Childhood Maltreatment and Differential Treatment Response and Recurrence in Adult Major Depressive Disorder

Kate L. Harkness
Queen’s University

R. Michael Bagby
University of Toronto

Sidney H. Kennedy
University Health Network and University of Toronto

Objective: A substantial number of patients with major depressive disorder (MDD) do not respond to treatment, and recurrence rates remain high. The purpose of this study was to examine a history of severe childhood abuse as a moderator of response following a 16-week acute treatment trial, and of recurrence over a 12-month follow-up. Method: Participants included 203 adult outpatients with MDD (129 women; age 18–60). The design was a 16-week single-center randomized, open label trial of interpersonal psychotherapy, cognitive-behavioral therapy, or antidepressant medication, with a 12-month naturalistic follow-up, conducted at a university psychiatry center in Canada. The main outcome measure was Hamilton Depression Rating Scale scores at treatment end point. Childhood maltreatment was assessed at the completion of treatment using an interview-based contextual measure of childhood physical, sexual, and emotional abuse. Multiple imputation was adopted to estimate missing values. Results: Patients with severe maltreatment were significantly less likely to respond to interpersonal psychotherapy than to cognitive-behavioral therapy or medication (OR = 3.61), whereas no differences among treatments were found in those with no history of maltreatment (ORs < 1.50). Furthermore, maltreatment significantly predicted a shorter time to recurrence over follow-up across treatment conditions (OR = 3.04). These findings were replicated in the sample with complete case data. Conclusions: Patients with a history of childhood abuse may benefit more from antidepressant medication or cognitive-behavioral therapy than from interpersonal psychotherapy. However, these patients remain vulnerable to recurrence regardless of treatment modality.

Keywords: major depression, childhood maltreatment, treatment response, recurrence

Cognitive-behavioral therapy (CBT), interpersonal psychotherapy (IPT), and antidepressant medication (ADM) have shown superior efficacy compared with placebo in several randomized controlled trials of unipolar major depressive disorder (MDD; e.g., DeRubeis, Gelfand, Tang, & Simons, 1999; Dobson, 1989; Elkin et al., 1989; Frank et al., 2000, 1990; Thase et al., 1997). A review of six trials comparing these modalities in intent-to-treat analyses yielded a mean response rate of 47.9% for psychotherapy (primarily CBT and IPT) and 46.2% for ADM, compared with a 27.7% placebo response (Casacalenda, Perry, & Looper, 2002).

Despite the significant advantage of CBT, IPT, and ADM over placebo, many patients with MDD do not respond to treatment, and recurrence rates remain high. Treatment nonresponse is associated with a longer duration of illness and higher levels of impairment (Petersen et al., 2004). Therefore, research that identifies reliable moderators of treatment response has the potential to prevent a life-long pattern of illness. A history of childhood maltreatment is strongly related to prognostic indicators such as depression severity (Harkness & Monroe, 2002), recurrence (Kessler & Magee, 1993), and comorbidity (e.g., Harkness & Wildes, 2002). Furthermore, it predicts a negative cognitive style (e.g., Gibb, 2002; Lumley & Harkness, 2007), disturbed interpersonal functioning (e.g., DiLillo, 2001), and altered neuromodulator function (e.g., Heim & Nemeroff, 2001), which are related to the hypothesized mechanisms of action of CBT, IPT, and ADM, respectively.

Childhood Maltreatment and Response to Treatment

There have been only a few published trials in which researchers have examined the effect of a childhood maltreatment history on treatment response in MDD. One of the first was conducted in the context of a large multisite randomized trial of Cognitive Behavioral Analysis System of Psychotherapy (CBASP), nefazodone, and their combination in 681 outpatients diagnosed with chronic depression (Nemeroff et al., 2003). Among those with early parental loss, physical abuse, sexual abuse, or neglect, CBASP alone...
had a higher response rate in comparison to nefazodone alone. In addition, in contrast to the efficacy results in the full sample (Keller et al., 2000), the combination of CBASP and nefazodone was only marginally superior to CBASP alone. The researchers speculated that CBASP may have provided maltreated patients with the skills necessary to function better in their interpersonal relationships. Medication, in contrast, clearly can only address issues of depression symptom severity.

Childhood maltreatment as a moderator of treatment response was also examined in three multisite randomized trials of adolescent depression. First was a trial that randomized depressed adolescents to systemic behavioral family therapy (SBFT), CBT, or nondirective supportive therapy (NDST). In the full sample, those in the CBT group were more likely to respond than those in the SBFT or NDST groups (Birmaher et al., 2000). However, among those with childhood maltreatment, response in CBT was no greater than in NDST (Barbe, Bridge, Birmaher, Kolko, & Brent, 2004). Second, in the Treatment of SSRl-Resistant Depression in Adolescents (TORDIA) trial, Asarnow et al. (2009) reported that adding CBT to medication yielded no benefit over medication alone among maltreated adolescents. In contrast, combined CBT + medication was associated with higher levels of response than the medication-alone group in the adolescents with no history of maltreatment. Similarly, in the Treatment of Adolescent Depression Study (TADS), Lewis et al. (2010) reported that adolescents with a history of maltreatment responded better to fluoxetine, or to the combination of fluoxetine and CBT, than to CBT alone. Indeed, the abused adolescents in the CBT arm failed to respond any better than those in the placebo condition. The results of these three trials in adolescents suggest that childhood maltreatment predicts poorer response to CBT.

Reasons for the discrepancy between the findings of Nemeroff et al. (2003) and those of the Birmaher et al. (2000), TADS, and TORDIA trials are likely complex. For example, adolescents may not yet possess the requisite emotional and cognitive skill to work through their trauma in psychotherapy, thereby accounting for the poor performance of CBT in these studies. Furthermore, childhood maltreatment is more proximal in time in the adolescent samples versus the adults in the CBASP trial who were reporting on adversities that may have occurred decades previously. Furthermore, in the TADS study, CBT excluded exposure techniques that may have been useful in adolescents with trauma. In addition, Lewis et al. (2010) note that CBT, which typically focuses heavily on psychoeducation, may not have provided the interpersonal content important in addressing abuse issues. In contrast, CBASP, conceptualized as a combination of CBT and IPT, may be more relevant for patients with a history of childhood trauma. In the present study, we attempt to address these inconsistencies by examining childhood maltreatment as a moderator of response to CBT, IPT, and ADM in an adult sample.

**Childhood Maltreatment and Depression Relapse and Recurrence**

In epidemiological studies of risk for depression over the life course, a history of childhood abuse has been found to strongly predict MDD onset (e.g., Kendler, Gardner, & Prescott, 2002; Kessler & Magee, 1994). However, more fine-grained analyses suggest that childhood maltreatment confers greater risk for a first onset of depression than for subsequent recurrences (e.g., Kessler & Magee, 1994). These studies focus on the etiological role of childhood maltreatment in new onsets of disorder over the naturalistic course of the syndrome. No study, to our knowledge, has examined the effect of childhood maltreatment in predicting MDD recurrences following successful treatment. This is a particularly germane question because it would suggest a basis upon which to differentially assign individuals to the therapies that have the greatest chance of keeping them well over the long term.

Research across several randomized controlled trials has demonstrated the superiority of CBT and IPT over ADM in preventing the relapse and recurrence of MDD over follow-up periods of 12–24 months (e.g., Dobson et al., 2008; Evans et al., 1992; Frank et al., 2000, 1990; Hollon et al., 2005; Shea et al., 1992; Simons, Murphy, Levine, & Wetzel, 1986). This effect may be attributable, at least in part, to (a) a lack of adherence to ongoing use of ADM over follow-up in those who were assigned to ADM (e.g., Melfi, Chawla, Croghan, Hanna, Kennedy, & Sredl, 1998) and (b) patients’ effective use of coping skills that they explicitly learn in CBT or IPT (Strunk, DeRubeis, Chiu, & Alvarez, 2007). The cognitive and interpersonal skills learned through psychotherapy may be particularly relevant in countering the depressogenic impact of an early abuse history.

The present investigation is the first to examine a history of childhood maltreatment as a moderator of treatment response and relapse/recurrence in adult outpatients with MDD. Patients were randomly assigned to 16 weeks of manualized CBT or IPT or ADM according to the 2001 Canadian Network for Mood and Anxiety Treatment guidelines (CANNMAT, 2001). Patients who met criteria for response were followed naturalistically for 12 months or until depression relapse or recurrence. Patients who completed the acute trial were interviewed regarding their childhood history. Childhood maltreatment was defined as a history of severe physical, sexual, or emotional abuse according to rigorous contextual guidelines (Bifulco, Brown, & Harris, 1994).

Because our sample comprised adult patients, we predicted that patients with a history of childhood maltreatment in the IPT and CBT conditions would show a significantly higher likelihood of response than maltreated patients randomized to receive ADM. In contrast, among those with no history of maltreatment, we expected no differences in response across the treatment groups. Second, we predicted that patients with a history of childhood maltreatment would be significantly less likely to suffer a relapse or recurrence over the follow-up period if they had received IPT and CBT than if they had received ADM. In contrast, we expected no differences in relapse/recurrence rates among those without maltreatment.

**Method**

**Participants**

Participants included 203 outpatients with MDD (74 men, 129 women) who participated in a larger one-site randomized trial (McBride, Atkinson, Quilty, & Bagby, 2006). Ethical approval for this study was obtained in 2001 by the Research Ethics Board at the University of Toronto. The study took place at the Centre for Addiction and Mental Health, University of Toronto from July 2001 to April 2007. All patients were competent to give consent
and provided written informed consent following complete description of the study procedures. No adverse events were reported.

All patients met *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (DSM–IV; American Psychiatric Association, 1994) criteria for MDD, were between the ages of 18 and 60 years, and had a minimum score of 16 on the Hamilton Rating Scale for Depression (Ham-D; Hamilton, 1967), which represents a moderate to severe symptom level (Müller, Himmerich, Kienzle, & Szegedi, 2003). All participants were free of ADM, had received a moderate to severe symptom level (Mu¨ller, Himmerich, Kienzle, & Szegedi, 2003). All participants were free of ADM, had received no electroconvulsive therapy in the past 6 months, did not have a concurrent medical illness, had a minimum of 8 years of education, and were fluent in reading English. Participants were excluded if they met DSM–IV criteria for bipolar disorder, a psychotic disorder, substance use disorders, or organic brain syndrome.

Figure 1 displays the CONSORT flow diagram. A total of 466 participants who were referred from general practitioners and mental health providers or recruited from advertisements took part in a clinic screen. Of these, 263 did not meet the inclusion criteria or declined participation prior to any data collection. A total of 203 were randomized to treatment using a random number generator stratifying on sex and number of previous episodes. A research assistant was responsible for generating the sequencing and assigning patients to treatment. The study investigators did not have access to the random assignment list. Twenty-nine patients refused their randomization assignment, and those who refused randomization assignment, and those who dropped out of treatment in terms of sex, \( \chi^2(2, N = 203) = 0.21, p = .90 \); age, \( F(2, 208) = 1.51, p = .22 \); occupation, \( F(2, 208) = 0.37, p = .69 \); number of previous episodes, \( F(2, 208) = 0.31, p = .73 \); age at first onset, \( F(2, 208) = 0.99, p = .37 \), or comorbidity, either current, \( \chi^2(1, N = 203) = 0.30, p = .59 \), or lifetime, \( \chi^2(1, N = 203) = 2.10, p = .15 \). Those who completed treatment (\( M = 16.42, SD = 2.27 \)) had significantly more years of education than both those who refused randomization (\( M = 14.86, SD = 3.85 \)) and those who dropped out (\( M = 15.06, SD = 2.36 \)), \( F(2, 208) = 7.39, p = .001 \). In addition, those who completed treatment (\( M = 17.84, SD = 3.63 \)) had a significantly lower baseline Ham-D scores than those who refused randomization (\( M = 19.93, SD = 2.62 \)), \( F(2, 208) = 4.73, p = .01 \).

Of the 140 patients who completed treatment, 94 were treatment responders and were entered into the follow-up phase. Of these 94 patients, 19 dropped out of follow-up, leaving a sample of 75 patients who completed all phases of treatment. Those who dropped out of follow-up were not differentially distributed across

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**Figure 1.** Flow diagram of patient progress through the acute treatment trial. IPT = interpersonal therapy; CBT = cognitive-behavioral therapy; ADM = antidepressant medication; CECA = Childhood Experience of Care and Abuse.
treatment conditions from those who completed, \( \chi^2(2, N = 94) = 2.08, p = .35 \). Furthermore, those who did not complete follow-up did not differ from those who did on any additional demographic or clinical variable (all \( ps > .10 \)).

The childhood maltreatment interview was administered following the end of acute treatment to minimize depressive bias in the recollection of childhood maltreatment and was part of a larger posttreatment assessment battery. Therefore, only treatment completers received the interview. We were unable to procure data from 28 patients, either because there was a malfunction with the recording (\( n = 12 \)) or because the patient could not be contacted to participate in the posttreatment assessment session or declined to be scheduled for the session when contacted (\( n = 16 \)). Patients who did versus did not receive the interview were not differentially distributed across treatments, \( \chi^2(2, N = 140) = 0.87, p = .65 \), nor did they differ on any of the above demographic or clinical variables (all \( ps > .10 \)). As a result, the sample of patients with complete case data for the acute phase of treatment was 112. The sample of patients with complete case data for the follow-up phase of treatment was 65 (i.e., 75 who completed follow-up minus 10 who were missing childhood maltreatment data).

**Measures**

**Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I/P; First, Spitzer, Gibbon, & Williams, 1995).** The SCID-I/P was used to assess the presence of MDD and comorbid Axis I disorders. The SCID-I/P is the gold standard for clinical diagnoses and has demonstrated strong reliability and validity (Williams et al., 1992). Interviews were conducted by doctoral-level clinical psychology students trained to “gold standard reliability status,” such that they matched the diagnoses of a gold standard rater (i.e., a SCID-trained clinical psychologist) on at least three consecutive SCID-I/P interviews (see McBride et al., 2006).

**The Ham-D (Hamilton, 1967).** The Ham-D is a semistructured, clinician-rated interview designed to assess severity of depression and is the most widely used measure of depression severity in clinical trials (Bagby, Ryder, Schuller, & Marshall, 2004).

**Childhood maltreatment.** Childhood maltreatment was assessed with the Childhood Experience of Care and Abuse (CECA; Bifulco et al., 1994) semistructured contextual interview. The CECA includes the following scales: (a) Antipathy—hostility and coldness directed toward the child; (b) Neglect—indifference to the child’s physical and emotional needs; (c) Physical Abuse—violence directed toward the child by parents; and (d) Sexual Abuse—nonconsensual sexual contact by any perpetrator. The CECA interview was administered following the end of acute treatment in treatment completers to minimize depressive bias in the recollection of childhood maltreatment. The interviewers were unaware of patients’ treatment assignment.

Following the interview, expert judges who resided at a separate institution and who were unaware of patients’ treatment assignment rated patients’ audiotaped narrative responses to the above scales on a 4-point threat scale (1 = marked, 2 = moderate, 3 = some, 4 = little/none) based on standardized criteria and with reference to a manual that contains hundreds of anchored case exemplars. According to CECA protocol (Bifulco et al., 1994), each variable was dichotomized to form severe (1 = marked or 2 = moderate) versus nonsevere (3 = some or 4 = little/none) levels. A composite “child maltreatment” variable was then created that represented the presence versus absence of severe antipathy and/or neglect and/or physical abuse and/or sexual abuse. Kappa coefficients for CECA ratings ranged from .86 to 1.00.

**Treatment Protocol**

**Treatment of index episode.** The acute treatment phase ran from July 2001 to December 2006. Patients received weekly sessions of CBT, using the Greenberger and Padesky (1995) “Mind Over Mood” manual, or IPT, using the Weissman, Markowitz, and Klerman (2000) “Comprehensive Guide to Interpersonal Psychotherapy” manual. The average number of sessions for completer patients in the CBT condition was 16.56 (SD = 3.22), and 17.15 (SD = 2.45) in the IPT condition. Patients in the IPT and CBT conditions were medication free throughout the study. Therapists were doctoral-level clinical psychologists or master of social work-level psychotherapists who had all received formal training in CBT or IPT and were supervised over the course of the trial.

A doctoral-level clinical psychologist with extensive experience evaluating CBT and IPT reviewed videotapes of two patient sessions for each therapist using the CBT and IPT scales of the Collaborative Study Psychotherapy Rating Scale (CSPRS; Hollon et al., 1988). The CSPRS includes a 28-item CBT scale and a 28-item IPT scale, each rated on 7-point Likert-type scale ranging from 1 (not at all) to 7 (thoroughly). The CSPRS has documented good psychometric properties (Hill, O’Grady, & Elkin, 1992; Shaw et al., 1999), with the internal consistency values in the present sample of \( \alpha = .97 \) for the CBT scale and \( \alpha = .96 \) for the IPT scale. All therapists achieved higher total scores for the scale that corresponded to their treatment modality. A mixed model analysis of variance (ANOVA) revealed a significant Treatment Modality \( \times \) Scale Score interaction, \( F(1, 19) = 171.42, p < .001, \eta^2 = .90 \), such that therapists in the CBT group had significantly higher mean item scores on the CBT scale than the IPT scale (\( M_S = 4.12, 1.67; SD_S = 0.97, 0.30 \)), whereas therapists in the IPT group had significantly higher mean item scores on the IPT scale than the CBT scale (\( M_S = 4.23, 1.56; SD_S = 0.68, 0.43 \)). Scores of the CBT therapists on the CBT scale did not significantly differ from scores of the IPT therapists on the IPT scale, \( t(19) = 0.29, p = .77 \).

Patients who completed the ADM condition were seen by a study psychiatrist once every 2 weeks for 16 weeks for medication management and supportive care. All of the study psychiatrists were expert pharmacotherapists employed in an academic setting, and all had previous experience treating patients in the context of a clinical trial. Patients received an ADM chosen at the discretion of the study psychiatrist, with reference to the Canadian Network for Mood and Anxiety Treatment guidelines (CANNMAT, 2001). These Canadian national guidelines are similar to the Texas Medication Algorithms (TMAP; Trivedi, Shon, & Crismon, 2000) in content and purpose and include a wide range of ADMs, effective dosages, and dosage ranges. Table 1 provides a list of medications used in the present study. Twenty-two patients (49%) saw their medication dosages increased over the course of the 16-week trial, and 15 patients (33%) switched to a different medication at least
once on the basis of the CANMAT protocols. Medication augmentation (i.e., use of more than one medication at the same time) was not permitted in the protocol.

All treatment providers were unaware of the study hypotheses and results of the CECA interview. A trained research assistant who remained unaware of patients’ childhood maltreatment history and treatment assignment throughout the protocol administered the Ham-D to all patients to monitor progress. Response was defined as a 50% or more decrease in Ham-D scores from baseline to treatment end point and a final Ham-D score of less than 8.

Note. All dosages fall within the guidelines prescribed by the Canadian Network for Mood and Anxiety Treatment guidelines.

### Data Analysis

To account for both missing childhood maltreatment data and patient attrition across the acute and follow-up phases of the study, multiple imputation (MI; Rubin, 1987) was performed. MI is a Monte Carlo technique that generates multiple values for each missing data point (Schafer & Graham, 2002). The MI method of estimating missing values is preferred to other approaches to missing data, such as deletion of missing cases or using the last observation carried forward (Schafer & Graham, 2002). This approach addresses biases inherent in deleting patients who drop out of treatment, and ultimately allows for the inclusion of a larger and more representative sample in the analyses. The Markov Chain Monte Carlo (MCMC) method in SPSS 18 was used, under the assumption that the data were missing at random (Rubin, 1987), to produce 20 imputed data sets for the acute phase (i.e., imputing missing data for childhood maltreatment and treatment response), and a separate set of 20 imputed data sets for the follow-up phase (i.e., imputing missing data for childhood maltreatment and recurrence).

Imputed values were generated from multivariate linear and logistic regression models using pretreatment and posttreatment Ham-D scores, age, sex, occupation status, years of education, number of previous episodes, age at first depression onset, chronicity, and comorbidity as potential predictors. Each set of multiple imputation results was then pooled in SPSS using Rubin’s (1987) rule to obtain a single set of parameter estimates for each analysis. Rubin’s rule derives one single pooled parameter estimate by taking into consideration the variance both within and between imputations (see also Schafer, 1997).

Due to the extent of missing data, all descriptive statistics and inferential models are presented separately below for the MI samples and for the samples with complete case data. For the dependent variable of treatment response, the sample size for the MI analyses was 203, and the complete case sample size was 112. A logistic regression model was created that included an effects-coded maltreatment variable (−1: absence; 1: presence) and two contrast-coded treatment condition variables plus the Maltreatment × Treatment Condition interaction (see Cohen, Cohen, West, & Aiken, 2003). A priori orthogonal contrasts were specified to test the present hypothesis regarding the interaction of group and condition. According to the present hypotheses stated above, it was expected that among those with maltreatment, patients receiving CBT should fare better than ADM. However, no differences among treatment conditions should be evident among those with no maltreatment.

For the dependent variable of depression recurrence, the sample size for the MI analyses was 94, and the complete case sample size was 65. Cox regression survival analysis was performed with time to recurrence estimated hierarchically, including potential covariates on the first step of the model, and childhood maltreatment on the second step.

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1 Four patients had a switch from citalopram to bupropion, one from venlafaxine to bupropion, one from sertraline to bupropion, two from bupropion to venlafaxine, one from bupropion to trazodone, one from fluvoxamine to bupropion, two from citalopram to venlafaxine, one from citalopram to sertraline, one from sertraline to citalopram, and one from fluoxetine to bupropion.

2 We performed 20 imputations because the fraction of missing information was large in these data. When the fraction of missing information is large, a greater number of imputations are necessary to bring the pooled estimates closer to the idealized estimates. The relative efficiency values for all parameters approached 1 (all > .975), indicating that the estimates approached the theoretical estimate computed using an infinite number of imputations (see Rubin, 1987). The fraction of missing information for analyses predicting treatment response ranged from .28 to .51. For analyses predicting depression recurrence, the fraction of missing information ranged from .31 to .34.
Results

Preliminary Analyses

Table 2 presents demographic and clinical characteristics of the multiply-imputed full randomized sample (n = 203) and the complete case sample (n = 112) stratified by treatment group and history of childhood maltreatment. Our Ethics Review Board, consistent with the Charter of Rights and policy of our institution, would not allow us to collect patient ethnicity data.

Multiple imputation analyses. In the full sample of 203 patients, the estimate of the frequency of severe childhood maltreatment was 91 (45%). Maltreatment history was not significantly differentially distributed across treatment conditions, χ²(2, N = 203) = 7.82, p = .28. Furthermore, those with maltreatment did not differ significantly from those without in terms of sex, χ²(1, N = 203) = 0.64, p = .42; age, t(166) = 1.84, p = .07; years of education, t(n1) = 0.007, p = .99; occupation status, t(74) = 1.49, p = .14; age at onset of first episode, t(n79) = 0.30, p = .77; depression chronicity (chronic vs. nonchronic), χ²(1, N = 203) = 3.35, p = .07; current, χ²(1, N = 203) = 2.05, p = .15, or lifetime comorbidity, χ²(1, N = 203) = 3.93, p = .14; or baseline, t(n63) = 0.19, p = .85, or end-point, t(n88) = 0.59, p = .55, Ham-D scores. However, those with maltreatment had a significantly higher number of previous episodes than those without (Ms = 3.39, 2.42; SEs = 0.39, 0.19), t(133) = 2.23, p = .03.

Completer analyses. In the sample of patients with complete data (n = 112), 53 (47%) reported a history of severe childhood maltreatment. Similar to the results reported in the MI sample, maltreatment history was not significantly differentially distributed across treatment conditions, χ²(2, N = 112) = 1.21, p = .55. Furthermore, those with maltreatment did not differ significantly from those without in terms of sex, χ²(1, N = 112) = 0.58, p = .45; years of education, t(n109) = 0.67, p = .51; occupation status, t(n108) = 1.41, p = .16; age at onset of first episode, t(n109) = 0.12, p = .91; number of previous episodes, t(n109) = 1.82, p = .07; depression chronicity, χ²(1, N = 112) = 1.52, p = .22; current, χ²(1, N = 112) = 1.03, p = .31, or lifetime comorbidity, χ²(1, N = 112) = 3.93, p = .14; or baseline, t(n109) = 0.24, p = .81, or end point, t(n110) = 0.72, p = .47, Ham-D scores. However, those with maltreatment were significantly older than those without (Ms = 45.44, 39.61; SEs = 1.49, 1.52), t(n110) = 2.74, p = .007.

Childhood Maltreatment and Differential Treatment Response

Multiple imputation analyses. The estimated response rate in the multiply-imputed sample of 203 was 63% (n = 127). Response rates across the IPT, CBT, and ADM conditions were 54%, 60%, and 72%, respectively. Responders and nonresponders did not differ in terms of sex, χ²(1, N = 203) = 1.27, p = .26; age, t(n50) = 0.33, p = .75; years of education, t(n46) = 0.37, p = .72; occupation, t(n64) = 0.27, p = .79; number of previous episodes, t(n166) = 0.59, p = .56; age of first onset, t(n37) = 0.85, p = .40; depression chronicity, χ²(1, N = 203) = 1.54, p = .70; current, χ²(1, N = 203) = 0.15, p = .70, or lifetime comorbidity, χ²(1,

Table 2
Descriptive Characteristics by Child Maltreatment and Treatment Group in Imputed (n = 203) and Case-Complete (n = 112) Samples

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Note. IPT = interpersonal psychotherapy; CBT = cognitive-behavioral therapy; ADM = antidepressant medication; No. = Number; Ham-D = Hamilton Depression Rating Scale.

* Fraction of missing information = .23–.60; relative efficiency = .97–.99.
A logistic regression model was conducted with number of previous episodes on the first step, childhood maltreatment and treatment group on the second step, and the interaction of maltreatment and treatment group on the third step. Over and above the effect of previous episodes, parameter estimates on the second step revealed no significant effect of maltreatment, \( OR = .97, p = .94, 95\% \text{ CI} [.44, 2.14] \). Furthermore, the contrast parameter estimates revealed no significant differences among treatments \( OR = .57–.58, p = .17–.36, 95\% \text{ CI} [.26, 1.91] \).

However, as displayed in Figure 2a, there was a significant interaction between history of maltreatment and treatment group. Specifically, among those with maltreatment, there was a significant relation of treatment group to response, \( \chi^2(2, N = 91) = 7.82, p = .04 \), such that patients with a history of maltreatment were significantly less likely to respond in the IPT condition than in the ADM or CBT conditions \( OR = 3.61, p = .04, 95\% \text{ CI} [1.06, 12.35] \), whereas the difference between the ADM and CBT conditions was not significant \( p = .48 \). In contrast, response rates were not differentially distributed across treatment groups among those with no history of child maltreatment, \( \chi^2(2, N = 112) = 7.82, p = .49 \) \( ORs < 1.50, ps > .45 \).

**Completer analyses.** The response rate in the case-complete sample of 112 was 68% \( (n = 76) \). Response rates across the IPT, CBT, and ADM conditions were 54%, 67%, and 84%, respectively. Responders and nonresponders did not differ in terms of sex, \( \chi^2(1, N = 112) = 1.45, p = .23 \); age, \( t(110) = 1.05, p = .29 \);

![Figure 2. Relation of child maltreatment to response status by treatment group in the (a) full randomized sample \( (n = 203) \) and (b) case-complete sample \( (n = 112) \). IPT = interpersonal therapy; CBT = cognitive-behavioral therapy; ADM = antidepressant medication.](image-url)
years of education, $t(110) = 1.05, p = .30$; occupation, $t(110) = 0.18, p = .86$; number of previous episodes, $t(110) = 0.32, p = .75$; age of first onset, $t(110) = 0.88, p = .38$; depression chronicity, $\chi^2(1, N = 112) = 0.96, p = .33$; current, $\chi^2(1, N = 112) = 0.36, p = .55$, or lifetime comorbidity, $\chi^2(1, N = 112) = 0.003, p = .96$; or baseline Ham-D scores, $t(110) = 0.46, p = .65$.

Results of the logistic regression model predicting treatment response from childhood maltreatment history, treatment group, and their interaction largely replicated the MI results reported above. In the model with the complete sample, we applied the Firth correction to the odds ratios to address biases in these estimates as a result of small cell sizes (see Firth, 1993). However, the contrast parameters revealed that response rates were significantly lower in the IPT condition than in the ADM and CBT conditions ($OR = 3.05 p = .04, 95\% CI [1.08, 8.62]$).

Furthermore, replicating the MI results reported above, there was a significant interaction between history of maltreatment and treatment group. Again, those with a history of maltreatment were significantly less likely to respond in the IPT condition than in the ADM and CBT conditions ($\chi^2(2, N = 54) = 9.66, p = .008, OR = 7.87, p = .008, 95\% CI [1.61, 22.73]$), whereas the difference between the ADM and CBT conditions was not significant ($p = .26$). Neither of these contrasts was significant among those with no history of maltreatment ($ORs < 1.50, ps > .50$). This pattern is displayed in Figure 2b.

**Childhood Maltreatment and Recurrence**

**Multiple imputation analyses.** In the imputed sample of 94 who started follow-up, the pooled frequency of recurrence was 24 (26%). Those who recurred did not differ significantly from those who maintained remission status in terms of sex, $\chi^2(1, N = 94) = 0.14, p = .71$; age, $t(114) = 0.30, p = .77$; years of education, $t(271) = 0.34, p = .73$; occupation status, $t(355) = 1.89, p = .06$; number of previous episodes, $t(425) = 1.12, p = .26$; age at first onset, $t(292) = 0.55, p = .58$; current comorbidity, $\chi^2(1, N = 94) = 0.26, p = .61$; lifetime comorbidity, $\chi^2(1, N = 94) = 3.39, p = .07$; chronicity, $\chi^2(1, N = 94) = 0.002, p = .96$; baseline Ham-D scores, $t(299) = 0.02, p = .98$, or end-point Ham-D scores, $t(100) = 1.13, p = .26$.

Recurrence rates did not differ significantly by treatment condition, $\chi^2(2, N = 94) = 7.82, p = .97$. Therefore, the Cox regression survival analysis predicting time to recurrence from severe childhood maltreatment was modeled collapsing across treatment condition. Over and above the effect of age, the model was significant, $\chi^2(1, N = 94) = 5.92, p = .01$, and the pooled estimate for the hazard ratio indicated that patients with severe childhood maltreatment were 3.04 times more likely to suffer a recurrence in follow-up than those without (95% CI [1.98, 3.11]).

**Completer analyses.** In the sample of 65 patients with complete data through follow-up, 12 (18%) suffered a recurrence. The mean time to recurrence was 29.17 weeks (range = 8–57 weeks; $SD = 15.09$). The follow-up period lasted an average of 48.89 weeks ($SD = 12.49$). Those who recurred versus those who maintained remission status did not differ significantly in terms of sex, $\chi^2(1, N = 65) = 0.16, p = .69$; age, $t(63) = 0.13, p = .88$; years of education, $t(63) = 0.52, p = .60$; number of previous episodes, $t(63) = 2.16, p = .06$; age at first onset, $t(63) = 0.57, p = .57$; current comorbidity, $\chi^2(1, N = 65) = 0.68, p = .41$; chronicity, $\chi^2(1, N = 65) = 0.02, p = .89$; baseline Ham-D scores, $t(63) = 0.48, p = .63$; or end-point Ham-D scores, $t(63) = 1.90, p = .06$. However, those who recurred had higher lifetime comorbidity rates, 57% versus 25%, $\chi^2(1, N = 65) = 5.68, p = .02$, and lower occupation status ($M_S = 30.22, 45.18; SE_s = 7.57, 2.90$), $t(63) = 2.08, p = .04$, than those who did not.

Again, recurrence rates did not differ significantly by treatment condition, $\chi^2(2, N = 65) = 0.44, p = .80$. Cox regression survival analyses of time to recurrence were modeled hierarchically, with lifetime comorbidity and occupation status entered on the first step and childhood maltreatment entered on the second step. Over and above the contribution of these clinical and demographic variables, childhood maltreatment significantly predicted recurrence, $\chi^2(1, N = 65) = 6.48, p = .04$, such that the presence of maltreatment was associated with 2.89 times the risk of recurrence (95% CI [1.02, 8.22]).

**Discussion**

In the present sample of patients randomized to IPT, CBT, or ADM, severe childhood maltreatment was associated with a significantly lower response rate to IPT compared with ADM and CBT, with the highest response rate in the ADM condition. Furthermore, in those who responded to treatment, severe childhood maltreatment significantly and preferentially predicted greater risk of recurrence over a 12-month follow-up period collapsed across treatment conditions. Therefore, childhood maltreatment may remain a risk factor for depression recurrence even in the context of successful treatment.

**Childhood Maltreatment and Treatment Response**

The overall response rate was 63% for the sample randomized to treatment and 67% for those who completed treatment. These rates are comparable to those reported in previous randomized trials of IPT, CBT, and ADM (Casacalenda et al., 2002). Response rates did not differ across treatments in the multiply-imputed sample randomized to treatment, which is also consistent with previous trials comparing these modalities (e.g., Elkin et al., 1989). In the complete sample, however, patients in the ADM condition saw a very high rate of response (84%). It is possible that our high response rate in the ADM condition is a function of patient expectancies. Given the high rates of randomization refusal and attrition in our ADM condition, those remaining would be expected to do well. This possible source of bias in the data highlights the importance of estimation techniques that allow us to impute response data for patients who either refused their randomization assignment or dropped out of treatment. We note in the present study that our results regarding childhood maltreatment as a moderator of treatment response and recurrence fully replicated across both the multiply-imputed and completer samples, thereby suggesting that the effects are valid and robust.

The significant interaction of treatment condition and childhood maltreatment on differential response to treatment is particularly intriguing. All treatments were equally efficacious for patients with no history of child maltreatment. This is good news for
clinicians, as it suggests that depressed patients with no abuse histories are likely to benefit from empirically supported and rigorously implemented treatment regardless of modality. At the same time, response rates were well below 100%, suggesting that other moderators of treatment response are likely operating in this group and require further study (e.g., Bulmash, Harkness, Stewart, & Bagby, 2009). Our results may also suggest that differences across previous studies in rates of childhood maltreatment, and a failure to take maltreatment history into account, may help to explain inconsistencies in prior reports of differential treatment response across therapeutic modalities.

In the present study, the superior efficacy of ADM, and to a lesser extent CBT, compared with IPT was only present among those with a history of severe maltreatment. Our results are consistent with those of the TADS and TORDIA trials (Asarnow et al., 2009; Lewis et al., 2010), which also found that response rates were highest for patients with maltreatment in the ADM arm. This pattern contrasts, however, with the CBASP-nefazodone trial in adults with chronic depression, which showed that those with childhood trauma fared significantly better with a psychotherapy that combined aspects of IPT and CBT than nefazodone (Nemeroff et al., 2003).

The reasons for the discrepancy between the results of the CBASP trial and those of our trial and the TADS and TORDIA trials are unclear and require further investigation. Our methodology is more similar to that of the TADS and TORDIA trials given that we administered standard psychotherapies and pharmacotherapies. In contrast, a medication was used in the CBASP trial that has since been discontinued, and a psychotherapy that was specifically developed to treat chronic depression. Furthermore, the CBASP trial included only patients with chronic depression, whereas the majority of patients in our study and in the two adolescent trials were suffering from episodic MDD (see Table 2). Episodic MDD responds more favorably than chronic depression to treatment, in general (Klein, Taylor, Dickstein, & Harding, 1988b), and is distinguishable from chronic depression on several key prognostic indicators, including family history of depression, comorbidity, and negative personality traits (Klein, Taylor, Dickstein, & Harding, 1988a; Klein et al., 1988b). As such, the moderators of treatment response may be different in these two patient groups.3

In the present study, we were surprised to find such low rates of response in maltreated patients randomized to IPT. Indeed, in previous research, maintenance IPT has been found to lessen the depressogenic impact of stress on recurrence (Harkness et al., 2002). It is possible that childhood maltreatment is an especially unique and impactful stressor that may be associated with patient characteristics that portend a negative response in an interpersonally based psychotherapy. For example, a history of childhood maltreatment is significantly associated with an avoidant and ambivalent style of attachment (e.g., Cicchetti & Toth, 2005). Study of adult MDD has found that patients who report high levels of avoidance and ambivalence failed to benefit from the explicit use of the therapeutic relationship as a model for the patient’s relational functioning. In contrast, patients with maltreatment may have fared better in ADM and CBT given their more prescriptive and structured nature that relies less on the therapeutic alliance as a mechanism for change. This possibility runs counter to research investigating common factors and their relation to outcome (e.g., Martin, Garske, & Davis, 2000) by suggesting that the therapeutic relationship may not be helpful to patients with particular characteristics. More research is needed that focuses beyond gross indicators of response to examine in a more fine-grained manner the common and specific mechanisms of treatment that portend poor response in patients with maltreatment histories and other risk characteristics.

A further potential explanation for our results is that perhaps remission was not feasible with the short-term therapy format of the present design in patients whose histories of child maltreatment emerged and needed to be addressed over the course of treatment. For example, individuals with severe abuse have more rigidly consolidated negative schemas than those without (Lumley & Harkness, 2007), and work with schemas to achieve symptom remission is theorized to require longer term therapy (see Padesky, 1994). In contrast, these issues are not relevant in ADM treatment given its focus on symptom relief and management of side effects. There is surprisingly little research investigating therapy processes and mechanisms in patients with abuse histories. These represent important variables to consider in future research that could help to more fully understand why patients with a maltreatment history fare better with certain modalities over others.

Childhood Maltreatment and Depression Recurrence

To our knowledge, this study is the first to report that childhood maltreatment significantly predicts depression recurrence following successful treatment with IPT, CBT, or ADM. The mechanism mediating recurrence in those with a history of childhood maltreatment was not the focus of the present investigation and requires further research. Childhood maltreatment is associated with negative cognitive biases (e.g., Hankin, 2005) and heightened ruminati- nation (Raes & Hermans, 2008). As such, individuals with a history of maltreatment may have a lowered threshold of activation of dysphoric mood, thereby facilitating recurrence. Childhood maltreatment also predicts the generation of stressful life events, which can serve to trigger new episodes (Harkness, Lumley, & Truss, 2008). There are also many possible common factors that may mediate a lower durability of treatment in those with maltreatment (e.g., decreased likelihood to seek follow-up care, decreased resilience in the face of ongoing stress, etc.). Given the high prevalence of severe childhood maltreatment in samples of patients with MDD, these mediating mechanisms, if confirmed, can serve as fruitful relapse risk targets that could be incorporated

3 We do not believe that depression chronicity represents a confounding factor in interpreting the present results because, as noted above, those with chronic and nonchronic depression did not differ in response rates or maltreatment history. Furthermore, we have no evidence that those with chronic or nonchronic depression responded differentially across the three treatments. However, in the present sample, there were too few patients with chronic depression to fully stratify our models examining the relation of childhood maltreatment to response by depression chronicity. Therefore, this remains an important question for future studies designed to specifically investigate differential prescriptive indicators in episodic versus chronic MDD.
explicitly into psychotherapy or the clinical management component of ADM in patients who present with abuse histories.

The present results suggest that patients with maltreatment should be targeted for relapse and recurrence prevention strategies regardless of the type of acute treatment they receive. Such patients may also benefit from booster sessions and/or sequential therapeutic strategies. Targeting these strategies to those who need them most may help to improve the cost-effectiveness of depression treatment (Dobson et al., 2008).

Study Limitations

The present completer sample was small, thus limiting the generalizability of our findings and necessitating the imputation of a large amount of data. To account for the extent of missing data, we performed a high number of imputations and note that our relative efficiency values all approached 1. We also note that our results in the imputed sample randomized to treatment fully replicated the original results with the case-complete data. Therefore, we are confident in the robustness of our effects, assuming that missing data can be considered missing at random. Nevertheless, we suggest that future research investigating the relation of child maltreatment to differential treatment response randomize patients to treatment a priori on the basis of maltreatment history.

In addition, we did not have ethnicity data for our sample because our Ethics Review Board did not allow us to collect these data. However, this sample was drawn from the downtown core of the most ethnically diverse city in the world according to the United Nations, and, anecdotally, many of our participants hailed from diverse countries (e.g., Bangladesh, China, Columbia, Ireland). Furthermore, the participants in the present study were recruited primarily from advertisements, and thus the generalizability of the present results to samples of treatment-seeking and/or referred outpatients is unclear. It is also important to note that our design included a relatively short follow-up period, which may have limited our ability to detect recurrences.

Furthermore, our design excluded individuals with antisocial or borderline personality disorder, the latter of which is associated with both trauma history (e.g., G. R. Brown & Anderson, 1991) and a poor MDD treatment prognosis (Mulder, 2002). Therefore, its impact in further moderating the effect of childhood trauma on differential MDD treatment response and recurrence is an important question for future research.

Finally, the present study relied on retrospective reporting of childhood maltreatment. However, it is important to note that the CECA addresses the concern of both rater and respondent bias in a much better way than do traditional self-report questionnaire measures of childhood maltreatment (e.g., Bifulco et al., 1994; Brewin, Andrews, & Gotlib, 1993; G. W. Brown, Craig, Harris, Handleby, & Harvey, 2007). In terms of rater bias, independent judges who were unaware of participants’ treatment assignment rated responses according to factual indicators and clear behavioral anchors. In addition, the format of the CECA is well suited to priming autobiographical memory by probing for detailed positive and negative contextual information to support respondents’ impressions.

In summary, in a trial of IPT, CBT, and ADM, patients with a history of severe childhood maltreatment showed a significantly higher response rate in ADM and CBT compared with IPT. Furthermore, severe maltreatment significantly predicted depression recurrence over a 12-month follow-up period collapsed across treatment conditions. These results suggest that proper assignment of patients to treatment and rigorous follow-up of these patients at greatest risk for recurrence has the potential to prevent a life-long pattern of illness.

References


Klein, D. N., Taylor, E. B., Dickstein, S., & Harding, K. (1988). Primary early-onset dysthymia: Comparison with primary nonbipolar nonchronic major depression on demographic, clinical, familial, personality, and


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