# Symptomatic and Functional Outcomes and Early Prediction of Response to Escitalopram Monotherapy and Sequential Adjunctive Aripiprazole Therapy in Patients With Major Depressive Disorder: A CAN-BIND-1 Report

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## ABSTRACT

***Objective:*** To report the symptomatic and functional outcomes in patients with major depressive disorder (MDD) during a 2-phase treatment trial and to estimate the value of early improvement after 2 weeks in predicting clinical response to escitalopram and subsequently to adjunctive treatment with aripiprazole.

***Methods:*** Participants with MDD (N = 211) identified with the Montgomery-Asberg Depression Rating Scale (MADRS) and confirmed with the Mini-International Neuropsychiatric Interview were recruited from 6 outpatient centers across Canada (August 2013 through December 2016) and treated with open-label escitalopram (10-20 mg) for 8 weeks (Phase 1). Clinical and functional outcomes were evaluated using the MADRS, Quick Inventory of Depressive Symptomatology–Self-Rated (QIDS-SR), Sheehan Disability Scale (SDS), and Lam Employment Absence and Productivity Scale (LEAPS). Participants were evaluated at 8 and 16 weeks for clinical and functional response and remission. Phase 1 responders continued escitalopram while nonresponders received adjunctive aripiprazole (2–10 mg) for a further 8 weeks (Phase 2).

***Results:*** After Phase 1, MADRS response (≥ 50% decrease from baseline) and remission (score ≤ 10) were, respectively, 47% and 31%, and SDS response (score ≤ 12) and remission (score ≤ 6) were, respectively, 53% and 24%. Response to escitalopram was maintained in 91% of participants at week 16, while 61% of the adjunctive aripiprazole group achieved MADRS response during Phase 2. Response and remission rates with the QIDS-SR were lower than with the MADRS. The LEAPS demonstrated significant occupational improvement ($P < .05$). Early symptomatic improvement predicted outcomes with modest accuracy.

***Conclusions:*** This study demonstrates comparable symptomatic and functional outcomes to those of other large practical-design studies. There was a high response rate with the adjunctive use of aripiprazole in escitalopram nonresponders. Given the limited value of early clinical improvement to predict outcome, integration of clinical and biological markers deserves further exploration.

***Trial Registration:*** ClinicalTrials.gov identifier: NCT01655706

*J Clin Psychiatry 2019;80(2):18m12202*

***To cite:*** Kennedy SH, Lam RW, Rotzinger S, et al. Symptomatic and functional outcomes and early prediction of response to escitalopram monotherapy and sequential adjunctive aripiprazole therapy in patients with major depressive disorder: a CAN-BIND-1 report. *J Clin Psychiatry.* 2019;80(2):18m12202.

***To share:*** https://doi.org/10.4088/JCP.18m12202



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Major depressive disorder (MDD) is a highly prevalent condition worldwide with an average 12-month prevalence of 6%; it is associated with increased morbidity and mortality and results in a high socioeconomic burden.[1–3] There are many evidence-based treatments for MDD, but in real-world settings rates of symptomatic response and remission are low.[4] While functional outcomes are prioritized by patients, these were previously underreported as primary outcomes in clinical trials.[5] Given the positive impact of achieving

**Clinical Points**

- Medications to treat depression are prescribed with very little certainty about effectiveness in individual patients.
- Early improvement with escitalopram enhances the likelihood of sustained response and remission out to 16 weeks. Adjunctive aripiprazole is effective across 8 weeks in more than 50% of previous nonresponders to escitalopram.
- A combination of biomarkers and clinical data may enhance treatment selection and outcomes.

symptomatic remission on functional outcomes such as work productivity,[6] it is important to develop methods to select the right intervention at baseline and/or predict likelihood of response in the first few weeks of treatment. Although symptom variables at baseline, including depression severity,[7] anxious subtype,[8] and a composite measure of interest and activity,[9] have value in predicting outcomes, early symptom change may also have predictive value.[10]

Variability in prediction accuracy may reflect the heterogeneous nature of MDD. While the criteria for a major depressive episode (MDE) are restricted to a small set of symptoms, there are 227 combinations of symptoms that meet the diagnosis of MDE.[11] It is unrealistic to expect that clinical predictors of antidepressant response can account for all combinations of symptoms. Subtypes and clinical specifiers based on symptoms (eg, atypical, anxious, or melancholic features) have been utilized in an attempt to reduce heterogeneity, but have not proved to be reliable predictors of response.[12] For example, in the International Study to Predict Optimized Treatment in Depression (iSPOT-D)[13] involving over 1,000 MDD participants, there were no significant relationships between clinical specifiers and response or remission across 3 antidepressant treatments. These findings are similar to those of the STAR*D (Sequenced Treatment Alternatives to Relieve Depression) trial,[14] in which no clinical phenotypes were identified as aids for treatment selection.

One clinical predictor for antidepressant response, early improvement after treatment initiation, has been replicated in a number of clinical studies.[15] Early improvement, usually defined as a threshold reduction (eg, ≥ 20%–40% decrease from baseline) in score on a depression-specific scale 2–4 weeks after antidepressant initiation, was significantly associated with response and remission at 6–8 weeks.[10,16] In fact, a recent meta-analysis[17] of 17 randomized controlled trials (RCTs) of antidepressants concluded that early improvers were 8 times more likely to become responders and 6 times more likely to become remitters compared to patients who were not early improvers. In general, specificity is more relevant than sensitivity and suggests that lack of early improvement is a more robust predictor of nonresponse,[10,15–17] a finding that has also been observed with repetitive transcranial magnetic stimulation for MDD.[18]

Similarly, by using receiver operating characteristic (ROC) analysis, investigations have been able to determine thresholds of early symptomatic and functional improvements (based on percentage change from baseline in depressive symptom and functional scales) to predict future response and symptom/functional remission for each respective scale.[19,20]

The first study of the Canadian Biomarker Integration Network in Depression (CAN-BIND-1) Program is designed to identify integrative biomarkers or biosignatures of antidepressant treatment response in patients with MDD. The clinical protocol involves open-label treatment with escitalopram for 8 weeks followed by aripiprazole augmentation in escitalopram nonresponders for an additional 8 weeks.[21] The goals of this report are (1) to present baseline characteristics and treatment outcomes for clinical and functional measures during the 16-week study and (2) to estimate the value of early improvement after 2 weeks of treatment with escitalopram or escitalopram plus aripiprazole to predict symptom outcomes.

## MATERIALS AND METHODS

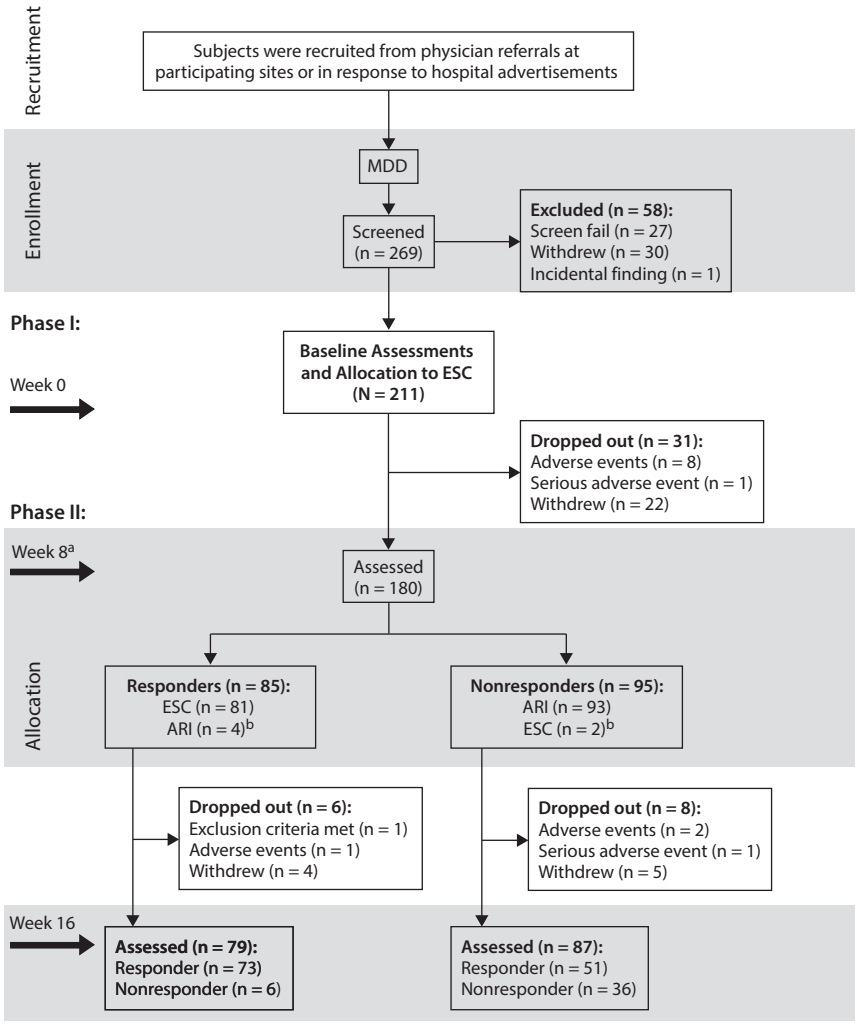
### Research Participants

Participants (N = 211) between 18 and 60 years of age who scored 24 or more on the Montgomery-Asberg Depression Rating Scale (MADRS)[22] were recruited from physician referrals or advertisements at 6 academic centers in Canada between August 2013 and December 2016. Participant flow, including total numbers of participants screened, enrolled, or excluded, is detailed in Figure 1. The Mini-International Neuropsychiatric Interview (MINI)[23] Version 6.1 was administered to confirm or rule-out MDD status and the presence or absence of other psychiatric comorbidities. Exclusion criteria included bipolarity, high suicidal risk, psychosis, pregnancy or breastfeeding, and failure to respond after 4 or more adequate pharmacologic interventions in the current episode or to a previous trial of escitalopram or aripiprazole. Adequate dose and duration were used to calculate the resistance scores using the Antidepressant Treatment History Form.[24] A score of 3 or higher constituted "resistance" for an individual. For a full list of inclusion and exclusion criteria, see Lam et al.[21] All participants provided written informed consent, and ethics approval was obtained at each center. The trial was registered at ClinicalTrials.gov (identifier: NCT01655706).

### Treatment Interventions

The protocol included 2 phases. In Phase 1, participants were treated with open-label escitalopram (10–20 mg/d, flexible-dosage) for 8 weeks. At baseline as well as at several time points in this period, they completed a comprehensive battery of structured assessments and self-report questionnaires outlined in the Study Visit Schedule (Supplementary Table 1). Participants also underwent neuroimaging, blood testing, and (at some centers) electroencephalography (EEG) at baseline, week 2, and week 8.[21] At the week 8 visit, individuals were classified as responders (≥ 50% decrease from baseline in MADRS score) or nonresponders (< 50% decrease in MADRS score from baseline). This dichotomy was used to define treatment outcomes (ie, response or nonresponse) and

**Figure 1. Flow of Participants**




[a]Week 8 responders, n = 83; nonresponders, n = 97. These numbers differ from those actually included in the 2 study groups because of inadvertent protocol deviations in drug allocation.
[b]Protocol deviations.
Abbreviations: ARI = aripiprazole, ESC = escitalopram, MDD = major depressive disorder.

allocation for Phase 2, in which Phase 1 responders continued to receive escitalopram monotherapy at the same dose while nonresponders received adjunctive aripiprazole (2–10 mg/d, flexible-dosage) for a second 8-week period (Figure 2). Of note, to maximize generalizability and to approximate real-world conditions, treatment was open-label and dosage adjustments within the treatment range were allowed if there were issues of tolerability or side effects.

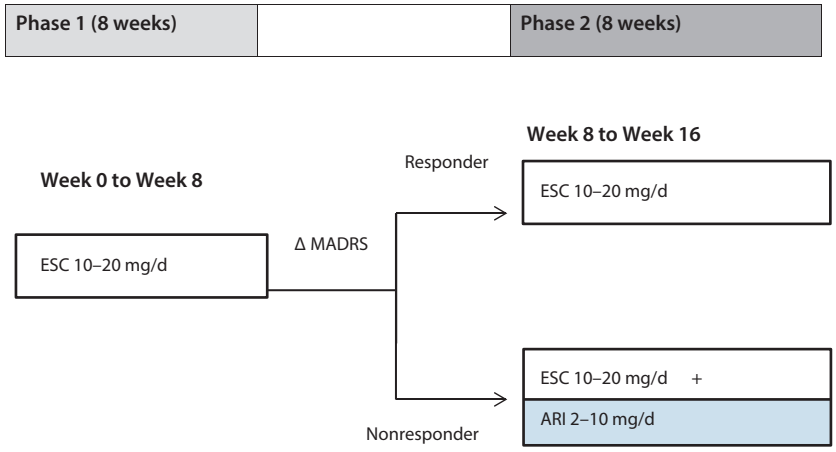
## Clinical Measurements

The following primary and secondary symptomatic and functional outcome measures were used: MADRS,[22] a 10-item clinician-administered questionnaire designed to assess depression severity; Quick Inventory of Depressive Symptomatology, Self-Rated (QIDS-SR),[25] a 16-item questionnaire designed to assess the severity of self-rated depressive symptoms; Clinical Global Impressions–Severity of Illness scale (CGI-S),[26] a 7-point scale rating illness severity; CGI-Improvement scale (CGI-I),[26] a 7-point scale assessing the clinical trajectory of illness (ie, improved or worsened outcomes); Sheehan Disability Scale (SDS),[27] a 5-item self-report tool that assesses functional impairment in work/school, social life, and family life; and Lam Employment Absence and Productivity Scale (LEAPS),[28] a 10-item self-rated scale assessing occupational impairment. Data were captured electronically in OpenClinica Enterprise (OpenClinica, Waltham, Massachusetts) and LimeSurvey (LimeSurvey, Hamburg, Germany) for entry into the Brain-CODE Platform.[29] A full list of measures is provided in Supplementary Table 1.

## Statistical Analysis

Descriptive statistics are presented as either number (percentage) or mean (SD). The demographic variables sex, age, education, and employment status were assessed, with additional clinical data on the number of previous episodes,

**Figure 2. CAN-BIND-1 Clinical Protocol[a,b]**




[a] ≥ 50% reduction.
[b] < 50% reduction.
Abbreviations: ARI = aripiprazole, CAN-BIND-1 = first study of the Canadian Biomarker Integration Network in Depression, ESC = escitalopram, Δ MADRS = change in Montgomery-Asberg Depression Rating Scale score.

current episode duration, and antidepressant use. Clinical outcome scores for the MADRS, QIDS-SR, SDS, and LEAPS were assessed for the full MDD cohort and subsequently for responders and nonresponders between week 0 and week 8 (Phase 1) and for both groups between week 8 and week 16 (Phase 2).

Three threshold levels of symptom reduction (≥ 20%, ≥30 %, and ≥ 40%) in MADRS scores from baseline to 2 weeks were used to examine the predictive value of early symptomatic change for escitalopram response in Phase 1; these thresholds were selected on the basis of previous literature.[17] To examine early improvement as a predictor of adjunctive aripiprazole response in Phase 2, these thresholds were applied to MADRS change scores from week 8 to week 10 to predict response and remission at 16 weeks. Sensitivity and specificity were calculated for each threshold. We also calculated the positive predictive value (PPV), ie, early improvers at 2 weeks that were responders at 8 weeks/all early improvers at 2 weeks, and negative predictive value (NPV), ie, early nonimprovers at 2 weeks that were nonresponders at 8 weeks/all early nonimprovers at 2 weeks. Analyses were performed using both (*a*) observed cases (OC) and (*b*) intent-to-treat (ITT) methods using mixed model for repeated measures (MMRM) to address missing values. In the OC analysis, only subjects with baseline and week 8 measures were included. Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS; SPSS Inc, Chicago, Illinois) version 20 and R,[30] version 3.4.3.

## RESULTS

### Participant Retention

In Phase 1, 211 participants completed the baseline visit and, for future publications, are considered the evaluable cohort. Of this group, 192 returned for at least 1 subsequent

**Table 1. Demographics and Clinical Characteristics of the MDD Cohort[a]**

| Characteristic | Patients With MDD (N = 211) |
|---|---|
| Female:male, n (% female) | 133:78 (63) |
| Age, mean (SD), range, y | 35.3 (12.6), 18–61 |
| Education, mean (SD), y[b] | 14.1 (2.0) |
| Age at MDD onset, mean (SD), range, y | 20.9 (10.5), 5–55 |
| No. of previous episodes | |
| 0 | 48 (22.7) |
| 1–2 | 56 (26.5) |
| 3–5 | 59 (28.0) |
| 6 or more | 35 (16.6) |
| Unknown/not reported | 13 (6.2) |
| Current episode duration | |
| < 12 mo | 110 (52.1) |
| 1–2 y | 23 (10.9) |
| > 2 y | 64 (30.3) |
| Unknown/not reported | 14 (6.6) |
| Prior antidepressant treatment for current episode | |
| None | 132 (62.6) |
| No adequate treatment | 29 (13.7) |
| 1 adequate treatment | 46 (21.8) |
| 2 adequate treatments | 4 (1.9) |
| Comorbidities[c,d] | |
| Substance-related disorders[e] | 8 (3.8) |
| Anxiety disorders[f] | 99 (46.9) |
| Eating disorders[g] | 10 (4.7) |
| Stable medical conditions[h] | 53 (25.1) |

[a] Values are shown as n (%) unless otherwise noted.
[b] Source: National Adult Reading Test (NART) with Heaton correction applied (a citation for this test is included in the article by Lam et al[21]).
[c] Based on *DSM-IV-TR*, as determined by the Mini-International Neuropsychiatric Interview.
[d] Percentages may not add up to 100% because patients may have more than 1 comorbid condition.
[e] Includes alcohol abuse and substance abuse.
[f] Includes panic disorder, agoraphobia, social phobia, obsessive-compulsive disorder, posttraumatic stress disorder, and generalized anxiety disorder.
[g] Includes anorexia nervosa and bulimia nervosa.
[h] Includes blood and lymphatic system disorders, cardiac disorders, dental hygiene disorders, ear and labyrinth disorders, endocrine disorders, eye disorders, gastrointestinal disorders, musculoskeletal and connective tissue disorders, nervous system disorders, renal and urinal disorders, reproductive system and breast disorders, rheumatology disorders, and skin and subcutaneous tissue disorders.
Abbreviation: MDD = major depressive disorder.

**Table 2. Change in Symptom and Functional Measures**

| Measure/Endpoint Outcome[a] | n | Start Point, Mean (SD) | Endpoint, Mean (SD) | *t* | *P* | Cohen *d* (Effect Size) |
|---|---|---|---|---|---|---|
| Participant outcomes after Phase 1, stratified by MADRS response or remitter status (Phase 1: escitalopram, baseline to week 8) | | | | | | |
| MADRS | | | | | | |
| Responder | 85 | 29.5 (5.6) | 8 (5.0) | −31.7 | <.001 | 3.4 |
| Nonresponder | 95 | 30.5 (5.5) | 23.7 (7.3) | −10.0 | <.001 | 1.0 |
| Remitter | 55 | 28.1 (5.4) | 4.9 (3.0) | −26.3 | <.001 | 3.6 |
| Nonremitter | 125 | 30.8 (5.4) | 21.3 (7.8) | −13.6 | <.001 | 1.2 |
| All | 180 | 30 (5.5) | 16.3 (10.1) | −18.8 | <.001 | 1.4 |
| QIDS-SR | | | | | | |
| Responder | 85 | 15.2 (4.1) | 6.8 (3.6) | −16.4 | <.001 | 1.8 |
| Nonresponder | 95 | 16.6 (4.0) | 12.8 (4.7) | −9.1 | <.001 | 0.9 |
| Remitter | 55 | 14.6 (4.3) | 5.3 (2.8) | −14.3 | <.001 | 2.0 |
| Nonremitter | 125 | 16.6 (3.9) | 12 (4.6) | −11.8 | <.001 | 1.1 |
| All | 180 | 16 (4.1) | 10 (5.2) | −16.2 | <.001 | 1.2 |
| SDS | | | | | | |
| Responder | 85 | 17.5 (7.2) | 7.9 (6.0) | −11.2 | <.001 | 1.3 |
| Nonresponder | 95 | 20 (6.2) | 16.9 (7.3) | −4.2 | <.001 | 0.4 |
| Remitter | 55 | 16.4 (7.5) | 6.3 (5.5) | −9.3 | <.001 | 1.3 |
| Nonremitter | 125 | 19.9 (6.2) | 15.5 (7.4) | −6.4 | <.001 | 0.6 |
| All | 180 | 18.8 (6.8) | 12.7 (8.1) | −10.1 | <.001 | 0.8 |
| LEAPS[b] | | | | | | |
| Responder | 85 | 13.7 (6.0) | 4.5 (4.2) | −10.1 | <.001 | 1.3 |
| Nonresponder | 95 | 15.2 (5.7) | 12 (6.2) | −5.1 | <.001 | 0.8 |
| Remitter | 55 | 12.8 (6.4) | 3.7 (3.2) | −8.1 | <.001 | 1.3 |
| Nonremitter | 125 | 15.3 (5.5) | 10.9 (6.4) | −7.1 | <.001 | 0.9 |
| All | 180 | 14.3 (5.9) | 8.2 (6.4) | −10.4 | <.001 | 1.0 |
| Participant outcomes after Phase 2, stratified by MADRS response or remitter status (Phase 2: escitalopram, week 8 to week 16) | | | | | | |
| MADRS | | | | | | |
| Responder | 69 | 7.4 (4.7) | 4.9 (4.0) | −4.2 | <.001 | 0.5 |
| Nonresponder | 7 | 11.4 (5.1) | 22.3 (6.9) | 3.7 | <.01 | 1.4 |
| Remitter | 61 | 7.1 (4.6) | 3.9 (2.9) | −5.6 | <.001 | 0.7 |
| Nonremitter | 15 | 10.4 (4.9) | 17.1 (6.9) | 3.7 | <.01 | 1.0 |
| All | 76 | 7.7 (4.8) | 6.5 (6.6) | −1.7 | NS | 0.2 |
| QIDS-SR | | | | | | |
| Responder | 69 | 6.3 (3.3) | 4.8 (3.6) | −3.7 | <.001 | 0.4 |
| Nonresponder | 7 | 10.6 (4.0) | 12.7 (5.5) | 0.9 | NS | 0.4 |
| Remitter | 61 | 6 (3.2) | 4.3 (3.2) | −3.9 | <.001 | 0.5 |
| Nonremitter | 15 | 9.6 (3.8) | 10.6 (5.1) | 0.8 | NS | 0.2 |
| All | 76 | 6.7 (3.6) | 5.5 (4.4) | −2.7 | <.01 | 0.3 |
| SDS | | | | | | |
| Responder | 69 | 7.2 (5.8) | 5.6 (6.0) | −2.4 | <.05 | 0.3 |
| Nonresponder | 7 | 14.4 (5.2) | 18.1 (6.7) | 2.3 | NS | 0.9 |
| Remitter | 61 | 6.7 (5.6) | 5.2 (5.7) | −2.1 | <.05 | 0.3 |
| Nonremitter | 15 | 12.7 (5.5) | 13.3 (8.2) | 0.4 | NS | 0.1 |
| All | 76 | 7.9 (6.1) | 6.8 (7.0) | −1.6 | NS | 0.2 |
| LEAPS[b] | | | | | | |
| Responder | 69 | 4.7 (4.3) | 3.8 (4.0) | −1.4 | NS | 0.2 |
| Nonresponder | 7 | 3.2 (2.6) | 13.2 (10.0) | 1.9 | NS | 0.9 |
| Remitter | 61 | 4.3 (3.9) | 3.3 (3.5) | −1.6 | NS | 0.2 |
| Nonremitter | 15 | 5.8 (5.6) | 10.2 (7.4) | 1.7 | NS | 0.5 |
| All | 76 | 4.6 (4.2) | 4.5 (5.1) | 0 | NS | 0 |
| Participant outcomes after Phase 2, stratified by MADRS response or remitter status (Phase 2: escitalopram + aripiprazole, week 8 to week 16) | | | | | | |
| MADRS | | | | | | |
| Responder | 55 | 21.5 (5.8) | 8.5 (4.9) | −15.6 | <.001 | 2.1 |
| Nonresponder | 35 | 26.1 (8.6) | 21.9 (6.8) | −4.1 | <.001 | 0.7 |
| Remitter | 38 | 20.4 (5.1) | 6 (3.2) | −15.7 | <.001 | 2.5 |
| Nonremitter | 52 | 25.3 (8.1) | 19.4 (6.9) | −6.6 | <.001 | 0.9 |
| All | 90 | 23.3 (7.3) | 13.7 (8.7) | −12.2 | <.001 | 1.3 |
| QIDS-SR | | | | | | |
| Responder | 55 | 11.9 (4.1) | 8 (4.3) | −6.6 | <.001 | 0.9 |
| Nonresponder | 35 | 14.2 (5.1) | 12.8 (5.3) | −2.4 | <.05 | 0.4 |
| Remitter | 38 | 11.2 (3.6) | 6.4 (3.5) | −7.0 | <.001 | 1.1 |
| Nonremitter | 52 | 13.9 (5.0) | 12.3 (4.9) | −3.1 | <.01 | 0.4 |
| All | 90 | 12.8 (4.7) | 9.9 (5.3) | −6.6 | <.001 | 0.7 |
| SDS | | | | | | |
| Responder | 55 | 15.6 (7.0) | 9.5 (7.0) | −5.3 | <.001 | 0.7 |
| Nonresponder | 35 | 18.4 (7.5) | 16.8 (8.7) | −1.4 | NS | 0.2 |
| Remitter | 38 | 15.5 (7.0) | 8.5 (7.4) | −4.8 | <.001 | 0.8 |
| Nonremitter | 52 | 17.6 (7.4) | 15.3 (8.1) | −2.4 | <.05 | 0.3 |
| All | 90 | 16.7 (7.3) | 12.4 (8.5) | −5.0 | <.001 | 0.5 |
| LEAPS[b] | | | | | | |
| Responder | 55 | 10.9 (5.6) | 7 (5.3) | −5.3 | <.001 | 0.9 |
| Nonresponder | 35 | 13.3 (7.1) | 11.4 (7.3) | −1.3 | NS | 0.3 |
| Remitter | 38 | 9 (4.8) | 4.8 (3.8) | −4.6 | <.001 | 1.0 |
| Nonremitter | 52 | 13.7 (6.4) | 11.4 (6.4) | −2.6 | <.05 | 0.5 |
| All | 90 | 11.7 (6.2) | 8.4 (6.3) | −4.6 | <.001 | 0.6 |

[a]Responder and remitter status based on MADRS scores. [b]No response for individuals not working.
Abbreviations: CGI = Clinical Global Impressions scale, LEAPS = Lam Employment Absence and Productivity Scale, MADRS = Montgomery-Asberg Depression Rating Scale, NS = not significant, QIDS-SR = Quick Inventory of Depressive Symptomatology–Self-Rated, SDS = Sheehan Disability Scale.

visit after receiving escitalopram 10 mg/d. One hundred eighty participants completed Phase 1, of whom 85 were responders. There were 6 protocol deviations for drug allocation at Phase 2, in which 4 responders to escitalopram received adjunctive aripiprazole and 2 of the nonresponders remained on escitalopram monotherapy. These 6 individuals were included in the groups to which they had been inadvertently allocated. At week 16, the remaining 166 participants were reassessed for response or nonresponse status (see Figure 1).

### Baseline Demographics and Clinical Characteristics of MDD Cohort

Participants had a mean (SD) age of 35.3 (12.6) years, and 63% were female. The mean (SD) duration of education was 14.1 (2.0) years, and 65% were employed during the study period. Approximately 77% had recurrent depressive episodes, with the majority reporting up to 5 episodes of depression prior to enrollment. Current episode duration was less than 12 months in 52% of participants, while 30% met criteria for persistent depressive disorder based on current episode duration of greater than 2 years. Prior use of an antidepressant within the current episode was reported by 37.4% of the group. Comorbid anxiety disorders (46.9%), substance-related disorders (3.8%), and eating disorders (4.7%) were present at baseline, and 25% reported having at least 1 stable medical condition (see Table 1).

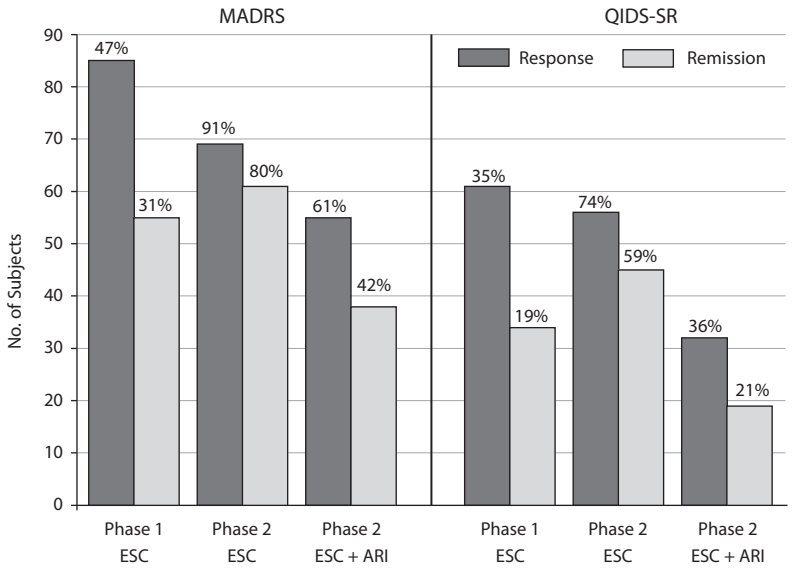
### Symptomatic and Functional Outcomes

Table 2 shows the change in symptomatic and functional measures during 8 weeks of escitalopram treatment for all subjects, who were also stratified according to response and remission outcomes. There was a significant reduction in all measures in each of the 3 groups (Phase 1). Among the 47% who were responders in Phase 1, the majority of participants (91%) had a sustained response at the end of Phase 2. Among nonresponders in Phase 1, 61% achieved response at week 16 and displayed significant reductions on the majority of clinical and functional measures, although nonresponders on the MADRS and QIDS-SR did not achieve significant reductions on functional measures (see Table 2 and Figure 3). There was a strong correlation between MADRS and QIDS-SR scores across all time points ($r = 0.80$, $P < .001$). Since analyses using MMRM and OC did not differ (see Supplementary Table 2), the OC results are presented in Table 2.

### Combined Symptomatic and Functional Response and Remission

Functional response and remission were also assessed using SDS criteria (SDS score ≤ 12 and

**Figure 3. Percentage of Responders and Remitters Based on Scores on the MADRS and QIDS-SR[a]**




[a]Remitters in Phase 2 include responders who were remitters or nonremitters in Phase 1. Percentages are based on a total of 180 subjects assessed at the start of Phase 2
Abbreviations: ARI = aripiprazole, ESC = escitalopram, MADRS = Montgomery-Asberg Depression Rating Scale, QIDS-SR=Quick Inventory of Depressive Symptomatology–Self-Rated.

**Table 3. Symptomatic, Functional, and Combined Response and Remission Rates During Phases 1 and 2[a]**

| Outcome | Phase 1 (Week 8), ESC | Phase 2 (Week 16) ESC | Phase 2 (Week 16) ESC + ARI |
|---|---|---|---|
| Response | | | |
| Symptomatic response (≥ 50% reduction in MADRS score) | 47 | 91 | 61 |
| Functional response (SDS score ≤ 12) | 53 | 80 | 53 |
| Combined | 35 | 77 | 40 |
| Remission | | | |
| Symptomatic remission (MADRS score ≤ 10) | 31 | 80 | 42 |
| Functional remission (SDS score ≤ 6) | 24 | 57 | 27 |
| Combined | 18 | 52 | 19 |

[a]All rates are shown as percentages.
Abbreviations: ARI = aripiprazole, ESC = escitalopram, MADRS = Montgomery-Asberg Depression Rating Scale, SDS = Sheehan Disability Scale.

**Table 4. Predictive Value of Symptom Reduction After 2 Weeks of Escitalopram or Escitalopram + Aripiprazole Treatment[a]**

| Threshold/Outcome | PPV | NPV | Sensitivity | Specificity |
|---|---|---|---|---|
| Phase 1: Predictive value of different threshold criteria for early improvement (change in MADRS score between baseline and week 2) for week 8 escitalopram response | | | | |
| ≥ 20% (n = 99) | | | | |
| Response | 60.6 | 69.1 | 70.6 | 58.9 |
| Remission | 44.4 | 86.4 | 80 | 56 |
| ≥ 30% (n = 67) | | | | |
| Response | 64.2 | 62.8 | 50.6 | 74.7 |
| Remission | 49.3 | 80.5 | 60 | 72.8 |
| ≥ 40% (n = 37) | | | | |
| Response | 78.4 | 60.8 | 34.1 | 91.6 |
| Remission | 62.2 | 77.6 | 41.8 | 88.8 |
| Phase 2: Predictive value of different threshold criteria for early improvement (change in MADRS score between week 8 and week 10) for week 16 escitalopram + aripiprazole response. | | | | |
| ≥ 20% (n = 57) | | | | |
| Response | 69.1 | 51.4 | 69.1 | 51.4 |
| Remission | 54.4 | 78.8 | 81.6 | 50 |
| ≥ 30% (n = 46) | | | | |
| Response | 71.7 | 50 | 60 | 62.9 |
| Remission | 58.7 | 75 | 71.1 | 63.5 |
| ≥ 40% (n = 33) | | | | |
| Response | 75.8 | 47.4 | 45.5 | 77.1 |
| Remission | 60.6 | 68.4 | 52.6 | 75 |

[a]All values are shown as percentages.
Abbreviations: MADRS = Montgomery-Asberg Depression Rating Scale, NPV = negative predictive value, PPV = positive predictive value.

SDS score ≤ 6, respectively).[31] Table 3 shows the response and remission rates for symptomatic (MADRS criteria), functional, and combined outcomes in Phases 1 and 2. In Phase 1, combined remission was achieved by 18% of patients. In Phase 2, this was achieved by 52% of the escitalopram continuation group and 19% of the adjunctive aripiprazole group. There was a significant positive correlation between MADRS and SDS total scores over all time points ($r = 0.71$, $P < .001$).

### Predictive Value of Early Symptomatic Improvement

Table 4 shows the sensitivity, specificity, PPV, and NPV for 20%, 30%, and 40% threshold criteria for early improvement after 2 weeks as predictors of response and remission to escitalopram at 8 weeks (0–2 weeks) and to adjunctive aripiprazole at 16 weeks (8–10 weeks). The 20% threshold provided the best balance between sensitivity and specificity for escitalopram response, while the 40% threshold had high levels of specificity and PPV but lower sensitivity and NPV. Similarly, PPV and specificity were highest at the 40% threshold in predicting response to adjunctive aripiprazole,

**Table 5. Comparison of Adverse Events During Phase 2 Treatment With Escitalopram Continuation or Escitalopram + Aripiprazole[a]**

| | Escitalopram | | | Escitalopram + Aripiprazole | | |
|---|---|---|---|---|---|---|
| Adverse Event | Week 10 | Week 12 | Week 16 | Week 10 | Week 12 | Week 16 |
| Decreased sleep | 4 | 10 | 10 | 24 | 23 | 12 |
| Drowsiness | 9 | 12 | 8 | 14 | 14 | 21 |
| Weakness | 8 | 9 | 6 | 14 | 12 | 24 |
| Nervousness | 8 | 4 | 3 | 13 | 9 | 15 |
| Sweating | 9 | 7 | 9 | 12 | 10 | 9 |
| Delayed ejaculation | 15 | 7 | 12 | 10 | 8 | 16 |
| Anorgasmia | 9 | 13 | 8 | 10 | 5 | 10 |
| Decreased libido | 12 | 10 | 6 | 10 | 8 | 14 |
| Weight gain | 4 | 4 | 5 | 9 | 6 | 12 |
| Agitation | 5 | 5 | 3 | 9 | 19 | 14 |
| Headache | 4 | 5 | 1 | 12 | 10 | 8 |

[a]All values are shown as percentages.

although the 30% threshold performed better overall than the 20% in this augmentation group. To further evaluate clinical utility of early improvement during treatment with escitalopram, an examination of areas under the ROC curves (AUC) showed values of 0.69 and 0.74, respectively, for response and remission at week 8. Similarly, treatment with escitalopram + aripiprazole yielded AUC values of 0.66 and 0.70, respectively, for response and remission at week 16.

### Tolerability and Safety

Side effect reporting is based on the Toronto Side Effects Scale (TSES).[32] During Phase 1, the most frequently reported side effects (occurring in > 10% of individuals) after 2 weeks of escitalopram were drowsiness (23%), nausea and headache (16%), weakness/fatigue (15%), nervousness/agitation (14%), and delayed ejaculation in men (14%). In general, these side effects decreased during treatment, with only delayed ejaculation (15%) and headache (12%) remaining above 10% at 8 weeks. Table 5 compares side effects in Phase 2 associated with escitalopram continuation in responders to those associated with adjunctive aripiprazole + escitalopram. In general, side effects diminished with escitalopram treatment during weeks 8–16, with only decreased sleep and delayed ejaculation in men remaining at 10% or higher. In the group who received adjunctive aripiprazole, weakness and drowsiness were reported in 24% and 21% of individuals, respectively, while 10%–20% of individuals reported symptoms of decreased libido (14%), delayed ejaculation (16%), agitation/nervousness (15%), and decreased sleep (12%).

Eight participants dropped out during Phase 1 due to adverse events such as decreased sex drive, appetite, or sleep as well as increased anxiety, tension, agitation, sadness, and incontinence; 1 participant made a hospital visit for chest tightness, dizziness, loss of balance, blurry vision, and chills (Figure 1). There was 1 serious adverse event, a death by suicide 3 days after a prescription for escitalopram was given at the baseline assessment; it is not known whether the prescription was filled or if any dose of escitalopram was ingested. Four participants dropped out during Phase 2 due to adverse events: 1 in the escitalopram continuation group and 3 in the adjunctive aripiprazole group, of whom 1 was classified as having a severe adverse event characterized by a hospital visit following a seizure.

## DISCUSSION

The aim of this report is to describe clinical characteristics and treatment outcomes for a population of 211 MDD outpatients who completed a 2-phase 16-week open-label treatment protocol. All participants also completed clinical, neuroimaging, EEG, and molecular measures,[21] which will be the focus of subsequent reports.

There are 4 key findings from this study: (1) response and remission rates after 8 weeks of escitalopram treatment were modest and comparable to those in other large practical-design trials; (2) response to escitalopram after 8 weeks was sustained in the majority of individuals at 16 weeks, and there was a greater overlap between functional and symptomatic outcomes at the end of Phase 2; (3) more than half of nonresponders to escitalopram at 8 weeks had a positive response to adjunctive aripiprazole at 16 weeks; and (4) in both escitalopram monotherapy and adjunctive aripiprazole phases, early symptomatic change after 2 weeks provided modest value in predicting subsequent response rates.

Response status (based on MADRS score reduction ≥ 50%) after 8 weeks of escitalopram treatment was used to assign participants to subsequent treatment arms. At the end of Phase 1, 47% were MADRS responders who continued on escitalopram for the remaining 8 weeks, and 91% of this subgroup maintained the response at 16 weeks. Meanwhile, among Phase 1 nonresponders, 61% achieved response with adjunctive aripiprazole. The cumulative response rate for all participants at the end of 16 weeks was 75%. The remission rate after Phase 1 was 31%, while after Phase 2 the remission rates for those who continued on escitalopram and for those who received adjunctive aripiprazole were 80% and 42%, respectively. In percentage terms, response and remission rates as measured by the QIDS-SR were lower than with the MADRS, with 35% of participants being rated as responders and 19% as remitters at 8 weeks. This finding is consistent with those of prior reports of clinician-rated and self-report questionnaires providing complementary information.[33]

Nevertheless, correlation between the 2 scales remained high, as has been reported elsewhere.[34]

Response and remission rates in Phase 1 are comparable to or lower than those of other large pragmatic design studies. For example, the response rate in the first stage of STAR*D,[35] in which patients received citalopram for up to 14 weeks, was 47% and remission was 33% (both based on the QIDS-SR). Somewhat higher rates were reported with acute escitalopram treatment (n = 233) in the iSPOT-D,[36] in which respective response and remission rates were 56% and 41% (also defined by QIDS-SR). This finding may be in part related to higher baseline scores on the QIDS-SR in our study.

As reported previously by Sheehan et al,[31] the correlation between functional and symptomatic improvement was not high; after Phase 1 in the current study, only 24% achieved functional remission by SDS criteria and 18% achieved combined symptomatic and functional remission. These results are comparable to those from a pooled analysis of duloxetine-treated MDD patients in which symptomatic (38%), functional (32%), and combined (23%) remissions were achieved after 8 weeks.[31] In Phase 2 of the current study, the adjunctive aripiprazole group achieved functional and combined remission rates of 27% and 19%, respectively. However, the escitalopram continuation group achieved considerably higher functional (57%) and combined (52%) remission rates at 16 weeks, confirming that it takes longer than 8 weeks to achieve functional remission in the majority of symptomatic responders.

The predictive value in Phase 1 of early improvement, as defined by ≥ 20% decrease in MADRS score from baseline to 2 weeks, showed a PPV of 61% and an NPV of 69%. This means that 60% of patients treated with escitalopram showing early improvement were responders at 8 weeks while 68% of those without early improvement were nonresponders. As expected, higher thresholds yielded higher sensitivity and lower specificity, but they did not improve on overall predictive accuracy. Although our results are not directly comparable because of the open-label treatment, they are similar to those reported in a systematic review and meta-analysis[17] of 17 antidepressant RCTs involving almost 17,000 patients, in which the PPV and NPV of early improvement (≥ 20% or ≥ 25% decrease in scores on a depression-specific scale at 2 weeks) as predictors of response were 63% and 77%, respectively. However, there also may be individual or class differences among antidepressants, as the meta-analysis found SSRIs had higher PPVs but lower NPVs than mirtazapine and tricyclic antidepressants.[17] Others[37] have questioned the utility of early improvement as a predictor of subsequent response, particularly in treatment-resistant depression.

The utility of early improvement during adjunctive aripiprazole therapy has been less frequently reported. In contrast to the Phase 1 results, the Phase 2 adjunctive aripiprazole group showed higher PPV (69%) than NPV (51%) for early improvement (defined as ≥ 20% decrease in MADRS score between week 8 and week 10) as a predictor for week 16 response. In a post hoc analysis of 3 placebo-controlled RCTs of aripiprazole augmentation of various antidepressants (n = 503), Muzina and colleagues[38] used the ≥ 20% criteria for early improvement to predict 6-week remission status. Compared to our results, they reported lower PPV (42% vs 69%) but higher NPV (91.5% vs 51%).

A significant strength of our study was the high retention rate (79%), which is noteworthy considering the rigorous protocol involving neuroimaging and blood sampling at frequent intervals. Although this study was not a placebo-controlled RCT, open-label treatment with escitalopram and adjunctive aripiprazole may better reflect real-world clinical practice. On the other hand, limitations include the lack of blinding and the relatively small sample size. As well, the choice of a binary approach to assigning participants in the second phase inevitably led to the occupation of different categories for subsequent treatment and analyses by some individuals with minimal differences (eg, 49% vs 51% reduction in symptoms). However, this approach facilitated exploration of response and remission rates following adjunctive aripiprazole in partial responders as well as robust nonresponders. However, the absence of a placebo-controlled group of escitalopram nonresponders in Phase 2 limits any conclusions about the efficacy of adjunctive aripiprazole.

In summary, the CAN-BIND-1 study found reasonable rates of symptomatic, functional, and combined response, but low rates of remission by all measures, in patients with MDD treated with standard escitalopram treatment followed by adjunctive aripiprazole treatment. Early improvement in symptoms after 2 weeks had reasonable PPV and NPV for later response and nonresponse, but the overall diagnostic accuracy is fair at best. The integration of clinical, neuroimaging, EEG, and molecular data in CAN-BIND-1 may help to identify a multimodal biosignature that can provide a more reliable predictor of response compared to the above clinical measures. The PPV and NPV of early improvement set at a threshold of 20% may be considered the benchmark against which the predictive value of any biosignature should be compared. In this regard, the ≥ 40% threshold for early improvement, although present only in a small subset of patients (37/180), achieved a PPV of almost 80% for response. It is suggested that a combination of biomarkers and clinical data may enhance treatment selection and outcomes.

***Submitted:*** February 21, 2018; accepted August 15, 2018.

***Published online:*** February 5, 2019.

***Potential conflicts of interest:*** **Dr Kennedy** has received research funding or honoraria from the following sources: Abbott, Alkermes, Allergan, AstraZeneca, Bristol-Myers Squibb (BMS), Brain Canada, Canadian Institutes of Health Research (CIHR), Janssen, Lundbeck, Lundbeck Institute, Ontario Mental Health Foundation (OMHF), Ontario Brain Institute, Otsuka, Pfizer, Servier, St. Jude Medical, Sunovion, and Xian-Janssen. **Dr Lam** has received honoraria for ad hoc speaking or advising/consulting or received research funds from Akili, Allergan, Asia-Pacific Economic Cooperation, BC Leading Edge Foundation, Brain Canada, CIHR, Canadian Depression Research and Intervention Network, Canadian Network for Mood and Anxiety Treatments (CANMAT), Canadian Psychiatric Association, CME Institute, Hansoh, Janssen, Lundbeck, Lundbeck Institute, Medscape, Mind Mental Health Technologies, Otsuka, Pfizer, St. Jude Medical, University Health Network Foundation,

and VGH Foundation. **Dr Milev** has been on the advisory board or consulted for Allergan, Bristol-Myers Squibb, Janssen, Lundbeck, Otsuka, Pfizer, Shire, Sunovion; has received research grants from Boehringer Ingelheim, Canadian Biomarker Integration Network in Depression (CAN-BIND), CIHR, Janssen, Lundbeck, OMHF, and Pfizer; and has been a speaker for BMS, Janssen, Lilly, Otsuka, Pfizer, and Sunovion. **Dr Blier** received grant funding and/or honoraria for lectures and/or participation in advisory boards for Allergan, AstraZeneca, BMS, Eli Lilly, Euthymics, Janssen, Lundbeck, Merck, Otsuka, Pfizer, Pierre Fabre, Servier, Shire, Takeda, and Valeant. **Dr Downar** reports research grants from CIHR, the National Institute of Mental Health (NIMH), Brain Canada, CAN-BIND , the Ontario Brain Institute, the Klarman Family Foundation, the Arrell Family Foundation, and the Buchan Family Foundation; travel stipends from Lundbeck and ANT Neuro; and in-kind equipment support for investigator-initiated trials from MagVenture and is an advisor for BrainCheck, TMS Neuro Solutions, and Restorative Brain Clinics. **Dr Evans** is employed by Indoc Research. **Dr Frey** has served on advisory boards for Lundbeck, Pfizer, and Sunovion and received research support from Pfizer. **Dr Giacobbe** has been a consultant or on an advisory board for St. Jude Medical and BMS. **Dr Ismail** has received grant support from or been on an advisory board/speaker's bureau for CIHR, National Institute on Aging, Canadian Consortium on Neurodegeneration and Aging, Brain Canada, University of Calgary Clinical Research Fund, Avanir, Janssen, Eli Lilly, Lundbeck, Merck, Otsuka, Pfizer, and Sunovion. **Dr McInerney** has received honoraria from Pfizer, Janssen, and Lundbeck in the last 5 years. He was part of the CANMAT guidelines for depression working group. **Dr MacQueen** has been a consultant or speaker for BMS, Lundbeck, Janssen, and Pfizer. **Dr Minuzzi** has received grants/research support and speakers bureau honoraria from Alternative Funding Plan Innovations Award, Brain & Behavioral Foundation, CIHR, Hamilton Health Sciences Foundation, Ontario Brain Institute, OMHF, BMS, Lundbeck, Sunovion, Canadian Psychiatric Association, and CANMAT. **Dr Parikh** has received honoraria for consulting from Assurex and Takeda, honoraria for speaking from CANMAT, and research grants from Assurex, Takeda, the Ontario Brain Institute, CIHR, and the Ethel and James Flinn Foundation and has shares in Mensante. **Dr Quilty** has received grant support from the American Foundation for Suicide Prevention, OMHF, Gambling Research Exchange Ontario, and CAMH Foundation as Principal Investigator (PI) and from the National Institutes of Health (NIH), CIHR, and Ontario Brain Institute as co-investigator. Dr Quilty has no personal affiliations or financial relationships with any commercial interest to disclose relative to the article. **Dr Ravindran** is not a major stockholder with any pharmaceutical companies, but has received grant and research support in the past from them. Past industry grant awards include AstraZeneca, BMS, Cephalon, Eli Lilly, GlaxoSmithKline, Janssen-Ortho, Lundbeck, Pfizer, Roche, Servier, and Wyeth. Dr Ravindran holds a current industry grant award from Janssen-Ortho as a co-investigator. He has served as a consultant for some of the above institutions and on their Advisory Boards. He has also participated in Continuing Medical Education programs sponsored by these and other pharmaceutical companies. Dr Ravindran also holds or has held peer-reviewed funding from CIHR, Grand Challenges Canada, Ontario Brain Institute, OMHF, Canadian Foundation for Innovation and Ministry of Economic Development and Innovation, and NIMH. **Dr Sassi** received consulting/advisory and speaker honoraria from BMS, Janssen, and AstraZeneca between 2012 and 2015, but has received none since. **Dr Soares** has worked as a consultant for Bayer, Pfizer, Sunovion, Otsuka, and Lundbeck. **Dr Strother** is a Chief Scientific Officer of ADMdx, Inc, Chicago, a medical neuroimaging analysis and diagnostics company. **Dr Turecki** is supported by grants from CIHR (MOP93775, MOP11260, MOP119429, and MOP119430, and the US NIH (1R01DA033684), by the Fonds de Recherche du Québec—Santé (FRQS) through a Chercheur National salary award and through the Quebec Network on Suicide, Mood Disorders, and Related Disorders, and through an investigator-initiated research grant from Pfizer. **Dr Vaccarino** is employed by Indoc Research. **Dr Vila-Rodriguez** reports research grants from CIHR, Brain Canada, Michael Smith Foundation for Health Research, and Vancouver Coastal Health Research Institute; reports receiving in-kind equipment support for this investigator-initiated trial from MagVenture; and has been on an advisory board for Janssen Pharmaceutical. **Dr Uher** declares no conflicts of interest, financial or other, and has no stakes in a pharma or biotech company and no consultancy or board membership. Dr Uher has received research funding from the Canada Research Chairs Program (award number 231397), the CIHR (grant reference numbers 124976, 142738, and 148394), the Brain & Behavior Research Foundation (NARSAD Independent Investigator Grant 24684), Nova Scotia Health Research Foundation (grants 275319, 1716, and 353892), and the Dalhousie Medical Research Foundation. **Drs Rotzinger, Farzan, Foster, Hall, Harkness, Hassel, Leri, Müller, Placenza,** and **Yu** have no conflicts to report.

***Funding/support:*** This research was conducted as part of the CAN-BIND, an Integrated Discovery Program supported by the Ontario Brain Institute, which is an independent non-profit corporation, funded partially by the Ontario Government. Additional funding was provided by CIHR, Lundbeck, BMS, and Servier. Funding and/or in kind support was also provided by the investigators' universities and academic institutions.

***Role of the sponsors:*** The sponsors had no role in study design, implementation, completion, analyses, or manuscript preparation.

***Disclaimer:*** The opinions, results, and conclusions are those of the authors and no endorsement by the Ontario Brain Institute is intended or should be inferred.

***Previous presentation:*** Preliminary data from this trial were presented by Dr Kennedy at the Canadian Psychiatric Association Annual Meeting; September 14, 2017; Ottawa, Ontario, Canada.

***Acknowledgments:*** We thank Amanda Ceniti (PhD Candidate, University of Toronto, St Michael's Hospital, Toronto, Ontario, Canada) and Trehani Fonseka, MSc (University Health Network, Toronto, Ontario, Canada), for assistance in preparation of this manuscript. We also thank Xiamin Leng, MSc (University Health Network, Toronto, Ontario, Canada); Helia Ghanean, MD, PhD (University Health Network, Toronto, Ontario, Canada); Keith Ho (PhD Candidate, University Health Network, Toronto, Ontario, Canada); and Wendy Lou, PhD (University of Toronto, Toronto, Ontario, Canada), for consultation and assistance with data analysis. All listed individuals are funded, at least in part, by CAN-BIND.

***Supplementary material:*** Available at PSYCHIATRIST.COM.

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# Supplementary Material

**Article Title:** Symptomatic and Functional Outcomes and Early Prediction of Response to Escitalopram Monotherapy and Sequential Adjunctive Aripiprazole Therapy in Patients With Major Depressive Disorder: A CAN-BIND-1 Report

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**DOI Number:** https://doi.org/10.4088/JCP.18m12202

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## Disclaimer

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## Supplementary Table 1: CAN-BIND-1 Study Visit Schedule

| | | Phase 1 | | | | | Phase 2 | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **PROCEDURE** | **Screening** | **Baseline** | **Week 2** | **Week 4** | **Week 6 (phone)** | **Week 8 / D/C** | **Week 10** | **Week 12** | **Week 14 (phone)** | **Week 16 / D/C** |
| **Informed Consent** | X | | | | | | | | | |
| **Demographics** | X | | | | | | | | | |
| **Medical, Psychiatric, Reproductive History** | X | | | | | | | | | |
| **ATHF** | X | | | | | | | | | |
| **MINI** | X | | | | | | | | | |
| **Physical Exam** [d] | X | | | | | | | | | |
| **Urinalysis, drug screen, screening blood work** | X | | | | | | | | | X [d] |
| **12 lead ECG (if indicated)** | X | | | | | | | | | |
| **Blood collection for pharmacogenetics** | | | | X | | | | | | |
| **Blood collection for drug levels** | | | X | | | | X | | | X |
| **Concomitant medication and adverse event review** | X | X | X | X | X | X | X | X | X | X |
| **Neuroimaging and EEG** | | X | X | | | X | | | | |
| **Blood collection for proteomics, genomics** | | X | X | | | X | | | | X |
| **Assessments and Scales - Clinician-Administered** | | | | | | | | | | |
| **MADRS** | X | X | X | X | X | X | X | X | X | X |
| **YMRS** | X | X | X | | | X | X | | | X |
| **CGI** | X | X | X | X | | X | X | X | | X |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **DID** | | **X** | | | | **X** | | | | |
| **CECA** | | | | **X**[b] | | | | | | |
| **TSES** | | | **X** | **X** | | | **X** | **X** | | **X** |
| **SexFX** | | **X** | | | | **X** | | | | **X** |
| **Assess for Response Status** | | | | | | **X** | | | | |
| **LEDS** | | | | | | | | | | **X**[c] |
| **NART** | X | | | | | | | | | |
| **Self-Reports** | | | | | | | | | | |
| **CNS Vital Signs** | | **X** | | | | **X** | | | | **X** |
| **QIDS-SR** | | **X** | **X** | **X** | | **X** | **X** | **X** | | **X** |
| **SDS** | | **X** | | | | **X** | | | | **X** |
| **LEAPS** | | **X** | | | | **X** | | | | **X** |
| **Q-LES-Q** | | **X** | | | | **X** | | | | **X** |
| **HCL** | **X** | | | | | **X** | | | | **X** |
| **SPAQ** | | **X**[a] | | | | | | | | |
| **GAD-7** | | **X** | **X** | | | **X** | **X** | | | **X** |
| **NEO-FFI** | | **X**[a] | | | | | | | | |
| **ECR-R** | | **X**[a] | | | | | | | | |
| **LTE** | | **X**[a] | | | | | | | | **X** |
| **SHAPS** | | **X** | | | | **X** | | | | **X** |
| **DARS** | | **X** | | | | **X** | | | | **X** |
| **BIS/BAS** | | **X** | **X** | | | **X** | **X** | | | **X** |
| **BPI** | | **X** | | | | **X** | | | | **X** |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **BRIAN** | | **X[a]** | | | | **X** | | | | **X** |
| **BDQ** | | **X** | **X** | | | **X** | | | | **X** |
| **IPAQ** | **x** | | | | | **X** | | | | **X** |
| **PSQI** | | **X** | | | | **X** | | | | **X** |
| **WHOQoL-BREF** | **x** | | | | | **X** | | | | **X** |
| **TREATMENT** | | | | | | | | | | |
| | **ESCITALOPRAM (10-20 mg)** | | | | | | | | | |
| | | | | | | **ARIPIPRAZOLE (2-10 mg) add-on for non-responders** | | | | |

ATHF = Antidepressant Treatment History Form; BDQ = Brief Diet Questionnaire; BIS/BAS = Behavioural Inhibition/Behavioural Activation Scale; BPI = Brief Pain Inventory; BRIAN = Biological Rhythm Interview of Assessment in Neuropsychiatry; CECA = Childhood Experience of Care and Abuse Questionnaire; CGI = Clinical Global Impression; DARS = Dimensional Anhedonia Rating Scale; DID = Depression Inventory Development Interview; ECR-R = Experiences in Close Relationships Questionnaire; EEG = electroencephalogram; GAD-7 = Generalized Anxiety Disorder 7-item scale; HCL = Hypomania Check-List; IPAQ = International Physical Activity Questionnaire; LEAPS = Lam Employment Absence and Productivity Scale; LEDS = Life Events and Difficulties Schedule; LTE = List of Threatening Experiences; MADRS = Montgomery–Åsberg Depression Rating Scale; MINI = MINI International Neuropsychiatric Interview; NART = National Adult Reading Test; NEO-FFI = NEO Five-Factor Inventory; PSQI = Pittsburgh Sleep Quality Index; SDS = Sheehan Disability Scale; SexFX = Sexual Side Effects Questionnaire; TSES = Toronto Side Effects Scale; QIDS-SR = Quick Inventory of Depressive Symptomatology; Q-LES-Q = Quality of Life, Enjoyment and Satisfaction Questionnaire; SPAQ = Seasonal Pattern Assessment Questionnaire; SHAPS = Snaith-Hamilton Pleasure Scale; WHOQoL-BREF = World Health Organization Quality of Life Assessment; YMRS = Young Mania Rating Scale

[a]= may be sent home; [b]= done at Week 2 for healthy comparison participants; [c]= done at endpoint (week 16 or early termination visit); [d] =patients only; phone interview by Harkness lab;

**Supplementary Table 2: Comparison of Observed-Case (OC) and Mixed-effect Model for Repeat Measurements (MMRM) for MADRS at Baseline, 8 weeks and 16 weeks***

| **Phase 1 – Escitalopram** | **MADRS Baseline** | | **MADRS Week 8** | |
|---|---|---|---|---|
| | **OC** | **MMRM** | **OC** | **MMRM** |
| All (n=192) | 30.0 (5.5) | 30.0 (5.5) | 16.3 (10.1) | 16.4 (9.9) |
| Responder (n=89, 46.4%) | 29.5 (5.5) | 29.5 (5.5) | 8.0 (5.0) | 8.1 (5.0) |
| Non-Responder (n=103, 53.6%) | 30.5 (5.5) | 30.5 (5.5) | 23.7 (7.3) | 23.5 (7.1) |
| Remitter (56, 29.2%) | 28.3 (5.4) | 28.3 (5.4) | 4.9 (3.0) | 4.9 (3.0) |
| Non-Remitter (136, 70.8%) | 30.8 (5.4) | 30.8 (5.4) | 21.3 (7.8) | 21.1 (7.6) |

| **Phase 2 Escitalopram Continuation** | **MADRS Week 8** | | **MADRS Week 16** | |
|---|---|---|---|---|
| | **OC** | **MMRM** | **OC** | **MMRM** |
| All (n=78) | 7.7 (4.8) | 7.8 (4.9) | 6.5 (6.6) | 6.7 (6.7) |
| Responder (n=71, 91.0%) | 7.4 (4.7) | 7.5 (4.8) | 4.9 (4.0) | 5.1 (4.2) |
| Non-Responder (n=7, 9.0%) | 11.4 (5.1) | 11.4 (5.1) | 22.3 (6.9) | 22.3 (6.9) |
| Remitter (n=61, 78.2%) | 7.1 (4.6) | 7.1 (4.6) | 3.9 (2.9) | 3.9 (2.9) |
| Non-Remitter (n=17, 21.8%) | 10.4 (4.9) | 10.6 (5.1) | 17.1 (6.9) | 16.8 (6.5) |

| **Phase 2 Adjunctive Aripiprazole** | **MADRS Week 8** | | **MADRS Week 16** | |
|---|---|---|---|---|
| | **OC** | **MMRM** | **OC** | **MMRM** |
| All (n=91) | 23.3 (7.3) | 23.1 (7.3) | 13.7 (8.7) | 13.6 (8.7) |
| Responder (n=56, 61.5%) | 21.5 (5.8) | 21.4 (5.8) | 8.5 (4.9) | 8.4 (4.9) |
| Non-Responder (n=35, 38.5%) | 26.1 (8.6) | 26.1 (8.6) | 21.9 (6.8) | 21.9 (6.8) |
| Remitter (n=39, 42.9%) | 20.4 (5.1) | 20.4 (5.0) | 6.0 (3.2) | 6.0 (3.2) |
| Non-Remitter (n=52, 57.1%) | 25.3 (8.1) | 25.3 (8.1) | 19.4 (6.9) | 19.4 (6.9) |

* There were no significant differences between OC and MMRM on any comparisons.