

*Pain severity and pain interference during major depressive episodes treated with escitalopram and aripiprazole adjunctive therapy: a CAN-BIND-1 report*

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# **Pain severity and pain interference during major depressive episodes treated with escitalopram and aripiprazole adjunctive therapy: a CAN-BIND-1 report**

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## **ABSTRACT**

Escitalopram may have pain-alleviating effects for patients with comorbid pain and depression. This study aimed to quantify improvements in pain for patients on escitalopram and adjunctive aripiprazole. A secondary analysis of the CAN-BIND-1 trial was conducted which only included participants with a current depressive episode and pain. Participants received escitalopram (10–20mg) for eight weeks and treatment response was defined as a reduction in Montgomery-Åsberg Depression Rating Scale (MADRS) of at least 50% from baseline. Non-responders at week 8 received adjunctive aripiprazole (2–10mg) for another eight weeks. The Brief Pain Inventory's pain severity (PSC) and pain interference (PIC) composite scores were measured at baseline, week 8, and week 16. Linear regression was used to determine how PSC and PIC differed between treatment responders and non-responders. Eighty-two participants with pain and depression received escitalopram. PSC and PIC decreased significantly regardless of treatment response at week 8, although responders had significantly lower PSC and PIC than non-responders. For the group receiving aripiprazole after week 8, neither PSC nor PIC improved further. Further research is needed to identify interventions that might treat both pain and depression symptoms.

**Key words:** depression, pain, SSRI, escitalopram, aripiprazole

## 1. INTRODUCTION

Pain and depression are frequently comorbid and synergistically disrupt health and quality of life for millions worldwide (Bair et al., 2003; Li, 2015). A review of literature has showed that pain symptoms are present in 15% to 100% of participants with depression, whereas the mean prevalence of depression symptoms in pain ranges between 18% to 52% across pain programs, psychiatric clinics, primary care clinics, and population-based settings (Bair et al., 2003). Those with comorbid pain and depression experience poorer quality of life and treatment response compared to those with one of the symptoms (Elliott et al., 2003; Emptage et al., 2005). Given the high comorbidity and negative impact, it is important to identify effective treatments that could minimize pain symptoms in major depressive disorder (MDD).

Antidepressants have been commonly used as an analgesic due to shared brain regions and neurotransmitters in the processing of depression and pain. These brain regions include the anterior cingulate cortex (ACC), prefrontal cortex (PFC), nucleus accumbens (NAc), hippocampus, and amygdala (Ressler and Mayberg, 2007). Specifically, imaging studies have identified that brain regions such as the ACC and the PFC process both the emotion-affective component of physical pain and psychological pain (Meerwijk et al., 2013). Studies have also found that patients with chronic pain have higher functional connectivity between the NAc and PFC, indicating that the reward circuitry may also play a role in this switch from sensory to affective focus in chronic pain (Baliki et al., 2012; Hashmi et al., 2013).

In addition to brain regions, there are also serotonin and norepinephrine pathways, originating from the dorsal raphe nucleus and locus coeruleus respectively, that are involved in pain and depression (Jann and Slade, 2007). The descending serotonin and norepinephrine pathways project to the spinal cord and suppress discomfort from limbs, organs, and other parts

of the body. Both neurotransmitters also have pathways that project to higher brain regions and regulate mood. Therefore, when serotonin and norepinephrine systems in the brain dysfunctions during MDD, the descending pain pathways would also likely dysfunction, which could explain the high comorbidity between depression and pain symptoms (Jann and Slade, 2007).

Given the importance of serotonin and norepinephrine in modulating pain, antidepressants that restore regular activity for both neurotransmitters could thus also act as an analgesic. These antidepressants include serotonin and norepinephrine reuptake inhibitors (SNRIs) and tricyclic antidepressants (TCAs), both of which have been recommended as first-line analgesics in primary care (Mu et al., 2017). The SNRI duloxetine, in particular, is one of the three FDA-approved antidepressants for treating diabetic peripheral neuropathy and fibromyalgia (Wright et al., 2010). It could provide a >50% direct analgesic effect independent of improvements in depression symptoms (Marangell et al., 2011).

In contrast to SNRIs and TCAs which increase both serotonin and norepinephrine levels, selective serotonin reuptake inhibitors (SSRI) increase only serotonin levels and are not recommended as first-line analgesic agents (Mu et al., 2017). Evidence supporting their analgesic effects is conflicting. For instance, a qualitative review of 36 RCTs studying SSRIs found that while 25 studies reported significant effects in pain reduction, the rest reported non-significant or inconclusive results (Patetsos and Horjales-Araujo, 2016). Although the results were mixed overall, the review also showed that fluoxetine, fluvoxamine, and escitalopram reduced pain more consistently compared to other SSRIs, such as citalopram. Therefore, certain SSRI agents may be promising candidates for treating pain.

Escitalopram, in particular, may be suitable for treating pain symptoms among patients with MDD. As an antidepressant, it is significantly more effective than a placebo in reducing

depression and anxiety symptoms (Bandelow et al., 2007; Cipriani et al., 2018; Kennedy et al., 2009, 2006). Most comparative studies have also found escitalopram to be superior, or at least non-inferior, to other SSRIs (e.g., sertraline and paroxetine) and SNRIs (e.g., duloxetine; Baldwin et al., 2006; Nierenberg et al., 2007; Ventura et al., 2007). With regards to its side effects profile, a study on MDD patients found that escitalopram recipients, compared to duloxetine recipients, experienced significantly less frequent nausea, dry mouth, vomiting, yawning, and irritability (Nierenberg et al., 2007).

While the literature examining the analgesic properties of escitalopram is limited, current evidence suggests that escitalopram may be effective for pain reduction. Evidence from RCTs have found that escitalopram was similar to duloxetine in reducing back pain (Mazza et al., 2010), more effective than placebo in reducing pain in multi-somatoform disorder (Muller et al., 2008) and polyneuropathy (Otto et al., 2008). However, these studies focused on illnesses other than MDD without appropriate subgroup analyses; therefore, it is still unclear whether escitalopram, or escitalopram used along with adjunctive agents, could reduce pain in patients with MDD.

The present study examined a cohort of outpatients with comorbid pain and MDD at baseline who were treated with escitalopram for 8 weeks. Within this cohort, a subgroup of participants who did not respond to escitalopram after 8 weeks and subsequently received aripiprazole adjunctive therapy for the following 8 weeks were also examined. Our objectives were two-fold: i) investigate whether pain severity are improved following 8 weeks of escitalopram monotherapy and aripiprazole adjunctive therapy. ii) investigate the relationship between changes in depression severity and pain severity during escitalopram monotherapy and aripiprazole adjunctive therapy.



## **2. METHODS**

### **2.1 Study design and participants**

The present study analyzes data from the first Canadian Biomarker Integration Network in Depression (CAN-BIND-1) trial, which was originally conducted to identify biomarkers predicting clinical responsiveness in MDD. The trial is registered at ClinicalTrials.gov (identifier NCT01655706). Adults between 18 and 60 years of age with a current major depressive episode lasting three months or longer and a Montgomery-Åsberg Depression Rating Scale (MADRS; Montgomery and Asberg, 1979) score of  $\geq 24$  were prospectively recruited by physician referral or advertisement from six academic centers across Canada. The full eligibility criteria are described in the original study (Lam et al., 2016). Ethics approval was obtained at each center and all participants provided written informed consent. Structured clinical interviews, self-report questionnaires, and psychological assessments were conducted at baseline and the end of each phase of the trial. In Phase 1, participants received escitalopram antidepressant therapy (10–20 mg daily, flexible dosing) for 8 weeks. In Phase 2, participants not responding to treatment in Phase 1, defined here as the decrease in MADRS total score from baseline to week 8 by less than 50%, received adjunctive aripiprazole (2–10 mg daily, flexible dosing) for 8 weeks while responders continued with escitalopram monotherapy.

### **2.2 Measures**

The Brief Pain Inventory – Short Form (BPI; Cleeland and Ryan, 1994) was administered to participants at baseline, week 8 (W8), and week 16 (W16). The BPI is a widely used and validated tool to assess the severity of pain and interference with daily life. For this study, the

four items of the BPI related to pain severity were considered, each rated from 0 (“no pain”) to 10 (“pain as bad as you can imagine”), as well as the seven items related to pain interference with different domains of life, each rated from 0 (“does not interfere”) to 10 (“completely interferes”). At baseline, W8, and W16 visits, the BPI was only administered to study participants who reported experiencing pain within the last day, excluding everyday pain symptoms described as “minor headaches, sprains, or toothaches.” Only the subset of participants who reported pain at their baseline visit and had subsequently completed the BPI was included in analyses. Scores on pain severity composite (PSC; average score of four items) and pain interference composite (PIC; average score of seven items) were the primary outcome variables for this study. Higher scores on PSC and PIC indicates more pain.

To measure depression severity, MADRS, a clinician-rated scale, was administered at baseline, W8, and W16. Response at W8 and W16 were defined as a  $\geq 50\%$  decline in the MADRS total score from baseline to week 8 and from week 8 to week 16, respectively.

### 2.3 Data analysis

Differences in baseline sociodemographic and clinical characteristics between the responder and non-responder groups were analyzed using independent samples *t*-tests for continuous variables or chi-square tests for categorical variables. The effect of age and sex on baseline PSC and PIC scores was explored using regression models and Pearson’s correlation (weak:  $\pm 0.1$ , moderate:  $\pm 0.3$ , strong:  $\pm 0.5$ ), where appropriate. Interaction effects between response status and age or response status and sex on baseline PSC or PIC scores were assessed using linear regression models. Statistically significant interaction terms were included in subsequent analyses.

To examine longitudinal changes in depression severity and pain severity, dependent samples *t*-tests were used to compare MADRS, PSC, PIC scores between baseline and week 8, separately for responders (R8) and non-responders (NoR8) at W8. In the aripiprazole adjunctive therapy cohort, dependent-sample *t*-tests were also used to compare MADRS, PSC, and PIC scores between weeks 8 and 16, separately for responders (R16) and non-responders (NoR16) at W16.

To examine the relationship between changes in depression severity and pain severity during escitalopram monotherapy, multiple variable linear regression was used. The dependent variable was PSC or PIC scores at W8. The independent variable of interest was treatment response status at W8. Covariates included baseline PSC or PIC scores, age, sex, and any significant interaction terms previously found. In addition, Spearman correlations were conducted between the baseline to week 8 change scores of MADRS and PSC or PIC.

To examine the relationship between changes in depression severity and pain severity during aripiprazole adjunctive therapy, multiple variable linear regression was also used. The dependent variable was PSC or PIC scores at W16. The independent variable of interest was treatment response status at W16. Covariates included W8 PSC or PIC scores, age, and sex. In addition, Spearman correlations were conducted between the week 8 to 16 change scores of MADRS and PSC or PIC.

Given the small sample size in Phase 2, the analyses associated with aripiprazole adjunctive therapy were exploratory. Significance for all analyses was tested through two-tailed tests at a *p*-value of 0.05. Data analyses were performed using R v3.5.2 (R Core Team, 2020). The sample size was based on the available data and no *a priori* power calculations were performed.

### 3. RESULTS

Two-hundred eleven participants meeting the criteria for clinical depression were enrolled to receive escitalopram therapy, of whom 99 reported pain at their initial visit. After excluding those lost to follow up, 82 participants (mean age  $39.4 \pm 13.4$  years; 65.9% female, mean baseline MADRS  $30.6 \pm 6.1$ ) were included in the analysis (Figure 1). After 8 weeks of escitalopram, 43 (52.4%) participants achieved treatment response. Baseline demographic and clinical characteristics of the responder and non-responder groups are displayed in Table 1.

#### 3.1 Changes in pain severity after escitalopram and aripiprazole

Dependent *t*-tests showed that PSC and PIC scores were significantly lower at week 8 compared to baseline for both R8 and NoR8 ( $p < 0.05$ ). In Phase 2 of the trial, 39 participants in the NoR8 group received adjunctive aripiprazole therapy. By the end of this phase, 25 participants achieved antidepressant response (R16) and 14 did not (NoR16). Dependent *t*-tests showed that PSC and PIC scores did not change significantly from week 8 to week 16 for both R16 and NoR16 ( $p > 0.05$ ) on adjunctive aripiprazole therapy.

#### 3.2 Escitalopram: relation between baseline to W8 changes in pain and depression severity

There were no differences between R8 and NoR8 groups in baseline PSC (Table 2a) or PIC (Table 2b) scores. Baseline PSC score was significantly associated with age ( $B=0.05$ ; 95% CI: 0.02–0.08;  $p=0.001$ ), demonstrating moderate correlation ( $r=0.34$ ,  $p=0.002$ ). Baseline PIC score was similarly associated ( $B=0.08$ , 95% CI: 0.03–0.12,  $p < 0.001$ ) and moderately correlated ( $r=0.35$ ,  $p=0.001$ ) with age. However, there was no significant interaction between response status and age, so this interaction term was excluded from subsequent analyses. There was no

effect of sex on baseline PSC or PIC scores, nor was there a significant interaction between response status and sex; hence this interaction term was also excluded from subsequent analyses.

At W8, PSC and PIC scores showed an overall reduction. However, R8 displayed a greater reduction compared to NoR8. After adjusting for baseline PSC or PIC scores, age, and sex, multiple linear regression revealed that R8's PSC scores were 0.98 points lower (95% CI: -1.88 to -0.09,  $p=0.032$ ; Table 3a) and PIC scores were 1.37 points lower (95% CI: -2.22 to -0.52,  $p=0.002$ ; Table 3b) compared to NoR8.

In addition, Spearman correlations showed that baseline to week 8 change in MADRS score was significantly associated to baseline to week 8 changes in PSC ( $r=0.26$ ,  $p=0.022$ ) and PIC scores ( $r=0.22$ ,  $p=0.049$ ).

### **3.3 Aripiprazole: relation between W8 to W16 changes in pain and depression severity**

There were no differences between W16 responders and non-responders in PSC (Table 4a) or PIC (Table 4b) scores at any timepoint throughout the trial. After adjusting for covariates, multiple linear regression revealed no statistically significant differences in PSC or PIC between the two groups at W16 (Tables 5a and 5b). In addition, Spearman correlations between week 8 to 16 changes in MADRS score and PSC ( $r=0.29$ ,  $p=0.078$ ) or PIC ( $r=0.26$ ,  $p=0.115$ ) scores were also not significant.

## **4. DISCUSSION**

We conducted a secondary analysis of the CAN-BIND-1 trial, focusing on the cohort with comorbid depression and pain. There were three main findings: 1) participants receiving escitalopram therapy experienced a significant reduction in pain severity and pain interference scores after 8 weeks of treatment; 2) those who achieved a clinically meaningful antidepressant

response by the 8-week endpoint experienced a greater reduction in pain severity and pain interference scores compared to non-responders; 3) for participants who did not respond to escitalopram and switched to aripiprazole adjunctive therapy, there was minimal improvement in pain severity or interference, as well no significant difference in both pain measures between those who did and did not achieve response by the 16-week endpoint. Clinically, our findings support the use of escitalopram in reducing pain among patients with MDD.

To our knowledge, our study is the first to show that participants with comorbid MDD and pain can experience reductions in pain severity and interference after using escitalopram. These findings extend past results showing how escitalopram can reduce pain from chronic lower back issues (Mazza et al., 2010), polyneuropathy (Otto et al., 2008), and multi-somatoform disorder (Muller et al., 2008). Neurobiologically, escitalopram's ability to reduce pain may be due to how it regulates serotonin levels by inhibiting reuptake. This regulation allows the descending serotonin pathways to suppress pain more effectively. Given the fewer side effects escitalopram has compared to other antidepressants used for pain reduction (e.g., TCA and duloxetine; Dharmshaktu et al., 2012; Nierenberg et al., 2007), escitalopram may be a promising analgesic candidate. Future studies could continue to examine whether this reduction is in excess of a placebo effect by including a placebo control group.

Our study is also the first to show that, in participants with comorbid MDD and pain, responders to escitalopram can experience a greater reduction in pain than non-responders, suggesting that greater reduction in depression is associated to greater reduction in pain. Similar findings were identified in a study that found responders to duloxetine at 4 and 8 weeks having significantly greater reductions in PIC compared to non-responders (Sagman et al., 2011), despite several major differences in the study sample and the metrics: i) duloxetine, an SNRI

with known analgesic properties, was used; ii) participants were taking an SSRI or other SNRI agent for at least 4 weeks prior to study enrollment, whereas in our study, nearly half of the participants had not received prior MDD treatment; iii) participants were only included if they reported  $PIC \geq 3$  at baseline; iv) instead of MADRS, the Hamilton Depression Rating Scale was used to measure depression severity. Our parallel findings suggest that antidepressant response is more important than the specific agent or baseline severity/quality of pain in eliciting substantial improvements in pain-limited function. That being said, no other studies have examined this relationship, which limits the ability to perform a meta-analysis. Therefore, future research should conduct non-inferiority RCTs between escitalopram and other antidepressants with well-known analgesic properties (i.e., duloxetine or amitriptyline).

On the other hand, the present study did not find significant reductions in pain after aripiprazole adjunctive therapy, as well as significant differences in pain reduction between responders and non-responders to aripiprazole. Aripiprazole is a partial agonist of dopamine (D2 and D3) and serotonin (5HT1A) receptors (Pae et al., 2011). Since both neurotransmitters are involved in pain modulation, aripiprazole could have an analgesic effect (Jann and Slade, 2007; Wood, 2008). While this effect, to our knowledge, has not been studied in clinical trials, human case reports (Fei et al., 2012; LaPorta, 2007) and animal studies (Almeida-Santos et al., 2015) have supported its efficacy. The lack of pain reduction in the present study, therefore, goes against these previous findings. There are several potential reasons for this difference. First, there might be a drug interaction between aripiprazole and escitalopram that reduces the analgesic effect. Second, after escitalopram was administered for the first 8 weeks, pain already declined for both responders and non-responders; therefore, there is less capacity for pain to be further declined in the second 8 weeks. Third, the sample that received aripiprazole was small ( $n=39$ ) and may be

underpowered to detect differences. Future studies could design adequately powered RCTs to examine the analgesic effects of aripiprazole.

Future research could also investigate whether other forms of therapy could be used along pharmacotherapy to treat MDD patients with comorbid pain. One RCT recruited patients with co-occurring musculoskeletal pain and depression (Kroenke et al., 2009). The intervention cohort underwent 12 weeks of optimized antidepressant therapy, followed by a 12-week pain self-management program and a continuation phase of therapy (6 months). Compared to the non-intervention cohort, those who received the intervention had significantly lower PIC, PSC, and depression severity from the first month of care until the study endpoint (12 months). Thus, multimodal therapy with a biopsychosocial approach could effectively reduce co-occurring depression and pain. Since this RCT did not use escitalopram, future studies could investigate its efficacy when used in conjunction with pain self-management programs. Furthermore, by using a factorial model for the trial design, they could quantify the added benefits offered by such programs.

The aforementioned RCT study has also demonstrated that changes in pain could predict subsequent changes in depression severity, and changes in depression symptoms could predict subsequent changes in pain severity (Kroenke et al., 2011). Future studies could continue to identify other early bio- or clinical-markers that could predict depression and pain treatment outcomes among patients experiencing comorbid MDD and pain. Findings will support the early recognition of treatment response/non-responses, thereby allowing for earlier switching or augmentation of pharmacotherapy to minimize morbidity.

### Limitations



This study has several limitations inherent in its design and the methodology of the CAN-BIND-1 trial. First, the lack of randomization and a placebo group limits inferences on the efficacy of escitalopram or aripiprazole therapy. Second, since the study is a secondary analysis, a priori power analysis was not conducted. Small sample sizes, especially in the aripiprazole cohort, may have caused the analysis to be inadequately powered and reduced external validity, which indicates that larger samples may be warranted in the future. Third, our study cohort did not necessarily represent a chronic pain sample. In the analysis, we could only include participants who responded “Yes” to the first item of the BPI, which asked whether they had experienced any pain that day. This single gatekeeper question would not necessarily include all individuals with chronic pain nor exclude those without. Furthermore, the numerical scores alone cannot consider the chronicity, location, or quality of pain. These are all inherent shortcomings of using one-dimensional scores to characterize pain.

### Conclusions

In adults with depression and pain, pain severity reduced overtime in both responders and non-responders to escitalopram. Those responding to escitalopram therapy after 8 weeks showed greater reductions in pain severity and pain interference than non-responders. Beyond this period there was little improvement in pain, even if adjunctive aripiprazole therapy helped achieve an antidepressant response. This highlights the idea of a time-sensitive window for antidepressant therapy targeted at both pain and depression. Future studies should continue characterizing the analgesic effects of commonly prescribed SSRIs and identify predictors of earlier therapeutic response for this comorbid population.

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**Conflicts of interest:**

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#### **Ethical Standards:**

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. All participants provided written, informed consent.

#### **Availability of data:**

Data are not publicly available in accordance with ethics approval given by the ethics board from the participating university. Interested investigators may submit inquiries to the corresponding author.

**Author contributions:**

**Calvin Diep** conceptualized and conducted the statistical analysis and drafted the manuscript.

The study conceptualization, data analysis and manuscript preparation were overseen by **Wendy**

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**Table 1.** Baseline characteristics of study participants.

	<b>W8 Non-responders (n=39)</b>	<b>W8 Responders (n=43)</b>	<b>p-value</b>
<b>Baseline MADRS, mean <math>\pm</math> SD</b>	31.4 (6.19)	29.9 (6.07)	0.264
<b><u>Demographics</u></b>			
<b>Age (years), mean <math>\pm</math> SD</b>	41.2 $\pm$ 13.6	37.7 $\pm$ 13.1	0.236
<b>Female</b>	27 (69.2%)	27 (62.8%)	0.703
<b>Years of formal education, mean <math>\pm</math> SD</b>	16.7 $\pm$ 1.87	16.9 $\pm$ 2.41	0.661
<b>Currently employed or student</b>	20 (51.3%)	24 (55.8%)	0.850
<b>Currently married or common law</b>	14 (35.9%)	11 (25.6%)	0.439
<b><u>Psychiatric History</u></b>			
<b>Length of current MDE (months), mean <math>\pm</math> SD</b>	36.0 $\pm$ 41.5	25.1 $\pm$ 32.7	0.204
<b>Tried treatment for current MDE before this trial</b>	29 (74.4%)	21 (48.8%)	<b>0.043</b>
<b>Number of previous MDEs, mean <math>\pm</math> SD</b>	3.46 $\pm$ 1.84	4.31 $\pm$ 2.36	0.114

Values are displayed as n (%) unless stated otherwise.

t-test used to test significance between groups for continuous variables.

$\chi^2$ -analysis used to test significance between groups for categorical variables.

MADRS: Montgomery-Åsperg Depression Rating Scale.

MDE: major depressive episode.

**Table 2a.** Pain severity scores, by response to escitalopram at Week 8.

	<b>W8 Non-responders (n=39)</b>	<b>W8 Responders (n=43)</b>	<b><i>t</i>-statistic</b>	<b><i>p</i>-value</b>
<b>Composite score</b>				
Baseline	4.28 (1.79)	3.65 (1.95)	1.53	0.131
Week 8	2.83 (2.32)	1.45 (2.11)	2.81	<b>0.006</b>
Week 16	2.51 (2.44)	1.34 (2.14)	2.26	<b>0.027</b>
<b>1. Worst pain in last 24h</b>				
Baseline	5.36 (2.11)	4.72 (2.10)	1.37	0.174
Week 8	3.95 (3.15)	2.02 (2.91)	2.87	<b>0.005</b>
Week 16	3.50 (3.14)	1.78 (2.67)	2.61	<b>0.011</b>
<b>2. Least pain in last 24h</b>				
Baseline	3.18 (2.45)	2.51 (2.12)	1.31	0.193
Week 8	1.90 (1.89)	0.91 (1.54)	2.59	<b>0.012</b>
Week 16	1.55 (2.04)	0.95 (1.76)	1.40	0.166
<b>3. Average pain in last 24h</b>				
Baseline	4.23 (2.24)	4.00 (2.19)	0.47	0.639
Week 8	2.87 (2.35)	1.51 (2.28)	2.65	<b>0.010</b>
Week 16	2.53 (2.53)	1.37 (2.19)	2.17	<b>0.033</b>
<b>4. Pain right now</b>				
Baseline	4.33 (2.26)	3.35 (2.43)	1.90	0.061
Week 8	2.62 (2.37)	1.37 (2.07)	2.52	<b>0.014</b>
Week 16	2.47 (2.75)	1.27 (2.24)	2.13	<b>0.037</b>

Values are displayed as mean (SD).

Each of the four items is scored on a Numeric Rating Scale, from 0 (“no pain”) to 10 (“pain as bad as you can imagine”).

**Table 2b.** Pain interference scores, by response to escitalopram at Week 8.

	W8 Non-responders (n=39)	W8 Responders (n=43)	<i>t</i> -statistic	<i>p</i> -value
<b>Composite score</b>				
Baseline	4.33 (2.99)	3.86 (2.73)	0.75	0.458
Week 8	2.84 (2.67)	1.17 (1.84)	3.26	<b>0.002</b>
Week 16	2.41 (2.70)	0.99 (1.74)	2.73	<b>0.008</b>
<b>1. General activity</b>				
Baseline	4.36 (3.38)	3.91 (3.30)	0.61	0.543
Week 8	2.90 (2.89)	1.51 (2.46)	2.32	<b>0.023</b>
Week 16	2.55 (3.19)	1.13 (2.15)	2.30	<b>0.024</b>
<b>2. Mood</b>				
Baseline	5.03 (3.36)	4.30 (2.99)	1.03	0.308
Week 8	3.51 (3.04)	1.40 (2.15)	3.61	<b>&lt;0.001</b>
Week 16	2.58 (2.94)	1.35 (2.35)	2.03	<b>0.046</b>
<b>3. Walking</b>				
Baseline	3.82 (3.39)	3.19 (2.93)	0.90	0.369
Week 8	1.64 (2.52)	1.05 (2.00)	1.18	0.243
Week 16	2.00 (2.87)	0.80 (2.09)	2.10	<b>0.039</b>
<b>4. Work/tasks</b>				
Baseline	4.18 (3.28)	3.91 (3.21)	0.38	0.705
Week 8	2.92 (2.79)	1.40 (2.32)	2.68	<b>0.009</b>
Week 16	2.76 (3.17)	0.90 (1.92)	3.12	<b>0.003</b>
<b>5. Relationships</b>				
Baseline	3.26 (3.08)	2.95 (2.71)	0.47	0.639
Week 8	2.13 (2.55)	0.44 (1.14)	3.80	<b>&lt;0.001</b>
Week 16	1.61 (2.28)	0.55 (1.45)	2.42	<b>0.018</b>
<b>6. Sleep</b>				
Baseline	4.54 (3.28)	4.37 (3.20)	0.23	0.817
Week 8	3.26 (3.38)	1.28 (2.42)	3.02	<b>0.004</b>
Week 16	2.50 (2.96)	0.92 (1.83)	2.81	<b>0.007</b>
<b>7. Life enjoyment</b>				
Baseline	5.15 (3.51)	4.40 (3.55)	0.97	0.334
Week 8	3.49 (3.52)	1.12 (1.85)	3.76	<b>&lt;0.001</b>
Week 16	2.84 (3.19)	1.30 (2.55)	2.35	<b>0.022</b>

Values are displayed as mean (SD).

Each of the seven items asks about how pain is interfering with each domain of life and is scored on a Numeric Rating Scale, from 0 (“does not interfere”) to 10 (“completely interferes”).

**Table 3a.** Linear regression model predicting pain severity composite score (PSC) at week 8 (W8).

	<i>B</i>	95% CI	<i>p</i> -value
(Intercept)	-0.59	-2.43 to 1.25	0.532
W8 response: yes	-0.98	-1.88 to -0.09	<b>0.032</b>
Baseline PSC	0.38	0.13 to 0.63	<b>0.003</b>
Age	0.03	-0.01 to 0.06	0.123
Sex: female	0.89	-0.05 to 1.83	0.063
Model: $R^2 = 0.27$ , $F(4,81) = 7.06$ , $p < 0.001$			

**Table 3b.** Linear regression model predicting pain interference composite score (PIC) at week 8 (W8).

	<i>B</i>	95% CI	<i>p</i> -value
(Intercept)	-0.13	-1.81 to 1.54	0.878
W8 response: yes	-1.37	-2.22 to -0.52	<b>0.002</b>
Baseline PIC	0.36	0.20 to 0.52	<b>&lt;0.001</b>
Age	0.02	-0.02 to 0.05	0.381
Sex: female	1.09	0.18 to 1.99	<b>0.019</b>
Model: $R^2 = 0.39$ , $F(4,81) = 12.27$ , $p < 0.001$			

**Table 4a.** Pain severity scores, by response to escitalopram and aripiprazole at Week 16.

	W16 Non-responders (n=14)	W16 Responders (n=25)	t-statistic	p-value
<b>Composite score</b>				
Baseline	4.20 (1.85)	4.41 (1.69)	0.36	0.725
Week 8	2.73 (2.50)	2.87 (2.26)	0.17	0.866
Week 16	2.54 (2.73)	2.47 (2.40)	0.08	0.941
<b>1. Worst pain in last 24h</b>				
Baseline	5.00 (2.25)	5.68 (1.95)	0.95	0.353
Week 8	3.86 (3.25)	3.96 (3.16)	0.10	0.924
Week 16	3.21 (3.24)	3.48 (3.12)	0.25	0.805
<b>2. Least pain in last 24h</b>				
Baseline	3.43 (2.62)	3.20 (2.42)	0.27	0.791
Week 8	1.79 (2.04)	1.96 (1.84)	0.26	0.793
Week 16	1.86 (2.48)	1.44 (1.96)	0.54	0.593
<b>3. Average pain in last 24h</b>				
Baseline	4.36 (2.68)	4.20 (1.91)	0.19	0.848
Week 8	2.86 (2.57)	2.88 (2.28)	0.03	0.978
Week 16	2.50 (2.74)	2.52 (2.55)	0.02	0.982
<b>4. Pain right now</b>				
Baseline	4.00 (2.57)	4.56 (1.89)	0.71	0.483
Week 8	2.43 (2.56)	2.68 (2.29)	0.31	0.763
Week 16	2.57 (3.11)	2.44 (2.68)	0.13	0.895

Values are displayed as mean (SD).

Each of the four items is scored on a Numeric Rating Scale, from 0 (“no pain”) to 10 (“pain as bad as you can imagine”).

**Table 4b.** Pain interference scores, by response to escitalopram and aripiprazole at Week 16.

	W16 Non-responders (n=14)	W16 Responders (n=25)	t-statistic	p-value
<b>Composite score</b>				
Baseline	4.48 (3.15)	4.48 (2.83)	0.00	1.000
Week 8	2.24 (2.35)	3.05 (2.74)	0.97	0.341
Week 16	2.41 (2.78)	2.37 (2.71)	0.05	0.964
<b>1. General activity</b>				
Baseline	4.50 (3.32)	4.48 (3.34)	0.02	0.986
Week 8	2.07 (2.27)	3.36 (3.13)	1.48	0.149
Week 16	2.71 (3.24)	2.36 (3.20)	0.33	0.745
<b>2. Mood</b>				
Baseline	5.07 (3.34)	5.16 (3.31)	0.08	0.937
Week 8	2.64 (2.53)	3.92 (3.16)	1.38	0.177
Week 16	2.64 (3.15)	2.40 (2.86)	0.24	0.813
<b>3. Walking</b>				
Baseline	3.21 (3.70)	4.32 (3.06)	0.95	0.352
Week 8	1.29 (1.98)	1.72 (2.81)	0.56	0.577
Week 16	2.07 (2.73)	2.04 (2.96)	0.03	0.974
<b>4. Work/tasks</b>				
Baseline	4.43 (3.69)	4.28 (2.99)	0.13	0.899
Week 8	2.14 (2.32)	3.36 (2.98)	1.42	0.166
Week 16	2.36 (2.59)	2.88 (3.47)	0.53	0.597
<b>5. Relationships</b>				
Baseline	3.50 (3.13)	3.24 (2.99)	0.25	0.802
Week 8	2.00 (2.29)	2.00 (2.45)	0.00	1.000
Week 16	1.71 (2.40)	1.60 (2.29)	0.14	0.886
<b>6. Sleep</b>				
Baseline	5.29 (3.02)	4.48 (3.42)	0.76	0.452
Week 8	2.79 (3.33)	3.44 (3.38)	0.59	0.563
Week 16	2.57 (3.06)	2.32 (2.94)	0.25	0.805
<b>7. Life enjoyment</b>				
Baseline	5.36 (3.84)	5.40 (3.32)	0.04	0.972
Week 8	2.79 (3.04)	3.56 (3.73)	0.70	0.488
Week 16	2.79 (3.29)	2.96 (3.36)	0.16	0.876

Values are displayed as mean (SD).

Each of the seven items asks about how pain is interfering with each domain of life and is scored on a Numeric Rating Scale, from 0 (“does not interfere”) to 10 (“completely interferes”).

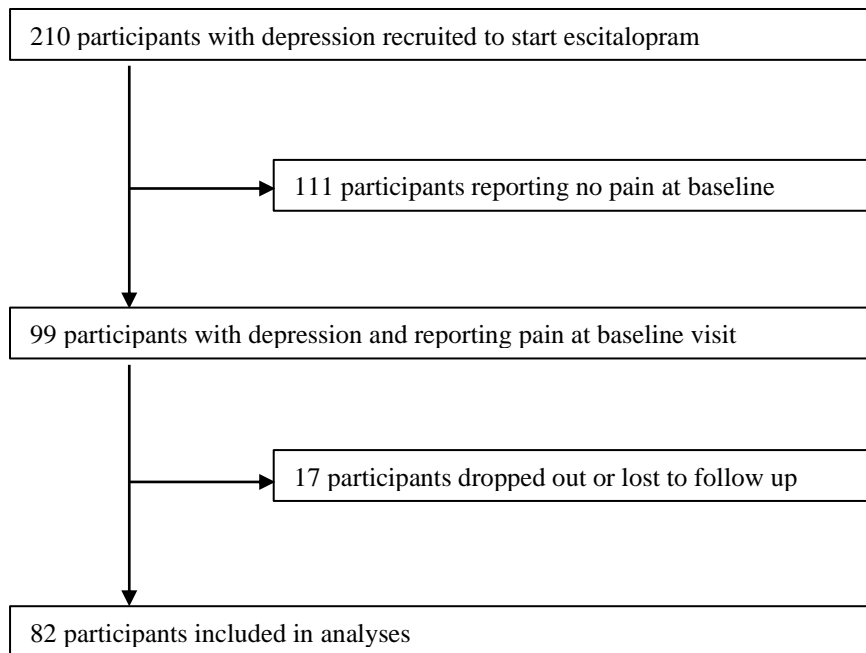


**Table 5a.** Linear regression model predicting pain severity composite score (PSC) at week 16 (W16).

	<i>B</i>	95% CI	p
(Intercept)	1.33	-6.59 to 9.24	0.742
W8 response: yes	-3.54	-7.42 to 0.35	<b>0.074</b>
Baseline PSC	0.45	0.18 to 0.73	<b>0.001</b>
Age	-0.01	-0.17 to 0.15	0.892
Sex: female	2.23	-1.82 to 6.27	0.281
Model: $R^2 = 0.20$ , $F(4,78) = 4.61$ , <b>p=0.002</b>			

**Table 5b.** Linear regression model predicting pain interference composite score (PIC) at week 16 (W16).

	<i>B</i>	95% CI	p
(Intercept)	4.15	-7.83 to 16.13	0.497
W8 response: yes	-9.10	-15.15 to -3.05	<b>0.003</b>
Baseline PIC	0.45	0.28 to 0.62	<b>&lt;0.001</b>
Age	-0.05	-0.30 to 0.21	0.725
Sex: female	1.62	-4.78 to 8.01	0.620
Model: $R^2 = 0.37$ , $F(4,77) = 10.94$ , <b>p&lt;0.001</b>			



**Figure 1.** CAN-BIND participants included in analyses.