INTRODUCTION

Globally, 405 million people experience depression and depression is a leading contributor to disability and lost productivity.\(^1\) Currently, less than 50% of major depressive disorder (MDD) patients achieve remission following treatment with antidepressants. There is an urgent need to understand what factors determine who is likely to benefit, and who is not, from commonly used first-line treatments. Childhood trauma, particularly due to abuse and neglect, is among the most significant contributors to the subsequent development of MDD.\(^2,7\) Despite this evidence, the rates of childhood trauma in outpatient depressed populations have not been well established and it remains unknown whether trauma predicts treatment outcomes in these outpatient populations. Thus, our aims were to establish the rates of trauma, overall and for individual types of trauma, in a large global sample of depressed outpatients and to assess whether exposure to these traumatic events is a general and/or differential predictor of outcomes following treatment with one of three commonly used antidepressants.

The exposure to significant traumatic stressors in childhood, including physical and sexual abuse and loss of parents, has been associated with an increased risk of depression.\(^3,5\) Exposure to early trauma and abuse increase the likelihood of meeting criteria for a major depressive episode at any point in life,\(^6\) compared with the absence of exposure to trauma. Childhood abuse predicts poorer outcomes, including earlier-onset depression, a higher risk of recurrent depression, more severe course of illness and greater chronicity.\(^2,8\)

Several studies suggest that a history of pre-pubertal abuse or trauma also moderates response to treatment, however, with variable results.\(^8\) Nemeroff et al.\(^9\) studied 681 patients with chronic depression and their response to an antidepressant (nefazodone) or CBASP (cognitive behavioral analysis of psychotherapy), a form of cognitive behavioral therapy (CBT). Patients without a history of

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pre-pubertal stressor had an equivalent response to psychotherapy and nefazodone, and the best response to the combination treatment. However, patients who reported a history of parental loss before the age of 15, parental neglect or childhood physical or sexual abuse were significantly less likely to respond to pharmacotherapy alone. Furthermore, combination treatment did not substantially improve the outcome versus CBT alone.

Some studies have suggested that specific types of abuse rather than a general history of trauma moderates treatment response. In the Treatment of Resistant Depression in Adolescents Study, 334 (ref. 11) adolescents who did not respond to a selective serotonin-reuptake inhibitor were randomized to receive 12 weeks of an alternative selective serotonin-reuptake inhibitor alone, or combined with CBT, or venlafaxine alone (a serotonin-norepinephrine reuptake inhibitor; SNRI) or with CBT. Those without a history of abuse did better on the combination treatment than on antidepressant monotherapy (62.8 vs 37.0%). Those with a history of sexual abuse responded equally to monotherapy and combination treatment (48.3 vs 42.3%), whereas those with a history of physical abuse responded substantially better to antidepressant monotherapy than combination treatment (52.4 vs 18.4%).

The Treatment for Adolescents with Depression Study compared the efficacy of 12 weeks fluoxetine, CBT, their combination and placebo in 427 adolescents with MDD, divided into four groups by their history: (1) no trauma; (2) trauma, no abuse; (3) physical abuse; and (4) sexual abuse. The no-trauma group responded to fluoxetine, with no effect of CBT over placebo. For teens with a history of trauma or physical abuse, no treatment was more effective than placebo. In the sexual abuse group, placebo appeared more effective than CBT. These findings are in contrast to Nemeroff et al., in which psychotherapy appeared to be more effective than medication in depressed adults with a history of trauma or abuse. The difference in participant population (chronically depressed and adult vs children) could explain the discrepancy. Pediatric studies have generally suggested that a history of childhood trauma predicted a poorer response to psychotherapy. A recent meta-analysis concluded that a history of early-life stress predicted poorer response to pharmacotherapy and combination pharmacotherapy/psychotherapy, and a trend for poor response to psychotherapy as well.

The international Study to Predict Optimized Treatment in Depression (iSPOT-D) enrolled nonpsychotic MDD patients into a real-world practical effectiveness trial, primarily to identify pre-treatment characteristics as general or differential predictors of response to antidepressants that could change how practitioners select among antidepressant medications.

In this study, we report on the effects of early-childhood trauma as a predictor of acute antidepressant treatment outcomes at 8 weeks post treatment in the 1008 depressed participants from iSPOT-D. Our aims were to test whether (i) the prevalence of early-life trauma differs in iSPOT-D MDD participants compared with matched healthy controls; (ii) the overall amount of ‘load’ of early-life trauma is a general predictor of acute antidepressant treatment outcomes defined by response, remission and change in symptom severity; (iii) exposure to a specific type of abuse is a specific predictor of acute antidepressant treatment outcomes; and (iv) overall ‘load’ of early-life trauma and exposure to a specific type of abuse are differential predictors of acute antidepressant treatment outcomes for different types of antidepressants.
The adverse event rates did not significantly differ across treatment arms.17

Treatment outcomes
The primary outcome was rate of response (≥50% decrease in HRSD17 scores from baseline to week 8) and remission (HRSD17 score ≤7) to treatment. Secondary outcomes included response and remission by the QIDS-SR16 (response: ≥50% decrease from baseline, remission: score ≤5).17,18 By the HRSD17, 62.2% of participants met the criteria for response at week 8, and 45.4% were in remission. By the QIDS-SR 16, 53.3% of participants responded and 37.6% were in remission (Saveanu et al.17). The response and remission rates did not significantly differ between the three treatment groups. We also assessed change in symptom severity on the HRSD17 and the QIDS-SR16 as a dimensional measure.

There was a 28.4% attrition rate that represented participants who were not medication adherent at week 8 or who withdrew from the study before week 8 (Figure 1).

Assessment of childhood trauma
We used the Early-Life Stress Questionnaire (ELSQ)19 to assess the role of childhood trauma in relation to antidepressant outcomes. The ELSQ comprises 18 items, which assess exposure to specific traumatic events in the first 17 years of life (Table 1) and which are equivalent to the trauma items assessed by the Child Abuse and Trauma Scale.20 These events represent previously identified categories of trauma, including interpersonal violation (physical, psychological and sexual abuse, neglect, domestic violence, bullying), family breakup (divorce, separation, conflict), family health (death, life-threatening illness), personal health (hospitalization, life-threatening illness or injury), disaster/war (natural disaster, war), birth complications or adoption.20–23 Each item is scored dichotomously for the presence/absence of exposure to each type of trauma. For each type of trauma endorsed as ‘present’, participants also reported the age range in which the trauma occurred or first occurred (0–3, 4–7, 8–12 or 13–17 years of age). Previously, reports of childhood trauma using the ELSQ have been shown to correspond to registry-reported prevalence, and that reported trauma is predictive of severity of depressive symptoms.19

Extent of exposure to traumatic events was not found to differ across site (chi-square = 10.954, df = 6, P = 0.090) or across country (chi-square = 6.134, df = 4, P = 0.189).

Statistical analysis
All analyses were conducted for the intention-to-treat sample. We established response and remission status based on the patients who completed treatment and the 8-week follow-up assessment (Figure 1). Responses to the ELSQ items were treated as categorical variables.

1. To test the hypothesis that prevalence of early-life trauma differs in MDD patients compared with controls, we used chi-square analysis and compared groups on each type of trauma.

2. We used logistic regression models to test whether overall trauma is a general predictor of acute treatment outcomes for response and remission defined by the HRSD17 and QIDS-SR16. Linear regression models were used to test prediction of dimensionally defined severity of symptoms at week 8, controlling for pre-treatment baseline severity.

3. We also used logistic and linear regression models to test whether abuse is a specific predictor of treatment outcomes. Given the focus on a particular trauma category, we used a corrected alpha level of 0.01.

4. We used logistic and linear regression models and included an interaction term for trauma by type of antidepressant to test whether...
overall trauma load or specific exposure to childhood abuse is a
differential predictor of treatment outcomes for different types of
antidepressants (escitalopram, sertraline, venlafaxine-XR).

In each regression model, clinical site, age and baseline level of
depressive severity (on the HRSD_{17} or QIDS-SR_{16}) were controlled for as
covariates.

On the basis of the exponential beta values in the regression models, we
generated the OR for each significant effect. The OR for interaction terms
reflects how much greater/lower the likelihood of response/remission is in
a multiplicative sense for treatment type.

**RESULTS**

Prevalence of early-life trauma

To confirm the absence of mental disorder meeting criteria for
DSM-IV, healthy controls were assessed by a MINI structured interview.
They also completed all the assessments and had the same visit schedule as MDD participants. MDD participants were
exposed to significantly more early-life stress than the healthy
controls (Table 1); 62.5% of MDD participants reported more than
two traumatic events compared with 28.4% of controls (Table 1).
Most notably, MDD participants had a fourfold or higher rate of
exposure to abuse (sexual, physical and emotional) than healthy
controls (Table 1). Other types of interpersonal violation (neglect,
witnessing domestic violence and bullying or rejection) were also
significantly increased. More than 40% of the MDD participants
reported experience of emotional abuse or bullying/rejection at
school compared with less than 10% and 20%, respectively for
controls. Having experienced parent divorce, separation from
family, conflict with family or undergone major surgery or
hospitalizations was also more frequent among MDD participants
than controls, whereas other potential traumatic events like death
in the family or natural disasters were not. Supplementary
analyses showed that the group difference in ELSQ scores did
not differ as a function of gender; hence, gender was not included
as an additional variable in subsequent analyses.

Overall presence of early-life trauma as a predictor of response
and remission

Of 1008 participants randomized to treatment, 286 dropped out
and 722 were assessed at week 8 (Figure 1). Overall presence of at
least one early-life traumatic event was not a significant predictor
of the percentage change in symptom severity from pre- to post-
treatment, assessed by the HRSD_{17} and QIDS-SR_{16}. Overall trauma
was also not a significant predictor of response or remission
defined categorically by the HRSD_{17} and QIDS-SR_{16}.

Specific contribution of abuse as a predictor of response and
remission

The experience of abuse was a significant predictor of both
HRSD_{17}-defined remission (chi-square = 49.782, df = 12, \( P < 0.0001 \))
and response (chi-square = 72.769, df = 12, \( P < 0.0001 \)). The
experience of abuse at the age of 4 to 7 years contributed
specifically and significantly to prediction for both HRSD_{17}-defined
response (\( P = 0.034 \); OR = 1.574) and remission (\( P = 0.032 \);
OR = 1.606), indicating that participants were about 1.6 times less
likely to achieve response or remission if exposed to abuse at this age (Figure 2).

| Table 1. Prevalence of early-childhood trauma in depressed patients and in healthy controls, according to the category and type of trauma |
|----------------------------------------------------------------------------------------------------------------------------------|
| **Category and type of trauma (ELSQ items: yes/no questions)** | **% Prevalence of trauma** | **Group difference** |
| | MDD N = 1008 | Control N = 336 | \( \chi^2 \) | P-value |
| **Abuse/interpersonal violation** | | | | |
| Were you physically abused? | 219 (21.7) | 18 (5.4) | 41.925 | < 0.001 |
| Were you sexually abused? | 164 (16.3) | 18 (5.4) | 27.758 | < 0.001 |
| Were you emotionally abused? | 433 (43.0) | 31 (9.2) | 113.225 | < 0.001 |
| Did you experience extreme poverty or neglect? | 186 (18.5) | 15 (4.5) | 36.118 | < 0.001 |
| Did you witness domestic violence within your family? | 326 (32.3) | 49 (14.6) | 36.560 | < 0.001 |
| Did you experience sustained bullying or rejection by schoolmates? | 452 (44.8) | 60 (17.9) | 82.231 | < 0.001 |
| **Family breakup** | | | | |
| Did your parents divorce or separate? | 408 (40.5) | 103 (30.7) | 11.894 | 0.02 |
| Were you separated for a long period from a parent, brother or sister? | 439 (43.6) | 61 (18.2) | 30.035 | < 0.001 |
| Was there sustained conflict within your family? | 516 (51.2) | 112 (33.3) | 70.875 | < 0.001 |
| **Family health/death** | | | | |
| Did one of your parents, a brother or sister die? | 92 (9.1) | 26 (7.7) | 5.403 | 0.25 |
| Did one of your parents, a brother or sister experience a life-threatening illness? | 168 (16.7) | 36 (10.7) | 6.818 | 0.15 |
| **Personal health** | | | | |
| Did you undergo major surgery or repeated hospitalization? | 168 (16.7) | 32 (9.5) | 9.559 | 0.05 |
| Did you experience a life-threatening illness or injury? | 100 (9.9) | 27 (8.0) | 5.227 | 0.27 |
| **Disaster/war** | | | | |
| Did you witness first-hand a natural disaster such as earthquake, flood or fire? | 121 (12.0) | 39 (11.6) | 4.229 | 0.38 |
| Did you witness warfare? | 29 (2.9) | 7 (2.1) | 0.357 | 0.55 |
| **Other traumatic events** | | | | |
| Were you born prematurely, or experience other birth complications? | 132 (13.1) | 29 (8.6) | 3.895 | 0.048 |
| Were you adopted? | 43 (4.3) | 8 (2.4) | 3.399 | 0.49 |
| Was your house destroyed by fire or other means? | 43 (4.3) | 14 (4.2) | 2.711 | 0.61 |

Abbreviations: ELSQ, Early-Life Stress Questionnaire; MDD, major depressive disorder.
Abuse occurring at age 4 to 7 years was also a predictor of percentage change in clinician-rated symptom severity assessed by the HRSD₁₇ (F = 2.787, P = 0.007; specific contribution of abuse at 4 to 7 years; t = 2.573, P = 0.01; 50% mean symptom improvement in patients exposed to abuse at 4 to 7 years versus 58% in those not exposed). Similarly, abuse occurring at age 4 to 7 years was a predictor of dimensional change in self-reported symptom severity assessed by the QIDS-SR₁₆ (F = 6.507, P < 0.0001; specific contribution of abuse at 4 to 7 years; t = 2.242, P = 0.025; 40% mean symptom improvement in patients exposed to abuse at 4 to 7 years versus 47% in those not exposed).

Early-life abuse as a predictor of response and remission for specific types of treatment

Overall, the presence of early-life stressors occurring before 18 years of age did not interact with the type of treatment to predict response or remission. However, exposure to the specific trauma of abuse did interact with types of treatment to predict response and remission. Abuse included physical, sexual and emotional abuse items, which have been shown to form a cohesive factor.¹⁹

The experience of abuse predicted HRSD₁₇-defined response according to type of treatment (omnibus chi-square = 49.421, df = 13, P < 0.0001), specifically due to abuse at 4 to 7 years of age (P = 0.043, interaction OR = 1.225). The experience of abuse also predicted HRSD₁₇-defined remission according to type of treatment (omnibus chi-square = 36.322, df = 13, P < 0.0001), specifically due to abuse at 4 to 7 years of age (P = 0.049, interaction OR = 1.260). For sertraline, in particular, participants who were abused at this age showed significantly less improvement in both clinician (P < 0.0001) and self-rated (P = 0.007) symptoms, than with escitalopram and venlafaxine-XR treatments.

**DISCUSSION**

The iSPOT-D is the first real-world practical trial to assess the prevalence of childhood trauma and its impact on antidepressant outcomes in an international sample of outpatient treatment seekers with MDD. These outpatients were found to have a fourfold higher incidence of childhood abuse than their healthy peers, and a twofold higher incidence of early exposure to other traumatic events. The greater the exposure to abuse in particular, the less likely these depressed patients were to remit following treatment with one of the three commonly prescribed antidepressants. Our results suggest that remission rates may be especially low when abuse occurs during the very early period of 4–7 years of age, and following treatment with sertraline.

Overall, the higher rate of trauma observed in the present MDD sample is in line with registry and observational studies.⁵,⁹ Thus, childhood trauma and especially abuse may contribute to the development of depression observed in routine practice in multiple outpatient settings spanning primary and specialist care settings. Our findings suggest that abuse in particular, and not overall exposure to traumatic events, predicts a lower rate of acute response and remission after antidepressant therapy. Sexual, physical and emotional abuse compared with other types of trauma (such as death of a parent/sibling, personal life-threatening illness/injury, or disaster), may have a specific impact on the neurobiological mechanisms of non-response to treatment. Neuroimaging studies suggest that there may be a differential effect of childhood sexual abuse on the subsequent functioning of emotional brain circuits in adulthood depression.²⁴ Childhood abuse has also been associated with a greater sensitivity to stress,⁶ cognitive impairment,²⁵ alterations in brain morphometry,²⁶–⁳⁰ and immune and metabolic abnormalities⁴¹ that may impact the course of depression and capacity to respond to antidepressants. It is also possible that abuse may recur and that it is the recurrence of the trauma that produces poor treatment outcomes.

In addition to the type of stressor, our results suggest that there is a critical period (4 to 7 years) in which childhood trauma occurs and has the most significant impact on subsequent poor response to antidepressants in adulthood. There is a rapidly growing body of work to suggest that gene polymorphisms and epigenetic modifications interact with childhood trauma to exert their effect on risk for depression,³²–³⁴ and that this effect is greatest at critical neurodevelopmental periods.⁷ This evidence is consistent with the view that the extent of brain plasticity varies during development, such that trauma occurring during critical neurodevelopmental periods may alter brain morphometry, circuit function, endocrine regulation, immune function and subsequent physiologic reactions to stress in an enduring way.⁹,¹⁶,³⁶–⁴⁰

Abuse occurring at age 4 to 7 years was associated with significantly poorer outcomes following the treatment with sertraline compared with the other selective serotonin-reuptake inhibitor escitalopram and the SNRI venlafaxine-XR. The participants who were abused at this age showed significantly less improvement in both clinician and self-rated symptoms following 8 weeks treatment with sertraline. Sertraline, in contrast to other serotonin-reuptake antidepressants, has an additional relatively specific effect on inhibiting dopamine.³⁸ There is some evidence that subgroups of patients are also characterized by dopamine circuit dysfunction³⁹ and number of traumatic events has been associated with higher ventral striatal dopamine response to amphetamine.⁴⁰ Although speculative, these lines of evidence support the view that childhood trauma may have a specific impact on the neurobiological mechanisms of non-response to treatment.
suggest that a possible dopamine-related mechanism might contribute to our specific observation of especially poor outcomes following sertraline in those exposed to early abuse.

Clinical translational signification

Here, we provide evidence from a well-powered study that outpatients with MDD have a fourfold higher incidence of childhood abuse than their healthy peers, and a twofold higher incidence of early exposure to other traumatic events. The greater the exposure to trauma, the less likely these depressed patients were to remit following antidepressant response. Thus, the translational signification of these findings is that in routine clinical management of depression it may be important to screen for childhood trauma to identify those patients that may not benefit from standard first-line antidepressants and may require additional therapy to more directly address the impact of trauma.

Limitations

The results should be interpreted within the context of several potential limitations of the study. First, there may be limitations due to sampling. We had a higher percentage of males relative to females than reported in previous studies such as STAR*D. This difference might be because we used a practical biomarker trial design and that males were more likely to report depression and trauma in this context. However, because women have previously been more likely to report trauma than men, future studies are required to establish the generalizability of our findings.

The study might also be limited due to the assessment of early-childhood trauma by the ELSQ. The scale is dependent on the recollection of the subject, and age 4–7 years may be the earliest reliable recollection rather than representing only a specific window of vulnerability. However, this limitation would not account for the lack of specific effect of abuse experienced after 7 years of age. Retrospective reports of childhood trauma, such as those assessed by the ELSQ, may have some bias but also tend to err on the side of false negatives rather than false positives. The prevalence of trauma reported retrospectively using the ELSQ is comparable with prevalence rates from archival records suggesting that such retrospective reports are also reliable. Nonetheless, it would be important to establish the reproducibility of our findings using additional and independent measures. Design limitations of this study include the reliance on only three first-step antidepressants, though they are commonly used in practice. Doses were lower than midrange of the recommended range, perhaps because the response and remission rates were large enough that further dose escalation was not warranted in many patients. Furthermore, as dose ranges were reflective of usual management practices and since primary care physicians prescribe about two-thirds of antidepressants, these ranges are an appropriate starting point for identifying predictors of outcome in real-world management settings. Although the present sample is well powered, we recognize that the findings are limited to this sample and that it would be beneficial to seek to replicate the findings in another sample. The iSPOT-D is designed to address future replication in a second cohort of a similar sample size.

CONCLUSION

Here we provide a systematic investigation to show that there is a fourfold increase in the rate of childhood trauma, especially physical, emotional and sexual abuse, in outpatients with depression. Abuse occurring before the age of 7 years predicts substantially poorer response and remission outcomes for commonly prescribed antidepressants. These outcomes may be poorest for sertraline. These results suggest that it is important to assess for childhood trauma in the outpatient management of depression, and to consider alternative or supplemental treatments for patients with a trauma history.

CONFLICT OF INTEREST

The iSPOT-D sponsor central management team managed the operations of the sites and the data storage and quantification. Interpretation of the data was undertaken independently from the study sponsor and preparation and review of the manuscript was undertaken by the academic authors. LMW has received consultant fees from Brain Resource and from Humana. CD has received research funding from Brain Resource, St. Jude, Jannsen, Assurex, Roche, Takeda and has received consultant fees from Pfizer and Genentech. A-MD has received research funding from Brain Resource. AFS has served as a consultant to Bay City Capital, BrainCells, CeNeRx, Cervel, Depomed, Eli Lilly, Forum, Genentech, Gilead, Jazz, Lundbeck/Takeda, McKinsey, Merck, MSL, Neurotensins, Novadel, OneCarbon, PharmaNeuroBoost, Sunovion, Synosyn and Xhale; he has received honoraria from Merck; he has equity in Amnestix, BrainCells, CeNeRx, Concept (co-founder), Delpor, Forest, Merck, Neurocrine, Novadel, Pfizer, PharmaNeuroBoost, Somaxon, Synosyn, Titan and Xhale; and he receives royalties from Stanford University for patents on mifepristone use and the pharmacogenetics of antidepressant response. In the last 3 years, CBN has received a Scientific Advisory Board/Board of Directors fee from PharmaNeuroboost, ClinLara/Brackett, Xhale, Taisho, Fortress, Takeda, Jannsen/Ortho-McNeil and George Weiden Mental Health Foundation. He holds stock or stock options in Xhale, ClinLara/Brackett, Seattle Genetics, Celgene, Titan and Network Life Sciences. CBN has patents for Methods and devices for the transdermal delivery of lithium (US 6 375 990 B1) and Method to estimate serotonin and norepinephrine transporter occupancy after drug treatment using patient or animal serum (provisional filing April 2001). LMW was the overall academic PI for iSPOT-D (2008–2013), CD is the PI for the Stanford iSPOT-D site, A-MD is co-I for the Ohio State iSPOT-D site, AFS is co-I for the Stanford iSPOT-D site and CBN is co-I for the Miami University iSPOT-D site. Analyses were undertaken by LMW, CD and CBN and all the authors participated in interpreting results and drafting the manuscript. CD and LMW had full access to all the data in the study and they take responsibility for the integrity of the data and the accuracy of the data analysis.

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