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Research paper

Efficacy of vortioxetine in patients with major depressive disorder reporting childhood or recent trauma

Michael Cronquist Christensen[a,*], Ioana Florea[a], Henrik Loft[a], Roger S. McIntyre[b]

[a] H. Lundbeck A/S, Valby, Denmark
[b] Mood Disorders Psychopharmacology Unit, University Health Network, University of Toronto, Toronto, ON, Canada

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ABSTRACT

Background: This analysis investigates the efficacy of vortioxetine in adults with major depressive disorder (MDD) who report childhood or recent trauma.

Methods: Patient-level data were analyzed from 4 double-blind, randomized, placebo-controlled short-term studies investigating the efficacy of vortioxetine (5–20 mg/day) versus placebo in patients (18–75 years old) with *DSM-IV-TR*–defined MDD. Changes from baseline to week 8 on the Montgomery-Åsberg Depression Rating Scale (MADRS), Hamilton Anxiety Rating Scale (HAM-A), Clinical Global Impression - Improvement (CGI-I), and Sheehan Disability Scale (SDS) were examined at the individual study level and as in meta-analysis. A long-term relapse prevention study of 5 and 10 mg of vortioxetine was also analyzed. Traumatic events history was recorded at baseline.

Results: Sixty-one percent of subjects (1113/1811) reported trauma history in the short-term studies. A significant effect vs. placebo was observed for vortioxetine on MADRS (10 mg, –2.2, $P = .025$; 20 mg, –4.4, $P < .001$), HAM-A (20 mg, –1.60, $P = .012$), CGI-I (5 mg, –0.3, $P = .028$; 10 mg, –0.3, $P = .013$; 20 mg, –0.50, $P = .009$), and SDS (20 mg, –2.3, $P = .007$) in patients with any trauma (childhood and/or recent). In the relapse prevention study, 51% (198/392) of subjects reported a history of trauma. Subjects with any trauma (childhood and/or recent) randomized to placebo were significantly more likely to relapse than subjects treated with vortioxetine (hazard ratio 2.8, $P = .0019$).

Limitations: An exploratory analysis.

Discussion: Vortioxetine showed significant short- and long-term efficacy on depressive and anxiety symptoms and overall functioning in this large subpopulation of MDD patients with a history of trauma. A significantly lower risk of relapse was also observed with vortioxetine.

1. Introduction

Childhood trauma is commonly reported in individuals with major depressive disorder (MDD) and is known to be a significant risk factor for incident depression in adulthood (Dube et al., 2005, 2003; Kendler et al., 1995). Results from the International Study to Predict Optimized Treatment for Depression (iSPOT-D) indicate that individuals with MDD are significantly more likely to report early life stress than controls (i.e., 62.5% of MDD participants reported >2 traumatic events compared with 28.4% of controls) (Williams et al., 2016). Furthermore, self-reported childhood trauma is associated with greater illness complexity in MDD, as evidenced by higher rates of suicidality (Fuller-Thomson et al., 2016).

Despite the high prevalence of a history of psychological trauma in patients with MDD, only a few studies have investigated the effectiveness of pharmacological treatments in this large, clinically important subpopulation. It is reported that response to antidepressants in adults with MDD is attenuated in individuals self-reporting childhood trauma (Williams et al., 2016; Nemeroff et al., 2003; Miller et al., 2015). Moreover, the iSPOT-D trial reported that abuse occurring at ≤7 years of age predicted poorer outcomes after 8 weeks of antidepressant treatment in adults. In addition to attenuated antidepressant efficacy with pharmacological treatment among individuals reporting trauma, the risk of recurrence of MDEs is reported to be higher in this subpopulation (Williams et al., 2016; Hovens et al., 2015). In a study of adults with chronic depression and childhood trauma (Nemeroff et al., 2003), participants exhibited attenuated responses to the antidepressant nefazodone, whereas individuals receiving manual-based

* Corresponding author.
E-mail address: MCRC@lundbeck.com (M.C. Christensen).

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cognitive behavioral therapy exhibited relatively higher responses. A meta-analysis of studies conducted before 2010 showed a generally poorer effect of monotherapy, combination therapy, and psychotherapy in adults with MDD and a history of childhood maltreatment (Nanni et al., 2012). Taken together, exposure to childhood trauma, perhaps via epigenetic mechanisms, results in a different biotype of MDD with a differential illness characteristics trajectory and response to treatments as compared to MDD with no trauma history (Lang et al., 2019; McIntyre et al. 2014a).

Most studies evaluating the influence of trauma on adult antidepressant treatment outcomes have focused on early childhood trauma. There is a paucity of studies that have sought to determine the influence of recent trauma on acute antidepressant outcomes. Although depression is twice as prevalent as posttraumatic stress disorder (Kessler et al., 2005), the existing literature on trauma disproportionately evaluates posttraumatic stress disorder presentations and outcomes rather than illness and treatment influence in MDD (Grosse et al., 2016).

Region-specific epigenetic changes in the central nervous system are a highly replicated observation in adults with MDD reporting childhood trauma, in accordance with preclinical studies evaluating the effect of stress on central nervous system molecular signatures (Weiss et al., 1999; Teicher et al., 2002, 2003; Deighton et al., 2018). Furthermore, the structural and functional interconnectivity in discrete brain circuits and networks is abnormal in individuals with MDD reporting distal trauma events (Bolsinger et al., 2018). For example, alterations in cognitive control and other task-positive networks as well as default mode networks are consistently identified with evidence of abnormal reciprocity and abnormal anticorrelation (Nakao et al., 2013). A separate and related body of evidence indicates that trauma during critical periods of development is associated with abnormalities in cognitive functions and measures of reward and motivation (Mackiewicz et al. 2018). A concatenation of study findings from both preclinical and clinical activities indicates that deficits in general cognition and measures of motivation and reward (e.g., anhedonia) are more likely to be observed in the context of past trauma (McLaughlin et al., 2015; Sasagawa et al., 2017; Blais and Geiser 2019).

A derivative of the foregoing set of observations is that treatments that are capable of exerting procognitive effects or mitigating deficits in motivation and reward may be particularly effective in individuals with MDD reporting childhood trauma. For example, the multimodal antidepressant vortioxetine has demonstrated both procognitive and antianhedonia clinical effects in patients with MDD (McIntyre et al. 2014b; Mahableshwarkar et al. 2015b; Cao et al., 2019). In preclinical paradigms, vortioxetine has also been shown to attenuate exaggerated fear responses in animal models (Hatherall et al., 2017; Mørk et al., 2013) and improve ability to cope with stressful conditions (Brivio et al., 2019; Sanchez et al., 2015). Moreover, vortioxetine treatment in remitted-depressed patients has been shown to attenuate exaggerated brain activity in select brain regions (e.g., hippocampus), suggesting changes of critical brain regions (Smith et al., 2018).

We sought to determine whether vortioxetine would be efficacious in adults reporting recent or childhood trauma. The impetus for this analysis was provided by the relatively small number of studies evaluating the association between antidepressant response (and relapse prevention) and childhood trauma, as well as the theoretical framework suggesting that vortioxetine, via effects on cognitive control networks, would be efficacious in this commonly encountered subpopulation of patients with MDD.

2. Methods

2.1. Study population

The study population was drawn from the following short-term, double-blind, randomized, fixed-dose, placebo-controlled, 8-week studies investigating the efficacy of vortioxetine versus placebo on depressive and anxiety symptoms as well as overall patient functioning in adults with moderate-to-severe MDD: (Mahableshwarkar et al., 2015a) (NCT01153009; vortioxetine 15 and 20 mg vs placebo); (Baldwin et al., 2012) (NCT00635219; vortioxetine 2.5, 5, and 10 mg vs placebo); Jacobsen et al. (2015) (NCT01163266; vortioxetine 10 and 20 mg vs placebo), and Boulenger et al. (2014) (NCT01140906; vortioxetine 15 and 20 mg vs placebo). In a long-term relapse prevention study by (Boulenger et al., 2012) (NCT00596817), the efficacy of vortioxetine 5 and 10 mg versus placebo was investigated with regard to relapse prevention, long-term efficacy on depressive and anxiety symptoms, and overall functioning and health-related quality of life. Only doses of vortioxetine in the therapeutic dose range (5–20 mg) were considered in the present analysis.

The study population in all 4 short-term studies and the relapse prevention study comprised adults (aged 18–75 years) with a primary diagnosis of MDD according to *DSM-IV-TR* criteria, current major depressive episode of ≥3 months' duration (confirmed using the Mini International Neuropsychiatric Interview), and a Montgomery-Åsberg Depression Rating Scale (MADRS) total score ≥26 at screening and baseline visits. Patients in study NCT1153009 (Mahableshwarkar et al., 2015a), and NCT01163266 (Jacobsen et al., 2015) were recruited at sites in the US between 2010 and 2012. Patients in study NCT01140906 (Boulenger et al., 2014) were recruited in Belgium, Estonia, Finland, France, Germany, Latvia, Lithuania, Norway, Russia, Slovakia, South Africa, Sweden and the Ukraine from May 2010 to September 2011. Patients in study NCT00635219 (Baldwin et al., 2012) were recruited in Australia, Bulgaria, Canada, the Czech Republic, Estonia, Finland, France, Hong Kong, India, the Republic of Korea, Latvia, Lithuania, Malaysia, the Philippines, Romania, Slovakia, Spain, Taiwan, Turkey and Ukraine from February 2008 to April 2009. Finally, subjects in study NCT00596817 (Boulenger et al., 2012) were recruited in Australia, Austria, Belgium, Canada, Finland, France, Germany, India, the Republic of Korea, Norway, Poland, South Africa, Sweden, Taiwan, Thailand, Turkey and the United Kingdom between December 2007 and September 2009.

Childhood or recent trauma history was assessed at baseline by the investigator, via interview with the patients according to categories inspired by the Childhood Trauma Questionnaire (Bernstein et al., 1994). Specifically, for childhood traumatic events, the investigator inquired for any of the following types of trauma before the age of 17 years: *[Death of a very close friend or family member?], [Any upheaval between the parents (such as divorce, separation)?], [A traumatic sexual experience (raped, molested, etc.)?], [Victim of violence (child abuse, mugged or assaulted other than sexual)?], [Extremely ill or injured?]*. If any of these types of trauma were indicated, the investigator also noted age of the subject at the time of the event. For recent trauma, the investigator inquired for any trauma the subject may have experienced within the past 3 years of the following types: [*[Death of a very close friend or family member?], [Major upheaval between the patient and his/her spouse?], [A traumatic sexual experience (raped, molested, etc.)?], [Extremely ill or injured?], [Major change in work (eg, new job, promotion, demotion, lateral transfer)?]*. All analyses were performed in the full study population (full analysis set) and for patients with any trauma (childhood or recent), patients with childhood trauma, and patients with recent trauma.

All studies were conducted in accordance with the principles of Good Clinical Practice (ICH, 1996) and the Declaration of Helsinki (World Medical Association, 2002) and approved by local research ethics committees. Eligible patients provided written informed consent before participating.

2.2. Clinical outcomes

Efficacy was assessed for depressive symptoms and anxiety symptoms using the MADRS and Hamilton Anxiety Rating Scale (HAM-A) in

all studies. Efficacy on overall clinical impression was assessed using the Clinical Global Impression scale (CGI), whereas the Sheehan Disability Scale (SDS) was used as an efficacy measure for overall functioning. For the CGI-Improvement (CGI-I), the scores range from 1 (very much improved) to 7 (very much worsened). For CGI-Severity (CGI-S), the scores range from 1 (normal) to 7 (among the most extremely ill). The SDS prompts patients to rate their own functioning on a scale from 1 to 10 in terms of work, social life, family life (total score of 30; higher score indicates worse functioning). Finally, in the relapse prevention study, (Boulenger et al., 2012) health-related quality of life was measured by the Short Form (36) Health Survey (SF-36).

2.3. Statistical analysis

Mean changes from baseline to endpoint in MADRS, HAM-A, SDS total scores, and SF-36 mental health component were analyzed using a mixed model for repeated measurements. Dichotomous outcomes of MADRS remission (MADRS total score ≤ 10) and CGI-I (CGI-$I \leq 2$) were analyzed by logistic regression, adjusting for baseline score and treatment using last observation carried forward data. A standard random effects meta-analysis for antidepressant response was performed using the MADRS results from each of the short-term placebo-controlled trials. The relapse prevention study was analyzed separately for risk of relapse using a Cox proportional hazards model. Furthermore, MADRS, HAM-A, CGI-S, SDS, and SF-36 were evaluated in the double-blind period by considering change from randomization up to week 48. All endpoints were analyzed at all time points by logistic regression, adjusting for baseline score and treatment using last observation carried forward. All analyses were made versus placebo.

2.4. Safety and tolerability assessments

At each visit, starting at baseline, patients were asked a nonleading question (such as, “How do you feel?”). All adverse events (AEs) observed by the investigator or reported spontaneously by the patient were recorded. Qualified personnel coded AEs using the lowest-level term according to MedDRA (Medical Dictionary for Regulatory Activities, version 14.0, 2011). Potential relationships between study drug and suicidality were assessed using the Columbia-Suicide Severity Rating Scale (C-SSRS) (United States Food and Drug Administration (FDA), 2010).

3. Results

3.1. Baseline characteristics

A total of 1811 patients were included in the full analysis set from the 4 short-term clinical studies (Table 1). The relapse prevention study included 396 patients randomized into the double-blind treatment period. In the short-term studies, 42% of patients ($n = 765$) indicated childhood trauma at baseline, and 48% ($n = 863$) reported recent trauma. In total, 61% reported a history of trauma in the sample, and 28.4% reported both childhood and recent trauma. Among patients with childhood trauma, 303 (39.6%) reported 2 or more types of childhood trauma, and 341 (39.5%) with recent trauma reported at least 2 types. In the relapse prevention study, 26.8% ($n = 105$) reported childhood trauma at baseline, and 42.1% ($n = 165$) reported recent trauma. In the short-term studies, patients with childhood trauma were on average 3 years younger than the overall study population, had a slightly higher mean number of major depressive episodes, and had longer duration of current episode. In the overall study population, 69.4% of the subjects were women, whereas this sex distribution was slightly different in patients with any type of trauma (71.8%) or childhood trauma (74.5%). In the relapse prevention study, patients with childhood trauma were also younger by ≈ 2 years and had slightly more previous major depressive episodes (Table 1). All subjects in all studies had a minimum MADRS total score of 26 at screening and baseline, and no major differences were observed between the overall study population and patients with history of trauma in terms of baseline severity of depressive symptoms, anxiety, or functional impairment.

MDD patients with a history of trauma reported at baseline more suicidal ideation and behavior across all 8 categories of the C-SSRS than MDD patients without such history. The biggest differences were observed in the categories of “wish to be dead,” “active suicidal ideation with any method (no plan) without intent to act,” and “non-fatal suicide attempt” (Supplementary Table 1).

In terms of the type of traumatic events, traumatic sexual experience, upheaval between parents, and death of a friend were the most common types of trauma among patients with childhood trauma, whereas death of a friend, major change in work situation, and major upheaval between patient and spouse were the most common types in patients with recent trauma (Fig. 1A). A history of trauma was substantially higher in patients recruited at sites in the United States than elsewhere in the world, both for childhood and recent trauma (Figs. 1B and 1C).

3.2. Clinical outcomes

In the short-term studies , the difference versus placebo on the MADRS was –2.3 for vortioxetine 5 mg ($P = .099$), –2.2 for 10 mg ($P = .025$), –2.8 for 15 mg ($P = .069$), and –4.4 for 20 mg ($P < .001$) in patients with any trauma (childhood and/or recent) (Table 2). For vortioxetine 20 mg, the effect on MADRS total score was –3.7 ($P < .001$) in patients with childhood trauma, whereas in patients with recent trauma, the effect was –5.0 ($P < .001$). In patients with multiple childhood traumas (≥ 2 types), the effect of vortioxetine 15 and 20 mg on MADRS total score was –5.1 ($P = .032$) and –4.8 ($P = .005$), respectively. In patients with multiple recent traumas, the effect of vortioxetine 20 mg was –3.7 ($P = .014$). In terms of the effect on anxiety symptoms, the difference versus placebo on HAM-A total score was –1.9 for vortioxetine 5 mg ($P = .089$), –0.5 for 10 mg ($P = .587$), 0.03 for 15 mg ($P = .961$), and –1.6 for 20 mg ($P = .012$) in patients with any trauma (Table 3). In patients with childhood trauma, the effect of vortioxetine on HAM-A total score was significant for 5 mg (–4.1, $P = .008$) and for vortioxetine 20 mg in patients with recent trauma (–1.8, $P = .028$). For global clinical impression after 8 weeks of treatment, the difference versus placebo on CGI-I total scores was –0.3 for vortioxetine 5 mg ($P = .028$), –0.3 for 10 mg ($P = .013$), –0.4 for 15 mg ($P = .089$), and –0.5 for vortioxetine 20 mg ($P = .009$) in patients with any trauma. In patients with childhood trauma, the effect of vortioxetine 15 mg and 20 mg on CGI-I score was –0.4 ($P = .020$) and –0.4 ($P = .004$), respectively, whereas in patients with recent trauma the effect was significant for vortioxetine 20 mg (–0.5; $P = .015$). Remission rates according to MADRS (total score ≤ 10) were significantly higher for vortioxetine 20 mg in both patients with any trauma ($P = .024$) and with childhood trauma only versus placebo ($P = .019$) (Supplementary Table 1). Significant differences in response rates according to CGI-I (CGI-$I \leq 2$) were observed at 5 mg (odds ratio [OR] = 2.9, $P = .033$), 15 mg (OR = 1.8, $P = .023$), and 20 mg (OR = 1.8, $P = .010$) in patients with childhood trauma and at 15 mg (OR = 1.7, $P = .035$) and 20 mg (OR = 1.9, $P = .033$) in patients with recent trauma (Supplementary Table 1). Finally, in terms of overall functioning, the effect versus placebo on SDS total score was 0.3 for vortioxetine 5 mg ($P = .811$), –1.1 for 10 mg ($P = .245$), –1.7 for 15 mg ($P = .270$), and –2.3 for 20 mg ($P = .007$) in patients with any trauma. In patients with recent trauma, the effect of vortioxetine on the SDS total score was significant for 20 mg (–2.4; $P = .016$) (Table 3).

In the relapse prevention study, the hazard ratio for the total study population was 2.0 (95% CI, 1.3–3.2; $P < .0035$; Fig. 2A). Subjects with any trauma (childhood and/or recent) randomized to placebo were significantly more likely to relapse than those randomized to

Table 1
Demographics and baseline clinical characteristics (FAS).

	All individuals		Patients with history of any trauma		Patients with history of childhood trauma		Patients with history of recent trauma	
	Mean ± SD	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD	n
Short-term MDD studies								
Age, y	44.3 ± 13.0	1811	43.1 ± 12.7	1113	41.7 ± 12.7	765	43.7 ± 12.3	863
Sex,% female	69.4	1811	71.8	1113	74.5	765	71.1	863
MADRS total	31.9 ± 4.1	1811	32.1 ± 4.3	1113	32.2 ± 4.3	765	32.1 ± 4.3	863
HAM-A total	20.0 ± 6.3	1811	20.3 ± 6.3	1113	20.0 ± 6.1	765	20.4 ± 6.4	863
SDS total	19.7 ± 5.9	1351	19.7 ± 6.0	840	19.9 ± 5.9	580	19.7 ± 6.0	638
CGI-S	4.7 ± 0.7	1810	4.7 ± 0.7	1112	4.7 ± 0.6	764	4.7 ± 0.7	862
Number of MDEs	2.6 ± 2.2	1811	2.7 ± 2.4	1113	2.9 ± 2.4	765	2.7 ± 2.3	863
Age at first event (if childhood), y	NA	NA	NA	NA	8.5 ± 4.3	626	NA	NA
Duration of current MDE, wk	36.8 ± 53.0	1807	39.6 ± 54.3	1110	41.4 ± 52.6	763	39.0 ± 47.2	861
MDD relapse prevention study								
Age, y	44.5 ± 12.4	646	43.4 ± 11.9	334	42.0 ± 12.6	184	43.6 ± 11.3	268
Sex,% female	62.1	646	62.6	334	63.6	184	61.9	268
Number of MDEs	2.1 ± 1.7	645	2.2 ± 1.6	334	2.4 ± 1.7	184	2.1 ± 1.4	268
Age at first trauma event (if childhood), y	NA		NA		9.3 ± 4.6	216	NA	
Duration of current MDE, wk	22.7 ± 23.0	646	23.6 ± 26.3	334	23.7 ± 28.8	184	24.1 ± 26.0	268
HAM-A total I	22.6 ± 6.6	646	23.4 ± 6.7	334	23.6 ± 6.5	184	23.2 ± 6.7	268
HAM-A total II	4.8 ± 3.7	404	4.8 ± 3.6	205	4.8 ± 3.9	109	4.7 ± 3.6	168
SDS total I	20.8 ± 5.7	550	21.5 ± 5.5	285	22.0 ± 5.6	157	21.4 ± 5.3	229
SDS total II	9.1 ± 7.4	379	8.8 ± 7.6	189	8.1 ± 7.4	103	9.1 ± 7.8	156
MADRS I	32.3 ± 4.1	646	32.3 ± 4.3	334	32.1 ± 4.2	184	32.4 ± 4.3	268
MADRS II	4.8 ± 3.1	404	4.4 ± 3.0	205	4.3 ± 3.0	109	4.5 ± 3.1	168
CGI-S I	4.8 ± 0.7	646	4.9 ± 0.7	334	4.9 ± 0.7	184	4.9 ± 0.7	268
CGI-S II	1.6 ± 0.7	404	1.5 ± 0.7	205	1.5 ± 0.7	109	1.5 ± 0.7	168

Abbreviations: CGI-S, Clinical Global Impression-Severity; FAS, full analysis set; HAM-A, Hamilton Anxiety Rating Scale; MADRS, Montgomery-Åsberg Depression Rating Scale; MDD, major depressive disorder; MDE, major depressive episode; NA, not applicable; SD, standard deviation; SDS, Sheehan Disability Scale. I: first baseline score at study entry. II: baseline score after 20 weeks of treatment and before randomization.

vortioxetine 5 or 10 mg, with a hazard ratio of 2.8 (95% CI, 1.5–5.4; $P = .0019$; Fig. 2B). In patients with childhood trauma, the hazard ratio was significant at 2.4 (95% CI, 1.0–5.8; $P = .0446$; Fig. 2C). In patients with recent trauma, the hazard ratio was also significant at 2.6 (95% CI, 1.3–5.2; $P = .0097$; Fig. 2D). The difference in MADRS total score for vortioxetine versus placebo in change from baseline in the double-blind period (after 12 weeks of open-label treatment) was –4.1 ($P = .0048$) in patients with any trauma. In patients with childhood trauma and recent trauma, the effect of vortioxetine was –4.0 ($P = .0715$) and –4.2 ($P = .0115$), respectively (Table 4). In terms of anxiety symptoms, a significant effect of vortioxetine versus placebo on HAM-A total score after randomization was observed in patients with any trauma (–2.6, $P = .0173$). Significant improvement with vortioxetine treatment was also observed in patients with any trauma on both CGI-Severity (–0.6; $P = .0042$) and overall functioning SDS (–2.4; $P = .0471$). For the SDS social life component, a significant effect with vortioxetine was observed both in patients with childhood trauma (–1.4; $P = .0376$) and those with recent trauma (–1.2; $P = .0051$). Finally, in terms of health-related quality of life, a significant effect of vortioxetine versus placebo was observed in patients with any trauma (2.5; $P = .0087$), childhood trauma (4.1; $P = .0090$), and recent trauma (2.3; $P = .0290$) on the SF-36 mental health index (Table 4).

3.3. Tolerability

In the short-term studies, in patients with any traumatic event, the most common AEs reported by at least 5% of patients treated with either 5, 10, 15, or 20 mg of vortioxetine and for which the incidence was numerically higher than for patients treated with placebo were nausea, headache, dizziness, dry mouth (only with 20 mg dose), diarrhea, constipation, vomiting, nasopharyngitis, insomnia (only with 5 mg dose), dyspepsia, and hyperhidrosis (Supplementary Table 3). AEs reported by at least 5% of patients in the long-term, double-blind, placebo-controlled, relapse-prevention study are presented in Supplementary Table 2. Pretreatment C-SSRS scores in patients with any trauma indicated more events in each of the C-SSRS scores than in patients without traumatic events. During the study, in patients with any trauma there were also more reports of events in the C-SSRS scores than in patients without trauma. There was no difference in shift from none to any form of suicidal ideation or behavior between the placebo and vortioxetine treatment groups (placebo, $n = 9$, 5.7%; vortioxetine 10 mg, $n = 3$, 5.1%; vortioxetine 15 mg, $n = 4$, 4.1%; vortioxetine 20 mg, $n = 4$, 2.6%).

4. Discussion

Herein, we replicate previous study results showing that a large percentage of adults with MDD present with childhood trauma or recent trauma (Williams et al., 2016). This analysis, the first to ascertain the efficacy of vortioxetine on depression and anxiety symptoms as well as on overall functioning in people with MDD reporting childhood or recent trauma, indicates that vortioxetine (5–20 mg) is highly effective as a short-term treatment and relapse prevention strategy in this patient population. In short-term (8 weeks) studies, significant effects were observed on depressive symptoms, anxiety, global clinical impression, and overall functioning. MDD patients with trauma treated with vortioxetine 5 or 10 mg were also significantly less likely to relapse than patients given placebo. Long-term treatment with vortioxetine further improved anxiety symptoms, overall functioning, and health-related quality of life in MDD patients with childhood and/or recent trauma. AEs reported in patients with any traumatic event in the vortioxetine group were in accordance with the overall study population in terms of type of events reported and the incidence of events.

The translational value of our findings into clinical practice is manyfold. First, clinicians often encounter patients with MDD who self-report childhood trauma or recent life stressors. Available evidence indicates that these populations are not only commonly encountered across clinical settings but exhibit diminished responses to selective serotonin reuptake inhibitor therapy (Williams et al., 2016). It is further reported that patients reporting trauma are not only more likely to exhibit

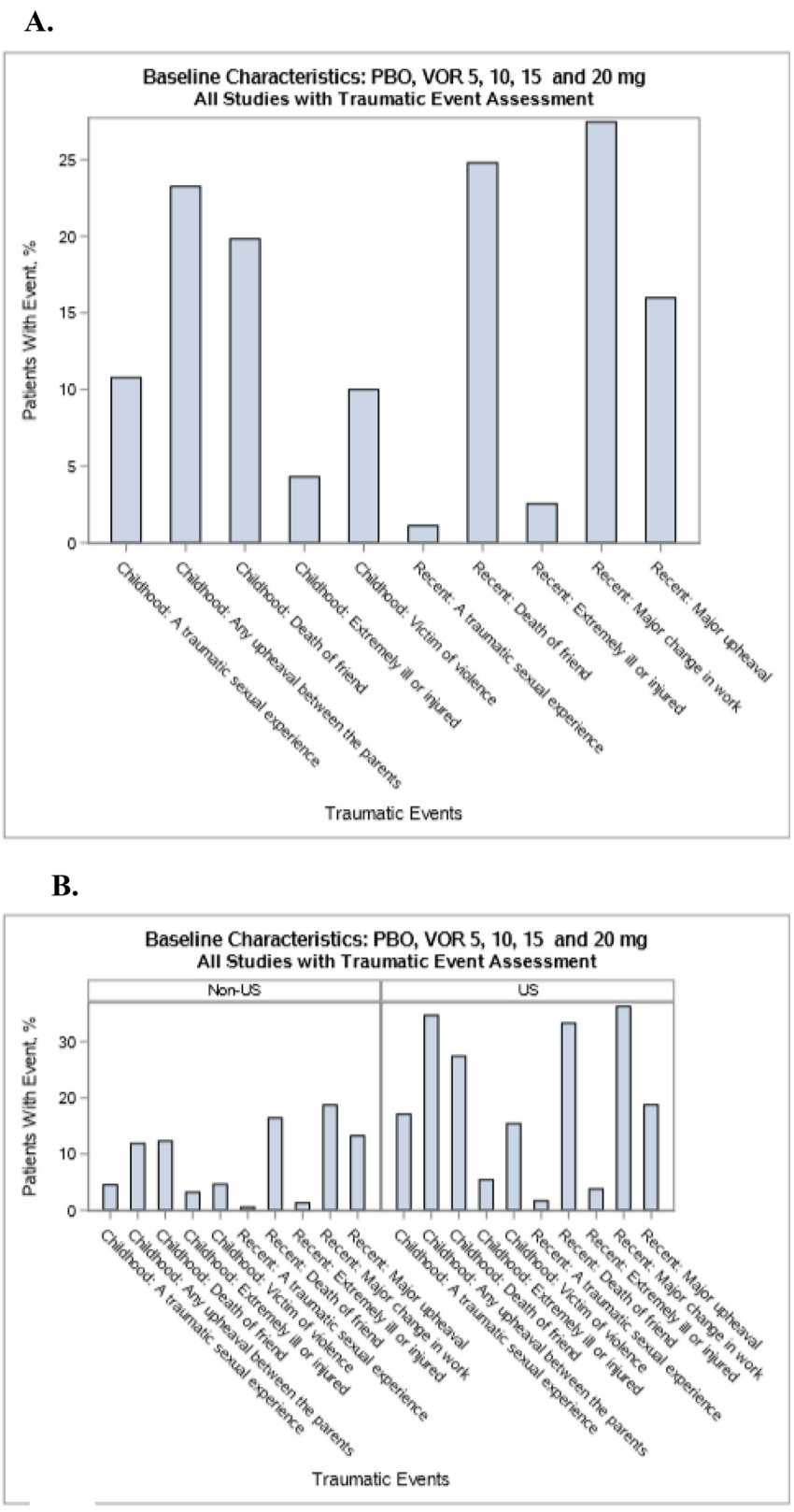

Fig. 1. Distribution of types of traumatic event at baseline in all short-term studies (NCT01153009, NCT00635219, NCT01163266, NCT01140906, and NCT00596817). (A) Percentage of patients with types of traumatic event categorized as any trauma (childhood or recent), childhood trauma, and recent trauma. (B) Percentage of patients with type of traumatic event categorized as any trauma (childhood or recent), childhood trauma, and recent trauma, by region (US vs non-US).

suboptimal treatment response but are also at greater risk of non-recovery, suicidality, psychiatric and medical comorbidity, chronicity, and health services utilization (Goldberg et al., 2019). Available evidence also suggests that adults with MDD reporting trauma are more likely to benefit from manual-based psychotherapies than conventional antidepressant therapy (Cook et al., 2017). Unfortunately, access and availability to manual-based treatments is often limited, or there are barriers (e.g., cost) that limit their widespread application.

Table 2
Change from baseline to week 6/8 in MADRS total score (Difference vs Placebo) according to trauma status (FAS, MMRM, OC)[a].

Study (NCT Identifier #) Dose	All patients (n = 1476)		Patients with any trauma (n = 914)		Patients with childhood trauma (n = 630)		Patients with recent trauma (n = 708)	
	Mean ± SE	*P* Value	Mean ± SE	*P* Value	Mean ± SE	*P* Value	Mean ± SE	*P* Value
11984A (NCT00635219)								
5 mg	**–2.5 ± 1.1**	**.018**	–2.3 ± 1.4	.100	–3.8 ± 2.1	.070	–0.6 ± 1.6	.737
10 mg	**–2.7 ± 1.1**	**.014**	–2.8 ± 1.5	.052	–3.0 ± 2.0	.129	–2.0 ± 1.7	.230
13267A (NCT01140906)								
15 mg	**–5.5 ± 1.1**	**<0.001**	**–4.4 ± 1.6**	**.006**	–3.4 ± 2.2	.126	–3.4 ± 2.0	.081
20 mg	**–7.1 ± 1.1**	**<0.001**	**–6.3 ± 1.7**	**<0.001**	**–6.1 ± 2.4**	**.012**	**–7.2 ± 2.1**	**<0.001**
315 (NCT01153009)								
15 mg	–1.5 ± 1.2	.224	–1.3 ± 1.4	.348	–2.0 ± 1.6	.201	–1.1 ± 1.6	.493
20 mg	**–2.8 ± 1.2**	**.023**	**–2.8 ± 1.4**	**.044**	–2.9 ± 1.6	.067	–2.7 ± 1.6	.087
316 (NCT01163266)								
10 mg	–2.2 ± 1.2	.058	–1.7 ± 1.4	.211	–1.1 ± 1.5	.482	–1.6 ± 1.5	.297
20 mg	**–3.6 ± 1.2**	**.002**	**–4.6 ± 1.3**	**<0.001**	**–3.4 ± 1.6**	**.030**	**–5.7 ± 1.5**	**<0.001**
Meta-analysis								
	N = 122		N = 63		N = 27		N = 51	
5 mg	**–2.5 ± 1.1**	**.018**	–2.3 ± 1.4	.099	–3.8 ± 2.1	.068	–0.6 ± 1.6	.736
	N = 243		N = 150		N = 109		N = 121	
10 mg	**–2.4 ± 0.8**	**.002**	**–2.2 ± 1.0**	**.025**	–1.8 ± 1.2	.136	–1.8 ± 1.1	.113
	N = 231		N = 141		N = 104		N = 107	
15 mg	–3.5 ± 2.0	.080	–2.8 ± 1.5	.069	–2.5 ± 1.3	.053	–2.0 ± 1.2	.102
	N = 359		N = 228		N = 169		N = 174	
20 mg	**–4.5 ± 1.4**	**<0.001**	**–4.4 ± 0.9**	**<0.001**	**–3.7 ± 1.0**	**<0.001**	**–5.0 ± 1.3**	**<0.001**

Abbreviations: FAS, full analysis set; MADRS, Montgomery-Åsberg Depression Rating Scale; MMRM, mixed model for repeated measurements; OC, observed cases; SE, standard error.
[a] Values in bold are statistically significant.

Consequently, there is an ongoing need to ascertain whether select antidepressants are effective in these patients. Moreover, the acceptability of antidepressants in MDD may be very different for people reporting childhood adversity (Cipriani et al., 2018).

Not dissimilar from MDD in general, the mechanisms whereby vortioxetine is efficacious in adults with MDD and childhood trauma are not known. Convergent lines of evidence indicate that exposure to trauma results in functional and structural alterations in select brain regions (e.g., hippocampus) and in discrete networks and circuits subserving cognition and reward (Teicher et al., 2002). Vortioxetine's ability to improve general cognitive functions and mitigate anhedonia, as well as exact effects in brain regions subserving cognitive control, provides a basis for hypothesizing that the benefits observed in our analysis across depression/anxiety symptoms and general psychosocial function with vortioxetine are mediated by modulatory effects on cognitive control and possibly by reward circuits (McIntyre et al. 2014b; Cao et al., 2019). The observation that vortioxetine exerts region-specific and circuit-level effects in individuals with depression would be in accordance with this testable hypothesis (Sanchez et al., 2015; Smith et al., 2018).

In this study, we observed remarkable differences in the reporting of both childhood and recent trauma between subjects recruited from the United States vs subjects outside of the United States (74.2% vs 48.6%). For childhood trauma, the differences were particularly remarkable for sexual abuse, upheaval between parents, death of a friend, and victim of violence. For recent trauma, major differences were observed for trauma related to death of a friend and traumatic experiences in a major change of work. Our study is unique in being the first of its kind in patients with MDD to investigate such differences, and also in its size and meticulous collection of data on these events, as well as clinician assessment of severity. It is conjectured that perhaps the differential drug-placebo differences observed internationally (i.e., attenuated

Table 3
Change from baseline to week 6/8 in HAM-A total score, CGI-I total score, and SDS total score (Difference vs Placebo) according to trauma status (FAS, MMRM, OC)[a].

Outcome Measure – Meta-analysis	All patients		Patients with any trauma		Patients with childhood trauma		Patients with recent trauma	
	Mean ± SE	*P* Value	Mean ± SE	*P* Value	Mean ± SE	*P* Value	Mean ± SE	*P* Value
HAM-A Total								
5 mg	**–1.9 ± 0.8**	**.025**	–1.9 ± 1.1	.089	**–4.1 ± 1.5**	**.008**	–0.6 ± 1.3	.674
10 mg	–0.9 ± 0.8	.235	–0.5 ± 0.9	.587	–0.4 ± 1.6	.821	–0.2 ± 0.8	.822
15 mg	–1.3 ± 1.2	.296	0.0 ± 0.7	.961	–0.1 ± 0.9	.870	0.6 ± 0.8	.436
20 mg	**–2.0 ± 1.0**	**.046**	**–1.6 ± 0.6**	**.012**	–0.9 ± 0.6	.154	**–1.8 ± 0.8**	**.028**
SDS Total								
5 mg	–0.5 ± 1.0	.612	0.3 ± 1.4	.811	–2.1 ± 2.4	.392	2.3 ± 1.5	.127
10 mg	**–1.8 ± 0.7**	**.015**	–1.1 ± 0.9	.245	–1.5 ± 1.3	.219	–0.4 ± 1.0	.732
15 mg	–1.6 ± 1.6	.306	–1.7 ± 1.6	.270	–1.0 ± 1.2	.384	–2.6 ± 2.3	.252
20 mg	**–2.4 ± 0.9**	**.006**	**–2.3 ± 0.8**	**.007**	–1.6 ± 0.9	.094	**–2.4 ± 1.0**	**.016**
CGI-I Total								
5 mg	**–0.3 ± 0.1**	**.021**	**–0.3 ± 0.2**	**.028**	–0.4 ± 0.2	.072	–0.2 ± 0.2	.176
10 mg	**–0.3 ± 0.1**	**.003**	**–0.3 ± 0.1**	**.013**	–0.2 ± 0.2	.160	–0.2 ± 0.1	.056
15 mg	–0.4 ± 0.3	.154	–0.4 ± 0.2	.089	**–0.4 ± 0.2**	**.020**	–0.2 ± 0.2	.211
20 mg	**–0.5 ± 0.2**	**.047**	**–0.5 ± 0.2**	**.009**	**–0.4 ± 0.1**	**.004**	**–0.5 ± 0.2**	**.015**

Abbreviations: FAS, full analysis set; CGI-I, Clinical Global Impression-Improvement; HAM-A, Hamilton Anxiety Rating Scale; MMRM, mixed model for repeated measurements; OC, observed cases; SDS, Sheehan Disability Scale; SE, standard error.
[a] Values in bold are statistically significant.

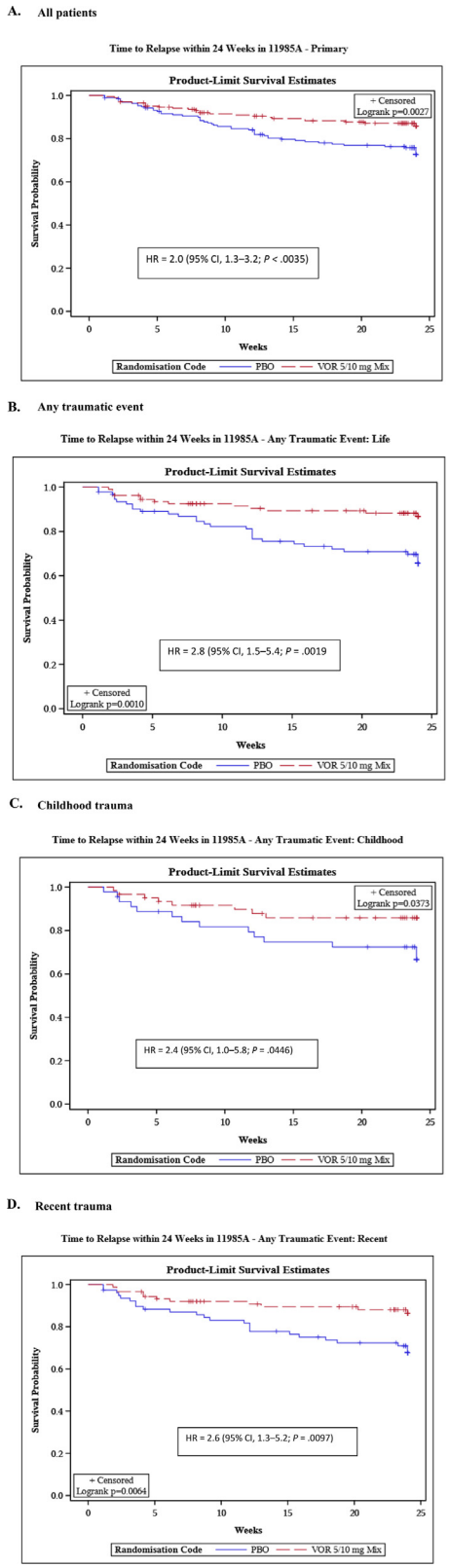

Fig. 2. Time to relapse within 24 weeks in the 11985A (Relapse Prevention) study (NCT00596817). Time to relapse within 24 weeks in (A), all patients; (B) patients with any traumatic event; (C) patients with childhood traumatic event; and (D) patients with recent traumatic event. Abbreviations: CI, confidence interval; HR, hazard ratio; PBO, placebo; VOR, vortioxetine.

differences in US-based studies) might in some cases be moderated by the higher frequency of self-reported abuse in the United States.

Cultural differences in perception and reporting of traumatic events cannot be ruled out in trying to understand these differences. The fact that our data are based on clinical interview and investigator assessment, and not direct patient reports, does not rule out such cultural differences; however, the method of data collection should at least make cultural differences in perception and reporting less likely to explain the entire difference. Our findings are in line with other reports of differences in trauma between the United States and other high-income countries (Benjet et al., 2016; Mercy et al., 2003). In a recent comprehensive assessment of violence in the United States (fatal and nonfatal), substantial progress appears to have occurred over the past two decades; however, homicide rates and firearm-related deaths are still substantially higher by international comparison, and ≈13% of US children are still estimated to experience child maltreatment before the age of 18 years (Wildeman et al., 2014; Finkelhor et al., 2013).

The World Health Organization (WHO) published the *World Report on Violence and Health* in 2002 to bring international attention to the epidemiology of violence and provide recommendations for violence prevention at global, national, and local levels (Krug et al., 2002). The report considered violence in terms of child abuse and neglect by caregivers, youth violence, intimate partner violence, sexual violence, elder abuse, self-inflicted violence, and collective violence (such as war or terrorism). In a follow-up assessment report in 2014 (Mercy et al., 2003), the WHO noted progress in terms of public health investments in violence prevention, yet at a level much lower than the actual burden. The WHO report highlights social determinants of violence, such as poverty and education, greater enforcement of laws to prevent violence, establishment of nonviolent norms, and great investments in health services to help victims of violence (WHO 2014).

This study has some limitations. First, all analyses were conducted post hoc, preventing any conclusive statements on the unique effect of vortioxetine in MDD patients with childhood or recent trauma. Nevertheless, the analysis is based on a large sample of individuals (≈60% of the total study population), and consistent effects were observed on clinical endpoints and across studies, including the long-term study. The effect seen was not driven by a difference in placebo response. In the short-term studies, a similar decrease from baseline was observed in MADRS total score in the vortioxetine active arms in subjects with and without a trauma event history. In the relapse prevention study, however, there was a tendency toward higher relapse rates in patients randomized to placebo compared with patients given vortioxetine 5 or 10 mg. Second, a direct statistical comparison between MDD patients with and without childhood or recent trauma in terms of efficacy on depressive and anxiety symptoms, overall global clinical impression, and functioning could also be of scientific interest. However, this study was not designed to address this comparison between subgroups. Third, it is unknown if all subtypes of trauma can be considered equal in terms of neurobiological correlates, for instance sexual abuse and neglect in childhood versus upheaval between parents. Fourth, in a meta-analysis like this in subgroups on several endpoints for four doses, one should be careful not to over-interpret the result of a single analysis, i.e., one endpoint for one dose. Rather the overall pattern of results should be considered for the different endpoints within each subgroup. The number of patients on each dose differed depending on the doses used in the different studies, and therefore it was expected that the usual dose-response of 5 mg to 20 mg vortioxetine would not be observed for all clinical endpoints in all the subgroups in this research. Finally, our research is limited by the general limitations associated with randomized clinical trials in MDD, such as study participants are not necessarily representative of patients with MDD seen in usual clinical practice.

This is the first report to evaluate the efficacy of vortioxetine on measures of depressive and anxiety symptoms, overall global clinical impression by clinicians, and overall functioning in adults with MDD

Table 4
Efficacy in relapse prevention study: change from baseline II to week 48 (Difference vs Placebo) according to trauma status (FAS, ANCOVA, LOCF)[a].

	All Patients (N = 392)		Patients With Any Trauma (N = 198)		Patients With Childhood Trauma (N = 104)		Patients With Recent Trauma (N = 164)	
	Mean ± SE	P Value	Mean ± SE	P Value	Mean ± SE	P Value	Mean ± SE	P value
MADRS total score	**–3.3 ± 0.9**	**.0004**	**–4.1 ± 1.4**	**.0048**	–4.0 ± 2.2	.0715	**–4.2 ± 1.6**	**.0115**
HAM-A total score	**–2.2 ± 0.7**	**.0018**	**–2.6 ± 1.1**	**.0173**	–2.7 ± 1.7	.1168	–2.3 ± 1.3	.0677
CGI-S	**–0.5 ± 0.1**	**.0004**	**–0.6 ± 0.2**	**.0042**	–0.7 ± 0.3	.0516	**–0.7 ± 0.2**	**.0079**
SDS total	**–2.1 ± 0.8**	**.0060**	**–2.4 ± 1.2**	**.0471**	–3.9 ± 2.1	.0729	–2.2 ± 1.3	.0920
SDS work	**–0.7 ± 0.3**	**.0161**	–0.8 ± 0.4	.0713	–1.4 ± 0.8	.0719	–0.7 ± 0.5	.1608
SDS social	**–0.9 ± 0.3**	**.0006**	**–1.0 ± 0.4**	**.0079**	**–1.4 ± 0.6**	**.0376**	**–1.2 ± 0.4**	**.0051**
SDS family	**–0.6 ± 0.2**	**.0127**	**–0.7 ± 0.4**	**.0429**	–1.2 ± 0.6	.0631	–0.7 ± 0.4	.1003
SF-36 Mental Health Index	**2.4 ± 0.6**	**<0.0001**	**2.5 ± 0.9**	**.0087**	**4.1 ± 1.5**	**.0090**	**2.3 ± 1.0**	**.0290**

Abbreviations: ANCOVA, analysis of variance; CGI-S, Clinical Global Impression-Severity; HAM-A, Hamilton Anxiety Rating Scale; MADRS, Montgomery-Åsberg Depression Rating Scale; SDS, Sheehan Disability Scale; SE, standard error; SF-36, Short Form (36) Health Survey.
[a] Values in bold are statistically significant.

that takes into account the patients' traumatic experience (childhood or recent) before their participation in the clinical research. The ability of vortioxetine to exert symptomatic relief in this population, in contradistinction to certain selective serotonin reuptake inhibitors, suggests that differential biotypes of MDD exist with differential response characteristics across mechanistically dissimilar antidepressants. Recent study results in bipolar disorder suggest that exposure to childhood trauma is associated with diminished response to conventional treatment and higher response to anti-inflammatory treatment (McIntyre et al., 2019). It may be relevant that vortioxetine in vitro affects inflammatory pathways (Talmon et al., 2018). Although the mechanism of action of vortioxetine is not fully understood, it is suggested that its efficacy in traumatized patients may involve other non–monoamine-based targets (McIntyre 2014). Compared with previous reports on the efficacy of vortioxetine in the general MDD population, a consistent (and for some endpoints, higher) effect was observed in MDD patients who had experienced past trauma.

In conclusion, a large percentage of adults with MDD present with a history of childhood trauma. Vortioxetine showed short- and long-term efficacy on depressive and anxiety symptoms and overall functioning in this large subpopulation of MDD patients, as well as demonstrating a significantly lower risk of relapse among these patients.

Trial registration

ClinicalTrials.gov identifiers: NCT01153009, NCT00635219, NCT01163266, NCT01140906, NCT00596817.

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CRediT authorship contribution statement

Michael Cronquist Christensen: Conceptualization, Formal analysis, Writing - original draft. **Ioana Florea:** Conceptualization, Formal analysis, Writing - original draft. **Henrik Loft:** Conceptualization, Formal analysis, Writing - original draft. **Roger S. McIntyre:** Conceptualization, Formal analysis, Writing - original draft.

Declaration of Competing Interest

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jad.2019.11.074.

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