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Opioid Dependence during Pregnancy: Relationships of Anxiety and Depression Symptoms to Treatment Outcomes

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Abstract

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Declaration of Interest:
This study was funded by the National Institute on Drug Abuse and National Center for Research Resources, National Institutes of Health.
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Aims—To examine the relationship of anxiety and depression symptoms with treatment outcomes (treatment discontinuation, rates of ongoing use of illicit drugs, and likelihood of preterm delivery) in opioid-dependent pregnant women and describe their use of psychotropic medications.

Design and setting—Secondary data analysis from a randomized controlled trial of treatment for opioid dependence during pregnancy.

Participants—175 opioid-dependent pregnant women, of whom 131 completed treatment.

Measurements—Symptoms of anxiety and depression were captured with the 15-item Mini International Neuropsychiatric Interview (MINI) screen. Use of illicit drugs was measured by urine drug screening. Preterm delivery was defined as delivery prior to 37 weeks gestation. Self-reported use of concomitant psychotropic medication at any point during the study was recorded.

Findings—Women reporting only anxiety symptoms at study entry were more likely to discontinue treatment (adjusted OR = 4.56, 95% CI = 1.91–13.26, P = 0.012) while those reporting only depression symptoms were less likely to discontinue treatment (adjusted OR = 0.14, 95% CI = 0.20 – 0.88, P = 0.036) compared to women who reported neither depression nor anxiety symptoms. No statistically significant between group differences were observed for ongoing illicit drug use or preterm delivery. A majority (61.4%) of women reported use of concomitant psychotropic medication at some point during study participation.

Conclusions—Opioid-agonist-treated pregnant patients with co-occurring symptoms of anxiety require additional clinical resources to prevent premature discontinuation.

Keywords

tbc

INTRODUCTION

Opioid dependence occurring during pregnancy is a significant public health challenge resulting in potential risks to mother and fetus and enormous healthcare costs [1,2]. Co-occurring psychiatric symptoms complicate clinical management of an already vulnerable patient population [3]. Rates of co-occurring anxiety and depression in clinical samples of opioid-dependent pregnant women range from 65 to 73% [3,4] compared with only about 20% in epidemiologic samples of non-pregnant drug-dependent individuals [5]. Rates of depression during pregnancy, not complicated by drug-dependence, range from 7 to 16% [6].

An extensive literature on the relationship of co-morbid anxiety and depression disorders with substance abuse treatment outcomes among non-pregnant individuals reveals mixed findings regarding outcomes of addiction treatment [7–9]. The difficulty of differentiating anxiety and depression symptoms from complications of drug use, withdrawal, and protracted abstinence [10] to arrive at valid diagnoses along with the possibility that addiction treatment approaches for different drugs of abuse may indirectly exacerbate or mitigate symptoms of anxiety and depression make the findings of such outcome studies particularly challenging to interpret.

The effect of co-occurring psychiatric conditions in opioid-dependent pregnant women, has been less well studied and conclusions are even less clear as pregnancy itself presents a particularly vulnerable period for many women. A single study has examined the relationship of co-occurring anxiety and mood disorders to treatment outcomes in opioid-dependent pregnant women. Women in methadone-maintenance treatment with depression were more likely to discontinue comprehensive treatment while those with anxiety were more likely to remain in treatment longer and to attend more treatment hours/day [4]. Further analysis of the same cohort found that infants born to opioid-dependent women with depression compared to those without depression had an increased length of stay in the neonatal intensive care unit [11]. To our knowledge, no study has examined the relationship of anxiety or depression symptoms to treatment outcomes for buprenorphine-maintained pregnant women.

The goal of the current study was to examine the relationship of co-occurring symptoms of anxiety and/or depression identified at entry into a randomized controlled trial of methadone and buprenorphine with treatment outcomes in pregnant women with opioid dependence. We hypothesized that co-occurring symptoms of anxiety and/or depression would be associated with differing rates of treatment discontinuation, lower rates of abstinence from illicit drug use, and a greater likelihood of preterm delivery. We focused on anxiety and depression symptoms because of their prevalence in the sample and the availability of a wide-range of evidence-based treatment options for these conditions including psychotherapy and pharmacotherapy. In addition, we described the patterns of prescribed concomitant psychotropic medications in this group of participants.

METHODS

Additional details regarding the study protocol can be found in Jones, *et al*. (*Addiction*, this issue [12]) and prior publications [1,3,12,13].

Study Design

This is a secondary analysis of data collected during the Maternal Opioid Treatment: Human Experimental Research (MOTHER) study. The MOTHER study was an international multi-site double-blind, double-dummy, randomized controlled trial of the safety and efficacy of buprenorphine and methadone for treatment of opioid-dependence during pregnancy that enrolled patients between May 4, 2005 and October 31, 2008. All sites received approval from local Institutional Review Boards. Oversight was provided by a Data and Safety Monitoring Board.

Participants

Opioid-dependent women between 18 and 41 years of age, carrying a single fetus with estimated gestational age of 6 to 30 weeks, were eligible for screening. Of 1074 women screened for participation, 438 (40.8%) were eligible and available for further screening. Of those, 208 (47.5%) consented to participate. Thirty-eight of the 438 (8.7%) women were excluded due to psychiatric illness with severity resulting in significant safety concerns. Of 175 women randomized to receive study medication, 131 (74.9%) completed the study

(remaining in the study until delivery of a live infant). Prior to initiation of study drug, participants were stabilized as inpatients with immediate release morphine sulfate to facilitate induction to study medication.

Assessments

Structured Clinical Interview for DSM Disorders, Substance Use Disorders Module (SCID-E)—The SCID-E [14] was administered during screening to assess current and lifetime substance use disorders. Study participants were required to meet criteria for current opioid-dependence criteria and were excluded for current alcohol- or benzodiazepine-abuse or dependence due to potential medication interaction effects and known effects of these agents on neonatal outcomes.

Mini International Neuropsychiatric Interview (MINI)—To assess symptoms of other co-occurring psychiatric disorders, the screening version of the MINI [15] was administered at study entry. The MINI is a valid and reliable tool for diagnosis of co-occurring psychiatric conditions in opioid-dependent individuals [16,17]. The shorter 15-item screening tool was used in the current study to reduce response burden. The MINI-screen items are listed in our earlier work [13]. Individual symptoms were collapsed into categories based on symptom clusters. Items 1–4 described symptoms of major depression disorder, dysthymia, and suicidal thinking and were included in a depression symptom cluster. Items 7–13 and 15 described symptoms of panic, agoraphobia, social phobia, obsessive compulsive disorder, post-traumatic stress disorder, and generalized anxiety disorder and were included in an anxiety symptom cluster. An affirmative answer to any of the items in the cluster resulted in a positive screen for that cluster. Participants were then grouped into four categories based on their responses: neither symptom reported, anxiety symptoms only reported, depression symptoms only reported, or both symptoms reported.

Addiction Severity Index (ASI)—The ASI is an interview-based rating of severity of impairment in seven domains: alcohol use, drug use, employment, legal, family/social, medical, and psychological [18] administered at study entry. It does not distinguish quality of symptoms or psychiatric diagnoses that contribute to impairment severity. Interviewers were trained and periodically screened for reliable use of the instrument. This study focused on the psychological composite score and examined whether this variable was associated with treatment outcomes.

Use of concomitant medications—Participants were asked at study entry and weekly about use of any other medications in addition to the study medication. Concomitant medications were prescribed by a clinician of the participant's choosing, not necessarily study staff. The study protocol included a list of acceptable concomitant medications; however, participants may have received non-approved medications from physicians unrelated to the study. Such use was noted as a protocol deviation, but was not cause for termination of participation in the study. Current abuse or dependence on benzodiazepines (including physiological dependence related to prescribed use) or positive urine drug screen for benzodiazepines at study entry was exclusionary. Medications were grouped into categories based on typical indication rather than mechanism of action. Anxiolytic

medications reported by participants included buspirone, hydroxyzine, passedan-tropfen (Austria), and zolpidem as well as benzodiazepines (clonazepam, diazepam, lormetazepam, midazolam, and oxazepam). Antidepressants included selective serotonin reuptake inhibitors (citalopram, escitalopram oxalate, fluoxetine, paroxetine, sertraline), mixed neurotransmitter reuptake inhibitors (buproprion, trazodone), and a tricyclic antidepressant, doxepin. Antipsychotics included olanzapine and quetiapine. Mood stabilizers included lithium and lamotrigine. Self-reported concomitant medication data were available for 166 (94.8%) participants. Report of concomitant medication use at any point during the study was coded as positive use.

Treatment Provided during the Study

The study protocol ensured that comprehensive care was provided for all participants at each site. In addition to daily on-site administration of study medication, study participants received individual and/or group counseling, additional psychiatric treatment as needed, and obstetric and medical care. While access to psychiatric treatment was available, such care was not always provided by a clinician affiliated with the study. Data regarding the frequency and specific nature of any adjunct services pursued by participants in this multi-site study were not collected. Contingency management was implemented to encourage abstinence from alcohol and other concomitant illicit drug use during the study. Patients earned monetary vouchers for providing drug-negative urine samples [12].

Treatment outcomes

Treatment discontinuation—The primary outcome of this secondary dataanalysis was discontinuation of study participation prior to delivery of a live infant. Women who discontinued participation were referred to local resources for ongoing treatment. Great effort was made to maintain women in treatment in the study, including considerable outreach efforts and rescheduling appointments for the convenience of each woman. Transportation to daily medication visits was provided when needed. At study entry, each participant provided contact information for three individuals who could be contacted in the event of a missed appointment to help encourage adherence to treatment. In spite of these efforts, 44 (25.1%) participants discontinued treatment prior to delivery. The reason for treatment discontinuation was voluntary for 36 participants (dissatisfaction with medication, missing more than 5 consecutive dosing days, or other reason for withdrawal), and involuntary for 8 participants (administrative discharge, loss of pregnancy, incarceration, other medical reason) [1].

Urine drug screening—Participants were asked to provide urine samples three times weekly throughout their participation in the study. Urine drug screening included tests for cocaine, benzodiazepines, marijuana, and opioids (excluding methadone and buprenorphine in order to protect randomization blinding). A positive urine drug screening test for any drug at any point during the study was considered as a positive result for this outcome variable. Refusal to provide a urine sample was coded as a positive screen. Participants received vouchers for negative screens. One participant in the group of women who reported no symptoms had missing urine drug screen data and was not included, resulting in a sample size of 130 for this analysis.

Preterm delivery—Preterm was defined as delivery before 37 weeks of gestation.

Data Analysis

Statistical analyses were performed using SPSS 18.0 and Stata 10. Descriptive statistics were used to summarize sample characteristics and psychiatric symptoms. Univariate differences in baseline characteristics among the psychiatric symptom groups were assessed using likelihood ratio chi-square tests of independence for discrete data distributions and analysis of variance for continuous data. Characteristics found to differ among the psychiatric symptom groups were not associated with any of the outcome variables. Hierarchical multiple logistic regression analysis was used to generate adjusted associations of the presence of anxiety and/or depression symptoms with treatment discontinuation. Replicating the approach used in the primary study, this hierarchical analysis controlled for site of participation (U.S. urban *vs*. U.S. rural *vs*. European) and randomized medication assignment, age, education, and race. An α of 0.05 was used for determining statistical significance.

RESULTS

Sample Characteristics

A description of participants can be found in the primary outcome paper for the MOTHER study [1]. A majority of participants (62.3%) reported some symptoms of anxiety or depression at study entry, with 19.4% reporting only anxiety symptoms, 10.9% reporting only depression symptoms, and 32.0% reporting both anxiety and depression symptoms. Table 1 describes characteristics of the participants in each symptom group at screening. Participants who reported no symptoms were younger ($P = 0.018$) and had completed fewer years of education ($P = 0.002$) than those in the other groups. There were no statistically significant differences between groups for the other characteristics summarized. As expected, the ASI composite score rating was associated with the presence of self-reported anxiety and/or depression symptoms ($P < 0.001$).

Anxiety and depression symptoms and retention in treatment

The rate of study discontinuation for women in the group reporting no symptoms was 18.2% compared with 47.1% in the group reporting only anxiety symptoms, 10.5% in the group reporting only depression symptoms, and 25.0% in the group reporting symptoms in both clusters ($P < 0.01$, Figure 1). We used logistic regression to further characterize the relationship of anxiety and depression symptoms with treatment discontinuation adjusting for study site, randomized medication assignment, age, race, and years of education. Compared to women reporting no anxiety or depression symptoms, women reporting symptoms of anxiety at study entry, had a 4.6 fold increase in likelihood of study discontinuation (adjusted OR = 4.56, 95% CI = 1.39–14.95, $P = 0.001$, see Table 2). In contrast, women reporting symptoms of depression were considerably less likely to discontinue the study than women with no symptoms (adjusted OR = 0.14, 95% CI = 0.02–0.88, $P = 0.036$). There was no statistically significant difference in the probability for discontinuation in the group with both depression and anxiety symptoms compared to those

reporting no such symptoms. No statistically significant association was found between the overall ASI psychological composite and treatment discontinuation (P = 0.472).

Psychiatric symptoms and illicit drug use

The proportion of women with positive urine drug screens at any point during the study was 46.9% for the group as a whole and 35.8% for women with no anxiety or depression symptoms, 38.9% for women with only anxiety symptoms, 52.9% for women with only depression symptoms, and 61.9% for women with symptoms of both anxiety and depression, but these differences did not reach the threshold for statistical significance (P = 0.07).

Psychiatric symptoms and preterm delivery

We observed no statistically significant association between the presence of symptoms of anxiety or depression at study entry and the likelihood of preterm birth (delivery prior to 37 weeks). The number (proportion) of preterm deliveries was 18 (13.7%) for the group as a whole and 3 (5.6%) for women with no anxiety or depression symptoms, 4 (22.2%) for women with only anxiety symptoms, 4 (23.5%) for women with only depression symptoms, and 7 (16.7%) for women with symptoms of both anxiety and depression (P = 0.10).

Prescription medications for anxiety and depression

Data regarding self-reported use of prescribed concomitant medication were available for 166 (94.9%) randomized participants. A majority of women (61.4%) reported taking psychotropic medication at some point during the study; however, not all of those taking medication had reported symptoms of anxiety or depression at study entry (Table 3). Women who reported symptoms of anxiety or depression were significantly more likely to report use of psychotropic medication (P < 0.001). A large proportion (40.3%) of women who reported no symptoms of anxiety or depression at study entry reported using one or more psychotropic medication at some point during the study. Anxiolytic medications were most frequently reported for all groups of participants except those who reported only symptoms of depression, for whom antidepressants were most frequently reported. Antipsychotic medication use was reported by 12 (7.2%) participants. The rate of reported use of mood stabilizers (lamotrogine or lithium) was 4.8%. Of women who reported symptoms of both anxiety and depression at study entry, 23.6% reported that they had taken no additional prescribed psychotropic medications throughout the entire study duration.

DISCUSSION

The major findings of this secondary analysis of MOTHER study data are that symptoms of anxiety and depression were associated with significant differences in treatment discontinuation in opioid-dependent pregnant women participating in a clinical trial of methadone and buprenorphine. Differences in rates of ongoing use of illicit drugs and preterm delivery did not meet the threshold for statistical significance. Women reporting anxiety symptoms at study initiation were significantly more likely to discontinue treatment prior to delivery while women reporting depression symptoms were less likely to discontinue treatment prematurely. Women reporting both anxiety and depression symptoms

had no appreciable difference in treatment retention compared with women reporting no symptoms.

These findings contradict those of a previous study in a similar population treated with methadone in which anxiety was associated with improved treatment retention, and depression with poorer retention [4]. Several methodological differences between the two studies may explain the contradictory findings. First, the current study was a randomized clinical trial of methadone and buprenorphine while the prior report studied women enrolled in a methadone-maintenance program. Second, the effects of buprenorphine on symptoms of anxiety and depression are not well understood and treatment with this medication may have contributed to treatment discontinuation for women with anxiety. Third, symptoms of anxiety may have contributed to a greater difficulty tolerating treatment in a randomized controlled trial setting in which participants did not know which medication they were receiving.

It is important to note that the threshold for anxiety and depression symptoms used in this study was considerably lower than would be required for formal diagnosis of an anxiety disorder or a depression disorder. Women who endorsed just one relevant screening item on the MINI at study entry were categorized as having symptoms of anxiety or depression. Thus, the current study may underestimate the influence of such symptoms on successful treatment of opioid dependence during pregnancy. This clinical trial was not designed to make a formal diagnosis of anxiety or depression or to measure severity of such symptoms; therefore, we were unable to examine the relationship between anxiety or depression symptom severity and treatment outcomes.

In this clinical sample, ASI psychological composite score at study entry was associated with reported MINI symptoms, but did not predict treatment retention, perhaps due to the opposing relationships of anxiety and depression. The ASI is helpful in providing an overview of the severity of psychological and other impairment, but it does not provide information regarding psychiatric causes of distress, thus the addition of another qualitative tool like the MINI screen adds clinically useful information that allows for a clearer understanding of individual needs of patients.

Women who reported depression symptoms were more likely, and women who reported anxiety symptoms were less likely to produce urine samples that were positive for illicit drugs compared to women who reported no symptoms at study entry, but these differences did not meet our threshold for statistical significance. These results are complicated by the differing rates of study discontinuation, EGA at time of study entry, and duration of pregnancy at delivery--women who remained in the study longer had a greater number of opportunities to provide urine samples for drug screening. Further investigation of the relationship of anxiety and depression symptoms with ongoing illicit drug use during treatment with opioid replacement during pregnancy is warranted.

The current study reveals interesting information about medication prescribing by physicians to opioid-dependent patients during pregnancy. First, nearly 25% of women who reported symptoms of anxiety or depression at study entry received no medication other than

study drug throughout the study duration. On the other hand, many of the women to whom medications for anxiety and depression were ultimately prescribed had not reported such symptoms at study entry. For these women, symptoms may have been present, but well managed with medication and therefore not reported at study entry, symptoms may not have been captured by responses to the MINI questions, or these women may have developed symptoms later during the course of their pregnancy and treatment for opioiddependence. Symptoms of anxiety and depression can be challenging to diagnose during pregnancy and change over time making ongoing assessment of co-occurring symptoms of anxiety and depression essential in this vulnerable population. The design of the current study did not allow for further assessment of the relationship of concomitant psychotropic medication to psychiatric diagnosis, opioid treatment retention, or pregnancy outcomes.

There are several limitations of this secondary analysis of data collected as part of a randomized controlled trial. First, due to the need to reduce response burden, this study employed only a brief screening tool for psychiatric symptoms. Use of the screening tool did not allow for confirmative diagnosis of psychiatric disorders or for designation of a primary disorder when symptoms of both depression and anxiety were present. Second, screening for psychiatric symptoms was performed only upon study entry without a longitudinal measure of how such symptoms changed over the course of pregnancy and treatment. Third, while each site employed contingency management to enhance treatment adherence and minimize other substance use, the study protocol for this multi-site medication trial did not standardize psychosocial treatments provided at each site. Therefore, adjunctive treatments may have varied between sites. Because details regarding which adjunctive services were provided to individuals in the study were not collected, the effects of psychosocial interventions on outcomes could not be evaluated. The analysis of birth outcomes was possible only for study completers, limiting the ability to detect any relationship with psychiatric symptoms. Finally, because the current study is a secondary analysis of data collected from a randomized controlled trial, statistical power to address the current research questions is limited and results should be considered as exploratory.

In spite of these limitations, this study reveals a statistically significant association between self-reported co-occurring symptoms of anxiety on entry into this clinical trial and likelihood of premature treatment discontinuation, emphasizing the importance of early identification of such symptoms to the provision of optimal care for such patients. Further work is needed to better understand the impact that treatment of depression and anxiety may have on obstetric, neonatal and drug related treatment outcomes. Future studies should examine the specific psychopharmacologic effects of methadone and buprenorphine in women with and without co-morbid depression and anxiety. Another important question is the timing of study discontinuation to determine at what point women are most vulnerable to discontinue treatment allowing for additional services to increase treatment adherence. Also, additional research is needed to better understand psychosocial factors influencing treatment adherence in this particularly vulnerable population. Finally, study of both pharmacologic and non-pharmacologic approaches to treatment of depression and anxiety symptoms in this population is needed to attain the ultimate goal of improving outcomes for the opioid-dependent mother and her newborn.

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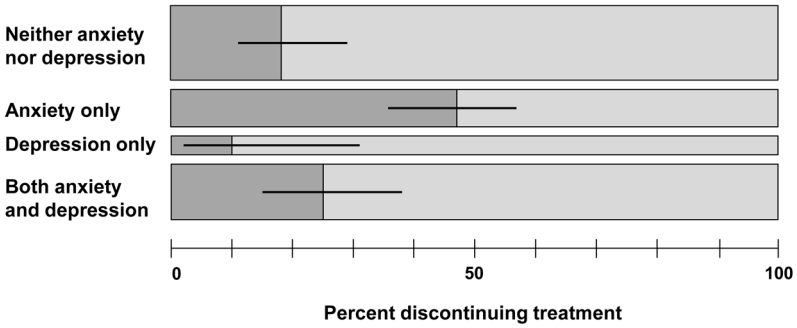

Figure 1. Treatment discontinuation by symptom groups (n = 175)

Opioid-dependent pregnant women reporting anxiety only were more likely and those reporting depression only were less likely to discontinue treatment prior to delivering an infant than women reporting symptoms in neither category. Symptoms of anxiety and depression were determined at study entry using the 15-item MINI screen. Width of each bar is proportional to the number of participants in each group. Error bars represent 95% confidence interval.

Table 1

Characteristics of participants at study entry by psychiatric symptom group (n=175)

	Reported Symptoms at Screening n (%)				
Characteristics	**Neither**	**Anxiety**	**Depression**	**Both**	**P**
	66 (37.7)	34 (19.4)	19 (10.9)	56 (32.0)	
Maternal age, years M(SD)	25.5 (5.4)	28.6 (5.5)	28.5 (6.6)	28.2 (6.0)	0.018
EGA, weeks M(SD)	18.4 (6.7)	19.2 (7.0)	19.2 (5.8)	18.5 (5.7)	0.902
Maternal education, years M(SD)	10.1 (1.9)	12.0 (1.4)	11.0 (1.6)	11.7 (1.9)	0.002
Non-White n (%)	6 (9.1)	6 (17.6)	7 (36.8)	10 (17.9)	0.053
Married n (%)	10 (15.2)	7 (20.6)	2 (10.5)	4 (7.1)	0.277
Employed n (%)	11 (16.7)	3 (8.8)	3 (15.8)	6 (10.7)	0.636
ASI Psychological Composite n (%)					< 0.001
No problem	42 (63.6)	8 (24.2)	7 (36.8)	6 (10.7)	
Slight problem	10 (15.2)	7 (21.2)	4 (21.1)	7 (12.5)	
Moderate problem	9 (13.6)	11 (33.3)	4 (21.1)	20 (35.7)	
Considerable/extreme problem	5 (7.6)	7 (21.2)	4 (21.1)	23 (41.1)	

Note: EGA: estimated gestational age

Table 2

Associations of baseline depression and anxiety with treatment discontinuation (n = 175)

Psychiatric symptoms reported	Adjusted OR (95% CI)	P
Anxiety only	4.56 (1.91–13.26)	0.012
Depression only	0.14 (0.20–0.88)	0.036
Anxiety and Depression	0.68 (0.12–2.18)	0.680

Note: Association analyzed by hierarchical logistic regression with neither anxiety nor depression group as referent category. Covariates included site, randomized medication assignment, age, race, and years of education.

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Table 3

Prescribed psychiatric medications by self-report corresponding to reported anxiety and depression symptoms

	Reported Symptoms at Screening				
	Neither (n = 62)	**Anxiety (n = 31)**	**Depression (n = 18)**	**Both (n =55)**	**All Cases (n = 166)**
Any medication*	25 (40.2)	21 (67.7)	14 (77.8)	42 (76.4)	102 (61.4)
Medication class [a]					
Anxiolytic	19 (30.6)	17 (54.8)	7 (38.9)	26 (47.3)	69 (41.6)
Antidepressant	10 (16.1)	8 (25.8)	8 (44.4)	23 (41.8)	49 (29.5)
Antipsychotic	4 (6.5)	1 (3.2)	2 (11.1)	5 (9.1)	12 (7.2)
Mood stabilizer	1 (1.6)	1 (3.2)	0 (0.0)	6 (10.9)	8 (4.8)

Note:

*$P < 0.001$,

[a]Participants may have been prescribed more than one type of medication; therefore, the column frequencies (percentages) are not mutually exclusive.