

THE IMPACT OF TRAUMA HISTORY ON ACUTE TREATMENT OUTCOMES IN
PEDIATRIC MAJOR DEPRESSIVE DISORDER

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DEDICATION

*In loving memory of my father, Marvin Louis Daniel,
whose intelligent and adventurous spirit has always inspired me.*

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PEDIATRIC MAJOR DEPRESSIVE DISORDER

by

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The impact of childhood trauma on depression in youth was examined through a secondary analysis of pooled data from three studies of Major Depressive Disorder (MDD) in youth. A total of 292 children and adolescents ages 7 to 18 (53% male, 70% Caucasian, mean age = 12.83), received open treatment with fluoxetine for a period of 6 to 12 weeks. Youth were separated into three trauma history groups: no trauma, trauma—no abuse, and abuse. Associations between trauma history and demographic and clinical characteristics of depression were examined. The effects of trauma and abuse history on depression severity and remission rates following acute treatment with fluoxetine were explored using depression severity scores from the Children's Depressive

Rating Scale-Revised (CDRS-R) and remission status, defined as a score of ≤ 28 on CDRS-R and a Clinical Global Impressions (CGI) Improvement score of 1 or 2. Abuse history was associated with older age, older age of depression onset, longer length of illness, and suicidal ideation and behavior at baseline. Abuse history was also associated with some differences in initial depressive symptom profiles among children. The hypothesis that youth with a history of abuse would demonstrate lower remission rates at the end of acute treatment was partially supported. Odds ratios indicated that youth without a history of abuse were twice as likely to have remitted at the end of acute treatment when compared to those with no abuse history. This finding did not remain significant after controlling for the effects of age and family history of depression. No differences were found in depression severity across the acute phase of treatment based on trauma history. Additionally, trauma history was not associated with a difference in youth's time to achieve remission. Results should be considered in context of small sample sizes and limited assessment of trauma in the current study. These results suggest the importance of thoroughly assessing for trauma history, especially abuse, and considering the impact of these events on youth's depressive presentation and treatment needs.

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LIST OF ABBREVIATIONS

CBT	Cognitive Behavioral Therapy
CDRS-R	Children’s Depression Rating Scale-Revised
CE	Current Episode
CGI	Clinical Global Impressions Scale
IRB	Institutional Review Board
K-SADS-PL	Kiddie Schedule for Affective Disorders and Schizophrenia- Present and Lifetime Version
MDD	Major Depressive Disorder
OR	Odds Ratio
PTSD	Posttraumatic Stress Disorder
RR	Childhood Depression: Relapse and Remission, Principal Investigator—G.J. Emslie
RP	Relapse Prevention CBT, Principal Investigator—B.D. Kennard
SES	Socio-economic status
STS	The Sequential Treatment Study of Pediatric Depression, Principal Investigators—G.J. Emslie, B.D. Kennard
UTSW	University of Texas Southwestern Medical Center at Dallas

CHAPTER ONE
Introduction

BACKGROUND OF THE STUDY

Major Depressive Disorder (MDD)

Depression affects a substantial number of youth, with prevalence rates ranging from 3% among children to 20% among adolescents (Lewinsohn, Rohde, & Seeley, 1998). The illness contributes to significant impairment in youth's academic, family, and social functioning, and has a negative impact on development that can contribute to longstanding impairment and increased risk for psychopathology throughout the lifespan. Current research examining the treatment of depression in children and adolescents has provided evidence for the effectiveness of both antidepressant medication and cognitive behavioral therapy (CBT) in reducing depressive symptoms and preventing relapse (Birmaher, Brent, and AACAP Work Group, 2007).

Impact of Trauma on Depression

Extensive research has demonstrated that individuals with early adverse experiences are at increased risk for the development of depression and anxiety disorders. A recent examination of the National Comorbidity Survey found that childhood adversities, such as loss or separation from parents, abuse, and parental maladjustment, occur in approximately half of all childhood-onset disorders (Green et al., 2010). Several studies have examined the specific relationship between traumatic life events and risk for major depressive disorder. Approximately 50% of depressed adolescents have experienced two

or more severe life events in the year prior to onset of depression (Williamson et al., 1998). Thus, one important risk factor associated with the development of major depression is the experience of trauma or severe negative life events.

Trauma and Clinical Characteristics of Depression

Further research has examined the relationship between trauma history and depression. The experience of childhood trauma and other stressful life events is one variable related to several clinical characteristics of depression, including onset, severity, and length of illness (Bernet & Stein, 1999; Kessler, 1997; Klein et al., 2009; Miniati et al., 2009). Depressed adults with significant life stress may present with differing symptom patterns, including an increase in suicidality, when compared to those without a history of adverse events (Miniati et al., 2009; Monroe, Harkness, Simons, & Thase, 2001; Muscatell, Slavich, Monroe, & Golib, 2009). Initial research among youth has attempted to corroborate these findings, with mixed results (Barbe, Bridge, Birmaher, Kolko, & Brent, 2004; Lewis et al., 2010). Additionally, previous research has indicated that negative life events, particularly peer harassment, are associated with greater cognitive vulnerability to depression (Mezulis, Hyde, & Abramson, 2006). Early experiences of trauma may produce lasting changes in cognition, which then leads to increased risk of experiencing a major depressive episode (Gibb et al., 2001; Hammen, Henry, & Daley, 2000). These findings indicate the need to consider the experience of life stress and trauma as an important variable when assessing and treating individuals diagnosed with MDD.

Adult Studies Examining Impact of Trauma on Treatment Response in MDD

Adverse childhood experiences, particularly the experience of physical and/or sexual abuse, have been associated with differential treatment response for depression in adults. The presence of early adversity is associated with a poorer response to pharmacotherapy for depression (Klein et al., 2009). Patients with early adverse experiences are more likely to experience a persistence of mood symptoms throughout the life course (McLaughlin et al., 2010) and have a greater need for augmentation treatment (Miniati et al., 2009). Additionally, research has shown that psychotherapy was more effective than antidepressant monotherapy in treating depression among adults with early childhood trauma (Nemeroff et al., 2003). Another study considered the impact of experiencing physical, sexual, or emotional abuse during childhood or early adolescence on the addition of CBT aimed at reducing self-harming behaviors, with similar findings (Spinhoven, Slee, Garnefski, & Arensman, 2009). In these studies, results indicate that patients with a history of childhood trauma achieved a greater relief of their depression symptoms when treated with the addition of a cognitive behavioral form of therapy.

Childhood Studies Examining Impact of Trauma on Treatment Response in MDD

Fewer studies have examined the impact of trauma and other stressful life events on depression treatment during childhood or adolescence. Recent research has begun to examine trauma history as a potential moderator of treatment response. Adolescents with treatment-resistant depression who identified a history of abuse are less likely to achieve an adequate response to additional treatment with a combination of medication and CBT, as compared to those adolescents without a history of abuse; this difference is particularly

evident in youth with a history of physical abuse (Asarnow et al., 2009; Shamseddeen et al., 2011). Other studies have examined response to psychotherapy and found results that contrast the findings from the adult literature. In general, adolescents without a history of psychosocial adversity or abuse were more likely to respond to treatment and receive benefit from CBT, as compared to those with a history of abuse (Barbe et al., 2004; Jayson, Wood, Kroll, Fraser, & Harrington, 1998; Lewis et al., 2010). The current literature suggests that trauma history is associated with differential treatment response among adolescents with depression; however, the findings are not consistent.

STATEMENT OF THE PROBLEM

Although researchers have identified several characteristics associated with early childhood adversity among adults, less is known about the impact of trauma on the experience and treatment of depression among children and adolescents. Trauma history has been considered as a potential moderator variable in several randomized controlled trials comparing efficacies of various treatments for major depressive disorder, including pharmacotherapy, various psychotherapies, and combination treatment. Given the complex nature of many of the studies utilized to assess these relationships, the current findings are unclear and often limited by very small sample sizes. Additionally, the focus in the large trials has been on examining whether trauma history is associated with differential treatment response with less attention paid to the ability of trauma history to predict response to acute treatment. No known studies have specifically examined the relationship between trauma history and response to acute pharmacotherapy treatment among depressed adolescents. In their review of the psychiatric sequelae associated with

trauma in children and adolescents, Pine and Cohen call for studies examining the efficacy of SSRI's in treating both anxiety and depression associated with trauma history (2002). These authors point out that little evidence exists regarding the efficacy of treatment for disorders associated with the experience of trauma.

PURPOSE OF THE STUDY

The current study proposes to establish a link between trauma history and clinical characteristics in the presentation of major depression among youth. Potential variables that may be associated with trauma history include length of depressive illness, age at onset, initial severity, comorbidity, suicidality, and symptom pattern. Considering the current gap in the literature, this study will attempt to elucidate the relationship between trauma history and the characteristics of depressive presentation and acute treatment response among youths.

STUDY AIMS

This study aims to evaluate the relationship between trauma history and several baseline clinical characteristics of depression, including depression severity, age at onset, length of illness, suicidal ideation, hopelessness, and symptom pattern. After considering the impact of the experience of traumatic events on baseline demographic and clinical characteristics of depression, we will examine the relationship between trauma history and depression severity across time, including response to antidepressant medication. Specifically, this study will evaluate the relationship between trauma and depression severity across time during the acute phase of treatment among a sample of children and

adolescents diagnosed with MDD. Additionally, this study will determine whether trauma history is predictive of remission status or differences in time to remission following acute treatment with an antidepressant.

SCOPE

The study consists of children and adolescents, ages seven to eighteen, who presented on an outpatient basis for treatment of MDD. All patients met criteria for a major depressive episode at the time of evaluation and agreed to participate in a clinical research study, including treatment with antidepressant medication during the acute phase. Additionally, the patients all presented to the same outpatient clinic in Dallas, TX. Thus, the results may not generalize to children and adolescents in the community or those who may experience symptoms of depression or dysthymia, but do not meet full criteria for MDD. Other youth with a significant trauma history may present with psychological symptoms that do not meet criteria for MDD, but do meet criteria for an anxiety disorder or other disorder. These individuals were not included in the present study.

IMPORTANCE OF THE STUDY

The findings from this study have great potential impact for clinicians when faced with the task of determining the type and intensity of treatment for children and adolescents with depression. Additionally, the proposed aims of this study fit nicely with one of the primary strategic objectives outlined by the National Institute of Mental Health (NIMH). According to the 2008 *Strategic Plan*, the NIMH recognizes that “there is considerable individual variation in treatment response depending on a range of biological and

psychosocial factors” and calls for research to examine “individual patterns of intervention response.” This study will examine the impact of traumatic experiences on depression, as one potential factor that may be related to response to depression treatment in youth.

CHAPTER TWO
Review of the Literature
MAJOR DEPRESSIVE DISORDER

Characteristics

Major Depressive Disorder (MDD) is characterized by at least one episode of depressive symptoms that produce impairment in social, academic, or other important areas of functioning. To meet criteria for MDD, an individual must experience depressed mood and/or anhedonia (the loss of interest or pleasure in nearly all activities) along with any combination of other depressive symptoms, including: changes in appetite, sleep, psychomotor agitation or retardation, fatigue, poor concentration, feelings of worthlessness or guilt, and thoughts of death or suicide. In the current diagnostic manual, one distinction is made for children and adolescents; rather than acknowledging depressed mood, children may present with an irritable mood (APA, 2000). The diagnosis of MDD is appropriate for youth presenting with irritability in place of sadness.

Largely, the clinical presentation of depression remains consistent throughout the life span. However, based on developmental differences between children and adults, youth's experience of depression may differ somewhat from that of adults. Children may be less able to verbalize feelings of sadness and depression, thus they more often present with irritability, mood lability, and somatic complaints (Birmaher et al., 2007). The most frequently reported symptoms among children and adolescents include depressed or irritable mood, poor concentration, and vegetative symptoms, including changes in sleep, weight, or appetite (Lewinsohn et al., 1998). Clinicians need to be acutely aware of the

differences in clinical presentation to ensure children and adolescents receive the appropriate diagnosis and treatment.

Prevalence

Major depressive disorder occurring during childhood or adolescence poses a significant public health concern, especially due to the negative impact on normal growth and development, academic performance, and increased difficulties in interpersonal relationships. Estimated prevalence rates of major depressive disorder range from 2-4% among children and 4-8% among adolescents (Birmaher et al., 1996). Lifetime prevalence rates, i.e. the percentage of persons who have experienced a major depressive episode during their lifetime, are approximately 3% among children and 20% among adolescents (Lewinsohn, Clarke, Seeley, & Rohde, 1994; Lewinsohn et al., 1998). These community estimates coincide with lifetime prevalence estimates among adults, suggesting that depression affects a substantial proportion of youth and may continue into adulthood.

Mean age of MDD onset is 14.9 years and the risk increases substantially each year, especially during adolescence (Lewinsohn et al., 1994). Earlier onset of depression is associated with several factors: demographics (female gender, lower SES), psychopathology (comorbid psychiatric disorders, negative cognitive style), psychosocial factors (poor support, stressful life events), and family history of psychopathology (Birmaher et al., 1996; Lewinsohn et al., 1994). Depression occurs frequently among

children and adolescents and is associated with increased risk for ongoing psychopathology and impairment, even into adulthood.

Associated Risk

Suicide

Suicidal ideation and behavior is inherent within the diagnosis of MDD. While suicide is associated generally with any psychiatric disorder, youth with depression are at a significantly increased risk for suicidal ideation and suicide attempts (Bridge, Goldstein, & Brent, 2006; Lewinsohn et al., 1998). According to reports from the Centers for Disease Control and Prevention, suicide is the third leading cause of death among adolescents and young adults ages 10 to 24 years in the United States (Suicide, 2007). Although rates had been declining between 1990 and 2003, rates among younger adolescents, ages 10-19 years have recently begun to increase. Additionally, research among adults has shown that earlier onset of depression, particularly during the adolescent years, may be associated with an increased risk of suicide attempt when compared to normal controls (Weissman et al., 1999). Suicidal ideation and behavior has a strong relationship to depression and is considered one of the most adverse consequences of depression due to its associated morbidity.

Recurrence

Although treatments have shown some efficacy in relieving depressive symptoms and may lead to an adequate response or remission of depressive episode, relapse rates remain high (Kennard, Emslie, Mayes, & Hughes, 2006). Research indicates that recurrence of

depression may be associated with history of suicidal ideation and later (adolescent) onset (Lewinsohn et al., 1998). Initial data examining the efficacy of continuation and maintenance phase treatment indicates that rates of remission improve, while rates of relapse decrease, with continued treatment (Emslie et al., 2008; Kennard et al., 2008; Kennard et al., 2009). Children with major depressive disorder are at increased risk for adolescent depression (Birmaher, Arbelaez, & Brent, 2002). Additionally, as many as 50% of adults with depression report that their first depressive episode occurred as an adolescent. Children and adolescents who suffer at least one major depressive episode are at increased risk for recurrence and may be more prone to experiencing mental health disorders in adulthood.

Psychosocial Functioning

Given that childhood and adolescent depression occurs during prime developmental years, its impact on academic, social, and family functioning may persist over time. One study examining the impact of adolescent-onset MDD on clinical characteristics of adults revealed that adolescent depression was associated with poorer education attainment and continued functional impairment in work, social, and family life (Weissman et al., 1999). Treating depression during this critical developmental period may have substantial effects on these youths' psychiatric status and functional abilities as adults.

Evidence-based Treatment of MDD

Guidelines set forth by a recent practice parameter for treating depression among children and adolescents establish the efficacies of pharmacotherapy, psychotherapy, or its

combination in reducing depressive symptoms (Birmaher et al., 2007). Additionally, this parameter outlines the importance of continuation and maintenance phase treatment to assist youths in consolidating the treatment response acquired during the acute phase and preventing subsequent relapse.

Psychopharmacology

Several randomized controlled trials comparing antidepressant medication to placebo have documented the effectiveness of SSRI's in the acute treatment of major depression (Cheung, Emslie, & Mayes, 2005; Emslie and Mayes, 2001). Until 2009, fluoxetine was the only medication approved by the U.S. Food and Drug Administration (FDA) for the treatment of child and adolescent depression. Recently, escitalopram gained approval by the FDA, despite the absence of substantial research examining its efficacy and safety. As compared to other antidepressants, fluoxetine has shown a more consistently favorable response when compared to placebo in randomized controlled trials (Birmaher et al., 2007). Despite demonstrations of efficacy, a large number of youth do not adequately improve following implementation of the first line treatment. Adolescents with treatment-resistant depression, who did not respond to initial treatment with an SSRI, benefited from the combination of a medication switch (either to another SSRI or to venlafaxine) and the addition of CBT (Brent et al., 2008). Research supports the efficacy and safety of antidepressant use in treating adolescent depression, specifically the use of fluoxetine or another SSRI. However, many adolescents will not respond to first-line medication treatment and may benefit from other treatment modalities or a combination treatment strategy.

Psychotherapy

A recent meta-analysis of randomized controlled trials found that the effects of psychotherapy for the treatment of depression in youth were modest (mean effect size = 0.34) across all types of psychotherapy (Weisz, McCarty, & Valeri, 2006). Additionally, these authors found no difference between effect sizes for CBT and other types of therapy, including family therapy, IPT, and social skills training. However, in a subsequent article these authors noted that when CBT was compared to a control group, some effect sizes were higher than 1.0, indicating a large effect (McCarty & Weisz, 2007). They also note that both CBT and interpersonal therapy (IPT) have well-established efficacy among adolescents. For a review of the relevant components of psychotherapy considered to be important in treating depression, see McCarty and Weisz, 2007. Some of the components identified include psychoeducation, treatment orientation, promoting competence, enhancing relationship skills, teaching problem solving, cognitive restructuring, and behavioral activation.

A randomized clinical trial compared three types of psychotherapy directly: cognitive behavioral therapy, systemic behavioral family therapy, and nondirective supportive therapy. Researchers found that patients treated with CBT experienced a more rapid and complete relief of depressive symptoms and higher remission rates at the end of acute treatment than those receiving the other forms of psychotherapy (Brent et al., 1997). However, after a period of two years, most participants had recovered and there were no significant differences in long-term outcome based on the type of psychotherapy received (Birmaher et al., 2009).

Factors associated with poorer response to psychotherapy include comorbid anxiety disorders, higher levels of cognitive distortion and hopelessness, psychosocial adversity, and a history of sexual abuse (Brent et al., 1998; Barbe et al., 2004; Curry et al., 2006; Jayson et al., 1998). Thus, while psychotherapy has shown some effectiveness in treating depression among youth, the findings are somewhat mixed. Additionally, certain clinical and demographic characteristics may limit the effectiveness of psychotherapy among youth or call for additional treatment, such as the combination of pharmacotherapy and psychotherapy outlined below.

Combination Treatment

Recent evidence comparing treatments for adolescent depression through randomized clinical trials has demonstrated the increased efficacy of combination treatment with pharmacotherapy and psychotherapy (Brent et al., 2008; TADS Team, 2004). A recent NIMH sponsored, multicenter, randomized clinical trial, entitled the Treatment for Adolescents with Depression (TADS), compared the efficacy of fluoxetine alone, CBT alone, their combination, and placebo in 439 adolescents. Acute response rates were greatest for combination (71%), followed by fluoxetine alone (61%), CBT (43%), and placebo (35%). Combination treatment and fluoxetine alone were more effective than placebo, while CBT was not (TADS Team, 2004). These results provide support for the increased efficacy of combination treatment among a large, diverse sample of adolescents with depression.

In the Treatment of Resistant Depression in Adolescents study (TORDIA), researchers conducted a randomized controlled trial to examine the efficacy of treatments for adolescents who did not respond to initial pharmacotherapy with an SSRI (Brent et al., 2008). Adolescents were randomized to either a medication switch (a different SSRI or venlafaxine) or to a medication switch plus CBT. Results indicated higher response rates (55%) in the combination treatment as compared to a medication switch alone (41%). This study provides further support for the efficacy of combination treatment, even with a population who did not respond to initial pharmacotherapy.

Another study examined the effectiveness of treatment for a high-risk population of adolescents who had recently attempted suicide. When treated with a combination of pharmacotherapy (SSRI) and psychotherapy (CBT), the rate of improvement for these adolescents was consistent to rates established among adolescents without a recent history of suicide (Vitiello et al., 2009). While only a few studies have examined the increased efficacy of combination treatment, the initial evidence supports its superiority to either medication or psychotherapy alone. This treatment may be especially beneficial for adolescents who present with more complex cases or factors that have been associated with poor treatment response when administered pharmacotherapy or psychotherapy alone.

Continuation Treatment

Preliminary studies among youth primarily examined response to various types of acute treatment. Analysis of lasting effects indicated that remission rates are low at the end of

the acute phase. Studies have consistently found that remission rates are low following the acute phase of treatment, with rates ranging from 23% across treatment groups to 37% among adolescents treated with a combination of fluoxetine and CBT (Kennard, Silva et al., 2006). If full remission is not achieved, residual symptoms may be present that increase the risk for subsequent relapse of a depressive episode. Thus, recent support has been generated for continued treatment among youth to consolidate the benefits of treatment and prevent relapse. A study examining treatment with fluoxetine, CBT, or their combination found that when adolescents continue to receive ongoing treatment following the acute phase, remission rates more than double, such that approximately 60% of adolescents achieve remission by week 36 (Kennard et al., 2009). These findings support the need for continuation phase treatment.

Given the low remission rates, researchers sought to outline treatment strategies that would increase benefit to youths. Continuation of antidepressant treatment following the acute phase may be associated with relapse prevention (Birmaher et al., 2007; Emslie et al., 2008; Emslie, Mayes & Ruberu, 2005). Rather than discontinuing medication after the youth achieves an adequate response, research supports continuation of medication treatment. Similar results have been found when examining the long-term benefit of psychotherapy treatment. Short-term psychotherapy administered acutely does not show lasting effects, thus indicating the need for continuation treatment (Weisz et al., 2006). Preliminary results indicate that the addition of CBT during the continuation phase of treatment may further reduce the risk for relapse when compared with responders maintained on antidepressant treatment alone (Kennard et al., 2008). Research

examining the treatment of child and adolescent depression clearly indicates the need for continued treatment that combines the use of antidepressants and psychotherapy.

TRAUMA AND DEPRESSION

Definition of Trauma

A persistent difficulty arises when attempting to compare literature examining the impact of trauma and life stress on psychopathology; namely, the definitions and measures vary greatly between studies. According to the DSM-IV-TR, a traumatic event includes any event either experienced, witnessed, or learned about that involves death, injury, or threat to the individual or another person. Additionally, the individual responds to the event with intense fear, helplessness, or horror. The DSM-IV-TR clarifies that a child's response may involve disorganized or agitated behavior, as opposed to the emotions listed above (APA, 2000). Thus, traumatic events may include being involved in a severe car accident, witnessing domestic violence, learning of the death of a loved one, or being the victim of physical or sexual abuse, among many others.

While many researchers have parceled out particular types of abuse for study, e.g. sexual abuse, others have cautioned against studying the effects of single traumatic life events on a particular disorder. Rather, they suggest that the experience of traumatic events typically occurs in combination with other events (Green et al., 2010; Kessler, Davis, & Kendler, 1997). They found that a cluster of events termed maladaptive family functioning, which includes parental mental illness, family violence, physical abuse, sexual abuse, and neglect were the strongest correlates of onset of psychiatric disorders.

Trauma as a Risk Factor for Psychopathology

Extensive research has indicated an association between the experiences of traumatic or other stressful life events and psychopathology. Attempts have been made to connect individual types of abuse to specific disorders. Initial research demonstrated the relative specificity of reports of childhood emotional abuse to diagnosis of depressive disorders versus anxiety disorders (Gibb, Butler, & Beck, 2003). However, a subsequent study did not replicate this finding and concluded that there was little evidence for specificity of types of abuse and psychiatric diagnosis (Gibb, Chelminski, & Zimmerman, 2007). History of child abuse appears to be related to a diagnosis of PTSD and other psychiatric disorders, including MDD, but may not be specific to any one disorder. When controlling for comorbidity among psychiatric disorders, relationships between specific traumatic events and specific disorders decline (Kessler et al., 1997). Other researchers suggest that the development of PTSD, MDD, or other anxiety disorders, such as GAD, may be distinct reactions to trauma (Grant, Beck, Marques, Palyo, & Clapp, 2008). Further research examining the processes related to particular reactions and subsequent psychopathology following exposure to trauma is needed.

Trauma as a Risk Factor for Depression

Depression researchers noticed early on that a significant number of individuals with depression have histories of abuse and other traumatic experiences. Thus, substantial support has emerged in the literature for a relationship between trauma history and depression. Although trauma has been identified as a non-specific risk factor for psychopathology, relationships between trauma and mental disorders are particularly

strong for both anxiety and depressive disorders (Pine & Cohen, 2002). The current study will focus on the relationship between trauma and depression.

Trauma has been established as a risk factor for the development of depression among both youth and adult populations. Child abuse increases the odds of developing depression by two times among adults and three to four times among adolescents and young adults (Brown, Cohen, Johnson, & Smailes, 1999; Oquendo et al., 2005). In the year prior to onset of a depressive episode, depressed adolescents have a significantly higher percentage of experiencing severe life events (62%) as compared to normal controls (27%). Additionally, half of all depressed adolescents had experienced two or more severe life events in the year prior, while none of the normal controls had experienced more than one severe life event (Williamson et al., 1998). Even less severe life events occurring in adolescence, such as interpersonal difficulties at school or home, have been established as a risk factor of the diagnosis of MDD in adulthood (Pine, Cohen, Johnson, & Brook, 2002). Thus, adolescents who experience trauma or significant life stress may be at increased risk for developing depression, either during adolescence or later in adulthood.

Specific life events may contribute to the development of psychopathology in particular ways. For example, early loss-related life events, especially the experience of death or separation from a loved one, occur more frequently among adults with depression as compared to normal controls (Horesh, Klomek, & Apter, 2008). Likewise, loss, abuse, neglect, and ongoing life stressors have consistently been shown to relate to the onset and

recurrence of major depression among adolescents (Birmaher et al., 2007). Further research examining symptoms of PTSD and depression among adolescents experiencing parental loss indicated that loss of both parents is a significant risk factor for depression, but not for PTSD (Goenjian et al., 2009). Thus, the experience of loss increases risk for depression in adolescence or subsequent depression in adulthood.

Substantial evidence supports the experience of childhood abuse as a risk factor for depression among adults. Adults who experienced victimization as children, including the experience of physical abuse, traumatic exposure, or parental neglect, have an increased likelihood of experiencing a major depressive episode (MDE) in adulthood (Arboleda-Florez & Wade, 2001). Risk of MDE increases proportionate to the number of experiences of victimization during childhood. One type of victimization makes adults twice as likely to experience depression while two or three increases the risk to four times. Interpersonal traumatic events, especially sexual abuse, produced higher odds-ratios for depression than other traumatic events (Kessler et al., 1997).

In adolescents, similar research has considered the impact of interpersonal violence, including sexual abuse, physical abuse, or witnessed violence, on the risk of developing MDD, PTSD, or substance abuse. Physical assault was associated with increased risk of MDD, while sexual assault and witnessed violence were associated with increased risk of comorbid PTSD and MDD (Kilpatrick et al., 2003). Robust findings from the literature substantiate the relationship between physical and/or sexual abuse and depression.

A recent practice parameter established for the assessment and treatment of depression in youth iterates the importance of evaluating current and past stressors such as physical and sexual abuse, ongoing interpersonal conflicts, neglect, low SES, and exposure to violence (Birmaher et al., 2007). The parameter notes, “depression often results from an interaction between depressive diathesis and environmental stressors” and emphasizes the importance of recognizing these stressors when determining appropriate treatments for youth.

Relationship of Trauma to Clinical Characteristics in Adults

Trauma history has been associated with several demographic characteristics, including younger age and female gender, and clinical characteristics of depression, including length of illness, earlier onset, increased recurrence, increased baseline severity, suicidal ideation, comorbid disorders, hopelessness, and negative cognitive style, among others. Support for the relationships between trauma history and these characteristics are outlined below.

Gender

Among adults, the relationship between childhood adversity and psychiatric disorders tends to be stronger for women than men. Research among the PTSD literature indicates that females are more likely to experience PTSD even though males are more likely to experience traumatic events (Tolin & Foa, 2008). They clarify that females are more likely to be the victims of sexual abuse, while males are more likely to be exposed to accidents, disaster, or combat. One potential explanation for the difference in rates of

PTSD by gender may be that the trauma females experience more likely occurs during childhood, while males may witness/experience these traumatic events as young adults. Developmental processes may play a substantial role in the impact of trauma experiences on psychiatric sequelae. Research specific to depression clarifies that the relationship between physical and sexual abuse and depression is greater for women, such that women with a history of abuse are almost three times as likely to experience a major depressive episode as compared to those without an abuse history (MacMillan et al., 2001). Another study found that female gender increases risk of sexual abuse and maternal neglect, overcontrol, and abuse, but not other forms of childhood maltreatment (Klein et al., 2009). Gender may be one demographic variable associated with increased risk for the development of depression in response to trauma.

Onset

Studies among adults with early childhood adversity report earlier age of onset of depressive disorders. Severe childhood adversities have significant effects on early-onset depression (Bernet & Stein, 1999; Kessler, 1997; Klein et al., 2009; Miniati et al., 2009; Moskvina et al., 2007; Young, Abelson, Curtis, & Nesse, 1997). Research indicates that stressful life events may be more clearly associated with the first onset of depression and have less of a relationship to recurrent episodes (Horesh et al., 2008; Mitchell, Parker, Gladstone, Wilhelm, & Austin, 2003). Currently, it is unclear whether this finding will replicate among a population of children and adolescents, given the differences in the amount of time between the experience of the traumatic event and the depressive episode.

Severity

Several studies have connected trauma history or the experience of severe life events with increased severity of depressive symptoms (Bernet & Stein, 1999; Klein et al., 2009; Muscatell et al., 2009). Additionally, depressed patients with lifetime history of comorbid PTSD experienced higher levels of objective depression (Oquendo et al., 2005). In contrast, one study found no difference on depression severity scores at baseline, as measured by the Hamilton Rating Scale for Depression, between participants with or without a history of abuse (Miniati et al., 2009). Adult studies have demonstrated a substantial connection between trauma history and severity of depressive symptoms.

Length of Illness

Among adult women, a history of childhood adversity, defined as sexual abuse, physical abuse, and/or parental indifference, increases the odds of experiencing a chronic depressive episode by three times when compared to depressed women without a history of childhood adversity (Brown & Moran, 1994). Additionally, chronicity was associated with those women who experienced interpersonal difficulties during the course of their depressive episode. Prolonged depressive episodes were observed among adults reporting childhood sexual abuse (Zlotnick, Mattia, & Zimmerman, 2001). Other studies have demonstrated a clear relationship between reports of childhood adversity, length of illness, and increased number of lifetime depressive episodes (Bernet & Stein, 1999; Klein et al., 2009; Miniati et al., 2009). Patients experiencing significant trauma, specifically child abuse, may be prone to experiencing chronic depression. This may be, at least in part, due to poorer response rates to treatment among this population.

Comorbidity

Several studies have examined rates of comorbidity due to history of abuse. Examination of comorbidity rates has established that childhood adversity, specifically in the form of maladaptive family functioning, is a non-specific predictor of psychiatric disorders (Green et al., 2010). Considerable data suggests the greater incidence of comorbid psychiatric diagnoses in addition to MDD among individuals with trauma history. Adult patients with a history of childhood sexual abuse had higher rates of comorbidity, primarily consisting of PTSD diagnoses (Zlotnick et al., 2001). Similarly, among a large sample of adults, those with a history of emotional and/or physical abuse, experienced a higher burden of lifetime comorbidity when compared to those without such history (Miniati et al., 2009). Further, multiple types of childhood adversity are related to number of concurrent or lifetime comorbid disorders, with anxiety and substance abuse being most prevalent (Bernet & Stein, 1999; Klein et al., 2009). The most robust findings indicate that the experience of abuse increases the risk for comorbid anxiety disorders, especially PTSD.

Suicide

Depressed adults with a history of attempted suicide report significantly more childhood trauma, especially emotional abuse, as compared to those without suicide attempts in their history (Sarchiapone, Carli, Cuomo, & Roy, 2007). History of clinically significant abuse, including sexual abuse, is associated with a history of suicide attempts (Klein et al., 2009). Depression comorbid with PTSD enhances the risk for suicidal behavior (Oquendo et al., 2005). These studies all examined reports or incidences of suicide

attempts or behavior, as opposed to suicidal ideation. However, the findings imply that early childhood trauma is a risk factor for suicidality, even years after the abuse occurred.

Symptom Specificity

In addition to the general clinical characteristics, research has examined the association between the experience of significant life stress and the identification of specific symptoms of depression. Initial research examining this relationship focused on associations between subtypes of depression, with inconsistent findings (Kohn et al., 2001; Muscatell et al., 2009). Recent studies have examined the relationship between stressful life events and individual symptoms of depression. Adults who have experienced a severe life event prior to onset of their depressive episode were more likely to endorse cognitive-affective symptoms, including sadness, pessimism, suicidal ideation, and social withdrawal (Monroe et al., 2001) in combination with somatic symptoms (Muscatell et al., 2009). Another study found evidence for a relationship between childhood emotional and physical abuse with depressed mood, psychomotor retardation, and neurovegetative symptoms, including changes in appetite and sleep (Miniati et al., 2009). Additionally, among a sample of adolescents, cognitive-affective and somatic symptoms were associated with reported life events (Harkness & Stewart, 2009). No studies have examined these findings using a history of trauma or abuse, but rather have focused on stressful life events; thus, it is unclear whether these findings will generalize to a sample of youth with a history of trauma.

Relationship of Trauma to Clinical Characteristics in Youth

Most of the relationships between trauma and clinical characteristics of depression have been established among adult populations; however, some recent studies have begun to consider these relationships among youth. Initial research among a small sample of adolescents ($n = 72$) considered the impact of sexual abuse only ($n = 10$) on various demographic and clinical characteristics of depression, including age, gender, SES, age at onset, depression severity, prior suicide attempts, and comorbidity. They found no differences between groups on any of these characteristics (Barbe et al., 2004). However, given the small sample size, insufficient power may partially account for the lack of findings.

In the larger TADS study, evidence suggests that trauma may be associated with differences in demographics and clinical presentation at baseline. Specifically, females had more incidences of sexual abuse, while males had more incidences of physical abuse. Clinician-rated depression severity was not related to trauma history; however, self-reports of depression severity were related to a history of trauma, particularly sexual abuse (Lewis et al., 2010). In TORDIA, self-reported depression was also higher among individuals with physical abuse; however, these individuals did not differ from other youth on any demographic variables (Shamseddeen et al., 2011). Another study among adolescents found that exposure to interpersonal forms of violence, including physical or sexual abuse or witnessed violence, increased the risk of experiencing comorbid psychiatric disorders, especially PTSD, MDD, and substance abuse or dependence (Kilpatrick et al., 2003). Depression severity can be predicted by level of childhood

adversity, including early illness, parental psychopathology, parental loss, abuse, and others (Espejo et al., 2006). Overall, these results corroborate the findings from the adult literature.

Several studies have specifically examined the relationship between trauma history and suicide among adolescents. A longitudinal study following individuals from about age 5 through adulthood found that adolescents and young adults with a history of neglect, physical abuse, or sexual abuse, were 3 times more likely to become suicidal compared with those without early maltreatment (Brown et al., 1999). Additionally, sexual abuse history increased risk of repeated suicide attempts among adolescents by 15 times. Trauma history was associated with baseline suicidality among a sample of adolescents presenting for outpatient depression treatment (Lewis et al., 2010). In the Treatment of Adolescent Suicide Attempters (TASA) study, adolescents with a history of physical or sexual abuse exhibited a higher risk and earlier time to experiencing a suicide event when compared to other suicidal adolescents without a history of sexual abuse (Brent et al., 2009). The experience of stressful life events may increase adolescents' risk for a suicide attempt, especially in the period immediately following the life event(s). Researchers note that adolescents who have made a suicide attempt report experiencing significant stressful life events during the period immediately prior to their attempt (Horesh, Nachshoni, Wolmer, & Toren, 2009). Thus, adolescents with a history of trauma, especially sexual abuse, may be at increased risk for experiencing symptoms of suicidal ideation and making suicide attempts.

With regard to the relationship between trauma history and demographic and clinical characteristics of depression, literature among children generally corroborates the findings from the adult literature. However, fewer studies have examined these relationships, with mixed results (Barbe et al., 2004; Lewis et al., 2010; Shamseddeen et al., 2011). Further research needs to be conducted among youth to establish these relationships.

PREDICTORS OF TREATMENT RESPONSE IN MDD

Previous research has identified several clinical and baseline characteristics associated with differences in treatment response for depression. Depression severity and length of depressive episode have been identified as robust predictors of poor treatment response (Asarnow et al., 2009; Curry et al., 2006). In a large multi-site study examining treatment for adolescents with depression (TADS), researchers found that older age, chronicity, melancholic features, hopelessness, suicidal ideation, comorbid diagnoses (especially anxiety disorders), and poor expectations of treatment were associated with poorer response to acute treatment (Curry et al., 2006). Another study considered predictors and moderators of treatment response among adolescents with treatment-resistant depression following an adequate SSRI trial. Higher baseline severity, greater impairment, higher suicidal ideation, hopelessness, self-injurious behaviors, and family conflict were associated with non-response to subsequent treatment (Asarnow et al., 2009). Perhaps the most robust predictors of response to treatment among adolescents include initial depression severity, suicidal ideation, and length of depressive illness.

Trauma as a Predictor of Treatment Response in Adults

While many studies have considered a wide range of clinical characteristics and other psychosocial factors as predictors of depression treatment, few have specifically examined the impact of trauma or early childhood adversity on treatment response. In a large study (n=808) of adults diagnosed with chronic forms of MDD, researchers considered whether a history of childhood adversity would predict remission when treated according to a 12-week algorithm guided pharmacotherapy model (Klein et al., 2009). Childhood adversity predicted a lower probability of remission at each time point during the acute phase of treatment with pharmacotherapy. Additionally, the probability of remission increased across time for patients without a history of childhood adversity, but not for those patients who had experienced clinically significant abuse (Klein et al., 2009). This study supports the hypothesis that child abuse is an important predictor of response to pharmacotherapy in depression treatment. Additionally, while the benefit from pharmacotherapy tends to increase over time, patients with a history of abuse may not derive greater benefit from continued medication treatment.

Additional studies among adults have considered whether augmentation with psychotherapy may provide added benefit to patients with a history of abuse. When compared to those without a history of abuse, adult patients who experienced physical and/or emotional abuse evidenced a longer time to achieve remission and were more likely to require combination treatment (SSRI and IPT) to achieve remission (Miniati et al., 2009). Adolescents and young adults with a history of childhood sexual abuse achieved greater reduction in repeated deliberate self-harming behaviors when treated

with CBT as opposed to treatment-as-usual (Spinhoven et al., 2009). Of note, this study included participants who had recently engaged in self-harming behaviors, independent of psychiatric diagnosis.

A large, multicenter, randomized trial examined the efficacy of psychotherapy (Cognitive Behavioral Analysis System of Psychotherapy [CBASP]), pharmacotherapy, and combination therapy among adults with chronic forms of depression. The combination treatment was found to be superior to either monotherapy at the end of the acute phase of treatment (Keller et al., 2000). History of childhood trauma, including early parental loss, physical abuse, sexual abuse, or neglect, was associated with differential treatment response (Nemeroff et al., 2003). Those with a history of childhood trauma achieved a greater reduction in their depressive symptoms when treated with psychotherapy alone as compared to antidepressant therapy. Additionally, the combination treatment was no longer superior to psychotherapy alone, thus highlighting the importance of psychotherapy in treating adults with early childhood trauma.

Based on their review of the relevant literature, Craighead and Nemeroff propose that psychotherapy combined with pharmacotherapy may be the treatment of choice for adults with depression and a history of childhood abuse (2005). Additional studies aimed at replicating these results and gaining a better understanding of these relationships are warranted.

Trauma as a Predictor of Treatment Response in Youth

Similar research among adolescents has examined the relationships between trauma history and depression. In several randomized controlled trials of depression in adolescents, trauma and abuse history was not found to be associated with acute treatment response, irrespective of treatment type (Asarnow et al., 2009; Lewis et al., 2011). No known studies have examined the effects of trauma history on response to pharmacotherapy alone. The focus of these large trials has been centered on examining trauma or abuse history as a potential moderator of treatment response when comparing the effectiveness of pharmacotherapy, psychotherapy, or their combination.

While little is known about the impact of trauma on treatment with antidepressants, one small study looked at the experience of several psychosocial events as potential predictors. Researchers found that recent school difficulties predicted poorer response to fluoxetine, while other psychosocial stressors, including loss, death, or separation from a loved one, were not associated with treatment response (Kowatch et al., 1999). Due to a small number of participants, the authors stipulate that the lack of power may explain the finding that few variables were predictive of response. Additionally, these authors did not consider a history of witnessing or experiencing a traumatic event, including physical or sexual abuse.

Recently, researchers have examined whether a history of abuse moderates treatment response in randomized clinical trials comparing pharmacotherapy, psychotherapy, or their combination. A large multi-site randomized trial, the Treatment for Adolescents

with Depression Study (TADS), examined differences in treatment response based on receipt of treatment with fluoxetine, CBT, their combination, or a pill placebo. Preliminary findings indicated that the combination treatment was superior to fluoxetine and both of these were superior to CBT and placebo (TADS Team, 2004). Further analyses examined whether trauma moderated treatment outcome among depressed adolescents participating in the TADS study. The response of adolescents with no trauma history matched the primary efficacy findings with fluoxetine and combination treatment exhibiting superior efficacy to CBT and placebo. However, among adolescents with a history of trauma (excluding sexual abuse), the researchers observed no differences among the various treatment arms (Lewis et al., 2010). Further, among adolescents with a history of sexual abuse, a non-significant trend was found that suggested poorer response to CBT compared to the other treatment arms, which were equally effective. It is important to note that these findings suggest poorer response to CBT when compared to fluoxetine, combination treatment, or pill placebo. Small sample sizes may compromise these findings.

Another randomized clinical trial found that abuse history moderated treatment response. In the Treatment of Resistant Depression in Adolescents study (TORDIA), depressed adolescents who did not respond to treatment with an SSRI were randomized to receive an alternative SSRI, venlafaxine, an alternative SSRI plus CBT, or venlafaxine plus CBT. Primary findings indicated that a higher proportion of adolescents responded to the combination therapy than those treated with pharmacotherapy alone (Brent et al., 2008). Abuse history, assessed as the presence or absence of physical and/or sexual abuse,

moderated treatment response in the following manner. Youth with no abuse history were significantly more likely to respond to the combined treatment than to pharmacotherapy alone. In contrast, those with a history of abuse had a better response to pharmacotherapy alone than to the combination therapy (Asarnow, et al., 2009). A more recent article clarified the relationship between abuse history and treatment response (Shamseddeen, et al., 2011). When abuse was broken down into physical and sexual, the authors found that only physical abuse moderated treatment response. Even when controlling for other variables associated with abuse and response, the finding persisted; adolescents with a history of physical abuse were 10 times more likely to respond to medication monotherapy than to the combined treatment (medication plus CBT).

A few studies have specifically examined the impact of trauma or life stress on response to psychotherapy. In accordance with findings from the adult literature and theories of the connection between trauma, life stress, and depression, researchers initially hypothesized that adolescents with a history of psychosocial stressors would respond more favorably to psychotherapy. However, the recent literature indicates that these adolescents actually evidence a poorer treatment response to psychotherapy than those without a history of abuse or life stress. A small study (n=50) examined the effects of general psychosocial adversity, including abuse, on response to treatment with short-term cognitive behavioral therapy (Jayson et al., 1998). Researchers found that patients with increased psychosocial adversity were less likely to achieve remission of their depressive episode during a course of CBT as compared to adolescents reporting less psychosocial

adversity. Potential limitations from this study include a small sample size and failure to control for the relationship between psychosocial stress and severity of depression. Another study randomly assigned depressed adolescents to one of three forms of psychotherapy: cognitive behavioral therapy (CBT), systemic behavioral family therapy (SBFT), or nondirective supportive therapy (NST). Primary findings indicated that CBT was superior to both SBFT or NST in reducing depressive symptoms and increasing rate of remission. However, when examining the impact of a history of sexual abuse ascertained by a yes/no question, researchers found that abuse moderated the treatment effect, with CBT no longer being superior to NST. Among those treated with CBT, adolescents with a history of sexual abuse had a higher rate of MDD at the end of acute treatment when compared to nonabused participants treated with CBT. Authors suggest that the “efficacy of CBT may be markedly diminished in depressed adolescents with a history of sexual abuse” (Barbe et al., 2004). It is important to note that these findings were based on very small sample sizes; only five patients in the CBT group had a history of sexual abuse. Preliminary results among adolescents indicate that CBT is less efficacious in treating adolescents with a history of abuse, although these findings may be compromised due to small sample sizes.

HYPOTHESES

Trauma and Clinical Characteristics of Depression

1a. First, we will examine whether the experience of trauma is associated with several baseline clinical characteristics of depression, including age at onset, depression severity, length of depressive illness, and comorbidity. Individuals with a history of trauma may

display: younger age at onset (Bernet & Stein, 1999; Kessler, 1997; Klein et al., 2009; Miniati et al., 2009; Young et al., 1997), increased severity of depression (Bernet & Stein, 1999; Espejo et al., 2006; Klein et al., 2009; Lewis et al., 2010; Miniati et al., 2009; Muscatell et al., 2009; Oquendo et al., 2005), longer length of illness (Bernet & Stein, 1999; Brown & Moran, 1994; Klein et al., 2009; Miniati et al., 2009; Zlotnick et al., 2001), and higher rates of comorbidity (Bernet & Stein, 1999; Kessler et al., 1997; Kilpatrick et al., 2003; Klein et al., 2009; Lewis et al., 2010; Miniati et al., 2009; Zlotnick et al., 2001). We will also examine whether trauma history is associated with self-reported hopelessness (Gibb et al., 2001; Mezulis et al., 2006).

1b. We will also examine the relationship between trauma history and symptom pattern. Based on the literature, we predict that adolescents with a history of trauma will report more cognitive-affective symptoms, including sadness or irritability, feelings of worthlessness or guilt, and increased suicidality (Brown et al., 1999; Brent et al., 2009; David, Ceschi, Billieux, & van der Linden, 2008; Harkness & Stewart, 2009; Monroe, et al., 2001; Muscatell et al., 2009; Oquendo, et al., 2005). Examining these relationships will provide us with a better understanding of relevant factors of depression that may be associated with the youth's experience of trauma and abuse.

Trauma and Acute Treatment

2a. This study aims to examine the relationship between trauma history and depressive symptoms across time among children and adolescents in the acute phase of medication treatment with fluoxetine. Adolescents with a history of trauma will exhibit differences

in their severity of depressive symptoms and response to pharmacotherapy, as compared to adolescents with no trauma. In accordance with results from the adult literature and preliminary findings from studies among adolescents, we expect adolescents with a positive trauma history to evidence poorer response to pharmacotherapy and to exhibit greater depressive symptoms across time (Asarnow et al., 2009; Klein et al., 2009; Miniati et al., 2009; Nemeroff et al., 2003).

2b. The odds of achieving remission of the current depressive episode after adequate treatment with fluoxetine will be greater for those patients without a history of trauma (Klein et al., 2009; Miniati et al., 2009).

2c. We will also examine the time to achieve remission during acute antidepressant treatment, considering the impact of trauma history. Adolescents who have experienced trauma will require a longer time to achieve remission as compared to those with no trauma history (Klein et al., 2009; Miniati et al., 2009).

CHAPTER THREE

Methodology

DESIGN

Overview

The current study was conducted as a secondary analysis of pooled data from the acute phase of three continuation treatment studies of Major Depressive Disorder (MDD) in youth. These studies included: Childhood Depression: Relapse and Remission (RR; PI: Graham J. Emslie; n = 168; Emslie et al., 2008), Relapse Prevention CBT (RP; PI: Beth D. Kennard; n = 66; Kennard et al., 2008), and a study examining the Sequential Treatment of Pediatric Depression (STS; PIs: Graham J. Emslie and Beth D. Kennard; n = 58, ongoing). The design of each of these studies included an acute phase consisting of open treatment with fluoxetine and a randomization phase consisting of continuation treatment. The primary aims of these three studies were to assess factors associated with a reduction in relapse rates during the continuation phase of treatment for MDD. Primary factors assessed included continuation of antidepressant medication and augmentation with a relapse-prevention specific cognitive behavioral therapy (CBT). See Figure 1 for flow of participants in the three studies. While the figure shows the flow of patients throughout the entire course of the studies, the current study only examined participants' baseline characteristics and response to antidepressant treatment during the acute phase.

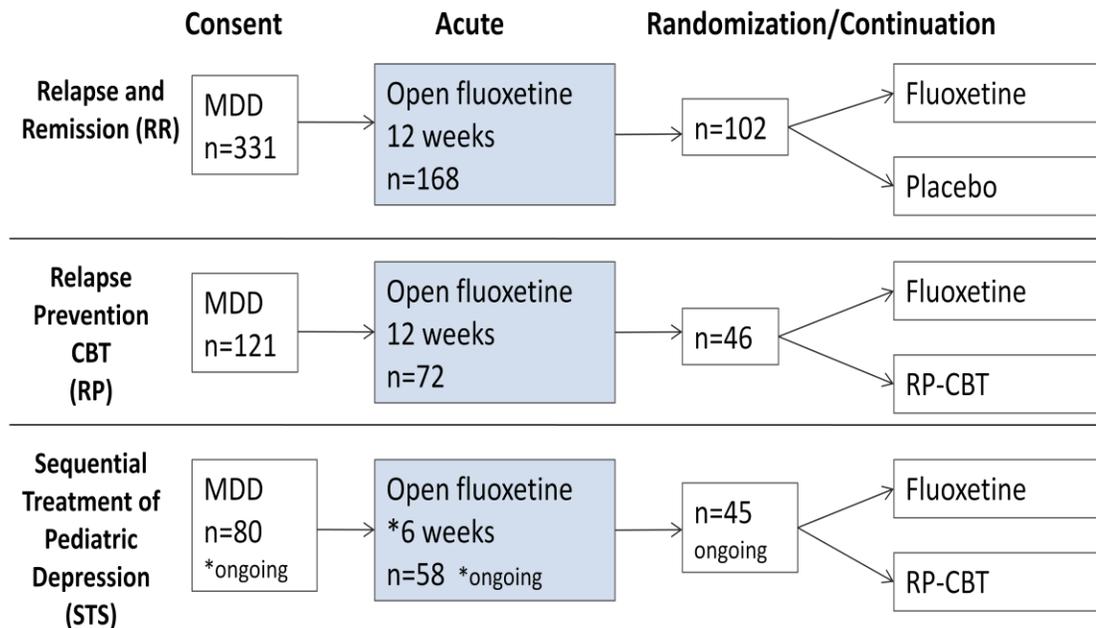


Figure 1. Participant flow chart in three studies of depression in youth. Note. RR: PI = G. Emslie; RP: PI = B. Kennard; STS: PIs = G. Emslie and B. Kennard

Acute Phase

Children and adolescents, ages 7 to 18, who presented for outpatient treatment of MDD, as defined by criteria outlined in the Diagnostic and Statistic Manual, 4th ed. (APA, 2000), were eligible for these studies. Participants were treated openly with fluoxetine during acute phase treatment, which ranged from 6 weeks (STS) to 12 weeks (RR and RP). Participants were evaluated by the clinician on a weekly basis for the first four weeks and a bi-weekly basis for the remainder of the acute treatment phase, with the exception of STS where participants attended weekly for the entire six weeks of acute treatment. If needed, two additional visits were allowed between the scheduled visits. Patients were typically started on 10 mg of fluoxetine and increased to 20 mg after one

week. If patients were not adequately responding to the medication after 4-6 weeks, physicians had the option of increasing the fluoxetine dose to 30 or 40 mg. The treating psychiatrist managed the dosing schedule. Given that the length of acute phases varied among the studies and most youths evidenced an antidepressant response early on, we examined response to pharmacotherapy during the first six weeks only. We also examined response to acute treatment within the first two studies across the entire 12-week acute phase of treatment.

Continuation Phase

Responders, defined as a Clinical Global Impressions-Improvement (CGI-I) score of 1 (very much improved) or 2 (much improved) and at least 50% reduction in depressive symptoms as measured by the Children's Depression Rating Scale Revised (CDRS-R), were randomized to continuation treatment for an additional 24 weeks. Participants were followed every two weeks through week 18 and every four weeks for the remainder of the continuation phase. Those randomized to receive CBT attended additional therapy appointments. In the RR study, participants were randomized to either placebo or continued medication management on fluoxetine. In the two latter studies, RP and STS, responders were randomized to receive either continued medication management (MM) or medication management plus relapse prevention cognitive behavioral therapy (MM+CBT) for six months of continuation treatment. Due to variations in continuation treatment, the current study will utilize data from the acute phase only.

Study Visits

Throughout the acute and continuation phases of treatment, clinicians completed measures of depression severity, global improvement, and suicidality at each visit. Adverse effects were monitored at each visit and any serious adverse events were reported to the Institutional Review Board (IRB). Additionally, self-report and parent reports were obtained to assess depression severity, medication compliance, and other measures of cognitions, social, and family functioning. An independent evaluator, blind to treatment assignment, assessed participants at baseline, every six weeks until study exit, and at the follow-up evaluations (1 year and 1.5 years post-exit). Any participants who did not respond to treatment or required exit from the study were provided appropriate referrals.

PARTICIPANTS**Recruitment**

Participants included children and adolescents who met DSM-IV criteria for MDD. Recruitment occurred from clinical referrals to the child and adolescent outpatient clinic at Children's Medical Center of Dallas and through advertisements in the community.

Inclusion Criteria

Children and adolescents, ages seven to eighteen and still attending school who presented on an outpatient basis for the treatment of MDD were considered for participation. Participants met criteria for a primary diagnosis of non-psychotic major depressive disorder, either single or recurrent, for at least four weeks as defined by DSM-IV.

Additionally, participants were required to have a CDRS score ≥ 40 and a CGI-severity score of ≥ 4 for depression. All participants were considered to be in good general medical health and of normal intelligence. Concerns regarding IQ were addressed during the diagnostic period, with an IQ > 80 required for study entry. Both participants and their parent/guardian(s) were English speaking, as the clinic did not employ a Spanish-speaking therapist at the time of the studies.

Exclusion Criteria

Participants were excluded from participation for the following mental health diagnoses: lifetime history of any psychotic disorder, lifetime history of bipolar disorder, lifetime history of anorexia nervosa or bulimia (in STS, only excluded if in the past year), severe suicidal ideation or previous history of serious suicide attempt (in STS, clarifies the additional requirement of need for more intense treatment, i.e. hospitalization), or alcohol or substance abuse or dependence within the six months prior to entry (in STS, only dependence was excluded). Youth meeting criteria for other comorbid mental health disorders, including anxiety, ADHD, conduct disorder, and others, were not excluded. Additionally, pregnant or lactating females and sexually active females not using medically acceptable means of contraception were excluded. Patients with first-degree relatives diagnosed with Bipolar I disorder, those with chronic medical illness who are deemed medically unstable and require regular medication, and those on medication with psychotropic effects such as anticonvulsants or steroids (STS allowed these medications if used to treat another stable medical condition) were also excluded. Given the method of acute treatment in the current study, previous failure of an adequate trial of fluoxetine

(≥ 4 weeks of at least 40 mg) excluded participants from the study. See Table 1 for a summary of inclusion and exclusion criteria.

Table 1

Summary of Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
Youth, ages 7 to 18	Lifetime history of psychotic disorder
Still attending school	Lifetime history of bipolar disorder
Diagnosis of non-psychotic MDD for at least 4 weeks	Lifetime history of anorexia nervosa or bulimia *in STS, only if in past year
CDRS score ≥ 40 and CGI-S ≥ 4	Severe suicidal ideation or history of serious suicide attempt *STS clarifies need for more intense treatment
English speaking	Alcohol or substance abuse/dependence within previous six months *STS only dependence
Normal intelligence	First-degree relatives with Bipolar I disorder
	Pregnant, lactating, or sexually active females without appropriate contraceptive use
	Chronic medical illness, deemed medically unstable
	Taking medications with psychotropic effects
	Previous failure of adequate trial of fluoxetine

ASSESSMENT AND MEASURES

Initial Evaluation

Consent

Patients referred to the study initially completed a phone screen administered by a research coordinator to assess presence of depressive symptoms and general suitability for the study. Appropriate participants were scheduled for an initial visit. Research coordinators provided informed consent and assent to both participant and parent, including educating participant and parent about the study, explanation of risks and benefits, and answering any questions. The IRB of the University of Texas Southwestern Medical Center at Dallas (UTSW) approved the consent forms and protocols for all studies prior to patient participation.

Screening

After obtaining written consent from the parent and assent from the youth, initial diagnostic evaluations were conducted. At the initial visit, a trained independent evaluator (IE) and a psychiatrist/psychologist separately evaluated each participant to determine whether he or she met criteria for a primary diagnosis of MDD as defined by the DSM-IV. Determination of this diagnosis was based on clinical judgment and information gathered from standardized administration of the Kiddie Schedule for Affective Disorders and Schizophrenia-Present and Lifetime Version (Kaufman, Birmaher, Brent, Rao, & Ryan, 1996; K-SADS-PL) and the Children's Depressive Rating Scale – Revised (Poznanski & Mokros, 1996; CDRS-R). In accordance with administration guidelines for the K-SADS-PL and CDRS-R, clinicians interviewed

patients and parents separately to ensure they obtained all relevant information. These evaluations included determination of diagnosis and severity of depression, presence of other psychiatric disorders, and consideration of medical, psychiatric, and family history. Additionally, labs were conducted upon recommendation by the study physician.

Consensus

Following the initial evaluation, participants returned one week later to assess for persistence of depression. To ensure rater reliability, a consensus committee reviewed diagnostic information obtained by the independent evaluator and psychiatrist. Principal investigator(s) reviewed and signed all consensus forms.

Participant Characteristics

During the baseline visit, demographic information and baseline clinical characteristics were documented. These included age, gender, ethnicity, socioeconomic status, family history of psychopathology, primary diagnosis, number of major depressive episodes, comorbid psychiatric diagnoses, age at onset of depression, length of current episode, length of total depressive illness, and global functioning of the child and family.

Participants also completed self-report measures assessing psychosocial characteristics, and cognitive, social, and family functioning.

Diagnostic Measure*Kiddie Schedule for Affective Disorders and Schizophrenia-Present and Lifetime Version (K-SADS-PL)*

The K-SADS-PL (Kaufman et al., 1997) is a semi-structured diagnostic interview designed to assess present and lifetime history of psychiatric illness according to DSM-IV criteria among children and adolescents (ages 7 to 17). Clinicians interview the parent and patient separately and combine these responses to obtain summary scores for each item. Adequate interrater agreement, test-retest reliability and validity have been established (Kaufman et al., 1997). Evaluators also administered the Affective Disorders Supplement to all participants at baseline in order to ascertain additional information regarding symptoms of depression and mania.

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

The Children's Depressive Rating Scale-Revised (CDRS-R; Poznanski & Mokros, 1996) is a 17-item clinician-rated interview designed to assess severity of depressive symptoms in youth (ages 6-18). This measure was modeled after the Hamilton Depression Rating Scale for adults. Items are rated on a scale ranging from 1-5 or 1-7, with 1 indicating absence of the symptom. Total scores range from 17-113, with a score of 40 or greater indicating depression. Research on the CDRS-R has established adequate interrater reliability, internal consistency, and test-retest reliability. Additionally, the CDRS-R has good research support as an outcome measure of adolescent depression (TADS, 2004). An exploratory factor analysis was performed to examine the factor structure of the

CDRS-R in children and adolescents (Guo, Nilsson, Heilingstein, Wilson, & Emslie, 2006). Five factors were identified, including: observed depressed mood, anhedonia, morbid thoughts, somatic symptoms, and reported depressed mood. These factors differ somewhat from the initial structure outlined by Poznanski and Mokros that were based on clinical experience (1996). In the current study, presence and severity of depression were assessed with the CDRS-R, which was completed by the clinician at each study visit and by the independent evaluator at baseline and follow-up visits. The five factors from the CDRS-R were utilized to gain an understanding of the impact of trauma history on differential symptom pattern.

Clinical Global Impressions (CGI)

The Clinical Global Impressions scale (Guy, 1976; CGI) assesses clinical severity (CGI-S) of psychiatric illness and global improvement (CGI-I), as compared to the initial assessment of illness. Each item is measured on a seven-point scale, with lower values indicating less severity and greater improvement. The CGI is a standard measure used to assess response to psychological treatment, with a CGI improvement score of 1 (very much), 2 (much) improved, or 3 (improved) considered to represent acceptable response. The CGI-I has adequate internal consistency and reliability (Guy, 1976), as well as considerable research support for its use in psychopharmacological studies. Severity and improvement of the depressive illness were documented at each visit through the CGI-S and CGI-I scores.

Definitions of Depression Outcome

The primary depression outcome measure for the current study was severity of depressive symptoms as measured by the CDRS-R completed by the clinician at each visit. In the current study, an adequate clinical *response* to treatment was defined as a CGI-Improvement (CGI-I) score of 1 (very much improved) or 2 (much improved) and at least 50% reduction in depressive symptoms from baseline, as measured by the CDRS-R. Participants not meeting these criteria were classified as nonresponders. *Remission* criteria include a CDRS-R score of 28 or lower and a CGI-I of 1 or 2.

Trauma Measures

Kiddie Schedule for Affective Disorders and Schizophrenia-Present and Lifetime Version (K-SADS-PL): Post-traumatic Stress Disorder Section (PTSD)

During the initial assessment, independent evaluators assessed trauma history using the PTSD section of the K-SADS-PL. The PTSD section asks participants whether they have ever experienced any of the following traumatic events: car accident, other accident, fire, witness of a disaster, witness of a violent crime, victim of a violent crime, confronted with traumatic news, witness to domestic violence, physical abuse, sexual abuse, or other. Criteria are included to assist the clinician in determining whether the event experienced was serious in nature or involved the actual or perceived threat of harm to self or others. The clinician completed a summary score based on agreement between parent and patient or clinical judgment as to whether the event met criteria for a traumatic event. Additional items were completed if the participant reported experiencing at least one traumatic

event. These items assessed the presence of specific symptoms in order to determine whether participants met criteria for PTSD.

In the current study, trauma was defined in the following manner. We separated the various traumatic events listed in the K-SADS-PL into three groups: (1) no trauma, (2) trauma—no abuse and (3) abuse, including both physical and/or sexual abuse. These categories are similar to the grouping proposed in a previous study utilizing the PTSD section of the K-SADS-PL (Lewis et al., 2010), with one minor exception. We have combined physical and sexual abuse into one category. This also allows us to maximize power given fewer incidences of abuse among the participants, and it is consistent with several other studies examining the impact of abuse (Asarnow et al., 2009; Klein et al., 2009; Nemeroff et al., 2003). Abuse history was operationally defined as a binary variable: no history of abuse versus history of physical and/or sexual abuse.

Hopelessness Scale for Children (HSC) and Hopelessness Scale for Adolescents (HSA)

The Hopelessness scales (Kazdin, Rodgers & Colbus, 1986) are self-report questionnaires adapted from the Beck Hopelessness Scale (BHS; Beck, Weissman, Lester, & Trexler, 1974). The HSC is for use with children ages 6-11, while the HSA is designed to assess hopelessness among adolescents ages 12-18. These scales have demonstrated adequate reliability as measured by ratings of internal consistency and validity, when correlated with other measures of depression and hopelessness (Beck et al., 1974; Kazdin et al., 1986). The current study will examine the relationship between hopelessness and trauma history at baseline.

Medication Compliance

Given the developmental age of most participants in the study, parents were primarily responsible for dispensing the medication. Compliance was emphasized through psychoeducation with the parents. Pill counts were conducted at each visit. Additionally, both parent and patient completed a brief measure of medication compliance by answering whether the patient had taken all the medication since the previous visit. The form also indicated the person primarily responsible for administering the medication, either patient or parent. Participants were discontinued if they were non-compliant with the medication regimen, defined as <70% of pills taken on two consecutive visits.

DATA ANALYSIS

Data Collection Procedures

In order to maintain confidentiality and protect data, all data were stored in locked filing cabinets in locked offices. Data were entered into the latest version of the Statistical Package for the Social Sciences (SPSS), Versions 16-19, updated annually. To ensure accuracy of data entry, all data were double-entered by separate research assistants. Values were compared using Microsoft *Excel*, according to the procedures outlined by Elliott, Hynan, Reisch, and Smith (2006). Any inconsistencies in the data entry were resolved by agreement between at least two research assistants and re-entered. Clean data were analyzed using SPSS, Version 19 and SAS.

Data Analysis Procedures

To avoid the effects of participant dropout and reduce potential biases, intent-to-treat analyses were conducted, with one minor caveat: participants who did not have at least one visit post-baseline were not included. The level of significance for all tests was set at $\alpha = .05$ (two-tailed). Given that the proposed analyses included data from a combination of three studies, we first examined whether any significant differences existed based on study participation. Dosing schedule of fluoxetine was evaluated as a potential covariate, especially since the length of the acute phase was shorter in the third study. We examined other potential differences between studies, including number of participants with a history of trauma, baseline severity, and other demographic and clinical characteristics. Any significant differences found between studies will be included as covariates in the relevant analyses described below.

Demographics and Clinical Characteristics

1a. Baseline characteristics of participants that entered the acute phase of treatment were examined to assess the relationship of trauma history to demographics (age, gender, ethnicity, SES) and clinical characteristics of depression (severity, age at onset, length of illness, comorbidity, suicidality). For continuous measures, one-way analyses of variance (ANOVA) were computed with trauma group (3 levels: no trauma; trauma, no abuse; abuse) as the independent variable. Chi-square tests were computed to determine whether trauma differs across gender, ethnicity, and socio-economic status (SES). Depending on characteristics of these variables as assessed by tests of normality, non-parametric tests were substituted as appropriate.

1b. To assess the relationship between trauma history and specific symptom identification, several analyses of variance were computed with trauma group as the independent variable and factor scores from the CDRS-R as separate dependent variables. The five factors include observed depressed mood, anhedonia, morbid thoughts, somatic symptoms, and reported depressed mood (Guo et al., 2006). Given the known relationship between gender and age (child vs. adolescent) on these factors, analyses controlled for these variables.

Trauma and Acute Treatment

2a. A 3 trauma group (no trauma; trauma, no abuse; abuse) \times 5 time point (weeks 1, 2, 3, 4, 6) mixed linear model analysis of repeated measures was applied to examine the relationship between trauma history and depressive symptoms across the 6-week acute phase of treatment with fluoxetine. The best fitting covariance structure was utilized. The primary outcome was measured by assessing depression severity on the CDRS-R across acute treatment. Initial depression severity (baseline CDRS-R) was included as a covariate in the mixed model. Other covariates, including age, gender, length of illness, among others, were added to the model based on their relationship to trauma at baseline and depressive outcome. The model included the main effects of trauma group and time and the interaction effect of trauma group by time. The Tukey procedure was used to examine the *post hoc* pairwise comparisons among the three levels of trauma group on CDRS-R. We also considered simple trauma group effects at each time point. An additional mixed linear model analysis of repeated measures was computed with abuse history as the primary grouping variable.

2b. To assess whether trauma history or abuse history is associated with remission following acute treatment with an SSRI (fluoxetine), binary logistic regression analyses were computed. Odds ratios indicated the likelihood of remission status at the end of the acute phase of treatment, based on trauma and abuse history. Remission status is a binary outcome variable (remitted or not remitted), with remission operationally defined by the following criteria: CDRS-R score of 28 or lower and a CGI-I of 1 or 2. Trauma history is a multinomial variable including three groups (no trauma; trauma, no abuse; and abuse, with “no trauma” as the reference group). The binary grouping variable of abuse history (abuse or no abuse) was also examined, given findings from the literature that abuse may be a better predictor of remission than other traumatic events. Potential covariates were included based on their association with remission and trauma history.

2c. Time to remission was examined by computing a Cox regression. Hazard ratios were examined to determine whether trauma or abuse history was associated with participants’ time to achieve remission during acute treatment with fluoxetine. We included potential confounding variables in the analysis that were known or found to be associated with remission, including age, initial depression severity, and others.

CHAPTER FOUR Results

DEMOGRAPHIC AND CLINICAL CHARACTERISTICS

Summary of Pooled Sample

Demographics

The pooled sample includes a total of 292 children and adolescents (ages 7-18) from three studies of depression in youth (RR, $N = 168$; RP, $N = 66$; STS, $N = 58$). The sample consists of 100 children (ages 7-11) and 192 adolescents (ages 12-18), with a mean age of 12.83. Gender was equally distributed in the sample; 156 (53.4%) of the participants were male and 136 (46.6%) were female. Ethnicity was distributed in the following manner: 206 (70.5%) White, non-Hispanic; 46 (15.8%) Hispanic; 28 (9.6%) African American; and 12 (4.1%) other ethnicity. Highest education level of the youth's parents was used as a measure of socio-economic status. More than half of the youth had at least one parent who graduated from college or obtained further education. See Table 1 for summary of demographic characteristics of the sample.

Clinical Characteristics

At baseline, 210 youth (72.2%) were in the midst of their first major depressive episode, while 81 youth (27.8%) exhibited a recurrent depressive episode. Mean scores of baseline severity of depression (CGI-S) placed most youth in the moderately ill to markedly ill range, $M = 4.95(0.65)$; CDRS-R, $M = 57.92(8.41)$. Evaluators determined the presence of comorbid psychiatric diagnoses during the youth's initial interview; 61% of youth met criteria for at least one comorbid diagnosis at baseline, excluding

dysthymia. The sample included a high rate of youth with a family history of depression. Approximately two-thirds of the participants had a first-degree relative (mother, father, or sibling) with a history of depression (196 versus 95 with no family history of depression). Approximately half of the sample identified experiencing at least one traumatic event (48.7%), with the breakdown by trauma group as follows: 142 youth (51.3%) reported no history of traumatic events, 97 (35.0%) reported experiencing at least one traumatic event, not including abuse, and 38 youth (13.7%) reported a history of physical and/or sexual abuse. Additional clinical characteristics are further outlined in Table 1.

Evaluation of Study Differences

Demographics by Study

Prior to completing additional analyses, we examined whether there were any significant differences in demographic and clinical characteristics of depression between the participants in any of the three studies. Participants did not differ between studies in gender, ethnicity, or parent's highest education level. An expected difference was found in the age representation between the studies as RP was designed to only include youth ages 11-18. See Table 2 for demographic characteristics separated by study involvement, including chi-square values and significance.

Clinical Characteristics by Study

Study participation was not associated with baseline depression severity (CDRS-R), family history of depression, number of comorbid diagnoses, or length of depressive illness. Additionally, the distribution of patients identifying a history of trauma or abuse

Table 2

Demographic and Clinical Characteristics of Pooled Sample (N = 292)

Characteristic	N (%)	Characteristic	M (SD)	Mdn (Range)
Gender		Age	12.83 (2.85)	
Male	156 (53.4%)	Severity (CDRS-R)	57.92 (8.41)	
Female	136 (46.6%)	Functioning (CGAS)	51.36 (6.10)	
Age Group		CE Duration (wk)	27.87 (24.16)	
Child	100 (34.2%)	CE Age of Onset	12.28 (2.77)	
Adolescent	192 (65.8%)	Age of Onset of MDD	11.53 (2.84)	
Ethnicity		Length of Illness (mo)	12.97(15.39)	
African American	28 (9.6%)	Hopelessness	7.37 (4.73)	
White	206 (70.5%)	Severity (CGI-S)	4.95 (.65)	
Hispanic	46 (15.8%)	CE Suicidal Behavior		2 (1-5)
Other	12 (4.1%)			
Highest Parent Education				
Less than HS	15 (5.5%)			
HS Graduate	40 (14.8%)			
Partial College	77 (28.4%)			
College Graduate	88 (32.5%)			
Graduate Training	51 (18.8%)			
Trauma History				
No trauma	142 (51.3%)			
Trauma, no abuse	97 (35.0%)			
Abuse	38 (13.7%)			
Primary Diagnosis				
Single Episode	210 (72.2%)			
Recurrent	81 (27.8%)			
Family History				
Depression	196 (67.4%)			
No depression	95 (32.6%)			
Comorbid Diagnoses				
0	114 (39.0%)			
1	120 (41.1%)			
2	44 (15.1%)			
3 or 4	14 (4.8%)			

Note. CE=Current Episode. HS=High School.

was the same across study involvement. Study involvement was significantly associated with youth's age of onset of the current episode $F(2, 292) = 23.85, p < .001$, and age of onset of youth's depressive illness $F(2, 292) = 23.11, p < .001$. However, analyses of covariance conducted to examine whether these differences remained when controlling for participants' age were non-significant (see Table 3 for adjusted F and p values).

Thus, differences in age of onset by study can be accounted for by the difference in mean age of youth participating in each of the three studies.

Table 3

Demographic Characteristics of Patients by Study Involvement

Characteristic	N (% within study)			χ^2
	RR (n = 168)	RP (n = 66)	STS (n = 58)	
Gender				3.29
Male	97 (57.7%)	33 (50.0%)	26 (44.8%)	
Female	71 (42.3%)	33 (50.0%)	32 (55.2%)	
Age Group				34.52***
Child	80 (47.6%)	6 (9.1%)	14 (24.1%)	
Adolescent	88 (52.4%)	60 (90.9%)	44 (75.9%)	
Ethnicity				12.30
African American	18 (10.7%)	3 (4.5%)	7 (12.1%)	
White	126 (75.0%)	47 (71.2%)	33 (56.9%)	
Hispanic	18 (10.7%)	14 (21.2%)	14 (24.1%)	
Other	6 (3.6%)	2 (3.0%)	4 (6.9%)	
Highest Parent Education				2.69 ^a
Less than HS	4 (2.5%)	4 (7.2%)	7 (12.4%)	
HS Graduate	34 (21.5%)	4 (7.1%)	2 (3.5%)	
Partial College	46 (29.1%)	17 (30.4%)	14 (24.6%)	
College Graduate	46 (29.1%)	23 (41.1%)	19 (33.3%)	
Graduate Training	28 (17.7%)	8 (14.3%)	15 (26.3%)	

Note. ^a represents results of chi-square statistic computed via Kruskal-Wallis method due to data being ordinal in nature. *** $p < .001$

Depression Severity by Study

While depression severity, as measured by symptoms on the clinician-administered CDRS-R, was found to be consistent across studies, severity on the seven-point CGI-S scale was not. A Kruskal-Wallis test was used to test for differences in CGI-S among studies because the data was organized in an ordinal fashion (normality was questionable) and sample sizes within some of the groups were small. The Kruskal-Wallis test was significant, $\chi^2(2, N = 292) = 21.36, p < .001$. *Post hoc* tests were performed by computing individual Mann-Whitney U tests between each of the study pairs. Severity ratings on the CGI-S at baseline were found to be significantly higher in STS than in RR and RP.

Current Depressive Episode by Study

An association between primary diagnosis (single versus recurrent) and study participation was also found, $\chi^2(2, N = 292) = 9.16, p < .05$. Examination of the cell frequencies showed that participants in STS were significantly more likely to be in the midst of their first depressive episode when compared to youth in the other two studies. Additionally, study participation was associated with length of the index depressive episode, $F(2, 292) = 5.73, p < .001$, with participants in STS exhibiting a significantly longer duration of their index depressive episode ($M = 37.31, SD = 31.22$) as compared to those in RR ($M = 25.30, SD = 21.10$) and RP ($M = 26.11, SD = 22.68$). Compared to youth in RR and RP, youth in STS were more likely to be in the midst of a first depressive episode of longer duration and greater severity. See Table 4 to examine

descriptives on the various clinical characteristics of depression separated by study involvement. Results of relevant statistical tests and p -values are reported.

Table 4

Differences in Clinical Characteristics of Depression in Patients by Study

Characteristic	RR	RP	STS	χ^2
	($n = 168$)	($n = 66$)	($n = 58$)	
	n (% within study)			
Primary Diagnosis				9.16*
Single Episode	116 (69.0%) _a	43 (66.2%) _a	51 (87.9%) _b	
Recurrent	52 (31.0%) _a	22 (33.8%) _a	7 (12.1%) _b	
Family History				2.26
Depression	119 (70.8%)	40 (61.5%)	37 (63.8%)	
No depression	49 (29.2%)	25 (38.5%)	21 (36.2%)	
Comorbid Diagnoses				13.84
0	68 (40.5%)	29 (43.9%)	17 (29.3%)	
1	65 (38.7%)	31 (47.0%)	24 (41.4%)	
2	26 (15.5%)	6 (9.0%)	12 (20.7%)	
3 or 4	9 (5.4%)	0 (0.0%)	5 (8.6%)	
Trauma History				6.42
No trauma	89 (54.3%)	27 (44.3%)	26 (50.0%)	
Trauma, no abuse	59 (36.0%)	23 (37.7%)	15 (28.8%)	
Abuse	16 (9.8%)	11 (18.0%)	11 (21.2%)	
	M (SD)			F
Severity (CDRS-R)	57.57 (7.31)	58.08 (9.71)	58.76 (9.81)	.442
Functioning (CGAS)	52.01 (6.04) _a	51.23 (5.51) _a	49.64 (6.59) _b	3.32*
CE Duration (wk)	25.30 (21.10) _a	26.11 (22.68) _a	37.31 (31.22) _b	5.73***
CE Age of Onset	11.40 (2.76)	13.74 (1.90)	13.16 (2.59)	2.143 ^a
Age of Onset of MDD	10.63 (2.70)	12.77 (2.38)	12.76 (2.74)	2.523 ^a
Length of Illness (mo)	14.64 (17.63)	9.32 (8.92)	12.25 (12.85)	2.96
Hopelessness	6.73 (4.50) _a	8.52 (5.37) _b	7.95 (4.40) _a	3.96*
	M (SD)			χ^2
Severity (CGI-S)	4.82 (.60) _a	4.98 (.67) _a	5.28 (.64) _b	21.36***
CE Suicidal Behavior	2 (1-5) _a	3 (1-5) _b	3 (1-5) _a	6.42*

Note. Subsets sharing a common subscript are not statistically different at $\alpha = .05$.

^a F value represents results of analysis of covariance, controlling for participants' current age. CE = Current Episode. * $p < .05$, ** $p < .01$, *** $p < .001$

Dosing Schedule by Study

Three Studies across 6-week Acute Phase

Given the differences in lengths of acute phase treatment between the studies, the mean dose of fluoxetine prescribed to patients at each week was examined. A repeated-measures analysis of variance was performed to compare the dose schedule between the three studies across the first four visits of the acute phase of treatment (visit 4 was the last clinician visit prior to the week 6 observation). The within-subject effect for dose across acute treatment was significant, $\Lambda = .032$, $F(4, 248) = 1814.75$, $p < 0.001$. Dose increased from baseline to visit 1, but remained steady through visit 4 for most participants. The interaction of study involvement by fluoxetine dose over time was also significant, $\Lambda = .795$, $F(8, 248) = 7.37$, $p < 0.001$. In STS, there was a significant difference in dose at visit 4 when compared to the other studies. Given the shorter acute phase in STS (6 weeks versus 12 weeks in RR and RP), clinicians may have been more likely to increase the youth's dose at visit 4. See Figure 2 for a graphical representation of dose by time across the three studies.

Additionally, the univariate between-subjects effect for study on overall mean fluoxetine dose was significant, $F(2, 248) = 6.20$, $p < 0.01$. Pairwise comparisons, using the Bonferroni method, indicate at the overall 0.05 level that there was a significant dose by study effect between STS [$M = 18.67(.20)$] and RR [$M = 17.96(.12)$] and RP [$M = 17.77(.22)$]. There was no difference in dose administered between RR and RP over the first six weeks of the acute phase of treatment.

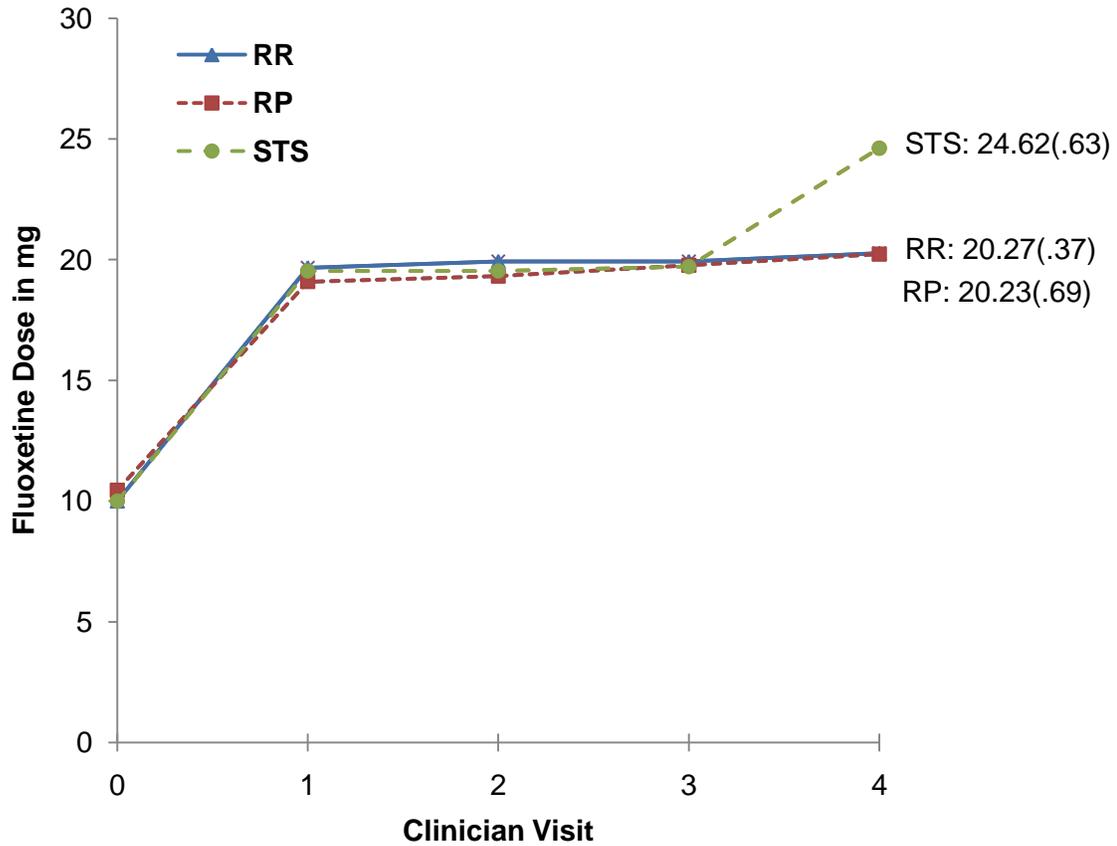


Figure 2. Plot of mean fluoxetine dose by study participation (RR, RP, STS) across first six weeks of acute treatment.

Two Studies across 12-week Acute Phase

An additional repeated measures ANOVA was computed to examine the dose schedule across the entire 12-week acute phase in RR and RP, excluding STS. The within-subject effect for dose across acute treatment was significant, $\Lambda = .035$, $F(7, 168) = 624.58$, $p < 0.001$. However, the interaction of study involvement by fluoxetine dose over time was

not significant, $\Lambda = .927$, $F(7, 168) = 1.78$, $p = .095$. See Figure 3 for a graphical representation of dose by time across the 12-week acute phase in RR and RP.

Furthermore, the between-subjects effect for study on overall mean fluoxetine dose was not significant, $F(1, 168) = 3.21$, $p = .075$. This analysis confirms that the dose schedule can be assumed to be equivalent in RR and RP.

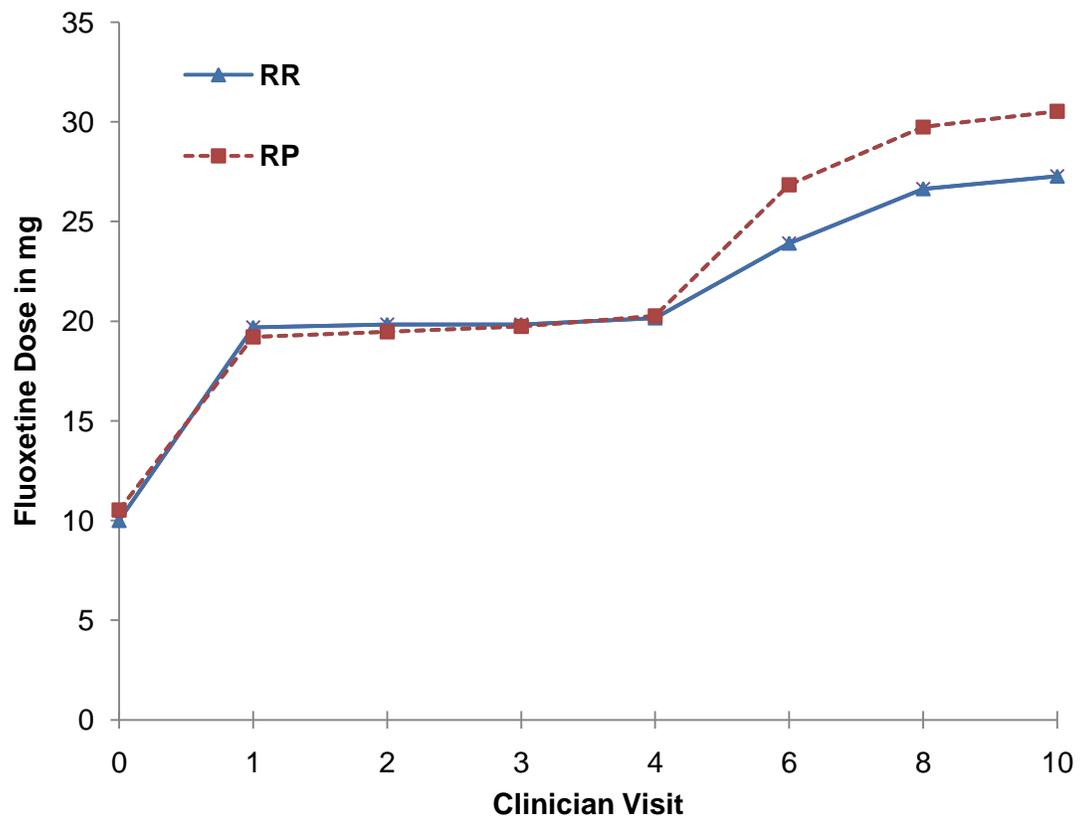


Figure 3. Plot of mean fluoxetine dose across 12-week acute phase in RR and RP

AIM I

Demographic Characteristics by Trauma History

Baseline characteristics of participants were examined to determine whether trauma history was associated with any demographic information or had an impact on relevant clinical characteristics of depression prior to acute treatment with fluoxetine. Chi-square tests (for categorical variables) and one-way analyses of variance (for continuous measures) were computed. A few of the baseline characteristics exhibited questionable normality, were organized in an ordinal fashion, or exhibited small sample sizes in some of the groups, thus non-parametric tests were substituted. Trauma history was not associated with participants' gender, ethnicity, or parent's highest level of education.

Age

The average age of youth was found to be different based on patient's trauma history, $F(2, 277) = 3.42, p < .05$. Follow-up tests were conducted to evaluate pairwise differences among the means. The Tukey multiple comparisons performed at the 0.05 significance level found that the mean age for participants with an abuse history ($M = 13.61, SD = 2.946, N = 38$) was significantly higher than that for the participants with no trauma history ($M = 12.44, SD = 2.882, N = 142$) but not significantly different than the participants with a trauma history but no abuse ($M = 13.15, SD = 2.655, N = 97$).

Additionally, age was broken down into two groups, children (ages 7-11) and adolescents (ages 12-18), and examined by computing a Chi-square test. Adolescents were more likely to have experienced a traumatic event, including abuse, than children, $\chi^2(2, N =$

277) = 9.02, $p < .05$. See Table 5 for a breakdown of demographic characteristics by report of trauma history, including chi-square and p -values.

Table 5

Differences in Demographic Characteristics of Patients by Trauma History

Characteristic	n (% within trauma group)			χ^2
	No trauma (n = 142)	Trauma, no Abuse (n = 97)	Abuse (n = 38)	
Gender				1.43
Male	81 (57.0%)	50 (51.5%)	18 (47.4%)	
Female	61 (43.0%)	47 (48.5%)	20 (52.6%)	
Age Group				9.02*
Child	60 (42.3%) _a	24 (24.7%) _a	10 (26.3%) _a	
Adolescent	82 (57.7%) _b	73 (75.3%) _b	28 (73.7%) _a	
Ethnicity				5.17
African American	13 (9.2%)	11 (11.3%)	4 (10.5%)	
White	106 (74.6%)	64 (66.0%)	24 (63.2%)	
Hispanic	16 (11.3%)	19 (19.6%)	8 (21.1%)	
Other	7 (4.9%)	3 (3.1%)	2 (5.3%)	
Highest Parent Education				3.28 ^a
Less than HS	4 (2.9%)	8 (9.4%)	3 (8.6%)	
HS Graduate	21 (15.4%)	14 (16.5%)	4 (11.4%)	
Partial College	39 (28.7%)	20 (23.5%)	14 (40.0%)	
College Graduate	41 (30.1%)	32 (37.6%)	10 (28.6%)	
Graduate Training	31 (22.8%)	11 (12.9%)	4 (11.4%)	

Note. Subsets sharing a common subscript are not statistically different at $\alpha = .05$.

^a value represents results of chi-square statistic computed via Kruskal-Wallis method due to data being ordinal in nature. * $p < .05$

Clinical Characteristics of Depression by Trauma History

Characteristics of depression found to be associated with trauma history include age of onset of depressive illness, duration of current depressive episode, and indication of suicidal thoughts and behaviors. No differences were found based on reported trauma history in participants' primary diagnosis (single vs. recurrent), family history of depression, number of depressive episodes, or number of comorbid diagnoses.

Additionally, depression severity at baseline, as measured both by the clinician CDRS-R and by the consensus agreement of the CGI-Severity rank, was not different between the participants with no trauma history, trauma history, or abuse. Participants' baseline functioning, as measured by the CGAS, age of onset of the current episode, length of total illness (from onset of first depressive episode), and level of self-reported hopelessness, were also equivalent between the trauma history groups. See Table 6 for additional information regarding the clinical characteristics of depression by trauma history. Significant findings are outlined below.

Comorbid Diagnoses

While MDD was the primary diagnosis for all youth participating in the current study, 73% of youth met *DSM-IV* criteria for other psychiatric disorders. When dysthymia was excluded, 61% of youth still met criteria for a comorbid disorder. Table 7 presents the percentage of children and adolescents meeting criteria for these disorders, separated by trauma history. No participants met criteria for bipolar, psychotic, eating disorders, or substance abuse/dependence, as these disorders were exclusionary. However, youth with a history of abuse were significantly more likely to meet criteria for a current diagnosis of

PTSD, $p < .001$. Approximately 10.5% of youth with a history of abuse met criteria for a diagnosis of PTSD and an additional 15.8% exhibited subthreshold symptoms, while only 5.9% of the remaining participants met subthreshold or threshold criteria for PTSD.

Trauma history was not associated with any other individual disorders or with anxiety, disruptive behavior disorders, or substance disorders, in general.

Age of Onset of MDD

Age of onset of the depressive illness (measured from incidence of first depressive episode) was significantly different between the trauma groups, $F(2, 276) = 3.73, p < .05$, with abuse history associated with later onset. However, an analysis of covariance conducted to examine whether these differences remained when controlling for participants' current age was non-significant (see Table 6 for adjusted F and p values). Thus, differences in age of onset of the depressive illness based on trauma history can be accounted for by the difference in mean age of youth who have experienced abuse.

Duration of Current Depressive Episode

A one-way analysis of variance found a significant difference in the length of the current depressive episode based on participants' history of trauma or abuse, $F(2, 277) = 4.12, p < .05$. Tukey multiple comparisons performed at the 0.05 significance level found that the mean length of current episode for participants with an abuse history, measured in weeks, ($M = 36.58, SD = 32.85, N = 38$) was significantly higher than that for the participants with no trauma history ($M = 24.80, SD = 19.82, N = 142$) and from those with a trauma history, but no abuse ($M = 27.16, SD = 21.16, N = 97$).

Table 6

Baseline Clinical Characteristics of Depression by Trauma History

Characteristic	No trauma (<i>n</i> = 142)	Trauma, no Abuse (<i>n</i> = 97)	Abuse (<i>n</i> = 38)	χ^2
	<i>n</i> (% within trauma group)			
Primary Diagnosis				.590
Single Episode	99 (69.7%)	71 (74.0%)	28 (73.7%)	
Recurrent	43 (30.3%)	25 (26.0%)	10 (26.3%)	
Family History				.826
Depression	94 (66.2%)	66 (68.8%)	23 (60.5%)	
No depression	48 (33.8%)	30 (31.3%)	15 (39.5%)	
Number of Episodes				4.153
1	99 (69.7%)	72 (74.2%)	28 (73.7 %)	
2	31 (21.8%)	22 (22.7%)	8 (21.1%)	
3 or 4	12 (8.4%)	3 (3.1%)	2 (5.2 %)	
Comorbid Diagnoses				4.167
0	50 (35.2%)	38 (39.2%)	17 (44.7%)	
1	65 (45.8%)	39 (40.2%)	12 (31.6%)	
2	21 (14.8%)	14 (14.4%)	7 (18.4%)	
3 or 4	6 (4.2%)	6 (6.2%)	2 (5.3%)	
	<i>M (SD)</i>			<i>F</i>
Severity (CDRS-R)	57.74 (8.30)	57.58 (7.89)	59.26 (9.49)	.607
Functioning (CGAS)	51.93 (6.39)	51.41 (6.02)	49.36 (4.93)	2.546
CE Duration (wk)	24.80 (19.83) _a	27.16 (21.16) _a	36.58 (32.85) _b	4.118*
CE Age of Onset	11.96 (2.78)	12.56 (2.61)	13.05 (2.99)	2.889
Age of Onset of MDD	11.13 (2.78)	11.83 (2.744)	12.39 (3.15)	.526 ^a
Length of Illness (mo)	12.96 (15.37)	12.97 (15.33)	13.41 (16.94)	.014
Hopelessness	7.01 (4.63)	7.40 (4.73)	7.70 (4.95)	.409
	<i>Mdn (Min-Max)</i>			χ^2
Severity (CGI-S)	5 (4-7)	5 (4-6)	5 (4-6)	.482
CE Suicidal Behavior	2 (1-5) _a	3 (1-5) _b	3 (1-5) _b	6.788*

Note. Subsets sharing a common subscript are not statistically different at $\alpha = .05$.

^a *F* value represents results of analysis of covariance, controlling for participants' current age. CE = Current Episode. * $p < .05$

Table 7

Current Psychiatric Comorbidities by Trauma History

Diagnosis	No Trauma	Trauma— No Abuse	Abuse
DSM-IV Diagnosis			
Attention-deficit/ Hyperactive	56 (39.4%)	32 (33.3%)	14 (36.8%)
Oppositional Defiant/ Conduct	14 (9.9%)	6 (6.2%)	3 (7.9%)
Separation Anxiety	7 (4.9%)	5 (5.2%)	1 (2.6%)
Generalized Anxiety	14 (9.9%)	15 (15.6%)	3 (7.9%)
Obsessive-Compulsive	3 (2.1%)	2 (2.1%)	0 (0.0%)
Posttraumatic Stress	0 (0.0%)	1 (1.0%)	4 (10.5%)
Dysthymia	40 (28.2%)	23 (24.0%)	14 (36.8%)
Summary Categories			
Anxiety	22 (15.5%)	22 (22.9%)	7 (18.4%)
Disruptive Behavior	63 (44.4%)	33 (34.4%)	14 (36.8%)
Substance Use	0 (0.0%)	0 (0.0%)	0 (0.0%)

Suicidal Thoughts and Behavior

To determine whether individuals with a trauma history (no trauma; trauma, no abuse; abuse) exhibited differences in suicidal thoughts or behavior (1=None, 2=Wishes, 3=Thoughts, 4=Plans, 5=Attempts) during their current depressive episode, a Kruskal-Wallis test was conducted due to the ordinal distribution of the variable (assumption of normality violated). The Kruskal-Wallis test for comparison of trauma history groups indicates that there is a statistically significant difference in the distribution of suicidal thoughts and behavior identified between the groups, $\chi^2(2, N = 276) = 6.788, p = < .05$. Follow-up tests were conducted to evaluate pairwise differences among the three groups by computing separate Mann-Whitney U tests of significance. The results indicated that youth with a history of abuse ($Mdn = 3, Range = 1-5$) were more likely to have

experienced more severe suicidal thoughts and behaviors than youth without a history of abuse ($Mdn = 2$, $Range = 1-5$); there were no differences between the other levels of trauma history on suicidal thoughts and behavior at baseline.

Symptom Identification by Trauma History

Separate analyses of variance were computed to determine whether a history of trauma influenced symptom identification on the five factors of the CDRS-R as outlined by Guo, et al., 2006 (observed depressed mood, anhedonia, morbid thoughts, somatic symptoms, and reported depressed mood). In each of these analyses, gender and age (child vs. adolescent) were included due to their known association with symptom identification. The interaction between these factors and trauma history was also examined. *Post hoc* tests were computed to examine where the differences lie. See Figure 4 for mean scores on each factor stratified by age group (children and adolescents).

Observed Depressed Mood

This factor includes three items based on the clinician's observation of the youth's depressed affect, tempo of speech, and level of activity. The interaction between trauma history and age was significant, $F(2, 277) = 3.56, p < 0.05$. In adolescents, there were no differences on observed depressed mood based on trauma history. However, among children, those with a history of trauma ($M = 5.81, SD = .55$) and/or abuse ($M = 6.05, SD = .84$) had lower scores on the observed depressed mood factor than children with no history of traumatic events ($M = 7.40, SD = .34$). The interaction between trauma history and gender approached significance, $F(2, 277) = 2.72, p = 0.068$, with males obtaining higher scores than females on observed depressed mood.

Anhedonia

Two items make up the anhedonia factor, including social withdrawal and capacity to have fun. There was a significant interaction between trauma history and age, $F(2, 277) = 3.43, p < 0.05$. Among children, those with a history of abuse ($M = 9.15, SD = .63$) obtained significantly higher scores on the anhedonia factor when compared to those with no trauma ($M = 8.11, SD = .25$). There were no significant differences between other levels of trauma history on anhedonia among children or adolescents.

Somatic

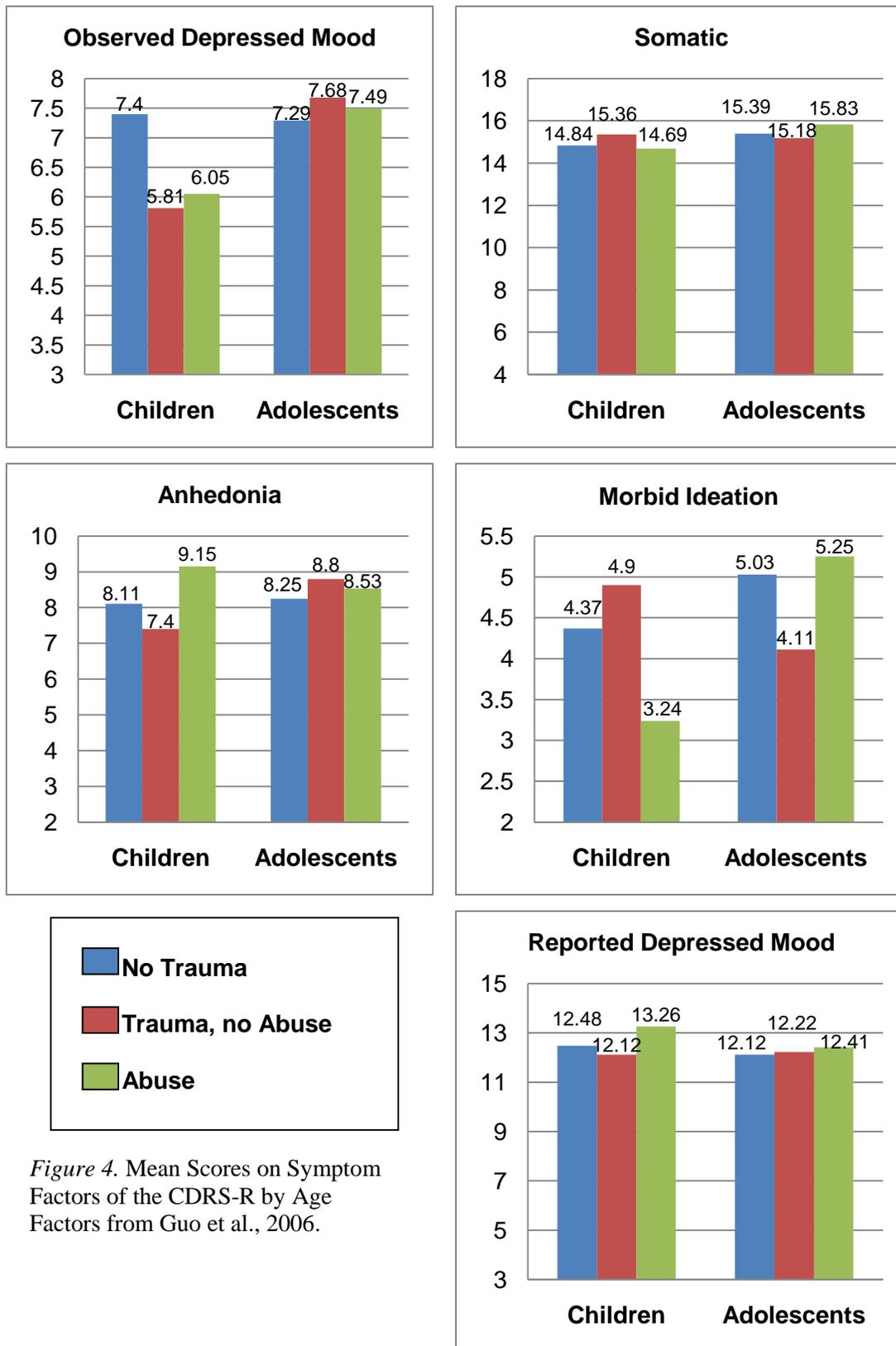
The somatic factor includes youth's reports of excessive fatigue, impaired sleep, physical complaints, and difficulties completing schoolwork (thought to be reflective of poor concentration and attention; Guo et al., 2006). There were no significant main effects or interactions found in trauma history, age, or gender on youth's somatic symptoms.

Morbid Thoughts

This factor includes the two items assessing morbid ideation and suicidal ideation. There was a significant interaction between trauma history and age, $F(2, 277) = 3.92, p < 0.05$. There were no differences in morbid ideation in those with no abuse history. However, in youth with a history of abuse, children had significantly lower scores on morbid ideation ($M = 3.24, SD = .76$) when compared to adolescents ($M = 5.25, SD = .45$).

Reported Depressed Mood

Items on reported depressed mood include depressed feelings, excessive weeping, and low self esteem. The main effect and interaction effects for trauma history and reported depressed mood were not significant.



AIM II

Rationale for Excluding STS

Given the significant difference in methodology (shorter acute-phase in STS), difference in administration of the fluoxetine dose in STS, and statistical differences found in baseline clinical characteristics between STS and the other two studies (severity on the CGI-S, primary diagnosis, and length of current episode), these three studies cannot be assumed to be equivalent. Thus, the remainder of the analyses will use the smaller sample of RR and RP, excluding those in STS. The exclusion of STS will allow us to examine participants' response throughout the entire acute phase of treatment, 12 weeks. Table 8 reports demographic information on the pooled sample of RR and RP (N = 234).

Factors Associated with Acute Outcome

Additional analyses were performed to determine whether any baseline demographic or clinical characteristics were associated with remission status at Week 12. Of the participants who entered the study, 80% remained at the end of the acute phase of treatment. Completion rates were similar between the three trauma history groups (81% of no trauma, 79% of trauma—no abuse, and 78% of abuse). As expected, age was found to be related to remission, such that children were more likely to have remitted than adolescents. Youth's first-degree family history of depression (mother, father, or sibling) was associated with remission status, such that youth with a positive family history of depression were more likely to remit when compared to youth with no family history of depression. SES, gender, and other clinical characteristics were not associated with remission status. See Table 9 for values of characteristics associated with acute outcome.

Table 8

Demographic and Clinical Characteristics of Two Studies, RR and RP (N = 234)

Demographic Characteristics		Clinical Characteristics	
	<i>N (%)</i>		<i>N (%)</i>
Gender		Trauma History	
Male	130 (55.6%)	No trauma	117 (51.8%)
Female	104 (44.4%)	Trauma, no abuse	82 (36.3%)
Age Group		Abuse	27 (11.9%)
Child	86 (36.8%)	Primary Diagnosis	
Adolescent	148 (63.2%)	Single Episode	159 (68.2%)
Ethnicity		Recurrent	74 (31.8%)
African American	21 (9.0%)	Family History	
White	173 (73.9%)	Depression	74 (31.8%)
Hispanic	32 (13.7%)	No depression	159 (68.2%)
Other	8 (3.4%)	Comorbid Diagnoses	
Highest Parent Education		0	97 (41.5%)
Less than HS	8 (3.8%)	1	96 (41.0%)
HS Graduate	38 (17.8%)	2	32 (13.7%)
Partial College	63 (29.4%)	3 or 4	9 (3.8%)
College Graduate	69 (32.2%)		
Graduate Training	36 (16.8%)		
	<i>M (SD)</i>		<i>M (SD)</i>
			<i>Mdn (Range)</i>
Age	12.59 (2.86)	Severity (CDRS-R)	57.71 (8.04)
		Functioning (CGAS)	51.81 (5.90)
		CE Duration (wk)	25.53 (21.51)
		CE Age of Onset	12.06 (2.75)
		Age of Onset of MDD	11.23 (2.78)
		Length of Illness (mo)	13.06 (15.89)
		Hopelessness	7.15 (4.89)
		Severity (CGI-S)	4.86 (.62)
		CE Suicidal Behavior	2 (1-5)

Note. CE = Current Episode. HS = High School.

Table 9

Demographic and Clinical Characteristics Associated with Remission at Week 12

Characteristic	Not Remitted	Remitted	χ^2
	(N = 52)	(N = 132)	
	N (% within characteristic)		
Age			6.521*
Child	13 (17.8%)	60 (82.2%)	
Adolescent	39 (35.1%)	72 (64.9%)	
Gender			.307
Male	28 (26.7%)	77 (73.3%)	
Female	24 (30.4%)	55 (69.6%)	
Highest Parent Education			.671
Less than HS	3 (6.4%)	5 (4.0%)	
HS Graduate	10 (21.3%)	20 (16.3%)	
Partial College	11 (23.4%)	38 (30.9%)	
College Graduate	14 (29.8%)	42 (34.1%)	
Graduate Training	9 (19.1%)	18 (14.6%)	
Primary Diagnosis			.304
Single Episode	35 (26.7%)	96 (73.3%)	
Recurrent	16 (30.8%)	36 (69.2%)	
Family History			16.72***
Depression	33 (21.9%)	118 (78.1%)	
No depression	18 (58.1%)	13 (41.9%)	
	<i>M (SD)</i>		<i>F</i>
Severity (CDRS-R)	58.25 (8.75)	57.13 (7.15)	.806
Functioning (CGAS)	51.55 (6.11)	52.09 (5.41)	.310
CE Duration (wk)	27.17 (22.80)	24.63 (21.33)	.510
CE Age of Onset	12.58 (2.73)	11.61 (2.76)	.778 ^a
Age of Onset of MDD	11.87 (2.69)	10.94 (2.85)	.024 ^a
Length of Illness (mo)	10.52 (8.82)	12.89 (16.19)	.999

Note. Subsets sharing a common subscript are not statistically different at $\alpha = .05$.

^a *F* value represents results of analysis of covariance, controlling for participants' current age. CE = Current Episode. * $p < .05$, ** $p < .01$, *** $p < .001$

Trauma History on Depressive Symptoms across Acute Treatment

Data from a total of 225 subjects in RR and RP were included in the following analysis. The change over time (Weeks 1, 2, 3, 4, 6, 8, 10, 12) in CDRS-R total score was compared between levels of trauma history (no trauma; trauma—no abuse; abuse) using a linear mixed model analysis of repeated measures. The model contained fixed effects terms for trauma history, time, and the interaction of trauma history by time. The intercept was included as a random effect. Baseline CDRS-R total score, age, gender, family history of depression, and total duration of depressive illness (in months) were included as covariates in the model. Restricted maximum likelihood estimation and Type III tests of fixed effects were used, with the Kenward-Roger correction (Kenward & Roger, 1997) applied to the spatial-power covariance structure for unequally-spaced repeated measures since CDRS-R scores were obtained every week through week 4 and bi-weekly weeks 6 through 12. Simple trauma group effects at each time period were also examined.

Results of the linear mixed model repeated measures analysis revealed a significant overall improvement in depressive symptoms (decrease in CDRS-R total scores) across the 12 weeks of treatment with fluoxetine (time effect, $p < .0001$). However, the main effect, interaction effect, and simple group effects of trauma history were not significant. Overall, across the entire 12 weeks, there were no significant differences between levels of trauma history (no trauma vs. trauma—no abuse vs. trauma—abuse) on the omnibus least squares mean CDRS-R Total scores [35.17 (SE=0.61) vs. 34.72 (SE=0.74) vs. 35.38 (SE=1.29), respectively, $F(2, 225) = 0.15, p = 0.8575$]. The trauma history by time

interaction effect also was non-significant, $F(14, 225) = 0.81, p = .6599$. Figure 5 displays adjusted least squares means of CDRS-R total score by week based on trauma history. Moreover, no significant (*post hoc*) simple trauma group effects emerged on the adjusted CDRS-R total scores at any subsequent week (p 's > 0.6019). See Table 10 for results of the best fitting model.

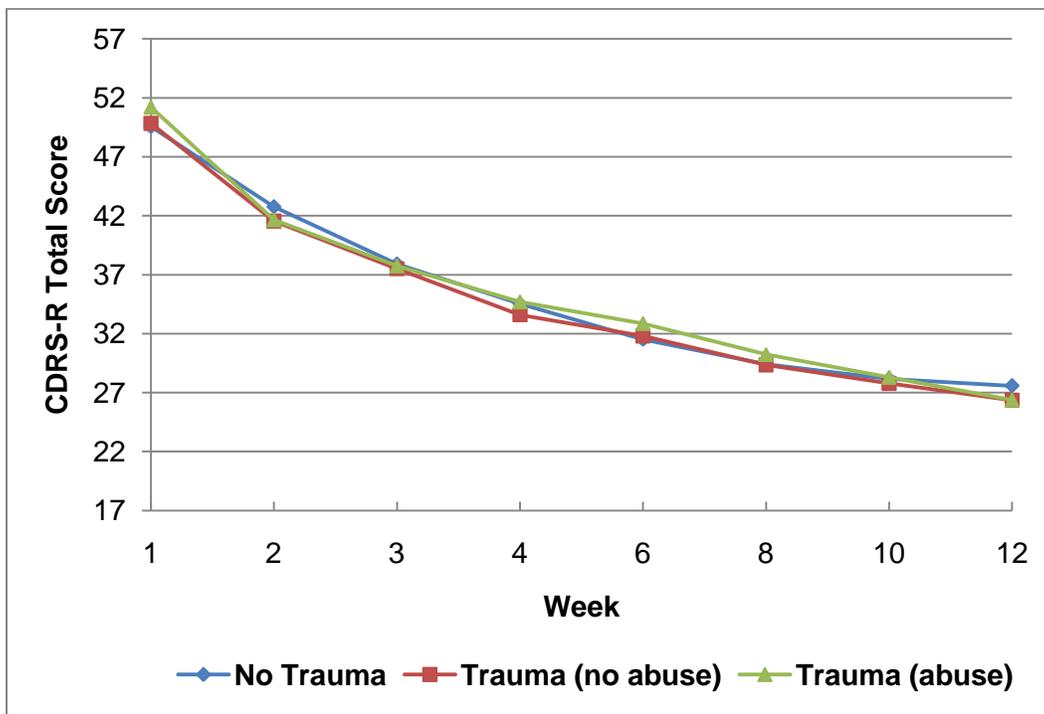


Figure 5. Plot of adjusted LS Means for CDRS-R total score across 12-week acute phase for each trauma group

Table 10

Linear Mixed Model Repeated Measures Analysis by Trauma History

Fixed Effects	Num df	Den df	F-value	p
Baseline Severity (CDRS-R)	1	206	65.68	< 0.0001
Age	1	197	16.98	< 0.0001
Gender	1	200	0.02	0.882
Family History of Depression	1	201	4.75	< 0.05
Length of Illness (months)	1	203	1.97	0.162
Trauma History	2	220	0.15	0.8575
Time (CDRS-R)	7	1072	131.66	< 0.0001
Trauma History*Time	14	1179	0.81	0.659

Abuse History on Depressive Symptoms across Acute Treatment

An additional linear mixed model analysis of repeated measures was computed to examine whether abuse history (no abuse, abuse) was associated with change over time (Weeks 1, 2, 3, 4, 6, 8, 10, 12) in CDRS-R total score. The model contained fixed effects terms for abuse history, time, and the interaction of abuse history by time. Covariates and model parameters remained the same as in the model described above. Results of the linear mixed model repeated measures analysis revealed a significant overall improvement in depressive symptoms (decrease in CDRS-R total scores) across the 12 weeks of treatment with fluoxetine (time effect, $p < .0001$). However, the main effect, interaction effect, and simple group effects of abuse history were not significant. Overall, across the entire 12 weeks, there were no significant differences between levels of abuse history (no abuse vs. abuse) on the omnibus least squares mean CDRS-R Total

scores [34.99 (SE=0.47) vs. 35.39 (SE=1.29), respectively, $F(1, 225) = 0.08$, $p = 0.7723$]. The abuse history by time interaction effect also was non-significant, $F(7, 225) = 0.69$, $p = .6775$. Figure 6 displays adjusted least squares means of CDRS-R total score by week based on abuse history. Moreover, no significant (*post hoc*) simple trauma group effects emerged on the adjusted CDRS-R total scores at any subsequent week (p 's > 0.4020). See Table 11 for results of the best fitting model.

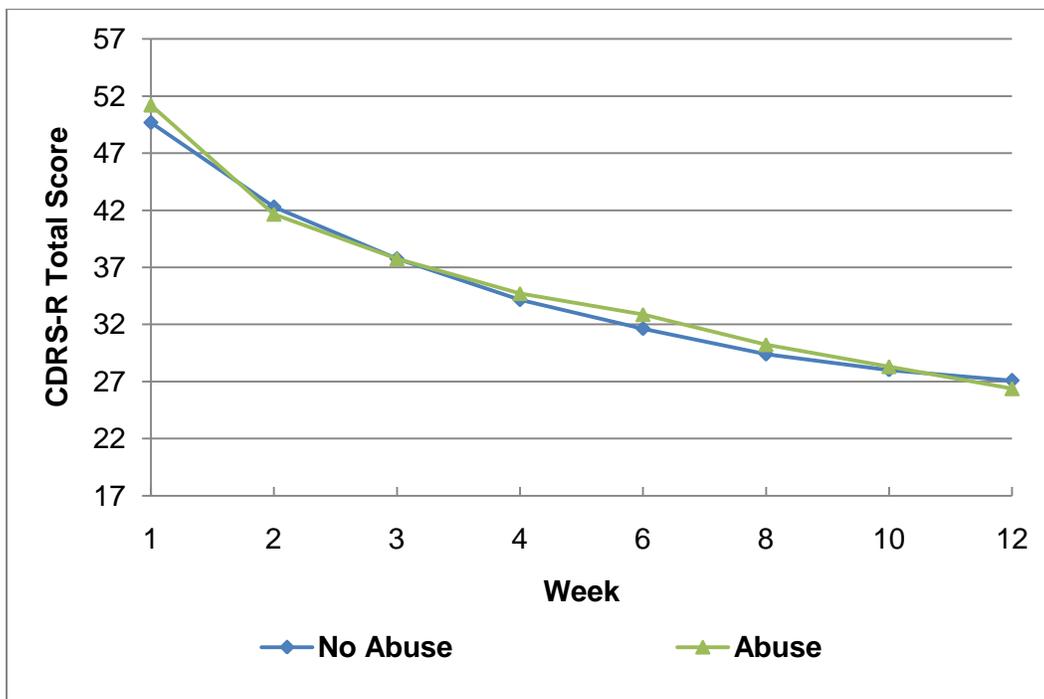


Figure 6. Plot of adjusted LS Means for CDRS-R total score across 12-week acute phase by abuse history

Table 11

Linear Mixed Model Repeated Measures Analysis by Abuse History

Fixed Effects	Num df	Den df	F-value	P
Baseline Severity (CDRS-R)	1	207	66.17	< 0.0001
Age	1	198	16.93	< 0.0001
Gender	1	201	0.02	0.8945
Family History of Depression	1	202	4.85	< 0.05
Length of Illness (months)	1	205	1.94	0.1656
Abuse History	1	222	0.08	0.7723
Time (CDRS-R)	7	1080	82.18	< 0.0001
Abuse History*Time	7	1080	0.69	0.6775

An additional linear mixed model repeated measures analysis was conducted to examine the interaction term for abuse history by family history of depression. The interaction effect for family history of depression and abuse history across time was not significant, $F(1, 221) = 1.88, p = .17$.

Trauma History on Remission Status

A logistic regression analysis was performed to assess prediction of remission status at the end of twelve weeks of acute treatment of MDD with fluoxetine, based on trauma history (no trauma; trauma—no abuse; abuse). Remission was defined as a CDRS-R total score of ≤ 28 and a CGI-Improvement score of 1 or 2. A simple model with trauma group as the predictor was not significant, $\chi^2(2, N = 181) = 3.938, p = 0.140$, indicating that trauma history was not a significant predictor of remission status at week 12.

To examine the effect of trauma history on remission status while accounting for other demographic and clinical characteristics on remission status, a logistic regression analysis was performed, including demographic (gender, age) and clinical characteristics (initial depression severity from baseline CDRS-R total score and family history of depression). Gender and initial depression severity were removed from the model because they did not have a significant effect on remission status. Age was a significant predictor of remission status when taken alone, $\chi^2(1, N = 181) = 6.307, p < 0.05$, with the odds of remission being 2.5 times more likely for children when compared to adolescents. A test of the full model with age, family history of depression, and trauma history was significant, $\chi^2(4, N = 181) = 20.593, p < 0.001$, indicating that the predictors as a set, reliably distinguished between participants who had remitted or not at week 12. Classification rates were 97.7% for remitted and 9.8% for not remitted, with an overall classification rate of 72.8%. Age was no longer significant in the full model. Trauma history also was not a significant predictor of remission status. In the full model, only family history of depression reliably predicted remission status. The odds of remission by week 12 are 3.25 times greater in youth with a positive family history of depression. Table 12 shows regression coefficients and chi-square tests of the variables of interest as well as odds ratios and the 95% confidence intervals around them, separated by models. Table 13 shows the relationship between remission status and the categorical predictors.

Table 12

Logistic Regression Analysis of Remission Status at Week 12 as a Function of Demographic, Clinical Characteristics and Trauma History

Variables	Model χ^2	p	B	S.E.	Wald	df	p	Exp (B)	95% CI	
									Lower	Upper
Trauma Group	3.938	.140			4.049	2	.132			
Trauma			-.125	.364	.118	1	.732	.883	.432	1.802
Abuse			-.989	.497	3.968	1	.046	.372	.140	.984
Demographic	6.811	< .05								
Age			.909	.369	60.62	1	< .05	2.481	1.204	5.114
Gender			-.046	.339	.019	1	.892	.955	.491	1.855
Clinical	15.523	< .001								
Baseline Severity (CDRS-R)			-.014	.022	.401	1	.527	.986	.944	1.030
Family Hx of Depression			1.319	.348	14.348	1	<.001	3.739	1.890	7.399
Full Model	20.593	< .001								
Age			.713	.392	3.299	1	0.069	2.040	.945	4.402
Family Hx of Depression			1.177	.356	10.944	1	<.001	3.245	1.616	6.518
Trauma Group					2.225	2	.329			
Trauma			.082	.396	.043	1	.836	1.085	.499	2.361
Abuse			-.705	.529	1.774	1	.183	.494	.175	1.394

Table 13

Remission Status at Week 12 as a Function of Age, Family History of Depression and Trauma History

	Remission Status—Week 12		Total <i>N</i>
	Not Remitted	Remitted	
Age			
Children	13 (17.8%) _a	60 (82.2%) _b	73
Adolescents	39 (35.1%) _a	72 (64.9%) _b	111
Family History of Depression			
No	28 (46.7%) _a	32 (53.3%) _b	60
Yes	23 (18.7%) _a	100 (81.3%) _b	123
Trauma History			
No Trauma	24 (25.3%) _a	71 (74.7%) _a	95
Trauma—No Abuse	18 (27.7%) _a	47 (72.3%) _a	65
Abuse	10 (47.6%) _a	11 (52.4%) _b	21
Total	52 (28.3%)	132 (71.7%)	184

Note. Each subscript letter denotes a subset of remission categories whose proportions do not differ significantly from each other at the 0.05 level.

Abuse History on Remission Status

While there were no differences in the three levels of trauma history, examination of the crosstabulations of trauma history and remission status indicated that abuse history may be associated with lower remission rates at Week 12. To examine this further, a logistic regression examining the effect of abuse history (abuse vs. no abuse) on remission at week 12 was significant, $\chi^2(1, N = 181) = 3.821, p = 0.05$, when compared to a constant-only model. Abuse history predicted remission status, $\chi^2(1, N = 181) = 3.940, p < 0.05$, odds ratio = 2.55. This indicates that a participant with no abuse history is 2.55 times more likely to have remitted at the end of acute treatment.

To account for other demographic and clinical characteristics on remission status, a logistic regression analysis was performed, including age (child vs. adolescent) and family history of depression; gender and baseline severity of depression were excluded because they did not contribute to the model as previously shown. A test of the full model with age, family history of depression, and history of abuse was significant, $\chi^2(3, N = 180) = 20.550, p < 0.001$, indicating that the predictors as a set, reliably distinguished between participants who had remitted or not at week 12. However, in the full model, only family history of depression remained a significant predictor of remission status; age and abuse history were no longer significant. Table 14 shows regression coefficients and chi-square tests of the variables of interest as well as odds ratios and the 95% confidence intervals around them.

Table 14

Logistic Regression Analysis of Remission Status at Week 12 as a Function of Demographic, Clinical Characteristics and Abuse History

Variables	Model χ^2	p	B	S.E.	Wald	df	P	Exp (B)	95% CI	
									Lower	Upper
Model 1	3.821	= .05								
Abuse History			.938	.472	3.940	1	< .05	2.554	1.012	6.447
Model 2	20.550	< .001								
Age			.695	.383	3.294	1	.070	2.005	.946	4.248
Family Hx of Depression			1.179	.356	10.976	1	<.001	3.251	1.618	6.529
Abuse History			.740	.501	2.186	1	.139	2.097	.786	5.595

Impact of Trauma History on Time to Remission

To assess the relationship between trauma history and time to remission after adjusting for the effects of other covariates, including age, gender, family history of depression, and baseline severity of depression (CDRS-R), a Cox regression survival analysis was performed. A total of 225 cases were included in the analysis, 9 were lost due to missing values. Survival time was fairly well predicted by the set of covariates, including age, gender, family history of depression, baseline severity of depression, and trauma history, $\chi^2(3, N = 225) = 23.124, p = < 0.001$. Table 15 shows regression coefficients, degrees of freedom, p values, and hazard ratios for each covariate. However, there was no statistically significant effect of trauma history (no trauma, trauma—no abuse, abuse) after adjusting for the covariates, $\chi^2(2, N = 225) = 0.094, p = .954$. Figure 7 illustrates cumulative survival proportions by trauma history. Age and family history of depression reliably predicted survival time at $\alpha = 0.05$. See Figure 8 for graphical display of cumulative survival based on participants' family history of depression. Youth with a positive family history of depression experienced a shorter time to remission (hazard ratio = 1.527). Additionally, each year in age of youth decreased the likelihood of remission (hazard ratio = 0.912). Earlier time to remission is associated with younger age and a positive family history of depression, but is not associated with initial depression severity or trauma history.

Table 15

Cox Regression Analysis of Trauma History and Covariates on Time to Remission

Covariate	<i>B</i>	<i>S.E.</i>	<i>Wald</i> χ^2	<i>df</i>	<i>P</i>	Hazard Ratio	95% CI for Exp(<i>B</i>)	
							Lower	Upper
Age	-.092	.030	9.416	1	< 0.01	0.912	.860	.967
Gender	.052	.166	.097	1	.755	1.053	.761	1.458
Family History of Depression	.423	.187	5.106	1	< 0.05	1.527	1.058	2.204
Baseline Severity	-.017	.011	2.559	1	.110	.983	.963	1.004
Trauma History			.093	2	.954			
Trauma vs. none	-.043	.174	.061	1	.806	.958	.682	1.347
Abuse vs. none	-.064	.264	.059	1	.809	.938	.559	1.573

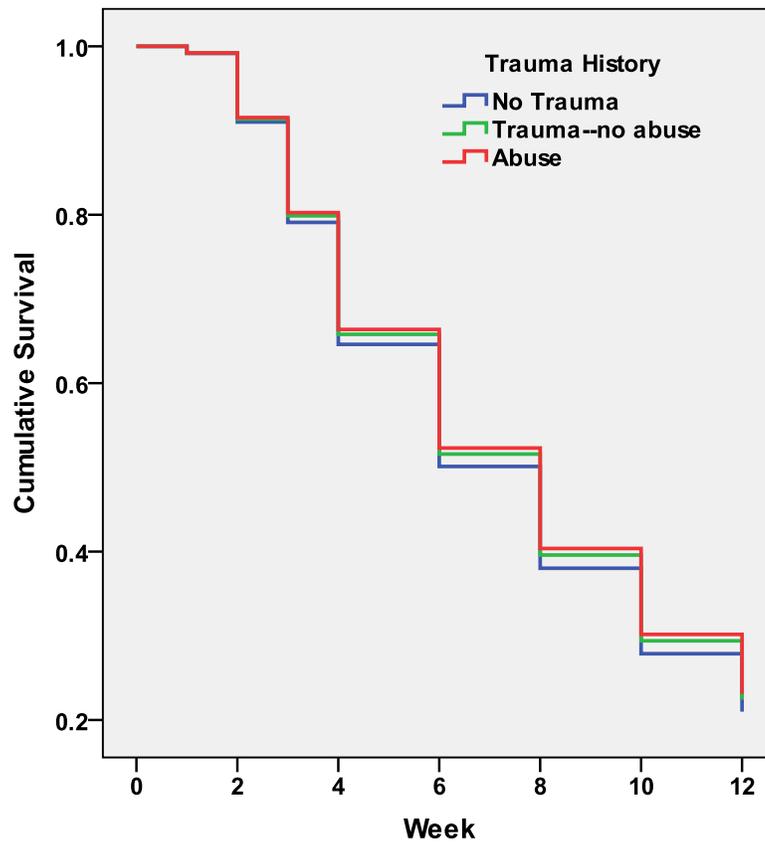


Figure 7. Survival Curve across 12 weeks acute treatment by Trauma History

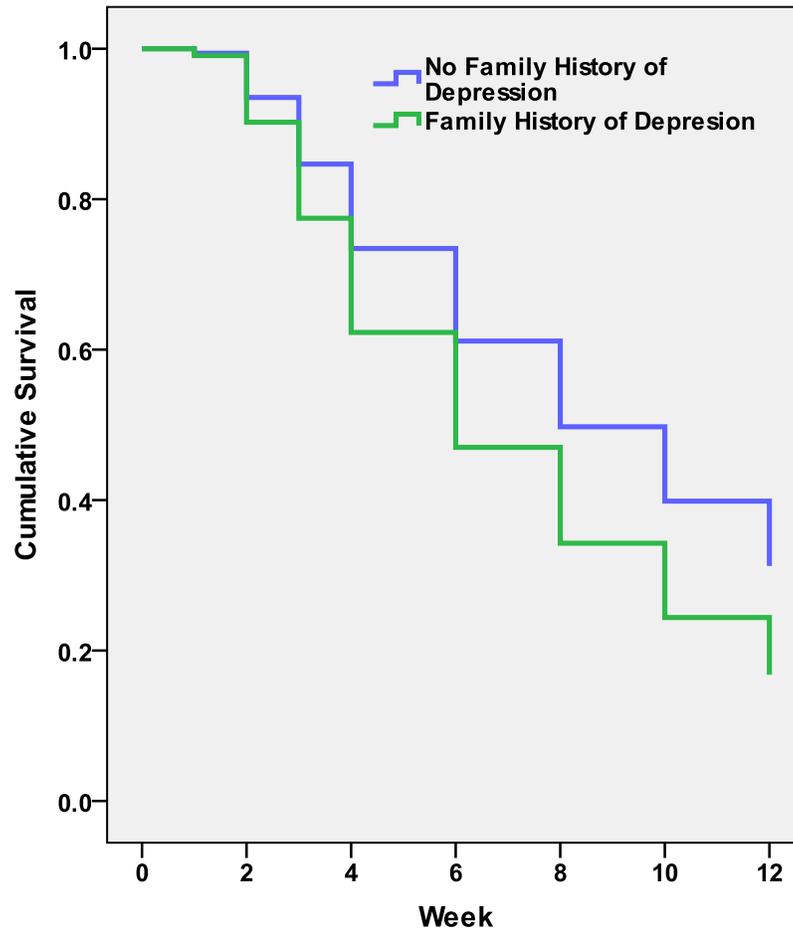


Figure 8. Survival Curve across 12 weeks acute treatment by first-degree Family History of Depression

CHAPTER FIVE

Conclusions and Recommendations

TRAUMA HISTORY AND DEPRESSION

Demographic and Clinical Characteristics

Children and adolescents were identified as either having a history of abuse, defined as physical or sexual abuse or both, a history of witnessing or experiencing another traumatic event, or no history of trauma. A history of trauma in general, excluding physical or sexual abuse, was not associated with any differences in baseline demographic or clinical characteristics of youth's depression; however, a history of abuse was associated with older age (adolescents versus children), later age at onset, longer length of current depressive episode, and suicidality at baseline. As expected, youth with a history of abuse were significantly more likely to meet criteria for a diagnosis of PTSD.

No gender differences were observed among youth reporting trauma or abuse history, which is consistent with other studies of trauma in youth (Barbe et al., 2004; Shamseddeen et al., 2011). While studies have shown that females are at greater risk of sexual abuse (Klein et al., 2009), males may be at greater risk of physical abuse and other types of trauma (Lewis et al., 2010; Shamseddeen et al., 2011). Our measure of abuse included both sexual and physical, which may explain why differences in gender were not observed based on trauma group. Additionally, as predicted, trauma history was not associated with differences in ethnicity or parents' highest level of education (an estimate of SES).

Age was associated with trauma history, with abuse history being more common among older youth in the study. Other studies of trauma in youth (TORDIA, TADS) have found no association between age and trauma history; however, these studies only included adolescents (Lewis et al., 2010; Shamseddeen et al., 2011). This is one of the first studies to include both children and adolescents. Our finding that trauma history is associated with older age may be a function of age itself, as older youth would have more occasions to have witnessed or experienced a significant traumatic event than children.

Additionally, trauma history was associated with an older age of onset of the depressive illness. When studying adults with depression, abuse and trauma history has been a consistent, significant predictor of an earlier age of onset of the depressive illness (Bernet & Stein, 1999; Kessler, 1997; Klein et al., 2009; Miniati et al., 2009; Young et al., 1997). This is likely due to the fact that the incidence of abuse or trauma may have occurred when these individuals were children or adolescents themselves and subsequently contributed to the development of a depressive disorder. We would expect to find a different association between age and onset when examining these individuals as youth. It is important to note that the age of onset of the depressive illness was not significant after controlling for participants' age.

Abuse history was also associated with a longer length of the present depressive episode, which may indicate a more chronic form of depression. This finding is supported from several studies among adults (Bernet & Stein, 1999; Brown & Moran, 1994; Klein et al., 2009; Miniati et al., 2009; Zlotnick et al., 2001), but has not previously been reported

among adolescents. Previous studies have linked chronicity to poor treatment response (Fournier et al., 2009). This suggests that individuals with a more chronic depressive course related to the experience of significant adversity may experience greater difficulty achieving remission.

While we expected youth with a history of trauma or abuse to exhibit higher severity of depressive symptoms prior to treatment, given significant associations found in the adult literature (Klein et al., 2009; Muscatell et al., 2009), no differences were found in the clinician-rated CDRS-R or in the consensus CGI-severity scores at baseline between the levels of trauma history. This finding is consistent with some studies of adversity and depression in adults (Miniati et al., 2009) and adolescents (Barbe et al., 2004; Lewis et al., 2010; Shamseddeen et al., 2011). Lewis et al. noted that adolescents in TADS with trauma, physical abuse, sexual abuse, or no trauma histories did not differ from one another on the CDRS-R (clinician-rated) measure of depression at baseline, but did differ on a self-reported measure of depression.

In concordance with the literature from both adult and adolescent studies of depression and abuse, we found that abuse history was associated with a greater indication of suicidal ideation and behavior at baseline. Suicidal ideation, attempts, and self-injurious behavior have been consistently linked to individuals' experience of trauma, especially emotional and sexual abuse (Sarchiapone et al., 2007; Klein et al., 2009; Brown et al., 1999; Lewis et al., 2010; Brent et al., 2009). In the current study, we found that abuse history, but not other traumatic events, was associated with more severe indication of

suicidal ideation, thoughts, or behaviors, when compared to individuals with no trauma history.

Trauma history was not associated with any other clinical characteristics of depression, including number of comorbid diagnoses identified, recurrence of depression, length of total depressive illness, or positive first-degree family history of depression.

Symptom Specificity

We found some differences in youth's initial depressive symptom profile at baseline by examining mean scores obtained on the five factors of the CDRS-R as outlined by Guo et al., 2009. While some reports among adults have indicated a relationship between severe life events and increased somatic and neurovegetative symptoms (Muscatell et al., 2009; Miniati et al., 2009), there were no differences observed in somatic symptoms based on trauma history in our sample of youth. Children with a history of abuse were more likely to report symptoms consistent with anhedonia, including social withdrawal and capacity to have fun. Based on previous findings, we expected youth with a history of trauma to identify more cognitive-affective symptoms of depression, including depressed mood, low self esteem, and suicidal ideation (Monroe et al., 2001; Harkness & Stewart, 2009). No differences were observed in youth's report of depressed mood; however, children with a history of abuse or trauma obtained lower scores on clinician's observation of their depressed mood. This finding was not observed among adolescents. Children with a history of abuse also obtained significantly lower scores on measures of morbid and suicidal ideation, as opposed to adolescents. The experience of traumatic

events often leads to withdrawal and avoidance (increased anhedonia) in combination with hypervigilance and anxiety. This hypervigilance may impact the child's interactions with clinicians, such that they appear less depressed. Children with an abuse history may also be more hesitant to identify or report morbid or suicidal thoughts, which could be related to attempts to not expose the severity of their condition. To our knowledge, symptom profiles have not previously been observed among youth with a history of trauma.

TRAUMA HISTORY AND ACUTE TREATMENT

The primary hypothesis that trauma history would impact youth's response to acute phase treatment with fluoxetine was partially supported. Youth who experienced a traumatic event, but no abuse, did not differ from youth with no trauma history in their rate of remission at the end of acute treatment. However, when youth with a history of abuse were compared to those without abuse, differences were observed in remission rates at the end of acute treatment. Individuals with a history of abuse, defined as physical or sexual abuse or the combination, were less likely to have remitted by Week 12 of acute treatment with fluoxetine. When controlling for age and family history of depression, this effect was no longer significant at the end of acute treatment. Odds ratios indicated that youth without a history of abuse were approximately twice as likely to achieve remission following acute treatment with fluoxetine, when compared to youth with a history of abuse.

The most robust predictor of remission following 12 weeks of acute treatment with fluoxetine was the indication of a positive first-degree family history of depression. Family history remained a significant predictor when controlling for other demographic and clinical characteristics. Youths with a positive family history of depression were approximately three times more likely to have achieved remission at the end of acute treatment when compared to those without a family history of depression. Additionally, family history of depression was associated with a quicker time to achieve remission. This finding was previously examined by looking at the sample from the Childhood Depression: Relapse and Remission study ($n = 168$; Tao et al., 2009). The authors suggested that family history may be an indication of a more “biological depression” that responds more favorably to medication treatment (Tao et al., 2009). It follows that individuals without a family history of depression may have a different etiology, such as environmental stressors, that responds less favorably to a biological treatment (antidepressant medication). These individuals may benefit from other forms of depression treatment, such as psychotherapy, that are able to focus more specifically on assisting youth develop coping and problem solving skills to better manage their environment and stressors. It is important to note that other researchers have consistently found an increased risk for psychopathology among children of depressed mothers (Wickramaratne, et al., 2011). In addition, children of mothers who receive treatment and achieve remission of their depression are likely to experience improvement themselves.

Additional analyses examined the hypothesis that youth reporting a history of trauma or abuse would differ in their responsiveness to fluoxetine throughout the acute phase. We expected that youth with a history of trauma or abuse might take longer to evidence a reduction in their depressive symptoms when compared to those without a trauma history, as previously found in adults (Klein et al., 2009; Miniati et al., 2009). A linear mixed model analysis of repeated measures was conducted to examine youth's depressive symptoms as measured by the CDRS-R at each week of acute treatment. Youth with or without a history of trauma or abuse experienced a similar reduction in their depressive symptoms across the acute phase. Youth's time to achieve remission of their current depressive episode was also examined by computing a survival analysis. When controlling for other factors, including age and family history of depression, youth with a history of trauma or abuse did not differ from the rest of the sample in the number of weeks it took to achieve remission on fluoxetine. Taken together, these findings indicate that trauma history may not impact the amount of time it takes for youth to respond to the medication treatment or achieve remission. This contrasts some findings from the adult literature (Klein et al., 2009; Miniati et al., 2009); however, no known studies among youth have examined the effect of trauma history on time to achieve response or remission with medication treatment.

LIMITATIONS OF STUDY

The above discussion should be considered within the context of the study's limitations. The current study was conducted through secondary data analyses; thus, no modifications to the methods or study procedures were made. The primary focus of the three studies

pooled for analysis was to evaluate the effectiveness of continuation-phase antidepressant medication and cognitive behavioral therapy in treating MDD and preventing relapse among children and adolescents. While the overall sample size in the current study was adequate to assess the primary findings of interest, the studies were not originally designed to examine the impact of youth's traumatic history on the nature of their depression or their response to antidepressant treatment. As a result, the number of individuals with a history of abuse was relatively small. The level of significance identified in some of the primary analyses may be reflective of a lack of power to detect these differences, especially when groups were further differentiated by age, gender, and other baseline characteristics.

Youth's experience of traumatic events was obtained through the PTSD portion of the K-SADS-PL, a structured interview completed by a licensed mental health professional at the initial visit. This interview includes both the child and the parent and asks questions regarding the experience of traumatic events and subsequent reactions and symptoms in order to make the diagnosis of PTSD. However, more detailed information regarding the youth's experience of trauma, including the age at which the traumatic event occurred, severity of the impact, duration and frequency of the trauma, and other factors that might be relevant in understanding the impact on youth (relationship to perpetrator in abuse) was not obtained. Many of these factors have been identified as important considerations in understanding the relationship between trauma and psychopathology (Pine & Cohen, 2002). Although this measure is limited in the information it provides regarding traumatic events, its use is consistent with the other recent studies of trauma in depressed

youth, including TORDIA and TADS (Asarnow et al., 2009; Lewis et al., 2010; Shamseddeen, 2011).

In addition, the percentage of depressed adolescents reporting the experience of abuse was small in the current sample. This may be reflective of recruitment strategies and characteristics of the clinical population at this site. Other sites may be more likely to obtain youth's with more significant and severe abuse histories that may be more likely to impact their development and treatment of depression. Given the limited assessment of trauma, it is unclear the extent to which abuse experiences impacted the youth in this study.

Other important forms of adversity that have been associated with the development of depression and differential treatment response were not assessed, in particular, emotional abuse and neglect (Gibb et al., 2003; Miniati et al., 2009; Sarchiaphone et al., 2007). Additionally, within the trauma and abuse categories, there may be wide variability in the nature, duration, and impact of the event(s) on the youth that could not be accounted for in the current study. For example, parental loss has been identified as an important stressful life event associated with psychopathology (Nemeroff et al., 2003). While some individuals with significant loss may have been included in the trauma group under the category of "confronted with traumatic news," these individuals may differ in important ways from individuals who experienced other types of trauma. Evaluators assessed for the presence of trauma only once—at the baseline visit prior to the participant entering

the study. Thus, the data does not include measures of traumatic events that may have occurred throughout the course of the study.

Additionally, previous research supports the separation of individuals experiencing abuse from those experiencing other forms of trauma. Furthermore, recent studies that have examined the effects of abuse on differential treatment response in adolescents with depression have found that physical and sexual abuse may have different effects on treatment response (Lewis et al, 2010; Shamseddeen et al., 2011). It is important to note that the abuse group in the current study includes youth presenting with either physical abuse or sexual abuse or their combination. While abuse was found to be a significant moderator of treatment response in the TORDIA study, further examination of individuals classified as having a history of abuse revealed that only those with physical abuse experienced a significant differential response to the treatments offered (medication monotherapy versus combination therapy). Thus, it's possible that the abuse category identified in the current study is made up of individuals with different forms of abuse that affect the individual's response to acute medication treatment in different ways. Small sample sizes prevent us from further breaking down the abuse category to examine these relationships.

CONCLUSIONS

The experience of traumatic events in general, not including abuse, does not appear to impact youth's depression; however, abuse history was found to be associated with youth's initial depressive presentation and remission rates following acute treatment with

fluoxetine. Older youth are more likely to have experienced trauma or abuse. These youth also demonstrated an older age of onset of the depressive illness, which suggests that the current depressive episode may be related in some way to their experience of trauma or abuse. In addition, youth identifying a history of abuse may present with a more chronic depressive episode and report more significant suicidal ideation and behavior. Previous research has noted that later age of onset (adolescence) and suicidal ideation are associated with increased rates of recurrence (Lewinsohn et al., 1998). Thus, in addition to being less likely to achieve remission, the impact of abuse on youth's clinical depressive presentation may also influence their likelihood to experience a recurrence. Children who reported an abuse history obtained lower scores on measures of observed depressed mood and morbid ideation, and higher scores on anhedonia. Abuse may impact children's depressive presentation such that they present as less depressed. No differences were observed in symptom pattern among adolescents.

Over the course of acute treatment with fluoxetine, a history of experiencing traumatic events or abuse does not appear to influence the individual's decline in depressive symptoms or time to achieve remission. However, abuse history may be associated with poorer remission rates at the end of acute treatment. It appears that this effect does not remain when youth's age and first-degree family history of depression are considered, as these factors are stronger predictors of remission following acute medication treatment. This may be at least partially accounted for by small sample sizes and variability within the abuse category. Previous studies among youth have not reported a relationship between trauma history and response to acute medication treatment; however, a few

recent studies have examined whether trauma history may moderate treatment response. In general, these studies have found that physical and sexual abuse may be related to poorer response when treated with CBT or combination therapy as opposed to medication alone (Lewis et al., 2010; Shamseddeen et al., 2011). Preliminary results from the current study, in combination with recent comparative studies of depression treatment in youth, indicate that youth with a history of abuse may experience greater difficulty achieving an adequate clinical response or remission of their depressive episode, when treated with medication, psychotherapy, or their combination. The most effective treatment may depend on the type of abuse experienced.

CLINICAL IMPLICATIONS

One of the primary objectives outlined by the NIMH calls for a better understanding of individual variation in treatment response based on various demographic, biological, and environmental factors (2008). Knowledge of an individual's experience of significant traumatic events, especially abuse, may influence clinician's considerations of their depressive presentation and treatment in the following manner. Children who present with a positive abuse history may present with more pronounced symptoms of anhedonia, yet appear to be less depressed. This symptom pattern may be related to the child's experience of abuse and reflective of the symptoms of avoidance and hypervigilance common following abuse. Individuals who appear to be less depressed may influence clinician's thought processes when making decisions regarding appropriate treatment, including medication dosing. Thus, abuse history should be an important consideration when assessing depression, particularly among younger children.

Given the relationship between abuse history and longer length of the youth's current depressive episode, these individuals may experience a more chronic course that is less responsive to treatment. Chronicity of depressive episodes among youth with a history of abuse may be related to poor or failed response to treatments or simply representative of a more severe course that was present prior to receiving any treatment. Chronicity, by definition, is associated with lower remission rates and may require a more aggressive or prolonged treatment regimen to achieve remission. Close examination of the youth's current depression, especially with regard to length and previous attempts made by youth to improve mood should be considered. These factors may impact clinician's decision making with regard to treatment and course.

Suicidal ideation and behavior are also more likely among children and adolescents reporting a history of abuse. While all depressed youth should be thoroughly screened and routinely followed with regard to morbid and suicidal ideation, self-injurious behavior, and suicidal behavior, clinicians should be more vigilant in the assessment of suicide among youth with a history of abuse. Other authors have noted that when treating individuals with suicidal ideation and behavior, a thorough assessment of the youth's trauma history and determination of the most appropriate treatment are imperative (Brent et al., 2009). These youth are more likely to experience an additional suicide event, thus additional suicide-specific treatments may be indicated in helping reduce risk (safety planning, instilling hope, etc.).

While this study only provided preliminary indication that abuse history may be associated with lower remission rates following acute treatment with fluoxetine, this finding might still be an important consideration for clinicians to consider when treating youth. Previous studies have indicated that early response to antidepressant medication, by about four to six weeks of acute treatment, is a strong predictor of remission (Tao et al., 2009). Thus, individuals with one or more factors associated with a low likelihood to remit, including positive first-degree family history of depression, abuse history, or poor response after six weeks of acute treatment, may benefit from a treatment augmentation or switch (medication and/or psychotherapy) earlier on in the acute phase.

In summary, clinicians treating youth with MDD would benefit from thoroughly examining youth's history of experiencing significant traumatic events, especially physical and/or sexual abuse. The experience of abuse may lead to a more chronic course associated with suicidal ideation, and may be more common among adolescents.

Additionally, abuse history may be one factor associated with lower remission rates at the end of acute treatment with fluoxetine, especially among adolescents. A recent practice parameter supports this suggestion, noting that the close assessment of abuse and other environmental stressors should be included in the clinical assessment of depression in youth (Birmaher et al., 2007). Given the known connection between both biological and environmental stressors in the development of depression, thorough assessment of such factors may assist clinicians in making informed treatment decisions.

FUTURE DIRECTIONS

In future studies of depression among youth, the inclusion of a more comprehensive measure of youth's trauma history may assist researchers in gaining a better understanding of the relationship between trauma history and depression. Additionally, other environmental stressors and significant life events, such as parental loss, divorce, neglect, family illness, among others, may also contribute to youth's development of depression and subsequently impact treatment response.

Two primary theories have been postulated to help explain the relationship between the experience of traumatic events and the development of depression. Scientists have noted that early childhood maltreatment may lead to specific and lasting neurophysiological changes in the brain, especially with regard to the stress response system, that may directly impact individual's risk for developing psychopathology (Nemeroff, 2004; Heim & Nemeroff, 2001). These changes may include sensitization of neuroendocrine and autonomic responses to stress, increased release of cortisol, and decreased hippocampal volume (Heim, Newport, Mletzko, Miller, & Nemeroff, 2008). Additionally, genetic vulnerability may play an important role in determining which abused children are likely to become depressed (Kaufman et al., 2006). Individuals with particular genetic vulnerabilities who sustain neurobiological changes as the result of abuse, may be more prone to exhibiting a heightened emotional response and experiencing significant symptoms of anxiety or depression in response to stress. First-degree family history of depression has been associated with remission rates in acute treatment of depression with fluoxetine, but more specific biological markers have not been clearly studied among

youth treated with antidepressant medication (Tao et al., 2009). Thorough assessment of relevant biological markers may provide a clearer picture of those individuals with a biological predisposition to depression that might respond more favorably to medication treatment. However, youth's experience of trauma may directly impact or interact with particular biological markers, as suggested by the literature; thus, trauma history should be thoroughly assessed.

Alternatively, early experiences of trauma may produce lasting changes in cognition, which then leads to increased risk of experiencing a major depressive episode. Cognitive style has been shown to mediate the relationship between childhood maltreatment and depression (Gibb et al., 2001). The experience of early adversity may sensitize individuals to stress, such that the individual is more likely to experience symptoms of depression in response to even low levels of stress (Hammen et al., 2000). Thus, in determining whether a history of trauma may be associated with changes in cognition that contribute to the development of depression or impact youth's response to depression treatment, it may be important to include more specific measures of youth's cognitive style. In summary, a more comprehensive assessment of potential links to etiology of depression in youth, including occurrence of environmental stressors, reports of youth's cognitive style, and relevant biological markers, may further elucidate the relationship between traumatic experiences and the course and treatment of depression in youth. In addition, several studies among youth have examined the relationship between abuse or trauma history and differential treatment response, including response to pharmacotherapy, CBT, and combination treatment (Asarnow et al., 2009; Lewis et al.,

2010; Shamseddeen et al., 2011). In future studies examining whether a history of trauma or abuse moderates treatment response, it may be helpful to examine the potential interaction of other biological markers and youth's cognitive style to assist in understanding these relationships.

While continuation treatment is recommended for all youth (Brent et al., 2007), it may be especially important for youth with a history of trauma or abuse. Given known relationships in the literature between remission, residual symptoms, and relapse, (Kennard et al., 2006), abuse history may also be one factor associated with an increased risk for relapse and recurrence. To date, no known studies have examined whether trauma history moderates treatment response during the continuation phase. Initial evidence suggests that youth with a history of abuse are less likely to respond to acute phase treatment with fluoxetine (as partially indicated in the current study), CBT (Lewis et al., 2010), or combination treatment (Asarnow et al., 2009; Shamseddeen et al., 2011). Thus, youth with a significant abuse history may require closely monitored continuation treatment or a trauma-specific therapy in order to achieve full remission and prevent relapse. Future studies may be able to determine the most effective treatment type and length to assist youth with a history of abuse in achieving recovery of their depression.

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