An Open-Label Clinical Trial Evaluating Sensitivity to Change in Cognition using the THINC-it following Treatment with Vortioxetine in Major Depressive Disorder

Investigator Initiated Trial

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BACKGROUND

Major depressive disorder (MDD) is a serious public health concern worldwide with ample documentation demonstrating that MDD is one of the leading contributors to the global burden of disease and is currently the leading cause of disability worldwide [1–3]. Moreover, the economic burden of MDD is estimated to total $210.5 billion with approximately 50% of the cost being attributable to impairment in role function (e.g., workplace performance: presenteeism, absenteeism, and short-/long-term disability) [4,5]. Accumulating evidence suggests that the treatment and resolution of mood symptoms among individuals with MDD is insufficient in facilitating full functional recovery among individuals affected by MDD wherein a highly reproduced observation is that impairments in cognitive function remain persistent, pervasive, and progressive during the "remitted" state [6–8]. The foregoing portrait of MDD as a multidimensional syndrome associated with cognitive impairment and differential functional implications, provides the impetus for evaluating the disparate domains commonly affected in this clinical population using valid and reliable measures/assessments capable of providing actionable information in the treatment and management of patients.

Hitherto, clinical awareness surrounding the pertinence of cognitive impairment in MDD and its impact on functional recovery has been limited with no "gold standard tool(s)" to detect cognitive impairments in adults with MDD. Moreover, although several screening/measurement instruments are currently available that have demonstrated sensitivity to cognitive impairments in select cognitive domains, only one tool, to the authors' knowledge, has been developed primarily to evaluate the four principal cognitive domains affected in adults (18-65) with MDD (i.e., executive function, learning and memory, processing speed, as well as attention/concentration) using a composite score.

The recently validated digitalized metric for assessing/screening cognitive deficits among adults

(18-65) with MDD - the THINC-integrated tool (THINC-it) - developed by the Global THINC Task Force, effectively demonstrated its ability to detect and measure cognitive performance. This tool is able to significantly differentiate between clinical (i.e., MDD) and healthy control populations based on measures of both objective and subjective cognition (McIntyre et al., 2017). The THINC-it is accessible via computers/tablets (downloadable, free of charge from the THINC-it website: http://thinc.progress.im/en/form/download-thinc-it-tool) and is comprised of the paradigms drawn from four objective measures of cognition: the Choice Reaction Time (CRT) (i.e., THINC-it: Spotter); the 0 N-BACK Working Memory Task (i.e., THINC-it: Symbol Check); the Digit Symbol Substitution Test (DSST) (i.e., THINC-it: Codebreaker); and the Trail Making Test- Part B (TMT-B) (i.e., THINC-it: Trails); in addition to the Perceived Deficits Questionnaire for Depression – 5 Item (PDQ-5-D) which assesses subjects' subjective experience of cognitive deficits.

The THINC-it was designed for patient self-administration in a clinical setting with no requirement for the tool to be delivered and/or scored by a psychometrist/psychologist. Patient results are made immediately available, taking approximately 30 minutes to complete. Instructions are conveyed in a manner that is commensurate with a grade 6 education and are not culture-bound. It is anticipated that the THINC-it tool will be available in the primary care and specialty setting in a digital format, providing actionable information for the treatment and management of patients with MDD.

The ideal gold standard tool for screening/assessing the presence of cognitive impairment in adults with MDD in the clinical ecosystem should include, but not be limited to, conceptual coverage of the cognitive domains affected in MDD (i.e., executive function, learning and memory, processing speed, and attention/concentration), validity and reliability, and minimal cultural/practice effects. The tool would also need to be brief and allow for easy administration and interpretation. Additionally, in order to make effective use of the information provided by the screening/assessment tool, it would also need to demonstrate sensitivity to change in cognitive function/performance following treatment. In keeping with this view, the objective herein is to establish sensitivity to change using THINC-it, as there is a need for an instrument

capable of tracking the progress of individuals receiving treatment for cognition dysfunction in MDD.

An 8-week, open-label, sensitivity to change study assessing alterations in cognitive function/performance, as measured by the THINC-it, in adults (18-65) with Diagnostic and Statistical Manual, Fifth Edition (DSM-5)-defined MDD treated with vortioxetine (10-20 mg flexibly dosed) is proposed. This study will be performed by the Brain and Cognition Discovery Foundation (BCDF). The BCDF is an organization based in Toronto, Ontario, Canada led by Dr. Roger S. McIntyre. Membership of the BCDF has developed and validated rating scales and metrics for adults with mood disorders for over 10 years. A member of the BCDF provides diagnoses and treatment for adults (age 18-65) with mood disorders and provides clinical care to the largest catchment area in Canada. The BCDF conducts clinical research according to the International Conference on Harmonization, Declaration of Helsinki, and Good Clinical Practice (GCP) guidelines. The study will be approved by the community Research Ethics Board.

HYPOTHESIS

The primary aim of this study is to establish sensitivity to change in cognitive function/performance using THINC-it tool in adults (18-65) with MDD treated with vortioxetine (10-20 mg flexibly dosed for 8 weeks). Secondary aims of the study include, but are not limited to: (1) determining whether early changes (i.e., Day 14; Week 2) in cognitive function/performance predict symptomatic improvements in mood (defined as a reduction of 50% or more on total mood score [as measured by the Montgomery Åsberg Depression Rating Scale [MADRS], at endpoint; and (2) determining whether early changes (i.e., Day 14; Week 2) in cognitive function/performance are capable of detecting the effect of vortioxetine treatment on secondary outcome measures assessing functional outcomes [e.g., Sheehan Disability Scale (SDS), Endicott Work Productivity Scale (EWPS), and the 5-Item World Health Organization Wellbeing Index (WHO-5)] at endpoint.

STUDY DESIGN

This is an 8-week, open-label, sensitivity to change study assessing alterations in cognitive function/performance, as measured by the THINC-it, in adults (18-65) with Diagnostic and Statistical Manual, Fifth Edition (DSM-5)-defined MDD treated with vortioxetine (10-20 mg flexibly dosed) (N=100) and (N=50) age, and sex-matched, Healthy Controls.

STUDY POPULATION

All patients will be enrolled at a single site, located in Toronto, Ontario, Canada.
The total planned number of participants is:

- ❏ 100 individuals with DSM-5-defined MDD (18-65 years of age)
- ❏ 50 Healthy Controls (18-65 years of age) matched on sex, and age

ELIGIBILITY CRITERIA

The eligibility criteria provided below do not unnecessarily filter and/or restrict select patients. The overarching aim of enrollment is to include representative patients to enhance the ecological validity of our results with careful consideration surrounding those patients likely to evince impairments/deficits in the dimension/domain of cognition. The rationale for the selection of those individuals with at least one prior major depressive episode (MDE), is based on extant literature indicating that individuals with recurrent MDD are at greater risk of inter-episodic "non-mood" symptoms including, but not limited to, cognitive impairments (e.g., indecision, difficulties with memory, and inability to concentrate) [8–11].

Similarly, the ideal participants would be antidepressant naïve and not receiving any psychotropic medication. However, the majority of patients with MDD seeking healthcare and/or utilizing healthcare systems have been prescribed and are taking at least one psychotropic medication including, but certainly not limited to, an antidepressant. Indeed, the possibility of

introducing potential confounds moderated by medication (i.e., iatrogenic artifacts) are raised when including patients taking antidepressants and/or other psychotropic/general medications; nonetheless, excluding patients currently receiving pharmacological treatment would significantly reduce the feasibility of a timely enrollment and would be liable to criticisms of non-representativeness. Therefore, participants would be evaluated by a study clinician on a case-by-case basis to determine the potential of pharmacodynamic interactions between the study intervention and the participant's current medication regimen as well as evaluating the likelihood of impacting study results.

Participants are advised to **NOT** use the THINC-it tool outside of the study, as to not affect study results during your participation.

Inclusion Criteria for Participants with MDD:

1. The participant is able and willing to provide informed consent.
2. The participant is male or female 18-65 years of age.
3. The participant has received a current diagnosis of a major depressive episode (MDE) as part of MDD as per DSM-5 criteria.
4. The participant's current MDE is confirmed by the Mini International Neuropsychiatric Interview (M.I.N.I 5.0.).
5. The participant is an outpatient of a psychiatric setting.
6. The participant has a MADRS score $\geq$ 20 at screening and baseline.
7. At least one prior MDE formally diagnosed by a healthcare provider or validated by previous treatment (e.g., guideline-informed pharmacotherapy and/or manual-based psychotherapy).

Exclusion Criteria for Participants with MDD:

1. Current alcohol and/or substance use disorder as confirmed by the M.I.N.I 5.0.
2. Presence of comorbid psychiatric disorder other than MDD that is a focus of clinical concern as confirmed by the M.I.N.I 5.0.
3. Medications approved and/or employed off-label for cognitive dysfunction

(e.g., psychostimulants).

4. Any medication for a general medical disorder that, in the opinion of the investigator, may affect cognitive function.

5. Use of benzodiazepines within 12 hours of cognitive assessments.

6. Consumption of alcohol within 8 hours of cognitive assessments.7 . Inconsistent use or abuse of marijuana.

8. Physical, cognitive, or language impairments sufficient to adversely affect data derived from cognitive assessments.

9. Diagnosed reading disability or dyslexia.

10. Clinically significant learning disorder by history.

11. Electroconvulsive therapy (ECT) in the last 6 months.

12. History of moderate or severe head trauma (e.g., loss of consciousness for >1 hour), other neurological disorders, or unstable systemic medical diseases that in the opinion of the investigator are likely to affect the central nervous system.

13. Pregnant and/or breastfeeding.

14. Received investigational agents as part of a separate study within 30 days of the screening visit.

15. Actively suicidal/presence of suicidal ideation or evaluated as being a suicide risk (as per clinical judgment using the Columbia-Suicide Severity Rating Scale).

16. Currently receiving treatment with Monoamine Oxidase Inhibitors (MAOIs) anti-depressants, antibiotics such as linezolid, or intravenous methylene blue.

17. Previous hypersensitivity reaction to vortioxetine or any components of the formulation. Angioedema has been reported in patients treated with vortioxetine.

18. Clinical worsening symptoms of depression and suicide risk – in both adult and pediatric age groups.

19. Serotonin syndrome

20. Abnormal bleeding

21. Previous history of mania/hypomania

22. Angle closure glaucoma

23. Hyponatremia

24. Moderate hepatic impairment

25. History of seizures and epilepsy

Inclusion Criteria for Healthy Controls:

1. No current or past history of mental disorder as evidenced by the M.I.N.I. 5.0 for DSM-IV.
2. No first-degree relative with an established diagnosis by a healthcare provider of a mood or psychiatric disorder.
3. No unstable medical disorders.

Exclusion Criteria for Healthy Controls:

1. Use of any medication for a general medical disorder and/or condition that, in the opinion of the investigator, may affect cognitive function (e.g., corticosteroids, beta-blockers).
2. Pregnant and/or breastfeeding.
3. Consumption of alcohol within 8 hours of THINC-it tool administration.
4. Inconsistent use or abuse of marijuana.

Transition to Enrollment

Patient will discontinue only antidepressants. Patients' existing antidepressant dosage will be decreased gradually over a course 10-14 days. At the same time, participants will be started on 10mg of Vortioxetine. It takes about 10-14 days for Vortioxetine to achieve steady states. For patients who are already taking antidepressants at the start of study, if they are abruptly discontinued, they are at risk for discontinuation syndrome. Therefore, both drugs will be co-prescribed for about 10-14 days and then the index antidepressant will be discontinued.

Serotonin syndrome or other additive side effects is very unlikely to be a concern. Should the patient's physician determine another optimal schedule, this will be followed instead. All MDD participants will be supervised by Dr. Roger McIntyre, prior to enrollment of the study. All partients will be monitored by a psychiatrist during the study. Furthermore, patients will have access to a 24-hour study number where they can contact research staff anytime, should they experience any adverse events. Therefore, there will always be an open line of communication between patients and the research staff.

The above mentioned procedures will only be carried out once participants have consented to take part in the research and signed the informed consent form.

Patients will be seen by a clinician on a biweekly basis for the antidepressant washout period. Clinician will be assessing the patient on adverse side effects, as well as mood.

ASSESSMENTS

Primary Assessment Instrument

- ❏ The THINC-it comprised of: Spotter, Symbol Check, Codebreaker, Trails, and PDQ-5-D
- ❏ The National Adult Reading Test (NART)

Secondary Assessment Instruments

- ❏ Montgomery Åsberg Depression Rating Scale (MADRS)
- ❏ Clinical Global Impression - Severity and Improvement (CGI-S/CGI-I)
- ❏ Columbia Suicide Severity Rating Scale (C-SSRS)
- ❏ Pen and paper Version of Digit Symbol Substitution Test (DSST)
- ❏ Pen and paper Version of the Trail Making Test B (TMT-B)
- ❏ Pen and paper Version of the Perceived Deficits Questionnaire for Depression (PDQ-5-D)

- ❏ Endicott Workplace Productivity Scale (EWPS)
- ❏ Sheehan Disability Scale (SDS)
- ❏ WHO-5 Well-Being Index (WHO-5)
- ❏ Snaith-Hamilton Pleasure Scale Questionnaire (SHAPS)
- ❏ International Physical Activity Questionnaire (IPAQ)
- ❏ Generalized Anxiety Disorder Assessment (GAD-7)
- ❏ THINC-it Satisfaction Questionnaire
- ❏ 36-Item Short Form Survey Instrument (SF-36)
- ❏ Insomnia Severity Index (ISI)
- ❏ Pittsburgh Sleep Quality Index (PSQI)
- ❏ Epworth Sleepiness Scale (ESS)
- ❏ Effort Expenditure for Rewards Task (EEfRT) - optional
- ❏ Changes in blood biomarkers (e.g. BDNF, cytokines, insulin etc.)

Data will be collected using paper based scales that will be administered by the rater or self-reported by the participant.

RATIONALE FOR SECONDARY ASSESSMENTS INSTRUMENTS

A critical question for addressing cognitive impairments in adults with MDD is not whether it exists, but rather determining whether these observed impairments in cognitive function/performance influence patient-reported, clinician-measured, and/or societally defined health outcomes. The answer to which additional testable hypotheses can be generated is to further investigate to what extent cognitive impairments affect these health outcomes and what methods of treatment are available to mitigate these cognitive symptoms. The pen and paper version of the DSST and PDQ-5-D will be administered as an additional measure of validity. Additionally, most individuals achieving remission continue to report/exhibit ongoing functional difficulties as well as significant reductions in quality of life, providing impetus for their measurement [14,15]. Consequently, the WHO-5 will be administered to assess overall quality of life and wellbeing.

Moreover, these deficiencies correlate with greater illness burden measures and costs, particularly in the workplace [16]. Likewise, it is recognized that cognitive function in adults with MDD represents a principal determinant of broad-based psychosocial function [15,17,18]. Taken together, the SDS and EWPS will be administered to allow for secondary evaluation of the relationship between global functional impairment/disability and health-related work productivity with cognitive function in adults with MDD, respectively. It has been amply documented that impairments in cognitive function are correlated with, but dissociable from, depressive symptom severity [18]. Hence, the relationship between measures of cognitive impairment and depressive symptoms severity will include the following secondary measures: the MADRS, the CGI-S/CGI-I, and the CSSRS.

PROCEDURES FOR PARTICIPANTS WITH MAJOR DEPRESSIVE DISORDER

Visit 1 (Screening)

The initial visit entails the provision of detailed study information to participant and obtainment

of informed written consent. A member of the research team will assess participants' eligibility based on inclusion/exclusion criteria and confirm a diagnosis of MDD with the M.I.N.I 5.0 and the Structured Clinical Interview for DSM-5 (SCID) to assess for mixed features symptomology. Demographics including date of birth, sex, and race will be recorded. Years of education will be recorded as well. Lifestyle factors (i.e. caffeine, exercise, alcohol, nicotine and marijuana) will also be recorded. Psychiatric and medical history, number of psychotropic medications received according to participant self-report/clinical chart review, as well as anthropometrics (including height, weight and waist circumference) will be measured. Resting heart rate and blood pressure will also be measured. Participants will be evaluated with the MADRS by a member of the research team trained in MADRS scoring to assure the severity threshold is indicative of non-remission (MADRS $\geq$ 20). The Columbia Suicide Severity Rating Scale (CSSRS) will also be used as part of participant assessment. In addition, participants will be asked to report any experience of adverse event(s) prior to study enrollment. Participants will be asked to complete the NART to estimate premorbid intelligence quotient (IQ). Upon confirmation of study eligibility, the participant will be scheduled for future appointments.

Visit 2 (Day 0: Week 0; Baseline)

Participant will be asked to report any adverse event(s) or any changes to medications. The Clinical Global Impression – Severity (CGI-S), MADRS, as well as the CSSRS scales will be used as part of participant assessment. Anthropometrics (including weight and waist circumference), resting heart rate and blood pressure will be measured. History of caffeine, alcohol, nicotine, exercise and marijuana use will be recorded as well. Participants will be provided with an opportunity to work through the modified THINC-it to minimize potential practice effects with a research team member. This will allow the participant with an opportunity to ask any outstanding questions. The THINC-it tool will be administered via tablet to evaluate objective and subjective measures of cognitive function. THINC-it tests will be consistently delivered in the following order: Spotter, Symbol Check, Codebreaker, Trails, and PDQ-5-D to all participants with a member of the research team instructing participants to read the tutorial

instructions preceding each of the THINC-it tasks. Participants will complete the pen-and-paper version of the Digit Symbol Substitution Test (DSST) and the Trail Making Test B (TMT-B).

Participants will also complete all secondary self-report assessments using paper-based scales/questionnaires and consist of the following scales: Endicott Workplace Productivity Scale (EWPS), Sheehan Disability Scale (SDS), Wellbeing Index (WHO-5), Snaith-Hamilton Pleasure Scale (SHAPS), Generalized Anxiety Disorder (GAD-7), Perceived Deficits Questionnaire for Depression (PDQ-5-D), International Physical Activity Questionnaire (IPAQ), 36-Item Short Form Survey Instrument (SF-36), Insomnia Severity Index (ISI), Pittsburgh Sleep Quality Index (PSQI), Epworth Sleepiness Scale (ESS) and THINC-it satisfaction questionnaire. All self reports will be administered by a member. All study procedures will take place in a quiet setting. Fasting (12-hours) clinical and research bloodwork will also be collected.

Participants will receive vortioxetine 10-20 mg (flexibly dosed) over the course of 8 weeks and to be taken once daily with the option to increase to vortioxetine 20 mg/day following visit 3 of the treatment based on clinical discretion (e.g. efficacy and tolerability). This dose was chosen based on extant evidence demonstrating improvements in cognitive function (i.e., executive function, attention/speed of processing, and memory), independent of improvement in depressive symptoms, over an 8-week period [19, 20]. Participants will be asked to store the medication at room temperature (i.e., 15-30 °C).

All participants will be fully informed of safety and tolerability concerns related to the treatment and will be instructed to report any treatment emergent adverse events (TEAEs) of concern to a member of the research team. Moreover, members of the research team will specifically probe and monitor all participants regarding side-effects at each visit. Participants will also be provided with a cell phone number accessible 24 hours a day, seven days a week. The cell phone will be carried on a rotating basis by individual members of the research team.

Visit 3 (Day 14; Week 2)

Participant will be asked to report any adverse event(s) or any changes to medications. The Clinical Global Impression – Severity (CGI-S), Clinical Global Impression – Improvement

(CGI-I), MADRS, as well as the CSSRS scales will be used as part of participant assessment. History of caffeine, alcohol, nicotine, and marijuana use will be recorded. Anthropometrics (including weight and waist circumference), resting heart rate and blood pressure data will be measured as well. THINC-it tool will be administered via tablet to evaluate objective and subjective measures of cognitive function. THINC-it tests will be consistently delivered in the following order: Spotter, Symbol Check, Codebreaker, Trails, and PDQ-5-D to all participants with a member of the research team instructing participants to read the tutorial instructions preceding each of the THINC-it tasks. Participants will complete the pen-and-paper version of the Digit Symbol Substitution Test (DSST) and the Trail Making Test B (TMT-B).

Participants will also complete all secondary self-report assessments using paper-based scales/questionnaires and consist of the following scales: Endicott Workplace Productivity Scale (EWPS), Sheehan Disability Scale (SDS), Wellbeing Index (WHO-5), Snaith-Hamilton Pleasure Scale (SHAPS), Generalized Anxiety Disorder (GAD-7), Perceived Deficits Questionnaire for Depression (PDQ-5-D), 36-Item Short Form Survey Instrument (SF-36), Insomnia Severity Index (ISI), Pittsburgh Sleep Quality Index (PSQI), Epworth Sleepiness Scale (ESS) and THINC-it satisfaction questionnaire. All self reports will be administered by a member. All study procedures will take place in a quiet setting.

Participants will receive vortioxetine 10-20 mg (flexibly dosed) over the next 2 weeks to be taken once daily with the option to increase to vortioxetine 20 mg/day based on clinical discretion (e.g. efficacy and tolerability). This dose was chosen based on extant evidence demonstrating improvements in cognitive function (i.e., executive function, attention/speed of processing, and memory), independent of improvement in depressive symptoms, over an 8-week period [19, 20]. Participants will be asked to store the medication at room temperature (i.e., 15-30 °C).

All participants will be fully informed of safety and tolerability concerns related to the treatment and will be instructed to report any treatment emergent adverse events (TEAEs) of concern to a member of the research team. Moreover, members of the research team will specifically probe

and monitor all participants regarding side-effects at each visit. Participants will be advised to contact a research member's 24hr study line in case of side effects. In the event of an emergency, participants are advised to contact their physician or visit the nearest emergency hospital.

Visit 4 (Day 28; Week 4)

A member of the research team will complete the MADRS, CGI-I, CGI-S, IPAQ and CSSRS with the participant as well as ask about any side-effects or changes to their medications. History of caffeine, alcohol, nicotine, and marijuana use will be recorded. Anthropometrics (including weight and waist circumference), resting heart rate and blood pressure data will be measured as well. Participants will receive additional vortioxetine for the following 4 weeks.

Visit 5 (Day 56; Week 8)

Participant will be asked to report any adverse event(s) or any changes to medications. Anthropometrics (including weight and waist circumference), resting heart rate and blood pressure will be measured as well. History of caffeine, alcohol, nicotine, and marijuana use will be recorded. The CGI-I scale, CGI- S scale, MADRS as well as the CSSRS will also be completed. Participants will be asked to complete the THINC-it to evaluate objective and subjective measures of cognitive function. Participants will complete the pen-and-paper version of the Digit Symbol Substitution Test (DSST) and the Trail Making Test B (TMT-B).

Participants will also complete all secondary self-report assessments using paper-based scales/questionnaires and consist of the following scales: Endicott Workplace Productivity Scale (EWPS), Sheehan Disability Scale (SDS), Wellbeing Index (WHO-5), Snaith-Hamilton Pleasure Scale (SHAPS), International Physical Activity Questionnaire (IPAQ), Generalized Anxiety

Disorder (GAD-7), Perceived Deficits Questionnaire for Depression (PDQ-5-D), 36-Item Short Form Survey Instrument (SF-36), Insomnia Severity Index (ISI), Pittsburgh Sleep Quality Index (PSQI), Epworth Sleepiness Scale (ESS) and THINC-it satisfaction questionnaire. Clinical and research bloodwork will also be collected. All self reports will be administered by a member. All study procedures will take place in a quiet setting. Participants will be required to return completed medication packets.

Effort Expenditure for Reward Task (MDD and HC)

Optional: Participants will be asked if they are interested in completing a 20-minute computer based behavioral task to explore effort-based decision-making, called "Effort Expenditure for Reward Task". This task has been added to objectively measure reward motivation among patients with MDD and HCs. Participants have to select between an Easy and a Hard task. Both tasks involve pressing the Spacebar for a predetermined amount of time. The Hard task offers more money (variable amounts: $1.24-$4.30) but is harder and takes twice as long. Participants make their selection knowingly under different win probabilities (i.e. they might not win money even if they are successful if the win probabilities are low).

Participants will be given the option to complete this task at endpoint (Week 8). This task is only done once. Participants will be awarded the monetary value of the amount they win from doing this task. This is a necessary component of the task, as a tangible incentive is required. 30 MDD and 30 HC participants will completed this task only.

Post Visits – Transition to Standard of Care

Upon completion of the study, patient will be seen by research team clinician to determine whether medication will be discontinued. If medication discontinuation is required, the patient will receive medication reduction by clinician for a period of one week, followed by a period of 1 week with no medication. Patient will be seen by physician 2 weeks post week 8, to monitor well being, including mood, adverse events and any suicide risks. This is a clinical visit with the psychiatrist and will undergo a full clinical psychiatric assessment to assure patient has a smooth

transition to standard of care with their main responsible physician. Should the patient need to see physician sooner, they are advised to contact the 24/7 study line to schedule an appointment. MDD participants will be followed up by physician but will not undergo ongoing provision of care after the study by the research physician.

MDD PATIENT SUMMARY CHART

Visit	Screening (Visit 1)	Week 0 ((Baseline, Visit 2)	Week 2 (Visit 3)	Week 4(Visit 4)	Week 8 (Endpoint, Visit 5)	Post-Study two weeks clinical visit for drug discontinuation. Additional visits will be scheduled as needed.
Consent	X					
Physician visit		X	X	X	X	X
Bloodwork		X			X	
Demographics	X					
Inclusion/ exclusion	X					
Adverse events	X	X	X	X	X	
Current Medications	X					
Medication Changes		X	X	X	X	
M.I.N.I 5.0	X					
SCID	X					
Psychiatric/Medical History	X					
Anthropometrics	X	X	X	X	X	
Lifestyle Factors	X	X	X	X	X	
Montgomery Åsberg Depression Rating Scale (MADRS) > 20	X	X	X	X	X	
THINC-it Practice		X				
THINC-it Cognitive test		X	X		X	
CSSRS	X	X	X	X	X	
DSST (pen/paper)		X	X		X	
TMT-B (pen/paper)		X	X		X	
NART	X					
CGI-I/CGI-S		X	X	X	X	
International Physical Activity Questionnaire (IPAQ)		X		X	X	
Vortioxetine Treatment		X	X	X		
Dispensing medication		X	X	X		
Effort Expenditure for Rewards Task (EEfRT) – optional					X	

Endicott Workplace Productivity Scale (EWPS)		X	X		X	
Sheehan Disability Scale (SDS)		X	X		X	
Wellbeing Index (WHO-5)		X	X		X	
Snaith-Hamilton Pleasure Scale Questionnaire (SHAPS)		X	X		X	
Generalized Anxiety Disorder (GAD-7)		X	X		X	
Perceived Deficits Questionnaire for Depression (PDQ-5-D)		X	X		X	
36-Item Short Form Survey Instrument (SF-36)		X	X		X	
Insomnia Severity Index (ISI)		X	X		X	
Pittsburgh Sleep Quality Index (PSQI)		X	X		X	
Epworth Sleepiness Scale (ESS)		X	X		X	
THINC-it satisfaction questionnaire		X				

PROCEDURES FOR HEALTH CONTROL PARTICIPANTS

Phone Screen

A member of the research team will assess participants' eligibility based on inclusion/exclusion criteria. Demographics including date of birth, sex, years of education and race will be recorded. Medical history, psychiatric history and lifestyle factors (i.e. alcohol use, nicotine history, caffeine and marijuana use) will also be taken during the phone screen. Participants will also be asked about any current medications that they are currently taking. The CSSRS will also be used

as part of participant assessment. In addition, participants will be asked to report any experience of adverse event(s) prior to study enrollment. Upon confirmation of study eligibility, the participant will be asked to scheduled for future appointment visits.

Visit 1 (Day 0: Week 1; Baseline)

The initial visit entails the provision of detailed study information to participant and obtainment of informed written consent. Participants will also be asked to report any experience of adverse event(s) in addition to lifestyle factors. Anthropometrics (consisting of height, weight and waist circumference), resting heart rate and blood pressure will be measured. The MADRS will be completed by a member of the research team trained in MADRS scoring to ensure the participant does not exhibit depressive symptoms (i.e., MADRS total score ≤ 6). Healthy control participants will be evaluated by the M.I.N.I 5.0 to confirm no diagnosis of mental disorder (including MDD). Participants will also be asked to complete the NART to estimate premorbid IQ.

Participants will be provided with a tutorial to work through the THINC-it. The THINC-it tool will be then administered to evaluate objective and subjective measures of cognitive function. The THINC-it will be consistently delivered in the following order: Spotter, Symbol Check, Codebreaker, Trails, and PDQ-5-D to all participants with a member of the research team instructing participants to read the tutorial instructions preceding each of the THINC-it tasks. Participants will complete the pen-and-paper version of the Digit Symbol Substitution Test (DSST) and the Trail Making Test B (TMT-B).

Participants will also complete all secondary self-report assessments using paper-based scales/questionnaires and consist of the following scales: Endicott Workplace Productivity Scale (EWPS), Sheehan Disability Scale (SDS), Wellbeing Index (WHO-5), Snaith-Hamilton Pleasure Scale (SHAPS), Generalized Anxiety Disorder (GAD-7), International Physical Activity Questionnaire (IPAQ), Perceived Deficits Questionnaire for Depression (PDQ-5-D), 36-Item Short Form Survey Instrument (SF-36), Insomnia Severity Index (ISI), Pittsburgh Sleep Quality Index (PSQI), Epworth Sleepiness Scale (ESS) and THINC-it satisfaction questionnaire. All self reports will be administered by a member. All study procedures will take place in a quiet setting.

Participants will also be provided with a cell phone number accessible 24 hours a day, seven days a week. The cell phone will be carried on a rotating basis by individual members of the research team.

Visit 2 (Day 14; Week 2)

Participants will also be assessed with the MADRS. Lifestyle factors, medication updates and adverse events will be recorded. Anthropometrics will be measured (consisting of height, weight and waist circumferenceheight), resting heart rate and blood pressure will be measured. Participants will be asked to complete the THINC-it to evaluate objective and subjective measures of cognitive function, in addition to the DSST and TMT-B pen-and-paper cognitive tests.

Participants will also complete all secondary self-report assessments using paper-based scales/questionnaires and consist of the following scales: Endicott Workplace Productivity Scale (EWPS), Sheehan Disability Scale (SDS), Wellbeing Index (WHO-5), Snaith-Hamilton Pleasure Scale (SHAPS), Generalized Anxiety Disorder (GAD-7), Perceived Deficits Questionnaire for Depression (PDQ-5-D), 36-Item Short Form Survey Instrument (SF-36), Insomnia Severity Index (ISI), Pittsburgh Sleep Quality Index (PSQI), Epworth Sleepiness Scale (ESS) and THINC-it satisfaction questionnaire. All self reports will be administered by a member.

Visit 3 (Day 14; Week 4)

Participants will be assessed with the MADRS . Lifestyle factors, medication updates and adverse events will also be recorded. Anthropometrics will be measured (consisting of height, weight and waist circumferenceheight), resting heart rate and blood pressure will be measured.The International Physical Activity Questionnaire (IPAQ) will be administered as well.

Visit 4 (Day 56; Week 8)

Anthropometrics (including weight and waist circumference), resting heart rate and blood pressure will be measured. Lifestyle factors will be measured. Participants will be assessed using the MADRS and be asked about any adverse events. Participants will be asked to complete the THINC-it to evaluate objective and subjective measures of cognitive function. Participants will complete the pen-and-paper version of the Digit Symbol Substitution Test (DSST) and the Trail Making Test B (TMT-B).

Participants will also complete all secondary self-report assessments using paper-based scales/questionnaires and consist of the following scales: Endicott Workplace Productivity Scale (EWPS), Sheehan Disability Scale (SDS), Wellbeing Index (WHO-5), Snaith-Hamilton Pleasure Scale (SHAPS), Generalized Anxiety Disorder (GAD-7), International Physical Activity Questionnaire (IPAQ), Perceived Deficits Questionnaire for Depression (PDQ-5-D), 36-Item Short Form Survey Instrument (SF-36), Insomnia Severity Index (ISI), Pittsburgh Sleep Quality Index (PSQI), Epworth Sleepiness Scale (ESS) and THINC-it satisfaction questionnaire. All self reports will be administered by a member.

HEALTH CONTROL SUMMARY CHART

Visit	Phone Screening	Visit 1 (Baseline, Week 0)	Visit 2 (Week 2)	Visit 3 (Week 4)	Visit 4 (Week 8)
Consent		X			
Demographics	X				
Inclusion/exclusion	X				
Adverse Events	X	X	X	X	X
M.I.N.I 5.0		X			
Psychiatric/Medical History	X				
Current Medications	X				
Changes in Medications		X	X	X	X
Anthropometrics		X	X	X	X
Montgomery Åsberg Depression Rating Scale (MADRS) 6>		X	X	X	X
NART		X			

Lifestyle Factors	X	X	X	X	X
DSST (Pen/Paper)		X	X		X
TMT-B (Pen/Paper)		X	X		X
THINC-it Practice		X			
THINC-it Cognitive test		X	X		X
Effort Expenditure for Rewards Task (EEfRT) – optional					X
International Physical Activity Questionnaire (IPAQ)		X		X	X
CSSRS	X				
SELF REPORTS					
Endicott Workplace Productivity Scale (EWPS)		X	X		X
Sheehan Disability Scale (SDS)		X	X		X
Wellbeing Index (WHO-5)		X	X		X
Perceived Deficits Questionnaire for Depression (PDQ-5-D)		X	X		X
Snaith-Hamilton Pleasure Scale Questionnaire (SHAPS)		X	X		X
Generalized Anxiety Disorder (GAD-7)		X	X		X
36-Item Short Form Survey Instrument (SF-36)		X	X		X
Insomnia Severity Index (ISI)		X	X		X
Pittsburgh Sleep Quality Index (PSQI)		X	X		X
Epworth Sleepiness Scale (ESS)		X	X		X
THINC-it satisfaction questionnaire		X			

OBJECTIVES

Primary Objective:

❑ To determine the sensitivity of the THINC-it to alterations in cognitive function/performance following intervention with vortioxetine over 8 weeks in adults aged 18-65 with MDD.

Secondary Objectives:

❏ To determine whether early changes (i.e., Day 14; Week 2) in cognitive function/performance, as measured by the THINC-it, predict symptomatic improvements in mood, defined as a reduction of 50% or more on total mood score (as measured by the MADRS), at endpoint.

❏ To determine whether early changes (i.e., Day 14, Week 2) in cognitive function/performance, as measured by the THINC-it, are capable of detecting the effect of vortioxetine treatment on secondary outcome measures of function (e.g., SDS, EWPS, WHO-5) at endpoint.

STUDY MEDICATION: VORTIOXETINE

Participants receiving vortioxetine will be provided 10 mg/day on days 1–14 of the treatment period, with the option to increase to vortioxetine 20 mg/day at the end of Week 2 based on investigator judgment. For the remaining 6 weeks, the dose of vortioxetine will be flexible at 10 or 20 mg/day as adjudicated by a research clinician.

Side effects

Most Common:

- Gastrointestinal adverse events; including nausea, vomiting, constipation/diarrhea. Highest incidence occurs during the first week of treatment. 21-32%
- Sexual dysfunction 14-34%

Less Common: 1-10%

- Dry mouth
- Dyspepsia (discomfort of the abdomen)
- Dizziness
- Somnolence/sedation
- Fatigue
- Insomnia
- Abnormal dreams
- Hyperhidrosis (increase sweating)
- Arthralgia (joint pain)
- Decreased appetite

Rare: %10>
- Nervous system disorders
- Skin and subcutaneous tissue disorders
- Psychiatric disorders

- Serotonin Syndrome has been reported with serotonergic anti-depressants (SSRIs, SNRIs, and others), including with Vortioxetine both when taken alone, but especially when coadministered with other serotonergic agents (including triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone, and St. John's Wort).

- Treatment with serotonergic antidepressants (SSRIs, SNRIs, and others) may increase the risk of abnormal bleeding. Patients should be cautioned about the increased risk of bleeding when Vortioxetine is coadministered with nonsteroidal anti-inflammatory drugs (NSAIDs), aspirin, or other drugs that affect coagulation.

- Activation of Mania/Hypomania can occur with antidepressant treatment.

- Angle Closure Glaucoma: Angle closure glaucoma has occurred in patients with untreated anatomically narrow angles treated with antidepressants.

- Hyponatremia can occur in association with the syndrome of inappropriate antidiuretic hormone secretion (SIADH).

Please see product monograph for full details.

Contraindications

Hypersensitivity to vortioxetine or any components of the formulation. Angioedema has been reported in patients treated with vortioxetine. The use of monoamine oxidase inhibitors (MAOI) intended to treat psychiatric disorders with vortioxetine or within 21 days of stopping treatment with vortioxetine is contraindicated because of an increased risk of serotonin syndrome. The use of vortioxetine within 14 days of stopping an MAOI intended to treat psychiatric disorders is also contraindicated.
Starting vortioxetine in a patient who is being treated with MAOIs such as linezolid or intravenous methylene blue is also contraindicated because of an increased risk of serotonin

syndrome.

Storage

Medication will be stored at room temperature and locked at a medical health care facility.

Rationale for Vortioxetine

It has been amply documented that vortioxetine has a beneficial effect on cognitive domains commonly reported to be negatively affected in MDD (i.e., executive function, attention/speed of processing, and memory) at a dose of 10-20 mg per day [10,19–21]. Moreover, vortioxetine is the only psychopharmacological agent currently available that has a regulatory label in the EU and many other countries in the world describing its benefit on cognitive dysfunction in patients with MDD [22].

Transition to Standard of Care

Patients will be informed of the transition to standard of care procedures (outlined here) post study prior to providing consent to participate in the study. These procedures will also be outlined in writing in the patient consent form itself.

Upon completing the 8-week course of vortioxetine, if patients benefit from this drug, they will be encouraged to continue the treatment with their most responsible physician (MRP). Patients will be notified prior to study consent that not all drug plans will cover the cost of vortioxetine. Should patients wish to continue to use this drug post-study when they do not have coverage, they will be personally responsible for the costs. There will be a gradual discontinuation of the medication for two weeks after the end of the study. However, participants will not have further access to this drug from the research team after study completion. If patients do experience side effects during the study, a physician will make a recommendation regarding the discontinuation or dose reduction of the medication for the remainder of the study. If patients do not experience

any improvement upon study completion in mood or cognition, the medication will be gradually discontinued over a two-week period upon study completion (week 8).

Vortioxetine discontinuation process

At visit 8, patients will be seen by a clinician and provided with half of current vortioxetine dosage for a period of 1 week. This down titration will assure there are no adverse side effects with discontinuation of vortioxetine. During the second week, patients will not be on medication and will be seen by the clinician at the end of two weeks, to ensure that there are no risks or adverse events during this time period. The visits with the clinician are post-study, and not part of the study visits. Patients are encouraged to contact the 24/7 study phone line in the event that they would like to be scheduled with the physician earlier. MDD patients will be seen by research clinician to ensure a safe transition into standard of care by their main responsible physician.

CONDITIONS FOR WITHDRAWAL FROM THE STUDY

Participants may discontinue from the study treatment and assessments at any time. Specific reasons for discontinuing a participant from this study are:

1. Voluntary discontinuation by the participant at any time without prejudice to further treatment.
2. Non-compliance to the protocol as judged by the investigator.
3. Participant becomes pregnant.
4. Increased risk of suicide ideation.
5. Any adverse event that, in the opinion of an investigator, puts the subject at risk.

RECRUITMENT

Membership of the BCDF provide consultation to approximately 20 new adult MDD patients per week. It is expected that approximately 10 participants per month will be eligible for the study herein. This estimate is based on previous experience in which a high proportion of persons referred to the THINC-it validation study met inclusion criteria. The clinical research experience of BCDF members demonstrates that it is possible (as evinced by publications) to recruit a minimum of two subjects per week for most studies conducted. Recruitment of all eligible subjects will be via media announcements in the general community. It is anticipated that the attrition rate will be 20%. Healthy controls will be consecutively recruited via media announcements and will be age-, sex- and education-matched in a 2-to-1 ratio.

The loss to follow-up rate in our program has been relatively low, based on previous experience. The estimated dropout rate in our experience has been approximately 20% for open-label studies. With this in mind, however, the present study has been sufficiently powered to achieve the primary aims and objectives.

STATISTICAL PLAN

Extant literature indicates that the effect size for cognitive deficits in first- and multiple-episode MDD patients is approximately 0.3-0.7 (Cohen's *d*). Notwithstanding the range of reported effect sizes, a modal estimate of 0.4 is instantiated by meta-analyses across disparate domains [23]. Based on an effect size of 0.4, it is estimated that a sample size of 110 evaluable subjects would be required (with a power level of 0.8 and a probability level of 0.05). Similarly, results from our recently completed validation study of the THINC-it demonstrated- temporal reliability of 0.7-0.8, suggesting that repeat-measure performance on the THINC-it between visits would be consistent in the study being proposed herein. Taken together, performance on all the THINC-it tool metrics will be collected in the healthy control group (N=50) for comparison with performance of patients with MDD treated with vortioxetine over an 8-week period, flexibly dosed 10-20 mg/day as adjudicated by a research clinician, to assess detectable differences between groups.

Participants with complete data from the 8 weeks of treatment will be included in analyses, which will be carried out using the Statistical Package for the Social Sciences (SPSS) software. The data will be preliminarily examined in exploratory analyses to obtain their distributional properties, examine any outlying data points, and explore bivariate relations between individual variables. Specific data analyses are subject to change based on the foregoing analyses, but in general we will set $\alpha = 0.05$, two-tailed, and $\beta = 0.20$.

Validation assessments will be employed based on previous psychometric validations of cognitive assessment, as reported by Harrison et al. (2007) wherein validation was informed by guidance regarding objective psychometric assessment by Ferris et al. (1997) stressing the importance of characterizing the reliability, validity, and sensitivity of cognitive measures; in addition, results from a recently completed validation study of the THINC-it completed by the BCDF will be used to determine the appropriate statistical measures required to perform the study herein.

An important consideration when determining issues such as temporal (or 'test-retest') reliability

is a reasonable expectation that the performance will not be impacted by disease or medication variables. Hence, it is necessary to conduct these analyses in a group of healthy controls (N=50) as compared to an intervention group (N=100) assessing sensitivity to change during vortioxetine treatment flexibly dosed 10-20 mg/day over an 8-week period.

Evidence to date indicates that average performance on cognitive tasks in patients with MDD fall approximately 0.5-1.0 standard deviations (SD) below healthy control normative data that is age, sex and education matched [17]. In this study, a comparison of performance in the healthy control group versus the treatment group with vortioxetine over an 8-week period, flexibly dosed 10-20 mg/day, will demonstrate both the deficit of magnitude as well as margin of improvement following 8 weeks of vortioxetine treatment in the latter group. Data from both groups will allow a comparison of overall THINC-it performance as well as improvement following vortioxetine treatment (sensitivity and specificity) on each test comprising the THINC-it tool.

Interim analysis will be conducted both at primary and secondary measures.

Test Sesitivity

Performance on the primary metric for each THINC-it tool test will be calculated to determine test sensitivity. Descriptive statistics for performance of i) the Healthy Control group and ii) that of the patients with MDD treated with vortioxetine over 8 weeks will be examined to determine:

- Mean difference in performance on each test
- Variance in performance for each test
- Additional measure of central tendency and variability
- Other descriptions of the data, including skewness and kurtosis
- Mean difference in group performance, characterised as a standardised effect size

Inferential statistical analysis will be conducted to determine significant difference in

performance within and between the two groups. An analysis of the sensitivity (true positive rate) and specificity (the true negative rate) of each test to the presence and subsequent improvement of cognitive impairment in patients with MDD will be conducted. Cut-off models designed to maximize sensitivity and specificity will be evaluated. The model will be optimized to obtain a pragmatic cut-off that maximizes the model with respect to levels of both sensitivity and specificity. In the event that no overlap is apparent, a threshold for determining impairment will be established. Secondary objectives will be addressed with correlative analysis between the total THINC-it tool and/or its components and the disparate secondary measures.

DATA HANDLING

Personal Data Protection

All data collection material will be de-identified. Participant records will be distinguished using participant identification (PID) numbers.

DATA RETENTION

Records and documents pertaining to the conduct of the study as well as all data collected as part of the study will be retained in a secure place for 25 years in accordance with Health Canada regulations. All data collected throughout the study will be kept with membership of the BCDF for 25 years.

PARTICIPANT PROTECTION

Participants will not be placed at any risk as a result of the study. Information obtained will be maintained in a secure and confidential fashion. No participant will be coerced and/or placed under duress to complete study procedures.

PARTICIPANT COMPENSATION

All participants (i.e., patients with DSM-5-defined MDD and healthy controls) will be provided with reasonable compensation (i.e., $150 CAD, plus modest out-of-pocket expenses for parking/public transit and food per visit maximum $30 CAD per visit) following successful completion of the clinical trial in its entirety. A cheque will be provided as reimbursement for every visit up to $30. Healthy participants will be reimbursed $100 CAD, plus up to $30 CAD for travel and food.

ADVERSE EVENTS

An adverse event (AE) is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver) or the abnormal results of an investigation (e.g., laboratory findings, electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

Serious adverse events

A serious adverse event (SAE) is an AE occurring during any study phase (i.e., run-in, treatment, washout, follow-up), and at any procedure, that fulfills one or more of the following criteria:

- ❏ Results in death
- ❏ Is immediately life-threatening
- ❏ Requires inpatient hospitalization or prolongation of existing hospitalization

- ❏ Results in persistent or significant disability or incapability
- ❏ Is a congenital abnormality or birth defect
- ❏ Is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above

The causality of SAEs (i.e., their relationship to study treatment) will be assessed by the investigator(s). Note that SAEs that could be associated with any study procedure should also be reported. For such events the causal relationship is implied as "yes".

Recordings of Adverse Events

Adverse events will be collected from baseline to endpoint. At each visit, subjects will be asked if they have experienced any health problems or side effects since the previous visit. All AEs will be recorded appropriately, whether or not considered related to the investigational product. This will include AEs spontaneously reported by the patient and/or observed by members of the research team as well as AEs reported in response to a direct question (e.g., "Have you experienced any health problems of side-effects since your last visit?").

For each AE, the following parameters will be described:

- ❏ Start and Stop date
- ❏ Action taken with regards to investigational product
- ❏ Outcome
- ❏ If the AE caused the patient to discontinue the investigational product
- ❏ A statement if the AE fulfills the criteria for a SAE or not
- ❏ The investigator's assessment of the causal relationship between the event and the investigational product
- ❏ Intensity of the AE
  - o Mild (awareness of sign or symptom, but easily tolerated)

- Moderate (discomfort sufficient to cause interference with normal activities)
- Severe (incapacitating, with inability to perform normal activities)

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not an SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be an SAE. Symptoms associated with overdose will be reported as AEs. Pregnancy in itself is not regarded as an AE. Follow-up of adverse events will be based upon the clinical judgment of the investigator.

Reporting of Adverse and Serious Adverse Events

The sponsor-investigator will comply with any and all national rules and regulations concerning safety reporting (adverse drug reactions or SAEs as required). All SAEs (according to the definition in ICH GCP) will be will be done by the investigator in accordance with local regulations and reported to the appropriate regulatory bodies.

References

[1] Holden C. Global Survey Examines Impact of Depression. Science 2000;288:39–40.

[2] Alonso J, Vilagut G, Chatterji S, Heeringa S, Schoenbaum M, Bedirhan Üstün T, et al. Including information about co-morbidity in estimates of disease burden: results from the World Health Organization World Mental Health Surveys. Psychol Med 2011;41:873–86.

[3] World Health Organization. SpringerReference, Berlin/Heidelberg: Springer-Verlag; 2011.

[4] Greenberg PE, Fournier A-A, Sisitsky T, Pike CT, Kessler RC. The economic burden of adults with major depressive disorder in the United States (2005 and 2010). J Clin Psychiatry 2015;76:155–62.

[5] Woo YS, Rosenblat JD, Kakar R, Bahk W-M, McIntyre RS. Cognitive Deficits as a Mediator of Poor Occupational Function in Remitted Major Depressive Disorder Patients. Clin Psychopharmacol Neurosci 2016;14:1–16.

[6] Jaeger J, Berns S, Uzelac S, Davis-Conway S. Neurocognitive deficits and disability in major depressive disorder. Psychiatry Res 2006;145:39–48.

[7] McIntyre RS, Soczynska JZ, Woldeyohannes HO, Alsuwaidan MT, Cha DS, Carvalho AF, et al. The impact of cognitive impairment on perceived workforce performance: results from the International Mood Disorders Collaborative Project. Compr Psychiatry 2015;56:279–82.

[8] Buist-Bouwman MA, Ormel J, de Graaf R, de Jonge P, van Sonderen E, Alonso J, et al. Mediators of the association between depression and role functioning. Acta Psychiatr Scand 2008;118:451–8.

[9] McIntyre RS, Cha DS, Soczynska JK. Cognition in Major Depressive Disorder. OUP Oxford; 2014.

[10] McIntyre RS, Lophaven S, Olsen CK. A randomized, double-blind, placebo-controlled study of vortioxetine on cognitive function in depressed adults. Int J Neuropsychopharmacol 2014;17:1557–67.

[11] Mocking RJT, Figueroa CA, Rive MM, Geugies H, Servaas MN, Assies J, et al. Vulnerability for new episodes in recurrent major depressive disorder: protocol for the longitudinal DELTA-neuroimaging cohort study. BMJ Open 2016;6:e009510.

[12] Lehrner J, Moser D, Klug S, Gleiß A, Auff E, Dal-Bianco P, et al. Subjective memory complaints, depressive symptoms and cognition in patients attending a memory outpatient clinic. Int Psychogeriatr 2014;26:463–73.

[13] Brewster GS, Peterson L, Roker R, Ellis ML, Edwards JD. Depressive Symptoms, Cognition, and Everyday Function Among Community-Residing Older Adults. J Aging Health 2016. doi:10.1177/0898264316635587.

[14] Culpepper L. Impact of untreated major depressive disorder on cognition and daily function. J Clin Psychiatry 2015;76:e901.

[15] Greer TL, Kurian BT, Trivedi MH. Defining and measuring functional recovery from depression. CNS Drugs 2010;24:267–84.

[16] Birnbaum HG, Kessler RC, Kelley D, Ben-Hamadi R, Joish VN, Greenberg PE. Employer burden of mild, moderate, and severe major depressive disorder: mental health services utilization and costs, and work performance. Depress Anxiety 2010;27:78–89.

[17] McIntyre RS, Cha DS, Soczynska JK, Woldeyohannes HO, Gallaugher LA, Kudlow P, et al. Cognitive deficits and functional outcomes in major depressive disorder: determinants, substrates, and treatment interventions. Depress Anxiety 2013;30:515–27.

[18] McIntyre RS. Cognitive Impairment in Major Depressive Disorder: Clinical Relevance, Biological Substrates, and Treatment Opportunities. Cambridge University Press; 2016.

[19] Harrison JE, Lophaven S, Olsen CK. Which Cognitive Domains are Improved by Treatment with Vortioxetine? Int J Neuropsychopharmacol 2016. doi:10.1093/ijnp/pyw054.

[20] McIntyre RS, Harrison J, Loft H, Jacobson W, Olsen CK. The Effects of Vortioxetine on Cognitive Function in Patients with Major Depressive Disorder: A Meta-Analysis of Three Randomized Controlled Trials. Int J Neuropsychopharmacol 2016. doi:10.1093/ijnp/pyw055.

[21] Citrome L. Vortioxetine for major depressive disorder: a systematic review of the efficacy and safety profile for this newly approved antidepressant--what is the number needed to treat, number needed to harm and likelihood to be helped or harmed? Int J Clin Pract 2014;68:60–82.

[22] Connolly KR, Thase ME. Vortioxetine: a New Treatment for Major Depressive Disorder. Expert Opin Pharmacother 2016;17:421–31.

[23] Pae C-U, Wang S-M, Han C, Lee S-J, Patkar AA, Masand PS, et al. Vortioxetine: a meta-analysis of 12 short-term, randomized, placebo-controlled clinical trials for the treatment of major depressive disorder. J Psychiatry Neurosci 2015;40:174–86.