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# Association Between Side Effects and Blood microRNA Expression Levels and Their Targeted Pathways in Patients With Major Depressive Disorder Treated by a Selective Serotonin Reuptake Inhibitor, Escitalopram: A CAN-BIND-1 Report

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## Abstract

**Introduction:** Antidepressant drugs are effective therapies for major depressive disorder; however, they are frequently associated with side effects. Although there is some evidence for a relationship between genetic variation and side effects, little is known regarding the role of dynamic molecular factors as moderators of side effects. The aim of this study was to assess microRNA (miRNA) changes associated with side effects during escitalopram treatment and their downstream effects on target gene expression.
**Methods:** A total 160 patients with major depressive disorder from the CAN-BIND-1 cohort were included. Side effects were assessed with the Toronto Side Effect Scale after 2 weeks of treatment with escitalopram. We assessed the relationship between side effects and changes in peripheral expression of miRNAs between baseline and week 2. For miRNA whose expression changed, we used target prediction algorithms to identify putative messenger RNA (mRNA) targets and assessed their expression.

## Significance Statement

While there are several studies focusing on genetic variation as predictors of side effects, there is little information on the possible role of dynamic molecular factors as side effect moderators. MicroRNAs (miRNA) are particularly good dynamic molecular factors to investigate for a relationship with antidepressant side effects. This study is the first, to our knowledge, to examine the role of miRNAs in the emergence of side effects during antidepressant treatment. We found negative associations between intensity of nausea and expression of miRNAs.

**Results:** Nausea was experienced by 42.5% of patients. We identified 45 miRNAs whose expression changed on initiation of escitalopram treatment, of which 10 displayed a negative association with intensity of nausea (miR15b-5p, miR17-5p, miR20a-5p, miR20b-5p, miR103a-3p, miR103b, miR106a-5p, miR182-5p, miR185-5p, and miR660-5p). Additionally, we found negative associations between 4 microRNAs (miR20a-5p, miR106a-5p, miR185-5p, miR660-5p) and mRNA targets. The expression of the miR185-5p target, CAMK2δ was significantly decreased [log 2 mean = –0.048 (0.233)] between weeks 0 and 2 ($P = .01$)].
**Conclusions:** We identified an overexpression of miR185-5p during escitalopram treatment of major depressive disorder, which was negatively associated with intensity of nausea, and identified a potential mRNA target that may mediate this effect.

**Keywords:** major depressive disorder, side effects, miRNA, antidepressant

## Introduction

Major depressive disorder (MDD) has a lifetime prevalence of approximately 20% in the general population (Hasin et al., 2018) and may evolve into a recurrent or chronic course (Eaton et al., 2008), with a negative impact on general functioning and quality of life (IsHak et al., 2015).

Antidepressant drugs are effective therapies for MDD (Cipriani et al., 2018). However, the majority of patients treated with antidepressants experience 1 or more side effects. These side effects, which demonstrate high variability among individuals, often create barriers to achieving remission of depressive symptoms and contribute to relapse and recurrence. Indeed, poor remission rates and high relapse and recurrence rates are associated with drug discontinuation or poor compliance due to side effects (Hodgson et al., 2012; Crawford et al., 2014; De las Cuevas et al., 2014; Fabbri et al., 2018). Although selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors have better safety profiles than classical tricyclic antidepressants (Wang et al., 2018), side effects are still reported frequently.

The most common side effects associated with SSRIs and serotonin-norepinephrine reuptake inhibitors are gastrointestinal, sexual dysfunction, weight gain, dry mouth, sweating, and hyponatremia (Wang et al., 2018). Additionally, they may occur at various time points following intake of antidepressants (Kelly et al., 2008). For example, SSRI-associated side effects such as insomnia, sexual dysfunction, and drowsiness are often considered acute but may still persist at 3 months. Some side effects such as nausea start early in the course of treatment but dissipate within 1–2 weeks. Other side effects such as weight gain are not present initially but emerge over time (Hu et al., 2004; Kelly et al., 2008). The prevalence of side effects associated with SSRI treatment can be up to 64% (Bet et al., 2013). Patient- and treatment-related factors like age (Naranjo et al., 1995; Draper and Berman, 2008; Stone et al., 2009; Bet et al., 2013), depression and anxiety severity (Uher et al., 2009; Bet et al., 2013), as well as drug class and dose (Trindade et al., 1998; Stahl et al., 2005; Watanabe et al., 2010) can influence the occurrence and severity of side effects.

Individual factors, such as genetic makeup, explain a part of the variance in antidepressant-related side effects (Tansey et al., 2013). For instance, poor metabolizer status of CYPP450 (2C19) associates with a higher risk of side effects early in treatment (particularly during the first 2–4 weeks) (Fabbri et al., 2018). Genetic polymorphisms in the serotonin transporter, serotonin receptor genes (Garfield et al., 2014; Basu et al., 2015), and the ABCB1 gene (Schatzberg et al., 2015; Bet et al., 2016) also seem to be associated with side effects.

While there are several studies focusing on genetic variation as predictors of side effects (Adkins et al., 2012; Clark et al., 2012; Schatzberg et al., 2015; Amitai et al., 2016; Fabbri et al., 2018), there is little information on the possible role of dynamic molecular factors as side effect moderators. MicroRNAs (miRNA) are particularly good dynamic molecular factors to investigate for a relationship with antidepressant side effects. These small, single-stranded, non-coding RNAs are 17 to 22 nucleotides in length and modulate the expression of messenger RNA (mRNA) through mRNA degradation and inhibition of protein translation. As such, they play a crucial role in regulating the processes leading to metabolite and protein production (Fiori et al., 2017, 2018). The aim of this study was to assess changes in miRNA expression associated with side effects emerging within the first 2 weeks of escitalopram treatment and their downstream effects on target gene expression.

## Materials and Methods

### Population

The cohort used in this study was previously described in detail (Kennedy et al., 2019). A baseline clinical assessment was completed by 211 participants with MDD who began treatment with escitalopram immediately following baseline assessment. Of this group, sequencing was performed on 205 participants at baseline and 170 after 2 weeks of escitalopram treatment. Participants between 18 and 61 years of age who scored 21 or more on the Montgomery-Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979) were recruited from

physician referrals or advertisements at 6 academic centers in Canada between August 2013 and December 2016. The Mini-International Neuropsychiatric Interview (Sheehan et al., 1998) Version 6.1 was administered to confirm or rule out MDD status and the presence or absence of other psychiatric comorbidities. Exclusion criteria included bipolar disorder, high suicidal risk, psychosis, drug dependency, 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. Adequate dose and duration were used to calculate the resistance scores using the Antidepressant Treatment History Form (Sackeim, 2001). A score of 3 or higher constituted "resistance" for an individual. All participants provided written informed consent, and ethics approval was obtained at each center. The trial was registered at ClinicalTrials.gov (identifier: NCT01655706).

## Clinical Assessment

In addition to the MADRS, the Toronto Side Effect Scale (TSES) (Vanderkooy et al., 2002), a 32-item instrument, was used to elicit adverse events after 2 weeks of treatment. The TSES is used to establish incidence, frequency, and severity of CNS, gastrointestinal, and sexual side effects. For each side effect, frequency (1 = never; 2 = sometimes; 3 = about half the time; 4 = often; 5 = everyday) and severity (1 = no trouble; 2; 3; 4;

5 = extreme trouble) were measured on a 5-point Likert scale. An "intensity" score was derived by multiplying frequency by severity for each side effect. At week 2, a total of 160 patients completed the TSES questionnaire, with 23 participants having missing subscores (Table 1). We did not include male-specific side effects in our analyses (we did not use the men's specific subscale of the TSES).

## Biological Assessment

At both the baseline visit (week 0) and after 2 weeks of treatment, blood and urine samples were obtained for molecular analysis.

## RNA Extraction

Whole blood for RNA analysis was collected at baseline and after 2 weeks in ethylenediaminetetraacetic acid tubes and filtered using LeukoLOCK filters (Life Technologies). Total RNA was extracted using a modified version of the LeukoLOCK Total RNA Isolation System protocol, which included DNase treatment to remove genomic DNA. The quality of RNA was assessed using the Agilent 2200 Tapestation, and only samples with an RNA integrity number ≥6.0 were used. The same RNA sample was used for both small RNA and mRNA sequencing.

**Table 1.** Population characteristics

| | | n | | Average (SD) | Minimum | Maximum |
|---|---|---|---|---|---|---|
| Age | | 160 | | 35.84 (12.64) | 18 | 61 |
| Gender | | 160 | Female: 100 (62.5%) Male: 60 (37.5%) | | | |
| MADRS week 0 | | 160 | | 29.82 (5.53) | 21 | 47 |
| Intensity side effects week 2 | Abdominal pain | 159 | | 11.89 (2.66) | 1 | 15 |
| | Agitation | 160 | | 3.02 (4.41) | 1 | 25 |
| | Anorgasmia | 156 | | 2.09 (3.47) | 1 | 25 |
| | Blurred vision | 160 | | 1.45 (1.75) | 1 | 15 |
| | Constipation | 159 | | 1.74 (2.45) | 1 | 16 |
| | Decreased appetite | 159 | | 3.03 (5.21) | 1 | 25 |
| | Decreased libido | 159 | | 2.65 (4.59) | 1 | 25 |
| | Decreased sleep | 159 | | 3.2 (5.21) | 1 | 25 |
| | Diarrhea | 159 | | 2.09 (2.95) | 1 | 16 |
| | Drowsiness/ somnolence | 159 | | 4.59 (5.95) | 1 | 25 |
| | Dry mouth | 160 | | 2.50 (3.48) | 1 | 25 |
| | Dyspepsia | 159 | | 2.50 (3.58) | 1 | 25 |
| | Dizziness | 160 | | 2.09 (2.95) | 1 | 20 |
| | Edema | 160 | | 1.28 (2.24) | 1 | 25 |
| | Flushing | 160 | | 1.48 (1.78) | 1 | 15 |
| | Headache | 159 | | 2.79 (3.22) | 1 | 20 |
| | Increased appetite | 160 | | 1.93 (3.12) | 1 | 20 |
| | Increased libido | 158 | | 1.22 (.98) | 1 | 9 |
| | Increased sleep | 160 | | 2.97 (4.82) | 1 | 25 |
| | Nausea | 159 | | 3.40 (3.94) | 1 | 20 |
| | Nervousness | 160 | | 3.13 (4.65) | 1 | 20 |
| | Other | 144 | | 1.85 (2.92) | 1 | 20 |
| | Postural hypotension | 160 | | 1.53 (1.80) | 1 | 15 |
| | Sweating | 159 | | 2.33 (3.50) | 1 | 20 |
| | Tremor | 160 | | 1.62 (1.92) | 1 | 15 |
| | Myoclonus | 160 | | 1.36 (1.58) | 1 | 12 |
| | Weight gain | 158 | | 1.30 (1.36) | 1 | 16 |
| | Weight loss | 160 | | 1.21 (1) | 1 | 9 |
| | Weakness/fatigue | 160 | | 3.73 (5.26) | 1 | 25 |

Abbreviations: MADRS, Montgomery-Asberg Depression Rating Scale.

## Small RNA Sequencing

All libraries were prepared using the NEB small RNA protocol following the manufacturer's instructions. Samples were sequenced at the McGill University and Genome Quebec Innovation Centre (Montreal, Canada) using the Illumina HiSeq4000 with 50nt single-end reads. All sequencing data were processed using CASAVA 1.8+ (Illumina) and extracted from FASTQ files. The Fastx toolkit was used to trim the Illumina adapter sequences. Additional filtering based on defined cutoffs was applied, including: (1) Phred quality (Q) mean scores higher than 30, (2) reads between 15 and 40 nt in length, (3) adapter detection based on perfect 10-nt match, and (4) removal of reads without detected adapter. Additionally, we used Bowtie (Song et al., 2014) to align reads to the human genome (GRCh37) (Kent et al., 2002) and ncPRO-seq (Chen et al., 2012) in combination with miRBase (V20) to match them to known miRNA sequences (Kozomara and Griffiths-Jones, 2011, 2014). Furthermore, all sequencing data were normalized with the Bioconductor-DESeq2 package (Love et al., 2014), using a detection threshold of 10 counts per miRNA.

## mRNA Sequencing

All libraries were prepared using the Illumina TruSeq mRNA stranded protocol following the manufacturer's instructions. Samples were sequenced at the McGill University and Genome Quebec Innovation Centre (Montreal, Canada) using the Illumina HiSeq4000 with 100-nt paired-end reads. FASTXToolkit and Trimmomatic were used for quality and adapter trimming, respectively. Tophat2 using bowtie2 was used to align the cleaned reads to reference genome. Reads that lost their mates through the cleaning process were aligned independently from the reads that still had pairs. Quantification on each gene's expression was estimated using HTSeq-count and a reference transcript annotation from ENSEMBL. Counts for the paired and orphaned reads for each sample were added to each other. Normalization was conducted on the resulting gene matrix using DESeq2.

## Target Prediction

We used 5 target prediction algorithms—miRWalk 2.0, miRanda, RNA22, RNAhybrid, and Targetscan (Rehmsmeier et al., 2004; Lewis et al., 2005; Miranda et al., 2006; Betel et al., 2010; Dweep and Gretz, 2015)—to identify putative mRNA targets of miRNAs and selected the top 100 targets for each miRNA. Although miRNAs can bind to other regions of mRNAs, we restricted our searches to the 3' untranslated region of target mRNAs.

## Statistical Analysis

Sociodemographic and clinical characteristics are presented using means and SDs for continuous variables and frequency distributions for categorical variables. We used log 2-transformed data for all miRNA and mRNA expression values. For each miRNA, we compared expression at each timepoint (week 0 and 2) with a repeated-measure ANOVA to identify those that changed significantly over time. For these miRNAs, we assessed the association between the change of expression of each miRNA (between week 0 and week 2) and course of intensity of each side effect between week 0 and week 2 (dependent variable) using linear regressions. To assess the role of miRNAs on predicted mRNA targets, we identified negative associations between week 0 and week 2 using linear regressions. For mRNA, we assessed the change of expression between week 0 and week 2 using a repeated-measure ANOVA. We used a false discovery rate threshold of 5% for each multiple comparison. Statistical analyses were performed with SPSS 25.0 (IBM Corp., released 2017. IBM SPSS Statistics for Mac, Version 25.0. Armonk, NY).

# Results

## Demographic Data

The sample included in this study comprised 160 patients who had TSES data available at week 2. Participants had a mean (SD) age of 35.84 (12.4) years, 62.5% were female, and their mean MADRS score prior to treatment was 29.82 (5.53) (Table 1). These patients were representative of the total sample (n = 211) included in the study at baseline (Kennedy et al., 2019) as they did not differ in age (35.84 [12.64] vs 35.34 [12.6], $P = .74$), sex ratio (female: 100 [62.5%] vs 133 [63%], $P = .95$), or mean baseline MADRS scores (29.82 [5.53] vs 29.98 [5.53], $P = .85$).

Side effects reported in this study primarily involved CNS, gastrointestinal, and sexual complaints (Table 1). The most common side effects experienced, at least occasionally, were drowsiness (45.9%), nausea (42.5%), and headaches (35.6%). Those with greatest severity were drowsiness (1.75; SD 1.11), nausea (1.60; SD 0.86), and weakness (1.57; SD 0.975).

## Change in miRNA expression between week 0 and week 2 following intake of SSRI (escitalopram) treatment

We detected 356 miRNAs that passed our filtering criteria at weeks 0 and 2. Of these, 45 displayed differential expression between weeks 0 and 2 (false discovery rate < 0.05) (supplementary Table 1).

## Association Between Side Effects and miRNA Expression Change Between Week 0 and Week 2

Among all side effects, only the intensity of nausea was associated with changes of miRNA expression between week 0 and week 2. Of the 45 miRNAs that showed significant changes between week 0 and week 2, we identified 12 where difference in expression between the 2 timepoints was significantly associated with reports of nausea (Table 2). Of these, 10 remained significant once covariates (age and gender) were accounted for. All were negatively associated with intensity of nausea (Table 2).

## Targets of Nausea-Associated miRNAs

We next tested for significant associations between these 10 miRNAs and their predicted mRNA targets. To generate a list of predicted mRNA targets, we used miRWalk, RNA22, miRanda, RNAhybrid, and Targetscan and identified a total of 19 targets that were predicted by all 5 algorithms (miR17-5p [3], miR20a-5p [1], miR20b-5p [2], miR106a-5p [3], miR185-5p [4], and miR660-5p [6]) (supplementary Table 2).

As miRNA primarily negatively regulates mRNA levels, we focused our analysis on miRNA-mRNA pairs that displayed negative correlations between week 0 and week 2. We found negative associations for (1) miR20a-5p with 1 mRNA (LDLRAD4), (2) miR106a-5p with 1 mRNA (CSNK1A1), (3) miR185-5p with 1 mRNA (CAMK2δ), and (4) miR660-5p with 2 mRNAs (HNRNPU, ASXL2) (Table 3).

**Table 2.** Association between nausea and change in miRNA expression (log 2) between week 0 and week 2

| miRNA (n = 160) | Week 0 (SD) | Week 2 (SD) | Delta week 0 week 2 (SD) | Nausea week 2 (n = 159) | Unadjusted | | Adjusted[a] | |
|---|---|---|---|---|---|---|---|---|
| | | | | | β | P value[b] | β | P value[b] |
| miR20b-5p | 9.09 (0.64) | 9.23 (0.6) | 0.14 (0.59) | 3.40 (3.94) | −0.278 | .009 | −0.262 | .011 |
| miR106a-5p | 7.98 (0.71) | 8.14 (0.67) | 0.17 (0.68) | | −0.276 | .009 | −0.248 | .011 |
| miR20a-5p | 11.49 (0.57) | 11.65 (0.57) | 0.16 (0.57) | | −0.264 | .009 | −0.266 | .011 |
| miR17-5p | 11.52 (0.49) | 11.65 (0.47) | 0.13 (0.48) | | −0.268 | .009 | −0.248 | .011 |
| miR185-5p | 12.85 (0.46) | 12.96 (0.45) | 0.11 (0.42) | | −0.253 | .009 | −0.238 | .027 |
| miR103a-3p | 13.87 (0.37) | 13.96 (0.35) | 0.1 (0.32) | | −0.231 | .019 | −0.209 | .039 |
| miR103b | 13.87 (0.37) | 13.96 (0.35) | 0.1 (0.32) | | −0.231 | .019 | −0.209 | .039 |
| miR1301-3p | 7.26 (0.53) | 7.13 (0.49) | −0.13 (0.56) | | 0.217 | .03 | 0.201 | .05 |
| miR182-5p | 11.7 (0.69) | 11.83 (0.69) | 0.13 (0.55) | | −0.217 | .03 | −0.181 | .028 |
| miR15b-5p | 11.53 (0.62) | 11.71 (0.58) | 0.16 (0.65) | | −0.211 | .008 | −0.17 | .034 |
| miR93-5p | 12.02 (0.45) | 12.15 (0.43) | 0.13 (0.41) | | −0.203 | .041 | −0.186 | .077 |
| miR660-5p | 6.57 (0.62) | 6.74 (0.58) | 0.17 (0.64) | | −0.200 | .041 | −0.21 | .013 |

Abbreviation: mRNA, microRNA.

False discovery rate (0.05) correction.

[a]Age and gender.

[b]False Discovery Rate (0.05) correction for multiple comparisons.

## Change of Target mRNA Expression Between Week 0 and Week 2

Expression of the miR-185-5p target CAMK2δ (log 2 mean = −0.048 [0.233]) decreased between weeks 0 and 2 (adjusted P = .01) (Figure 1). There were no changes in expression of the other target mRNAs over this period of time (Table 4).

## Discussion

To our knowledge, this study is the first to examine the role of miRNAs in the emergence of side effects during antidepressant treatment. We identified a negative association between the intensity of nausea and differential expression of 10 miRNAs between week 0 and week 2 of SSRI treatment. Additionally, we showed that the increased expression of miR185-5p was negatively associated with intensity of nausea and that its levels were negatively associated with the expression of a predicted target, calcium/calmodulin ($Ca^{2+}$/CaM)-dependent serine/threonine kinase 2δ (CAMK2δ), whose expression decreased between week 0 and week 2.

These findings are interesting when considering nausea/vomiting mechanisms. Nausea is one of the most prevalent side effects, occurring in up to 26% of patients treated with SSRIs (Trindade et al., 1998). Nausea and vomiting result in part from the stimulation of the chemoreceptor zone located in the fourth ventricle (area postrema) (David and Gourion, 2016). The tip of the fourth ventricle in the area postrema is free of blood-brain barrier, allowing access to toxins, chemicals, and also neurotransmitters (Miller and Leslie, 1994). This zone contains a number of different neurotransmitter receptors, but it is rich in serotoninergic 5-HT3 receptors. Drugs that produce nausea/vomiting activate the serotonin 5-HT3 receptors, among others, and stimulation of 5-HT3 receptors in the intrinsic plexus of the intestine or in the vagus induces vomiting (Nutt, 1997). It has also been suggested that the neurokinin receptor NK1 interacts with the 5-HT3 receptor to potentiate the signal (Navari and Aapro, 2016).

CAMKs constitute a family of 81 proteins in the human proteome that play a central role in cellular signaling by transmitting $Ca^{2+}$ signals (Manning et al., 2002). Kinases in this protein family are activated through binding of $Ca^{2+}$/CaM to regulatory regions that either flank the catalytic domain or are located in regulatory molecules (Swulius and Waxham, 2008). Four CAMK2 isozymes (α, β, γ, and δ) are expressed in humans. The α and β isoforms are brain specific (Erondu and Kennedy, 1985). The γ and δ isoforms are expressed in most tissues (Hudmon and Schulman, 2002; Rellos et al., 2010). There is some evidence to support a relationship between CAMK2 and vomiting through activation of the $Ca^{2+}$-CAMK2-ERK1/2 pathway (Zhong et al., 20142016). In our study, we found that onset of nausea was negatively associated with an increased expression of miR185-5p and that its levels were negatively associated with the expression of a predicted target, CAMK2δ, whose expression decreased between week 0 and week 2. Our results suggest that the negative association between increased expression of miR185-5p and intensity of nausea could be linked with the decreased expression of CAMK2δ.

This study investigated the expression of miRNAs and mRNAs in blood. While changes measured peripherally may not reflect the expression of these molecules in the brain, MDD is a systemic illness and side effects may arise as a result of treatment-induced peripheral molecular changes. Another limitation of this study is that we focused on side effects occurring early

**Table 3.** Association between change in miRNA and target mRNAs between week 0 and week 2 (negative correlations only)

| miRNA | Target (mRNA) | Linear regression (adjusted)[a] | |
|---|---|---|---|
| | | β | P value[b] |
| miR20a-5p | LDLRAD4 | −0.26 | .001 |
| miR106a-5p | CSNK1A1 | −0.29 | .003 |
| miR185-5p | CAMK2δ | −0.24 | .005 |
| miR660-5p | HNRNPU | −0.24 | .006 |
| | ASXL2 | −0.22 | .006 |

Abbreviations: mRNA, messenger RNA; miRNA, microRNA.
False discovery rate (0.05) correction.
[a]Age and gender.
[b]False Discovery Rate (0.05) correction for multiple comparisons.
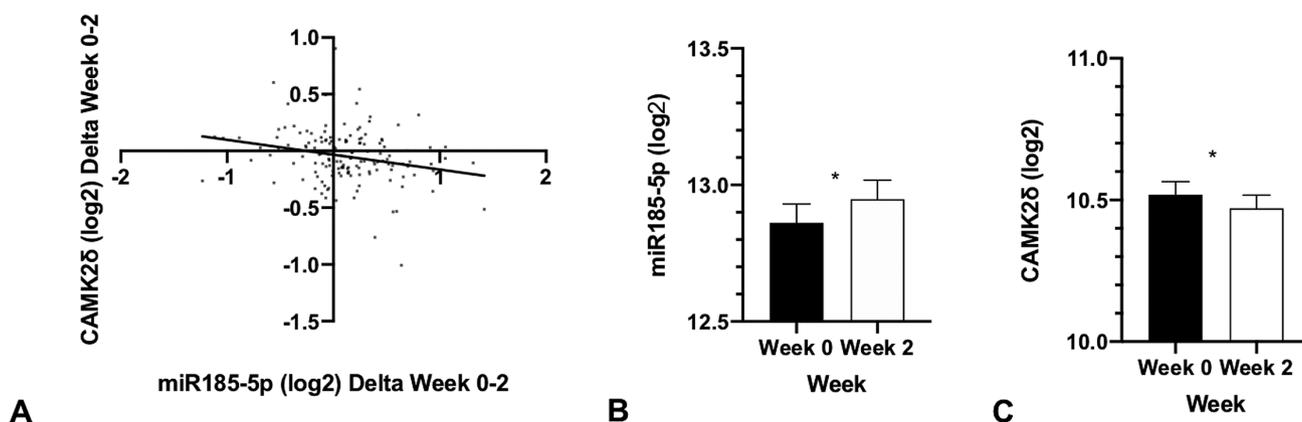


**Figure 1.** Changes in miR185-5p and CAMK2δ over time. (A) Association between miR185-5p and CAMK2δ. (B) Changes of miR185-5p expression (log 2) between week 0 and week 2. (C) Changes of CAMK2δ expression (log 2) between week 0 and week 2. *$P < .05$; CAMK2δ, calcium/calmodulin ($Ca^2+$ /CaM)-dependent serine/threonine kinase 2δ; miRNA, micro RNA.

**Table 4.** Change in mRNA expression (each miRNA selected) between week 0 and week 2.

| mRNA | miRNA | Week 0 (SD) | Week 2 (SD) | P value[a] |
|---|---|---|---|---|
| LDLRAD4 | miR20a-5p | 9.999 (0.288) | 9.988 (0.258) | .57 |
| CAMK2δ | miR185-5p | 10.519 (0.287) | 10.471 (0.290) | .01 |
| CSSNK1A1 | miR106-5p | 11.904 (0.185) | 11.890 (0.179) | .39 |
| HNRNPU | miR660-5p | 13.917 (0.177) | 13.904 (0.157) | .56 |
| ASXL2 | | 11.431 (0.410) | 11.416 (0.372) | .56 |

Abbreviations: mRNA, messenger RNA; miRNA, microRNA.
Log 2-adjusted counts are shown for expression.
[a]False discovery rate (0.05) correction for multiple comparisons.

after the initiation of SSRI treatment. Other side effects, such as weight gain, are known to occur later in the course of treatment. Thus, future research on this topic should include points of assessment later in the treatment course.

## Conclusions

We identified an overexpression of miR-185-5p during escitalopram treatment of MDD, which was negatively associated with intensity of nausea, and identified a potential mRNA target that may mediate this effect. Future studies are warranted to investigate the role of epigenetic factors in the mechanisms underlying side effects during antidepressant treatment in order to improve patient care and reduce discontinuation or poor compliance.

## Supplementary Materials

Supplementary data are available at *International Journal of Neuropsychopharmacology (IJNPPY)* online.

## Acknowledgments

## Statement of Interest

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