non-psychotic MDD, single and recurrent. Based on a CGI scale improvement rating of 1 or 2 (very much or much improved) to define response, 27 (56%) of 48 patients receiving fluoxetine treatment and 16 (33%) of 48 patients on placebo responded to treatment at exit from the study ($\chi 2 = 5.097$, df =1, P=.02) (Emslie, 1997).

The second study Emslie et al. (2002) is a multi-site trial consisting of 219 participant's ages 8-18 year-old. Eligibility requirements for participation in the trial included primary diagnosis of non-psychotic MDD (single or recurrent) as defined by DSM-IV criteria and depressive symptoms of at least moderate severity as defined by CDRS-R total score > 40, and a CGI-Severity rating of ≥ 4. Of those subjects 142 (65%) were labeled treatment responders (≥ 30% decrease in CDRS-R total score from first week of the 8 week trial to endpoint), and 90 (41.3%) were labeled treatment remitters (CDRS-R total score of ≤

28). There are no significant differences between treatment groups in patient demographics or clinical features.

Inclusion criteria: Outpatients 7-18 years of age at time of study entry who attended school during participation in the study. A primary diagnosis of non-psychotic major depressive disorder (single or recurrent) for at least four weeks as defined by DSM-IV criteria with a CGI-severity score >4 for depression and CDRS-R total score >40. Subjects were in good general medical health and of normal intelligence. While the MDD must be the primary cause for dysfunction, other concurrent disorders (anxiety, attention deficit (ADHD), or conduct) are not excluded (Emslie et al., 1997, 2002).

Exclusion criteria: Subjects were excluded for lifetime history of any psychotic disorder, including psychotic depression; bipolar I and II disorder; alcohol or substance abuse or dependence within the past six months; lifetime anorexia nervosa or bulimia; pregnant or lactating females, sexual 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 psychotropic effects (anticonvulsants, steroids, etc.); patients with first degree relatives with bipolar I disorder; or subjects with severe suicidal ideation or previous history of serious suicide attempt. Subjects who have failed on a previous adequate treatment of fluoxetine (defined as at least 40 mg/day for 4 weeks) were excluded (Emslie et al., 1997, 2002).

Measures

Due to the inconsistency in frequency of data collection between the two studies only the baseline and week 8 data are presented. The following measures were collected across studies:

The Diagnostic Interview for Children and Adolescents (DICA) (Welner, Reich, Herjanic, Jung, and Amado, 1987).

The Diagnostic Interview for Children and Adolescents (DICA) is a structured interview for children and adolescents ages 7-17 years, patterned after the National Institute of Mental Health Diagnostic Interview Schedule (DIS) and based on the DSM-III criteria. The DICA includes two separate interviews: DICA-C, a child interview, and DICA-P, a corresponding parent interview. Each interview is divided according to 18 of the DSM-III diagnostic categories. Essentially, one or more questions has been designed to fulfill each symptom from each disorder, and a method of determining current and past symptomatology, as well as severity, is included in some diagnostic categories. Each diagnostic section is followed by instructions that list the specific DSM-III criteria for arriving at diagnoses in that section (Welner, Reich, Herjanic, Jung, & Amado, 1987). Reliability and validity studies were conducted investigating parent child agreement based on the DICA-C and DICA-P, and inter-interview reliability by Welner et al., (1987). Agreement on diagnoses between 84 child and parent interviews was high, using kappa statistics to measure positive agreement that exceeds chance the study found; attention deficit disorder $\kappa = .66$, conduct disorder $\kappa = .80$, affective disorder $\kappa = .63$, enuresis $\kappa = .49$, and oppositional disorder $\kappa = .52$. The inter-interviewer reliability (N=27) was highest in categories of attention deficit disorder, conduct

disorder, and affective disorder, and the lowest agreement was found in anxiety disorders, κ = .76 which is still considered to be in the range of a good agreement.

The Children's Depression Rating Scale – Revised (CDRS-R) (Poznanski, et al., 1984).

The CDRS-R is a 17-item clinician-rated instrument, modeled after the Hamilton Depression Rating Scales for adults, and is used to measure the presence and severity of depressive symptomatology in children and adolescents. It is modified version of the CDRS (Poznanski, Cook, and Carroll, 1979) which was a diagnostic tool and severity measure of depression in children. It is a semi structured interview which can be administered to children, ages 6 to 12, adolescents, their parents, teachers, case workers, or other sources of information in approximately 30 minutes. Seventeen (17) symptom areas are assessed by the scale, the last three (3) of which are evaluated using the child's nonverbal characteristics. Each item is rated on a 1 to 5 or a 1 to 7 point scale, with a 1 describing absence of the given symptom. The CDRS-R yields a total score from 17 to 113, with a score of 40 or greater considered to be compatible with 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 .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 child interviewed (Poznanski et al., 1984). High inter-rater reliability, with four raters and 25 subjects, was evidenced by a product-moment correlation of .92 (Poznanski et al., 1984). The CDRS-R has been used successfully in psychopharmacology studies for

some time and allows for ready comparison to be made across studies. In a recent study, the CDRS-R has good inter-rater reliability with an intra class correlation of .95; it also correlated highly with global ratings of improvement (Emslie et al., 1997).

The Clinical Global Improvement Scale (CGI) (National Institute of Mental Health, 1985).

This scale is used as a clinician assessment of overall symptom severity and improvement, each with a seven point scale, with lower values being more favorable. It was developed during the PRB collaborative schizophrenia studies. The items are considered "universal" and formatted for use in pediatric and adult populations. Only clinical Global Severity (CGS) can be measured at intake. In subsequent assessments, both severity and clinical global improvement (CGI) will be rated. This is a standard scale for affective disorders treatment research, and CGI improvement score 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). In this study, subjects were rated as responders if they received a CGI score of 1 or 2. The intra class correlation for CGI improvement as a continuous variable in the above study was 0.93, and if used as categorical variable, was k=.95.

Procedure

Randomization was preceded by 3 evaluation visits that consisted of structured diagnostic interviews to participants and parent(s) using the Diagnostic Interview for Children and Adolescents (DICA), to establish diagnosis of MDD. Participants had to continue to meet established criteria of MDD, have a CDRS-R score > 40, and meet the previous inclusion-exclusion criteria to enroll in the 1-week single blind placebo run-in. No-

responders to placebo run-in were then randomized into the double-blind treatment phase of 20mg/day of fluoxetine (n=158) or placebo (n=157) if they continued to meet inclusion criteria. CDRS-R and CGI data were collected every visit. Due to inconsistencies of data collection between the studies only baseline and exit scores on the CDRS-R and CGI will be used in data analysis.

Following randomization, visits in the single-site trial were weekly for 8 weeks; visits for the multi-site trial were at weeks 1, 2, 3, 5, 7, and 9. Dosing for the single-site study was 20mg for the duration of the trial; dosing for the multi-site trial was 10mg for 1 week, and then increased to 20mg for the remainder of the study. For the purposes of these post hoc analyses, weeks of treatment are based on the number of weeks on 20mg of fluoxetine. Thus, week 8 refers to patients having been on 20mg for 8 weeks. (NOTE: subjects in the multi-site trial had one week of 10mg prior to increasing to 20mg; consequently, those patients will have actually had 9 weeks of total medication exposure.).

For the purposes of this study, remission is defined as CDRS-R $\leq$ 28, consistent with previous definitions of remission existing in the child and adolescent psychiatry literature (Emslie et al., 1997, 2002; Tao et al., 2005; & Kennard et al., in press). Response is defined by a CGI-I score of 1 or 2 (TADS Team, 2004; Kennard et al., in press). Remission in responders are those subjects who had a CGI-I score of 1 or 2 after 8 weeks of treatment and a CDRS-R $\leq$ 28, thus, this is a subset of the responder group. Residual symptom is defined as a CDRS-R individual item score $\geq$ 3 (Tao et al., 2005).

Statistical Design

All analyses follow an intent-to-treat approach. The baseline data are 100% complete for the CDRS-R and CGI-Severity. The completeness of the Week 8 post-randomization data is 69% (218/315). In the case of missing Week 8 data, the imputed data is the last observation carried forward (LOCF).

Statistical Analyses

End-of-treatment CDRS-R scores were used to dichotomize the sample into "remitted" (score ≤ 28) or "not remitted" (score>28). End-of-treatment CGI-I scores was used to dichotomize the sample into "responders" (CGI-I of 1 or 2) or "non responders (CGI-I ≥ 3). Chi-square was used to test significance. To assess residual symptoms, the responder group was analyzed for frequencies and type of residual symptoms at week 8 (CDRS-R ≥ 3). Logistic regression was used to identify baseline predictors of remission in responders at exit.

CHAPTER FOUR
Results

THE MAJOR STUDY HYPOTHESES

The purpose of this study was to investigate the presence and type of residual symptoms of depression in children and adolescents who participated in a RCT of fluoxetine 20mg/day. We also looked to establish baseline variables that could accurately predict remission in responders. The following paragraphs present the findings of this study.

Hypothesis I:

What are the remission rates in fluoxetine and placebo responders?

With end-of-treatment CGI-I score of 1 or 2 defining response and CDRS-R score ≤ 28 to define remission, the over all remission rates in responders was found to be 87 out of 143 (61%). In the fluoxetine-treated group 55 out of 86, and in the placebo-treated group 32 out of 57 meet end of treatment criteria as responders who remitted. More fluoxetine patients (64%) than placebo patients (56%) met proposed defined criteria for responders who remitted however the difference was not significant (p=.35).

Hypothesis II A:

What is the frequency of residual symptoms in fluoxetine and placebo responders?

Using the CDRS-R individual item scored of ≥ 3, 86 out of 157 (55%) fluoxetine-treated patients met criteria for response and 57 out of 158 (36%) placebo-treated patients meet criteria for response. Of those that responded to fluoxetine-treatment 41 (48%) displayed zero residual symptoms, 26 (30%) displayed one to two residual symptoms, and 19

(22%) displaying three or more residual symptoms with a maximum of ten residual symptoms. Of those that responded to placebo-treatment 20 (35%) displayed zero residual symptoms, 20 (35%) displayed one to two residual symptoms, and 17 (30%) displayed three or more residual symptoms with a maximum of nine residual symptoms. The difference between the frequency of residual symptoms experienced between the fluoxetine and placebo treatment groups was not found to be significant (p=.32). See Table 2 for frequency of residual symptoms at exit between treatment groups.

Hypothesis II B:

What are the types of residual symptoms in fluoxetine and placebo responders?

Using the CDRS-R individual item scores of ≥3, fourteen residual symptoms were positive (residual symptoms with >1% of occurrence) for the 86 fluoxetine responders, and eleven residual symptoms were positive for the 57 placebo responders. Residual symptoms displayed by the 86 fluoxetine treatment responders are impaired school work 18 (21%), hypoactivity 17 (20%), low self-esteem 17 (20%), difficulty having fun 12 (14%), irritability 12 (14%), sleep disturbance 11 (13%), excessive fatigue 10 (12%), physical complaints 9 (11%), social withdrawal 6 (7%), appetite disturbance 6 (7%), depressed feelings 6 (7%), depressed facial affect 5 (6%), excessive weeping 3 (4%), excessive guilt 2 (2%). Residual symptoms displayed by the 57 placebo treatment responders are low self-esteem 14 (25%), irritability 13 (23%), impaired school work 12 (21%), excessive fatigue 9 (16%), physical complaints 9 (16%), hypoactivity 9 (16%), difficulty having fun 8 (14%), sleep disturbance 8 (14%), social withdrawal 6 (11%), depressed feelings 5 (9%), and appetitive disturbance 4 (7%). The types of residual symptoms experienced are consistent with

previous research by Tao et al. (2005) and Kennard et al. (in press). See Figure 4 for percent of residual symptoms at baseline, and Figure 5 for percent of residual symptoms at exit.

Hypothesis III A:

Can baseline variables predict remission at the end of treatment in patients with MDD?

Using a logistic regression to evaluate baseline variables for predictors of responders who remitted two baseline variables were found to be predictive of responders who remitted. Having a lower CDRS-R baseline total score was found to be significantly correlated ($p<.001$) with remission in responders. The second variable to be correlated was having a current diagnosis of dysthymic disorder. It was found that patients that had dysthymic disorder were two times more likely to not meet the criteria of responders who remitted than all other patients ($p=.031$). See Table 4 for characteristics of dysthymic patients. Other variables tested but found to not be significant were age ($p=.560$), gender ($p=.07$), prior episodes ($p=.687$), and duration of illness ($p=.878$). See Table 3 for full report of analyses.

Hypothesis III B:

Within patients who respond to 8 weeks of treatment (fluoxetine or placebo), can baseline variables predict full remission?

Using available baseline variables in a logistic regression, two variables significantly correlated with the outcome of remission in responders defined as participants with a CGI-I score of 1 or 2 and a CDRS-R score ≤ 28 at exit. Having a lower CDRS-R baseline total score was found to be significantly correlated ($p<.001$) with remission in responders. Gender was also found to correlated showing that males are two times more likely to respond to

treatment, but not remit when compared to females (p=.021). Other variables tested but found to not be significant were age (p=.864), treatment group (p=.401), current dysthymic disorder (p=.058), and prior episodes (p=.449), duration of illness (p=.555). See table 5 for complete report of analysis.

CHAPTER FIVE
Conclusions and Recommendations

Research into residual symptoms and the long term effect it has on recovery from MDD is in its infancy. The purpose of this study was to establish that residual symptoms do occur in the child and adolescent population as it has been established in the adult population. The second purpose of this study was to establish predictive baseline variables for remission in responders.

Discussion of Hypothesis

Hypothesis I:

What are the remission rates in fluoxetine and placebo responders?

To the knowledge of this study no other research project has reported the rate of remitters in responders. Of the 143 fluoxetine and placebo patients who responded to treatment only 87 (61%) also remitted at end of treatment. However when compared to the entire sample only 28% of 315 responded and remitted to treatment. As predicted a higher number of fluoxetine treated patients responded and remitted to treatment than placebo, however the difference was not significant. This is a more stringent criterion to strive for in treatment outcomes. In using this more stringent criterion the research may be identifying a subset of patients that may have a better long term prognosis for remaining symptom free than those patients that only responded or only remitted.

Hypothesis II A:

What is the frequency of residual symptoms in fluoxetine and placebo responders?

This study successfully established that residual symptoms do occur in children and adolescents who responded to double-blind placebo controlled trial of fluoxetine for eight weeks of treatment. As predicted responders in the placebo treatment group had more participants that were experiencing residual symptoms at end of treatment. Only 20 out of 57 (35%) placebo responders experienced zero residual symptoms with 41 out of 86 (48%) fluoxetine responders experiencing zero residual symptoms this difference however was not significant. It is of note that the number of residual symptoms a single patient experienced was higher in the fluoxetine treatment group with one patient experiencing ten residual symptoms versus a max of nine residual symptoms in the placebo treatment group.

Hypothesis II B:

What are the types of residual symptoms in fluoxetine and placebo responders?

We have identified the types of residual symptoms responders exhibited after a double-blind placebo controlled trial of fluoxetine over eight weeks of treatment using the CDRS-R. Unexpectedly the fluoxetine treatment group displayed more types of residual symptoms (14) at exit than the placebo treatment group (11). The residual symptoms not experienced by the placebo group were excessive guilt, excessive weeping and depressed facial affect. However the placebo treatment group did have a higher percentage of patients experiencing residual symptoms with low self-esteem 14 of 57 (25%) and irritability 13 of 57 (23%) being the most frequent. This is inline with the previously stated hypothesis that the

placebo group would experience more mood related symptoms. However in the fluoxetine treatment group the most frequent residual symptoms where impaired school work 18 of 86 (21%), hypoactivity 17 of 86 (20%), and low self-esteem 17 of 86 (20%). It was predicted that sleep disturbance would be one of the most frequently exhibited residual symptoms in the fluoxetine treatment group, however only 11 of 86 (13%) experienced sleep disturbance.

Hypothesis III A:

Can baseline variables predict remission at the end of treatment in patients with MDD?

It was identified that low baseline CDRS-R total score is predictive of being a patient who responded and remitted at end of treatment. It was also identified that a diagnosis of dysthymic disorder made a patient twice as likely to not respond and remit at exit. Thus, factors associated with severity, greater symptomatology on CDRS-R and comorbid dysthymic disorder are associated with a less successful outcome. These variables are consistent with the previously stated hypothesis.

Hypothesis III B:

Within patients who respond to 8 weeks of treatment (fluoxetine or placebo), can baseline variables predict full remission?

It was identified that low baseline CDRS-R total score is predictive of meeting criteria for remission in responders at exit. Gender was identified to predict that males are more likely to respond, but not remit to treatment in comparison to females. Thus, greater symptom severity, and being male are associated with less successful outcome when evaluating remission in responders.

Generalizability of Data

This study has helped establish the presence of residual symptoms in children and adolescents who respond to a double-blind, eight week treatment of fluoxetine. Adult research has shown that residual symptoms increase the rate of relapse and recurrence of MDD in adults. With this established knowledge in the adult population and the evidence to support the presence of residual symptoms in children and adolescents from this study more specific long term studies can be developed to better understand the effect residual symptoms have in children and adolescent MDD.

Limitations of the Present Study and Future Recommendations

This study combined data from existing data sets evaluating the efficacy of fluoxetine treatment in children and adolescents. Due to the use of these preexisting data sets, this study was limited in the variables available to use in the analysis. Identifying variables such as socioeconomic status, and evaluation of home environment information could potentially increase the number of predictors of outcome. This study was also limited in having a relatively small sample to perform logistic regression analyses to evaluate baseline predictive variables.

This study does not include follow-up data to analyze the effect residual symptoms have on the rate of relapse of MDD in children and adolescents. Now that the presence of residual symptoms has been established in children and adolescents in this study and others (Kennard et al., in press and Tao et al., 2005), it would be beneficial to conduct a research project that specifically looked at residual symptoms and contained follow-up data to track the effect residual symptoms have on the rate of relapse. This is the next recommended step

in investigating the effects residual symptoms have in children and adolescent recovery from MDD. In addition, the use of a factor analysis to narrow down the types of residual symptoms exhibited would benefit by focusing the scope of future research.

Future studies would benefit from the use of the Kiddie-Sads-Present and Lifetime Version in combination with the CDRS-R to evaluate the type of residual symptoms exhibited. It would also be valuable to use a measure of self rated depressive symptoms to compare these results to clinician rated measures such as the Beck Depression Inventory (Beck and Steer, 1984), and the Childhood Depression Inventory (Kovacs, 1985).

Summary

One of the major risk factors for relapse or recurrence of MDD is childhood onset of the illness. MDD in childhood will most likely lead to MDD in adulthood. In using this data and future studies to better understand the part residual symptoms play in the relapse or recurrence process practitioners can treat at younger ages with better long term success. The goal of treatment is to have long term remission of MDD, however at this time we do not have a full understanding of the contributing factors to relapse.

This study achieved its goal of adding to the few studies published evaluating the presence of residual symptoms at the end of acute treatment. These studies represent beginning steps into fully understanding the effect residual symptoms may have in the child and adolescent population. With the information from this study and others it is now possible to design a full length study specifically designed to evaluate residual symptoms in children and adolescents, using adequate baseline data, and appropriate measures.

Through increasing our understanding of residual symptoms of MDD, and improving our ability to measure these symptoms should assist in develop and implement interventions to prevent relapse in youth with MDD.

Figure 1:

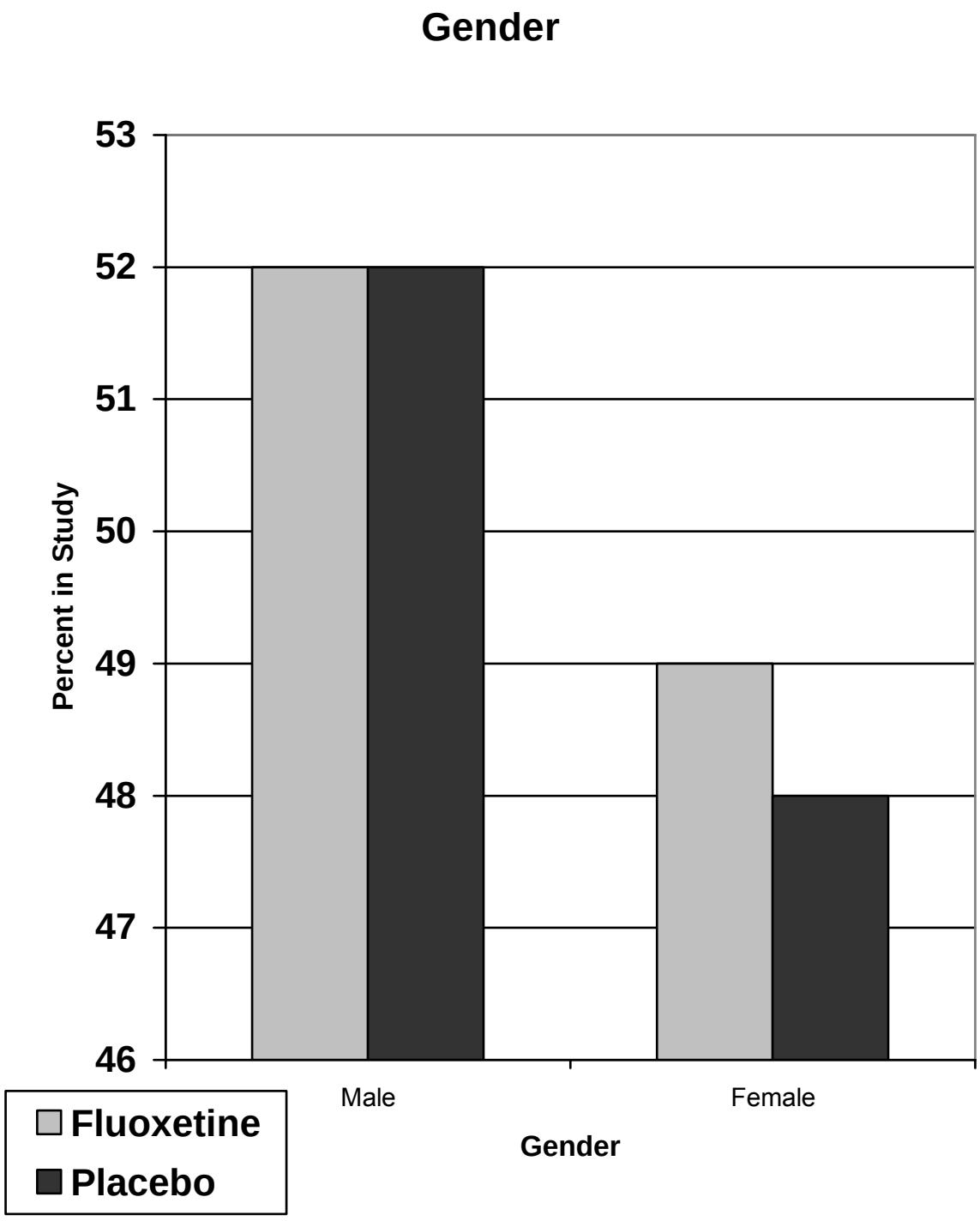
Gender
53
52
51
50
49
48
47
46
Percent in Study
Male
Female
Gender
Fluoxetine
Placebo

Figure 2:

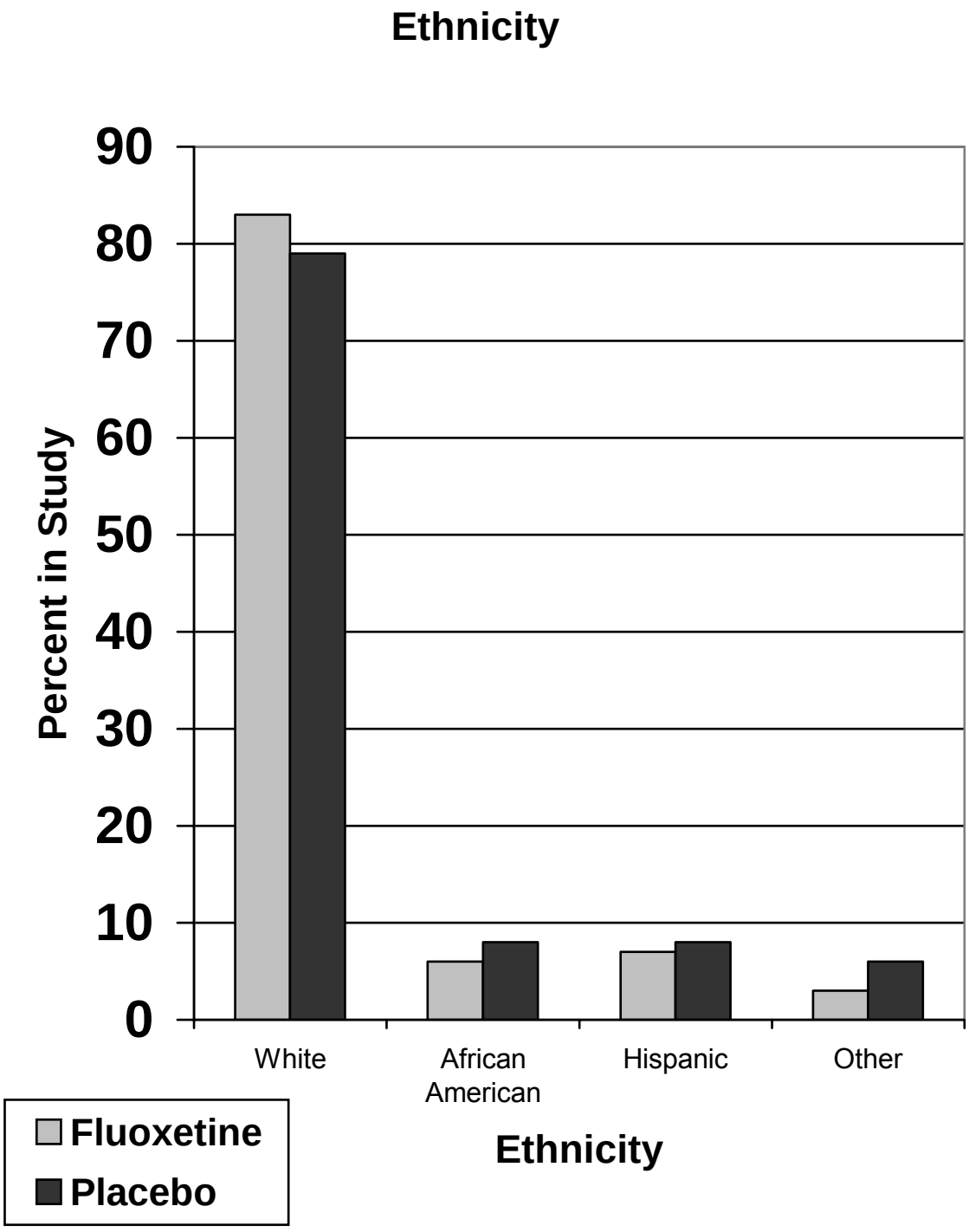
Ethnicity
90
80
70
60
50
40
30
20
10
0
Percent in Study
White
African American
Hispanic
Other
Ethnicity
Fluoxetine
Placebo

Figure 3:

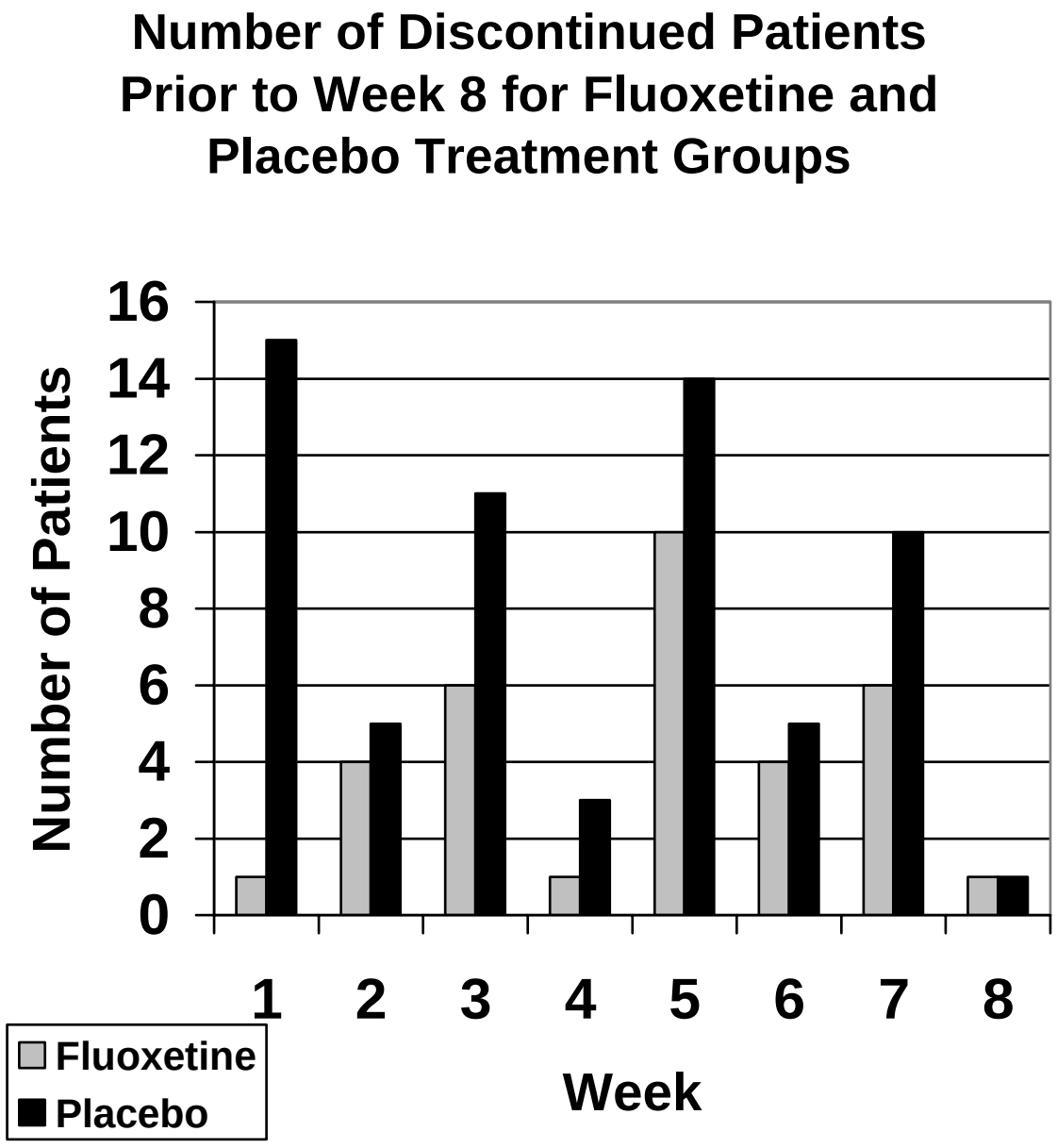
Number of Discontinued Patients Prior to Week 8 for Fluoxetine and Placebo Treatment Groups
Number of Patients
16
14
12
10
8
6
4
2
0
1
2
3
4
5
6
7
8
Week
Fluoxetine
Placebo

Figure 4:

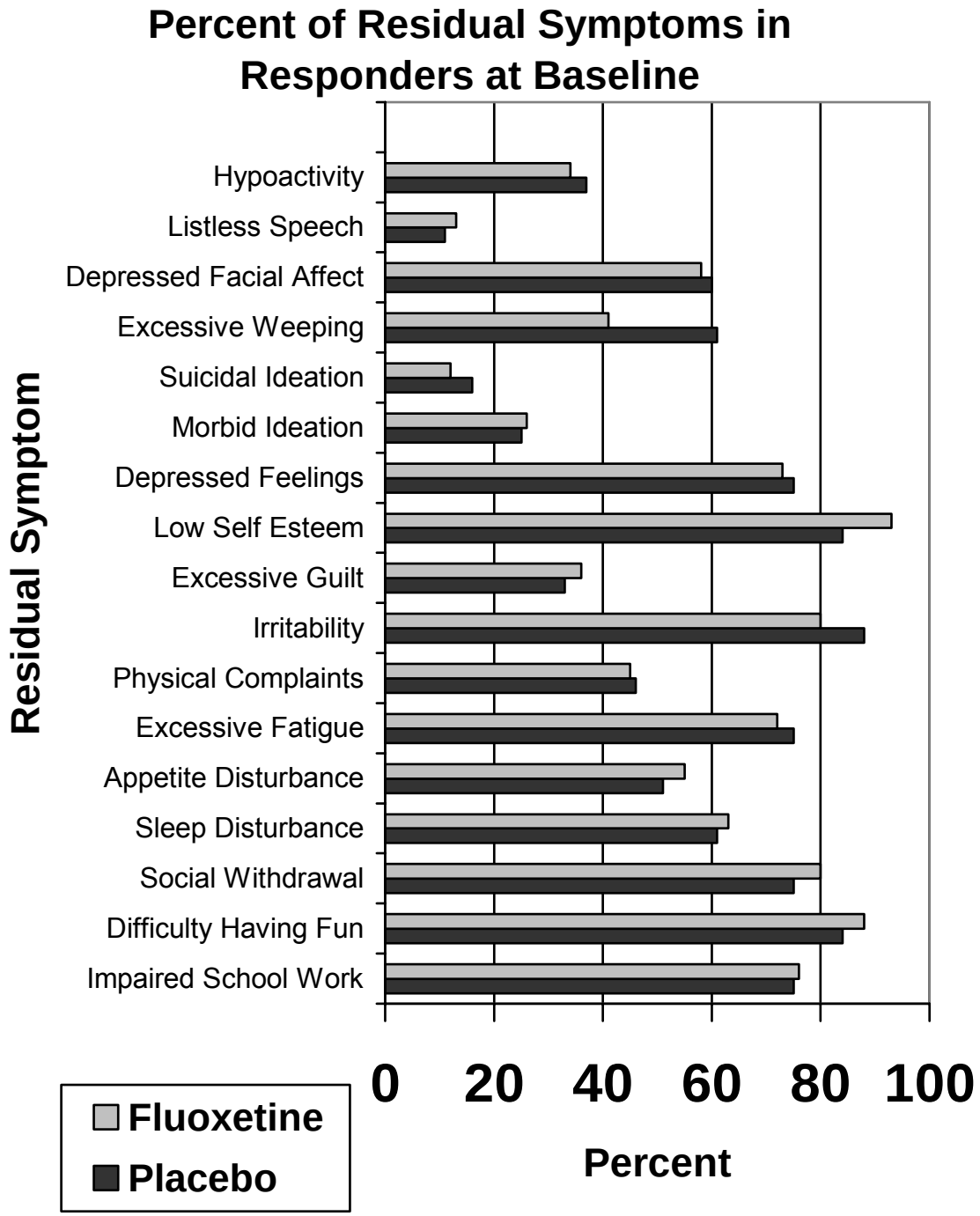
Percent of Residual Symptoms in Responders at Baseline
Residual Symptom
Hypoactivity
Listless Speech
Depressed Facial Affect
Excessive Weeping
Suicidal Ideation
Morbid Ideation
Depressed Feelings
Low Self Esteem
Excessive Guilt
Irritability
Physical Complaints
Excessive Fatigue
Appetite Disturbance
Sleep Disturbance
Social Withdrawal
Difficulty Having Fun
Impaired School Work
0
20
40
60
80
100
Percent
Fluoxetine
Placebo

Figure 5:

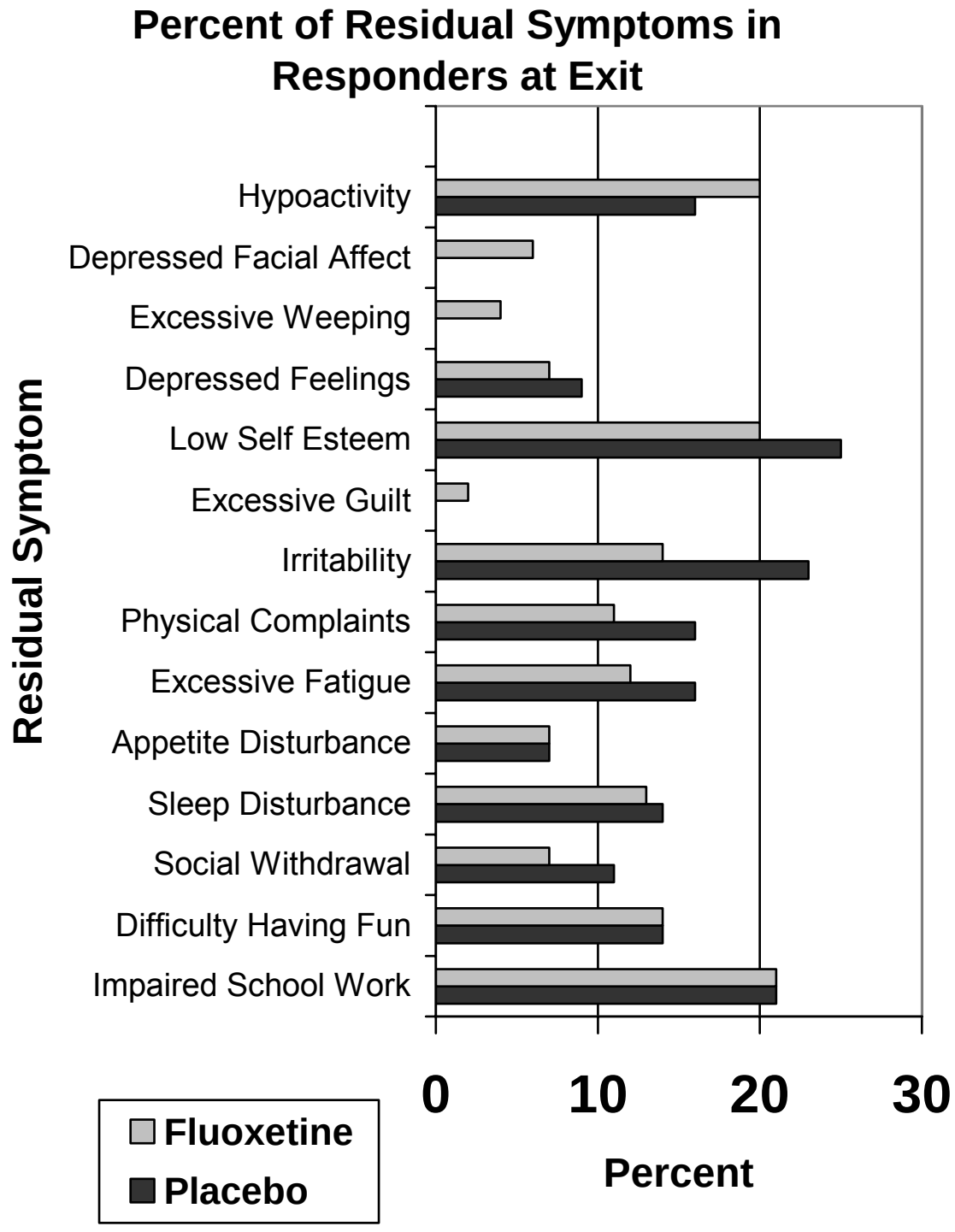
Percent of Residual Symptoms in Responders at Exit
Residual Symptom
Hypoactivity
Depressed Facial Affect
Excessive Weeping
Depressed Feelings
Low Self Esteem
Excessive Guilt
Irritability
Physical Complaints
Excessive Fatigue
Appetite Disturbance
Sleep Disturbance
Social Withdrawal
Difficulty Having Fun
Impaired School Work
0
10
20
30
Percent
Fluoxetine
Placebo

Table 1:

Clinical and Demographic Characteristics between Treatment Groups

Demographics	Fluoxetine (n=157)	Placebo (n=158)
Gender		
Male	81 (51.6%)	82 (51.9%)
Female	76 (48.4%)	76 (48.1%)
Age (years)	12.52 ± 2.6	12.67 ± 2.7
Ethnicity		
White	131 (83.4%)	125 (79.1%)
African American	10 (6.4%)	12 (7.6%)
Hispanic	11(7%)	12 (7.6%)
Other	5 (3.2%)	9 (5.7%)
Current Dysthymic		
No	117 (74.5%)	120 (75.9%)
Yes	40 (25.5%)	38 (24.1%)
Duration of Current Episode (weeks)		
Mean	46.42	46.82
Range	4-572	2-450
Number of Comorbid Diagnosis		
Zero	56 (35.7%)	67 (42.4%)
One	41 (26.1%)	41 (25.9%)
Two	32 (20.4%)	26 (16.5%)
Three	23 (14.6%)	15 (9.5%)
Four	3 (1.9%)	9 (5.7%)
Five	2 (1.3%)	0

Table 2:

Frequency of Residual Symptoms at Exit between Groups

Number of Residual Symptoms	Fluoxetine n=86	Placebo n=57
0	41 (47.7%)	20 (35.1%)
1	20 (23.3%)	12 (21.1%)
2	6 (7%)	8 (14%)
3	7 (8.1%)	8 (14%)
4	2 (2.3%)	5 (8.8%)
5	1 (1.2%)	1 (1.8%)
6	2 (2.3)	1 (1.8%)
7	2 (2.3)	1 (1.8%)
8	2 (2.3)	1 (1.8%)
9	2 (2.3)	1 (1.8%)
10	1 (1.2%)	0

Table 3:

What Predicts Patients who will Respond and Remit after 8 weeks of Treatment for MDD?

			95% CI for exp b		
	B (SE)	**p**	**Lower**	**exp b**	**Upper**
Included					
Age	-.031	.560	.872	.969	1.077
Gender	-.492	.069	.360	.612	1.040
Dysthymic	.802	.031	1.08	2.23	4.612
Number Previous Episodes	-.136	.687	.811	.965	1.148
Length of Illness	-.001	.878	.982	.999	1.016
CDRS-R Baseline Total	-.055	.000	.924	.946	.969

Table 4:

Characteristics of Dysthymic Responders

	Fluoxetine n=40	Placebo n=38
Age	12.50 ± 2.6	13 ± 2.77
Gender		
Male	21 (52%)	22 (58%)
Female	19 (48%)	16 (24%)
Race		
White	32 (80%)	30 (79%)
African American	5 (13%)	2 (5%)
Hispanic	1 (3%)	2 (5%)
Other	2 (5%)	4 (11%)
Responded	20 (50%)	12 (32%)
Remitted	9 (23%)	5 (13%)
Responders Who Remitted	9 (23%)	5 (13%)

Table 5:

What Predicts Remission in Responders after 8 Weeks of Treatment?

			95% CI for exp b		
	B (SE)	**P**	**Lower**	**exp b**	**Upper**
Included					
Age	.01	.864	.874	1.013	1.174
Gender	.915	.021	1.149	2.497	5.428
Treatment Group	.328	.401	.647	1.388	2.978
Dysthymic	.884	.058	.971	2.422	6.040
Number Previous Episodes	-.097	.449	.707	.908	1.166
Length of Illness	.007	.555	.985	1.007	1.029
CDRS-R Baseline Total	-.065	.000	.906	.937	.968

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VITAE

Morgan Michelle Sowell was born in Houston, Texas, on July 30, 1981, the daughter of Dale and Monica Sowell. After completing her work at McNeil High School, Austin, Texas in 1999 she enrolled at Texas Tech University in Lubbock, Texas. She received her Bachelor of Arts degree with a major in psychology and a minor in substance abuse counseling in December of 2002. After working as a substance abuse counselor she began graduate work at the University of Texas Southwestern Medical Center at Dallas in Rehabilitation Psychology in the fall of 2004. She will begin work in the fall of 2006 at Texas A&M University in the School Psychology doctoral program.

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