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Psychopharmacologic Management of Opioid-Dependent Women during Pregnancy

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Abstract

Illicit drug use during pregnancy presents complex clinical challenges, including reducing drug use and treating psychiatric disorders. Pharmacologic treatment of psychiatric disorders in a pregnant woman requires an evaluation of the balance between potential clinical benefit and the risk of potential neonatal consequences. This study describes psychiatric symptoms in 111 opioid-dependent pregnant women and their prescribed psychotropic medications. Hypomania, generalized anxiety disorder and depression were the most common disorders for which psychiatric symptoms were endorsed. Over half of women studied were prescribed some form of psychoactive medication during pregnancy. Pharmacologic vs. non-pharmacologic treatment approaches in this patient population are discussed.

Background

Opioid use during pregnancy is associated with adverse birth outcomes, which are most likely complications of a multitude of unfortunate life circumstances and the presence of coexisting medical and psychiatric conditions.[1] In a national survey of the prevalence of prenatal drug exposure, it was estimated that 5.5% of pregnant women used illicit drugs at some point in their pregnancy. Annually, 53,400 were estimated to have been exposed to heroin or nonmedically used opioid analgesics.[2] Arguably, because of the increase in nonmedical prescription opioid abuse, especially among women of childbearing age,[3,4] this earlier study

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most likely underestimates prenatal exposure to prescription opioids. A more current conservative estimate of opioid analgesic use during pregnancy comes from the National Survey on Drug Use and Health, which indicated that 4.4% of pregnant women aged 15 to 44 (or 109,000 women) used opioid analgesics without appropriate medical oversight in the past year, with 15–17 year old pregnant females having the highest estimate of all age groups reported (15%).[5]

Agonist treatment for opioid dependence is effective in reducing opioid abuse and has been utilized in pregnant women as part of a comprehensive management strategy. Methadone maintenance treatment is the standard of care for opioid dependence in pregnant women but has not been formally approved by the Food and Drug Administration (FDA).[6] Relative to active heroin addiction, methadone maintenance results in improved prenatal care, increased fetal growth, reduced fetal mortality, reduced foster care placement, and decreased risk of HIV infection, preeclampsia, and neonatal withdrawal.[7–13] Although comparable studies have not been conducted with pregnant women who are addicted to other opioid analgesics resulting from nonmedical use, support and structure associated with maintenance treatment are expected to be beneficial by bringing stability to an otherwise chaotic lifestyle.

Buprenorphine, a partial μ-agonist has been found to be as equally effective and safe as methadone in the outpatient treatment of opioid dependence in non-pregnant patients.[14–16] With regard to pregnancy, buprenorphine use is associated with good neonatal outcomes[17–19] and is being used more frequently for treatment of pregnant opioid-dependent women, though it is also not yet approved by the FDA for this patient population.[1] Both methadone and buprenorphine have been categorized by the FDA as Pregnancy Category C, but there is far more experience with methadone.

Complicating the clinical management of substance use disorders is the co-occurrence of a plethora of psychiatric conditions which may be exacerbated by the psychological and physiological stresses of pregnancy, a period widely considered a time of increased sensitivity to psychiatric disorders.[20–21] Knowledge of the prevalence of other psychiatric disorders in pregnant women with substance use disorders stems primarily from small studies of clinical samples. In one study, 10.3% of drug-using pregnant women had other psychiatric disorders compared to 1.4% of their non-using counterparts.[22] Among a clinical sample of substance-dependent pregnant patients, 73% met criteria for a current co-occurring Axis I disorder with 37% and 36% meeting criteria for a current mood or anxiety disorder, respectively.[23] Comparatively lower prevalence estimates have been reported among pregnant women who do not have a substance use disorder. Prevalence varies by ascertainment source (ie, community-based vs. clinical samples), the instruments used to make psychiatric diagnoses, and the psychiatric diagnosis of interest. For instance, major depression during pregnancy has been observed in 3 to 21% of pregnant women.[24–28]

In the past, most of our knowledge regarding treatment approaches for psychiatric disorders came from studies of non-pregnant patients. Much recent attention has been focused on the treatment of psychiatric disorders among pregnant women from the general population.[29,30] To our knowledge, specific issues regarding the treatment of pregnant women with co-occurring substance use disorders (in whom there are distinct pathophysiological and pharmacological concerns) have not been discussed.

There is now consensus that depression is very common among pregnant women in general and should be thoughtfully diagnosed and treated. If left untreated, maternal depression during pregnancy, even without a substance use disorder (SUD), can result in adverse consequences for mother and infant, including increased risk for pre-eclampsia,[31] low infant birth weight and delivery complications,[32] poor maternal weight gain, postpartum depression,[33] maternal

suicide,[34] as well as decreased maternal responsiveness and consequent impairment of infant socio-emotional functioning and development.[35] In addition, women with antenatal depression are more likely than non-depressed women to use alcohol, cigarettes, and other drugs during pregnancy.[36] In a large study using administrative data, Kelly et al.[37] demonstrated that psychiatric disorders and SUD are both independently associated with less prenatal care.

Given the degree of overlap between symptoms of substance abuse and other psychiatric disorders in women,[38] many clinical challenges exist when a pregnant patient presents for treatment. Most importantly, if psychiatric symptoms abate with adequate management of the drug use disorder (eg, with agonist maintenance treatment), it may not be necessary to treat such disorders independently and to expose the fetus to additional pharmacological agents which have their own levels of risk. Pharmacotherapy of pregnant women is complex because few clinical trials have been conducted to evaluate the safety and efficacy of most medications during pregnancy. Prescription of psychiatric medications, especially, are to be avoided, even when there is "no evidence of risk in humans" (Category C according to the FDA classification) due to poorly defined and understood behavioral teratogenesis.

This paper centers on the issue of clinical management of pregnant women who have opioid dependence. It has two objectives: 1) to estimate the frequency of psychiatric symptoms among a sample of opioid-dependent pregnant women; and, 2) to describe the types of pharmacologic agents prescribed to these women for the treatment of their psychiatric disorders.

Methods

Study Design

This study used cross-sectional data that were collected as part of the Maternal Opioid Treatment: Human Experimental Research (MOTHER) study. The MOTHER study is a double-blind, randomized clinical trial that is currently ongoing at eight clinical sites.* The major goal of the MOTHER project is to evaluate the safety and efficacy of buprenorphine and methadone in pregnant opioid-dependent women and their neonates[39] using standardized methods and procedures founded on extensive pilot research in pregnant women and their neonates.[18,40] All sites received local Institutional Review Board approval, and oversight is conducted by a Data and Safety Monitoring Board. For a more detailed description of site selection, study coordination, subject selection, and protocol details, see Jones et al.[39]

Subjects

Opioid-dependent pregnant women, between the ages of 18 and 41 years, who planned to deliver at one of the participating site hospitals, were considered for inclusion in the study. All women considered for entry met DSM-IV criteria for current opioid dependence, according to the E module of the Structured Clinical Interview for DSM-IV (SCID I),[41] and provided an opioid-positive urine sample indicating current opioid use or were currently on agonist treatment for opioid dependence. In addition, potential participants were required to have a single fetus pregnancy, with an estimated gestational age (EGA) of 6 to 30 weeks and a normal fetal heartbeat identified by sonogram.

Exclusionary criteria for the study are: (1) a medical condition making participation medically hazardous (eg, HIV, preterm labor, evidence of congenital fetal malformation, abnormal fetal

*The MOTHER clinical sites are: Johns Hopkins University School of Medicine, Baltimore, MD (lead site); Thomas Jefferson University, Philadelphia, PA; Vanderbilt University School of Medicine, Nashville, TN; Wayne State University, Detroit, MI; University of Vermont, Burlington, VT; Alpert School of Medicine at Brown University, Providence, RI; University of Vienna, Vienna, AUSTRIA; University of Toronto, Toronto, CANADA. As of this writing, all sites with the exception of Toronto contributed data from participants for the present analyses.

heartbeat); (2) an acute severe psychiatric condition in need of immediate treatment or which represented an imminent risk to the woman herself or others; (3) a current diagnosis of benzodiazepine or alcohol abuse or dependence according to the E module of the SCID I; (4) regular use of alcohol or benzodiazepines in the past 30 days (as determined by Addiction Severity Index); (5) a positive alcohol breath test or benzodiazepine positive urine during screening; or (6) pending legal action that could prohibit or interfere with participation. We wished to minimize exposure of the women to alcohol consumption or nonmedical benzodiazepine use because such exposure would confound our ability to quantify the major outcome variable of the study, namely the severity of opioid withdrawal in the neonates.

Potential enrollees in the clinical trial undergo a screening process before randomization. As of this writing, 256 potentially eligible women were approached for participation in the study. Of these, 120 (46.9%) consented to participate in the study, and 111 completed the screening assessment for psychiatric disorders. No women have yet to be excluded for having an acute severe psychiatric condition.

Assessment of Substance Use Disorder

The SCID-E[41] was administered during screening by a trained interviewer to assess current and lifetime substance use disorders. Training on the administration of the SCID-E included a didactic review of DSM-IV criteria for Axis I disorders, a standardized review of the SCID instrument, and observation of videotapes purchased from the test makers. In addition, two mock interviews were reviewed by an expert interviewer[39] for concordance between expert trainer and interviewer. Finally, trainees were required to pass a knowledge assessment pertaining to DSM-IV criteria for substance abuse and/or dependence. Ongoing review of the trained interviewers' administration of the SCID-E is conducted periodically.[39]

Screening for the Presence of Psychiatric Disorders

The Mini International Neuropsychiatric Interview (MINI), a short, structured diagnostic interview,[42] was administered to assess symptoms of DSM-IV Axis I psychiatric disorders. The MINI was designed as a screening instrument, and as such, it yields information that can be used to indicate whether further evaluation for the presence or absence of a psychiatric diagnosis is in order. It has been used in several studies to evaluate the presence of psychiatric conditions in opioid addicts,[43,44] and other substance users in treatment.[45,46]

Psychopharmacologic Medications

As part of the clinical trial, information is routinely gathered on concomitant medications that are prescribed to participants during the course of their pregnancy. This information is extracted from the patient record and transferred to the study's Coordinating Center in a standardized fashion on a weekly basis. Complete information on medications that were prescribed was available on 96 of the 111 women enrolled in the study at the time of this writing.

Analysis

Descriptive statistics on the frequency of putative psychiatric disorders and psychotropic medications were generated using SPSS, Version 13.0.

Results

Sample Characteristics

Table 1 presents the sociodemographic characteristics of the participants. At the time of this writing, these participants represent seven of the eight MOTHER clinical sites (The Toronto site had not yet begun participant screening). The mean age of the sample was 27.7 years old;

a majority had never been married, and approximately half (46.8%) had less than a high school degree. The vast majority were White and unemployed.

Psychiatric Diagnosis Screening Results

Table 2 presents the results from the MINI. The first column of percentages denotes the frequency with which each item was endorsed among the sample. The second set of percentages represents the proportion of the sample who met MINI screening criteria for needing further clinical evaluation of the corresponding psychiatric disorder. For example, a little less than a third of women (29.7%) endorsed that they were consistently depressed or down, most of the day, nearly every day, for the past two weeks, and 36.0% had lost interest in things that they previously enjoyed. Continuing with this example, 39.6% met screening criteria for major depressive disorder; namely, having an affirmative response to one or the other of the first two questions. In many cases, multiple symptoms were endorsed, suggestive of the presence of multiple psychiatric conditions.

In this sample, the most common putative psychiatric disorders suggested by subjects' endorsement of screening questions were Hypomania (45.9%), Generalized Anxiety Disorder (43.2%), Major Depressive Disorder and Dysthymia (both 39.6%). Approximately one-quarter of the sample met screening criteria for panic disorder (27.9%) and agoraphobia (26.1%). Less common were Bulimia (9.9%) and Obsessive-Compulsive Disorder (5.4%).

Prescribed Psychoactive Medications

Table 3 provides data on clinically prescribed medications at some point during pregnancy for the subset of 96 participants for whom complete concomitant medication data were available. As can be seen, among the entire sample, 54 participants (56.3%) were prescribed at least one type of medication. The most common class of medication prescribed was anti-anxiety agents (35.4%), followed by SSRIs (24.0%). Less common were mixed neurotransmitter reuptake inhibitors, tricyclics, anti-psychotics, and mood stabilizers. Also presented in Table 3 are the frequencies of prescribed medications within groups of participants with probable psychiatric diagnoses (based on the MINI). From the data available, we cannot determine with certainty if the medication prescribed was for a particular condition, but it is notable that almost three-quarters (71.4%) of participants with a probable diagnosis of major depressive disorder were prescribed some type of medication, with 45.7% prescribed an anti-anxiety agent and about one-third prescribed an SSRI (31.4%). Similarly, 80.0% of women reporting suicidal symptoms were prescribed some type of medication.

Discussion

The current study describes a sample of opioid-dependent pregnant women (n = 111) with respect to their psychiatric symptoms as identified by a brief screening instrument, the Mini-International Neuropsychiatric Interview (MINI) and psychoactive medications prescribed in this patient population. Hypomania, Generalized Anxiety Disorder, Major Depressive Disorder, and Dysthymia were the most common disorders for which psychiatric symptoms were endorsed. The fact that almost three-quarters of the women with symptoms suggesting either depression or generalized anxiety were prescribed medications at some point during their pregnancy suggests that there is little reluctance to treat these women with medication. Our data clearly cannot address the appropriateness of the selected psychopharmacological intervention[47] nor the important assessment of the balance of risk-to-benefit in opioid maintained substance-abusing pregnant women. Namely, the potential risk of pharmacotherapy must be weighed against the risk of untreated maternal psychiatric disorder for the fetus, beneficial effects of opioid agonists on depressive, anxiety, and somatic symptoms, and the availability of non-pharmacological psychosocial treatment approaches that

might offer benefits that persist beyond the treatment period. Nevertheless, this study is unique in that it is the first to report the extent to which opioid-dependent pregnant women are prescribed psychopharmacologic medications.

Several limitations of the study must be acknowledged. The first pertains to an obvious selection bias. Of the 256 women identified, 120 (47%) consented to participate in the study and of these an additional nine women did not complete the screening assessment for psychiatric disorders because of time constraints. Therefore, we cannot state with confidence that the women who provided data for analysis were representative of those who did not consent to participate in terms of manifested psychopathology. The use of the MINI for measurement of psychiatric symptoms is the second limitation of the study. To reduce response burden, the study did not employ extensive measures of psychiatric diagnoses. Rather, the MINI was employed as a screening instrument. Future studies should employ more extensive structured interviews to extend the findings herein. It is possible that the presence of an opiate or other type of substance use disorder exacerbates psychiatric symptoms such that the estimates from this study might overestimate the prevalence of psychiatric disorders. Moreover, it is difficult to disentangle whether psychiatric symptoms reported in our sample are related to significant neurobiological or physiological stresses of pregnancy *per se* or indicative of an underlying psychiatric condition. Ideally, future studies should prospectively measure psychiatric symptoms in the pre-pregnancy period as well as during and through the post-partum period to understand the course of psychiatric symptoms.

Another important limitation is that we did not examine detailed information with respect to the timing of medication during pregnancy, or dose, or whether or not the medication was used consistently. For example, we excluded women who had a diagnosis of benzodiazepine or alcohol abuse or dependence prior to entry into the study, regular alcohol consumption or nonmedical benzodiazepine use in the previous 30 days, or a positive alcohol breath test or benzodiazepine positive urine during the screening period. However, in spite of these selection precautions, some subjects were subsequently prescribed benzodiazepines while participating in the study to manage transient withdrawal and/or anxiety symptoms as shown in Table 3. Because this study is ongoing, future work with larger sample sizes will enable us to conduct more fine-grained analyses including the rationale for choice of benzodiazepines versus antidepressants in this high-risk population. Of note, is the interesting observation that approximately equivalent numbers of patients with putative major depressive disorder were prescribed an anti-anxiety medication (40%) as were prescribed an antidepressant (45.7%). Finally, the current analyses did not examine neonatal outcomes associated with the use of various medications. Subsequent to breaking the blind and examining our primary outcome variables with respect to methadone or buprenorphine exposure, we will have the opportunity to examine the relationship between pharmacologic treatment during pregnancy with antidepressants or anti-anxiety medicines and neonatal outcomes and perhaps the interaction between these agents and opioid agonists.

Given the paucity of literature on the topic of treatment approaches for the management of psychiatric disorders among substance-abusing pregnant women, it is clear that carefully controlled studies are needed to better guide clinical decision-making. Specifically, research is needed to describe the range of treatment approaches for psychiatric disorders in this special population, their relative effectiveness, and how individual characteristics are associated with treatment response. Some symptoms of depression for instance, may be resolved upon adequate treatment of the addiction. Although research data is sparse, it is likely that the presence of psychiatric symptoms during pregnancy would lead to noncompliance with prenatal care and maintenance therapy to reduce drug use.[23] Future prospective studies are needed to explore the degree to which women with co-occurring psychiatric disorders terminate addiction

treatment prematurely, or do not respond to contingency management protocols, for example, to reduce other substance use, such as alcohol, tobacco and cocaine.

As supported by the findings reported here, psychiatric symptoms are widespread and should be treated in the opioid dependent pregnant woman. Although our methods were intended predominantly to screen women who were likely to require further diagnostic assessment for the most common psychiatric diagnoses, the prevalence of *inferred* disorders observed in this sample are consistent with previous reports documenting psychiatric comorbidity in substance-dependent populations. The proportions of women meeting screening criteria for various psychiatric disorders in our study are understandably higher than previous studies of non-addicted pregnant women. Opioid-dependent pregnant women are likely to be experiencing a multitude of stressful life circumstances that serves to exacerbate any underlying psychiatric disorder and increases the likelihood of reporting psychiatric symptoms beyond those related to pregnancy itself.

This study serves as a starting point for thoughtful discussion regarding the balance of risk and benefit in substance-abusing pregnant women. A notable proportion of women who screened positive for psychiatric conditions were not treated with pharmacologic agents. We cannot determine whether upon further evaluation and assessment of the balance of risk and benefit, the clinician made a decision to treat the symptoms with non-pharmacologic interventions or whether the disorder was not severe enough to warrant pharmacotherapy. While pharmacologic agents are available and have been shown to be effective in non-pregnant samples, pregnancy and substance use disorder complicate the clinical picture significantly and change the risk-benefit equation. Given the adverse consequences of untreated mental illness and opioid addiction during pregnancy, the pharmacological treatment of pregnant women is an area of growing research. While older tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs) were presumed to be safe in pregnant women[48–50] and are traditionally the most commonly prescribed medications among pregnant and postpartum patients, clinicians still use this treatment during pregnancy and lactation with caution, as few medications are adequately evaluated for safety and efficacy during pregnancy.[51] Nevertheless, one study reported that as many as 35% of women use psychotropic medications during pregnancy.[52] Newer studies have shown that there are some teratogenic concerns with SSRIs.[53,54] Accordingly, it seems appropriate to also consider the demonstrated long-lasting beneficial effects of cognitive behavioral therapy (CBT) in psychiatric disorders,[55–58] and its potential role in pregnant opioid dependent women.

Another important consideration in the decision to use pharmacologic agents in pregnant women maintained on opioid-substitution therapies is the issue of pharmacologic interaction between methadone and antidepressants.[59–61] Although many studies have identified interactions between methadone and antidepressants in opioid dependent individuals, these results cannot be generalized to pregnant mothers receiving similar treatment. An unresolved issue is whether methadone *per se* (or other maintenance therapy) is associated with decreases in depressive symptoms in pregnant women. The risk/benefit considerations in psychopharmacotherapy remain in flux as our healthcare system changes so that the physician has less available time to see each patient. Recently conducted clinical trials of new antidepressant medications as they are developed show increasingly greater placebo effects, especially in patients in whom depression is complicated by substance use disorders or is not profound.[62] Therefore, it remains to be elucidated when medications beyond *adequate* opioid substitution are needed in depressed opioid dependent pregnant women who have access to good behavioral treatment with careful monitoring.

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References

1. Jones HE, Martin PR, Heil SH, et al. Treatment of opioid-dependent pregnant women: Clinical and research issues. J Subst Abuse Treat.
2. National Institute on Drug Abuse. National Pregnancy and Health Survey: Drug use among women delivering live births: 1992. 1996
3. Sander SC, Hays LR. Prescription opioid-dependence and treatment with methadone in pregnancy. J Opioid Manage 2005;1:91–97.
4. Substance Abuse and Mental Health Services Administration, Office of Applied Studies. The NSDUH Report: patterns and trends in nonmedical prescription pain reliever use: 2002 to 2005. Rockville, MD: Apr 6. 2007
5. Substance Abuse and Mental Health Services Administration, Office of Applied Studies. The NSDUH Report: substance use during pregnancy: 2002 and 2003 update. Rockville, MD: Jun 2. 2005
6. Substance Abuse and Mental Health Services Administration, Office of Applied Studies. Medication-assisted treatment for opioid addiction during pregnancy. In: Bataki, SL.; Kauffman, JF.; Marion, I.; Parrino, MW.; Woody, GE., editors. Treatment Improvement Protocol TIP; no. 43. Center for Substance Abuse Treatment. Medication-assisted treatment for opioid addiction in opioid treatment programs; Rockville, MD: 2005. p. 211-224.
7. Fischer G. Treatment of opioid dependence in pregnant women. Addiction 2000;95:1141–1144. [PubMed: 11092062]
8. Hulse GK, Milne E, English DR, Holman CD. The relationship between maternal use of heroin and methadone and infant birthweight. Addiction 1997;92:1571–1579. [PubMed: 9519499]
9. Hulse GK, Milne E, English DR, Homan CD. Assessing the relationship between maternal opiate use and neonatal mortality. Addiction 1998;93:1033–1042. [PubMed: 9744134]
10. Kandall SR, Doberczak TM, Jantunen M, Stein J. The methadone-maintained pregnancy. Clin Perinatol 1999;26:173–183. [PubMed: 10214548]
11. Kaltenbach K, Berghella V, Finnegan L. Opioid dependence during pregnancy: effects and management. Obstet Gynecol Clin North Am 1998;25:139–151. [PubMed: 9547764]
12. McCarthy JJ, Leamon MH, Parr MS, Anania B. High-dose methadone maintenance in pregnancy: maternal and neonatal outcomes. Am J Obstet Gynecol 2005;193:606–610. [PubMed: 16150249]
13. Fajemirokun-Odudeyi O, Sinha C, Tutty S, et al. Pregnancy outcome in women who use opiates. Eur J Obstet Gynecol Reprod Biol 2006;126:170–175. [PubMed: 16202501]
14. Johnson RE, Jaffe JH, Fudala PJ. A controlled trial of buprenorphine treatment for opioid dependence. JAMA 1992;267:2750–2755. [PubMed: 1578593]
15. Johnson RE, Eissenberg T, Stitzer ML, Strain EC, Liebson IA, Bigelow GE. Buprenorphine treatment of opioid dependence: clinical trial of daily vs. alternate-day dosing. Drug Alcohol Depend 1995;40:27–35. [PubMed: 8746921]
16. Ling W, Wesson DR, Charuvastra C, Klett J. A controlled trial comparing buprenorphine and methadone maintenance in opioid dependence. Arch Gen Psychiatry 1996;53:401–407. [PubMed: 8624183]
17. Johnson RE, Jones HE, Fischer G. Use of buprenorphine in pregnancy: patient management and effects on the neonate. Drug Alcohol Depend 2003;70:S87–S101. [PubMed: 12738353]
18. Jones HE, Johnson RE, Jasinski DR, Milio L. Randomized controlled study transitioning opioid-dependent pregnant women from short-acting morphine to buprenorphine or methadone. Drug Alcohol Depend 2005;78:33–38. [PubMed: 15769555]

19. Fischer G, Ortner R, Rohrmeister K, et al. Methadone vs. buprenorphine in pregnant addicts: a double-blind, double-dummy comparison study. Addiction 2006;101:275–281. [PubMed: 16445556]
20. Cox JL. Psychiatric morbidity and pregnancy: a controlled study of 263 semi-rural Ugandan women. B J Psychiatry 1979;134:401–405.
21. Evans J, Heron J, Francomb H, Oke S, Golding J. Cohort study of depressed mood during pregnancy and after childbirth. BMJ 2001;323:257–260. [PubMed: 11485953]
22. Kennare R, Heard A, Chan A. Substance use during pregnancy: risk factors and obstetric and perinatal outcomes in South Australia. Aust N Z J Obstet Gynaecol 2005;45:220–225. [PubMed: 15904448]
23. Fitzsimons HE, Tuten M, Vaidya V, Jones HE. Mood disorders affect drug treatment success of drug-dependent pregnant women. J Subst Abuse Treat 2007;32:19–25. [PubMed: 17175395]
24. Cutrona CE. Causal attributions and perinatal depression. J Abnorm Psychol 1983;92:161–172. [PubMed: 6863731]
25. Gotlib IH, Whiffen VE, Mount JH, Milne K, Cordy NI. Prevalence rates and demographic characteristics associated with depression in pregnancy and the postpartum. J Consult Clin Psychol 1989;57:269–274. [PubMed: 2785127]
26. Holcomb WL Jr, Stone LS, Lustman PJ, Gavard JA, Mostello DJ. Screening for depression in pregnancy: characteristics of the Beck Depression Inventory. Obstet Gynecol 1996;88:1021–1025. [PubMed: 8942846]
27. O'Hara MW. Social support, life events, and depression during pregnancy and the puerperium. Arch Gen Psychiatry 1986;43:569–573. [PubMed: 3707289]
28. Pajulo M, Savonlahti E, Sourander A, Helenius H, Piha J. Antenatal depression, substance dependency and social support. J Affect Disord 2001;65:9–17. [PubMed: 11426516]
29. Cott AD, Wisner KL. Psychiatric disorders during pregnancy. Int Rev Psychiatry 2003;15:217–230. [PubMed: 15276961]
30. Hilty DM, Kelly RH, Hales RE. Diagnosis and treatment of bipolar disorder in pregnant women. Primary Care Update for OB/GYNs 2000;7:105–112.
31. Kurki T, Hiilesmaa V, Raitasalo R, Mattila H, Ylikorkala O. Depression and anxiety in early pregnancy and risk for preeclampsia. Obstet Gynecol 2000;95:487–490. [PubMed: 10725477]
32. Steer RA, Scholl TO, Hediger ML, Fischer RL. Self-reported depression and negative pregnancy outcomes. J Clin Epidemiol 1992;45:1093–1099. [PubMed: 1474405]
33. Gotlib IH, Whiffen VE. Prospective investigation of postpartum depression: factors involved in onset and recovery. J Abnorm Psychol 1991;100:122–132. [PubMed: 2040762]
34. Lindahl V, Pearson JL, Colpe L. Prevalence of suicidality during pregnancy and the postpartum. Arch Womens Ment Health 2005;8:77–87. [PubMed: 15883651]
35. Weinberg MK, Tronick EZ. The impact of maternal psychiatric illness on infant development. J Clin Psychiatry 1998;59:53–61. [PubMed: 9559760]
36. Zuckerman B, Amaro H, Bauchner H, Coral H. Depressive symptoms during pregnancy: Relationship to poor health behaviors. Am J Obstet Gynecol 1989;160:1107–1111. [PubMed: 2729387]
37. Kelly RH, Danielsen BH, Golding JM, Anders TF, Gilbert WM, Zatzick DF. Adequacy of prenatal care among women with psychiatric diagnoses giving birth in California in 1994 and 1995. Psychiatr Serv 1999;50:1584–1590. [PubMed: 10577877]
38. Kessler RC, McGonagle KA, Zhao S, et al. Lifetime and 12-month DSM-IIIR psychiatric disorders in the United States: Results from the National Comorbidity Survey. Arch Gen Psychiatry 1994;51:8–19. [PubMed: 8279933]
39. Jones HJ, Arria AM, Baewert A, et al. Evolution and innovation in the agonist treatment of opioid-dependent pregnant women: Development of a multi-center randomized controlled clinical trial (*submitted*).
40. Jones HE, Johnson RE, Jasinski DR, et al. Buprenorphine versus methadone in the treatment of pregnant opioid-dependent patients: effects on the neonatal abstinence syndrome. Drug Alcohol Depend 2005;79:1–10. [PubMed: 15943939]
41. First, MB.; Spitzer, RL.; Gibbon, M., et al. Structured clinical interview for DSM-IV Axis I disorders. Biometrics Research, New York State Psychiatric Institute; New York, NY: 1996.

42. Sheehan DV, Lecrubier Y, Sheehan KH, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry 1998;59:22–23. [PubMed: 9881538]
43. Hides L, Lubman DI, Devlin H, et al. Reliability and validity of the Kessler 10 and Patient Health Questionnaire among injecting drug users. Aust N Z J Psychiatry 2007;41:166–168. [PubMed: 17464695]
44. Chiang S, Chan HY, Chang YY, Sun JJ, Chen WJ, Chen CK. Psychiatric comorbidity and gender difference among treatment-seeking heroin abusers in Taiwan. Psychiatry Clin Neurosci 2007;61:105–111. [PubMed: 17239047]
45. Gunter TD, Black DW, Zwick J, Arndt S. Drug and alcohol treatment services effective for methamphetamine abuse. Ann Clin Psychiatry 2004;16:195–200. [PubMed: 15702567]
46. Mitchell JD, Brown ES, Rush AJ. Comorbid disorders in patients with bipolar disorder and concomitant substance dependence. J Affect Disord 2007;102:281–287. [PubMed: 17291591]
47. American Academy on Pediatrics. Committee on Drugs. Use of psychoactive medication during pregnancy and possible effects on the fetus and newborn. Pediatrics 2000;105:880–887. [PubMed: 10742343]
48. Nulman I, Rovet J, Stewart DE, et al. Child development following exposure to tricyclic antidepressants or fluoxetine throughout fetal life: A prospective, controlled study. Am J Psychiatry 2002;159:1889–1895. [PubMed: 12411224]
49. Cohen LS, Rosenbaum JF. Psychotropic drug use during pregnancy: weighing the risks. J Clin Psychiatry 1998;59:18–28. [PubMed: 9559756]
50. Vaswani M, Linda FK, Ramesh S. Role of selective serotonin reuptake inhibitors in psychiatric disorders: a comprehensive review. Prog Neuropsychopharmacol Biol Psychiatry 2003;27:85–102. [PubMed: 12551730]
51. Battle CL, Zlotnick C, Miller IW, Pearlstein T, Howard M. Clinical characteristics of perinatal psychiatric patients: a chart review study. J Nerv Ment Dis 2006;194:369–377. [PubMed: 16699387]
52. Zeskind PS, Stephens LE. Maternal selective serotonin reuptake inhibitor use during pregnancy and newborn neurobehavior. Pediatrics 2004;113:368–375. [PubMed: 14754951]
53. Moses-Kolko EL, Bogen D, Perel J, et al. Neonatal signs after late in utero exposure to serotonin reuptake inhibitors. JAMA 2005;293:2372–2383. [PubMed: 15900008]
54. Chambers CD, Hernandez-Diaz S, Van Marter LJ, et al. Selective serotonin-reuptake inhibitors and risk of persistent pulmonary hypertension of the newborn. New Eng J of Med 2006;354:579–587. [PubMed: 16467545]
55. Hollon SD, Stewart MO, Strunk D. Enduring effects for cognitive behavior therapy in the treatment of depression and anxiety. Annu Rev Psychol 2006;57:285–315. [PubMed: 16318597]
56. DeRubreis RJ, Hollon SD, Amsterdam JD, et al. Cognitive therapy vs. medication in the treatment of moderate to severe depression. Arch Gen Psychiatry 2005;62:409–416. [PubMed: 15809408]
57. Brent D, Emslie G, Clarke G, et al. Switching to another SSRI or to venlafaxine with or without cognitive behavioral therapy for adolescents with SSRI-resistant depression. The TORDIA randomized controlled trial. JAMA 2008;299:901–913. [PubMed: 18314433]
58. Hollon SD, DeRubreis RJ, Shelton RC, et al. Prevention of relapse following cognitive therapy vs. medications in moderate to severe depression. Arch Gen Psychiatry 2005;62:417–422. [PubMed: 15809409]
59. Draper JC, McCance-Katz EF. Medical illness and comorbidities in drug users: implications for addiction pharmacotherapy treatment. Subst Use Misuse 2005;40:1899–1921. [PubMed: 16282085]
60. Hamilton SP, Nunes EV, Janal M, Weber L. The effect of setraline on methadone plasma levels in methadone-maintenance patients. Am J Addict 2000;9:63–69. [PubMed: 10914294]
61. Torrens M, Castillo C, San L, del Moral E, Gonzalez ML, de la Torre R. Plasma methadone concentrations as an indicator of opioid withdrawal symptoms and heroin use in a methadone maintenance program. Drug Alcohol Depend 1998;52:193–200. [PubMed: 9839145]
62. Nunes EV, Levin FR. Treatment of depression in patients with alcohol or other drug dependence. JAMA 2004;291:1887–1896. [PubMed: 15100209]

TABLE 1

Characteristics of sample (n = 111)

Demographic characteristics	***Mean***	***Sd***
Age	27.7	5.8
Estimated gestational age (weeks)	19.1	6.4
	n	%
Marital status		
Never married	75	67.6
Married	17	15.3
Widowed/divorced/separated	19	17.1
Educational level		
Less than 12 years	52	46.8
High school graduate	38	34.2
More than high school	21	18.9
Race/ethnicity		
White	94	84.7
Black/African American	17	15.3
Employment status		
Employed	14	12.7
Unemployed	95	86.4
Disabled	1	0.9
Missing	1	0.9
Other current drug dependence in addition to opioid dependence		
Cocaine	28	25.9
Cannabis	10	9.3

TABLE 2

Frequency of putative psychiatric disorders based on screening items from the mini-international neuropsychiatric interview (MINI) (*n* =111)

Individual MINI items	*n* ("yes")	%	Corresponding probable psychiatric diagnosis	*n*	%
1. Have you been consistently depressed or down, most of the day, nearly every day, for the past two weeks?	33	29.7	Major Depressive Disorder: yes" to #1 OR #2	44	39.6
2. In the past two weeks, have you been much less interested in most things or much less able to enjoy the things you used to enjoy most of the time?	40	36.0			
3. Have you felt sad, low or depressed most of the time for the last two years?	44	39.6	Dysthymia: "yes" to #3	44	39.6
4. In the past month did you think that you would be better off dead or wish you were dead?	18	16.2	Suicidality: "yes" to #4	18	16.2
5. Had you ever had a period of time when you were feeling 'up' or 'high' or 'hyper or so full of energy or full of yourself that you got into trouble, or that other people thought you were not your usual self? (Do not consider times when you were intoxicated on drugs or alcohol.)	26	23.4			
6. Have you ever been persistently irritable, for several days, so that you had arguments or verbal or physical fights, or shouted at people outside your family? Have you or others noticed that you have been more irritable or overreacted, compared to other people, even in situations that you felt were justified?	43	38.7	Hypomanic episode: "yes" to #5 OR #6	58	45.9
7. Have you, on more than one occasion, had spells or attacks when you suddenly felt anxious, frightened, uncomfortable or uneasy, even in situations where most people would not feel that way? Did the spells surge to a peak, within 10 minutes of starting?	31	27.9	Panic disorder: "yes" to #7	31	27.9
8. Do you feel anxious or uneasy in places or situations where you might have a panic attack or panic-like symptoms, or where help might not be available or escape might be difficult: like being in a crowd, standing in a line (queue), when you are away from home or alone at home, or when crossing a bridge, traveling in a bus, train, or car?	29	26.1	Agoraphobia: "yes" to #8	29	26.1
9. In the past month, were you fearful or embarrassed being watched, being the focus of attention, or fearful of being humiliated. This includes things like speaking in public, eating in public or with others, writing while someone watches, or being in social situations?	24	21.6	Social Phobia/Social Anxiety Disorder: "yes" to #9	24	21.6
10. In the past month, have you been bothered by recurrent thoughts, impulses, or images that were unwanted, distasteful, inappropriate, intrusive, or distressing? (e.g., the idea that you were dirty, contaminated or had germs, or fear of contaminating others, or fear of harming someone even though you didn't want to, or fearing you would act on some impulse, or fear of suspicions that you would be responsible for things going wrong, or obsessions with sexual thoughts, images	13	11.7	Obsessive-Compulsive Disorder: "yes" to #10 and #11	6	5.4

Individual MINI items	*n* ("yes")	%	Corresponding probable psychiatric diagnosis	*n*	%
or impulses, or hoarding, collecting, or religious obsessions.)					
11. In the past month, did you do something repeatedly without being able to resist doing it, like washing or cleaning excessively, counting or checking things over and over, or repeating, collecting, or arranging things, or other superstitious rituals?	20	18.0			
12. Have you ever experienced or witnessed or had to deal with an extremely traumatic event that included actual or threatened death or serious injury to you or someone else?	55	49.5	Post Traumatic Stress Disorder: "yes" to #12 and #13	20	18.2
13. During the past month, have you re-experienced the event in a distressing way (such as, dreams, intense recollections, flashbacks or physical reactions)?	22	20.0			
14. In the past three months, did you have eating binges or times when you ate a very large amount of food within a 2-hour period?	11	9.9	Bulimia Nervosa: "yes" to #14	11	9.9
15. Have you worried excessively or been anxious about several things over the past 6 months?	48	43.2	Generalized Anxiety Disorder: "yes" to #15	48	43.2

TABLE 3

Medication classes prescribed for participants by probable psychiatric diagnosis based on the MINI

Medication class[1] (total number of individuals prescribed)	Probable psychiatric diagnosis based on MINI											
	Major depressive disorder (*n*= 35)		Dysthymia (*n* = 38)		Suicidality (*n* = 15)		Mania (*n* =41)		Panic disorder (*n* = 35)		Social anxiety disorder (*n* = 18)	
	n	%	n	%	n	%	n	%	n	%	n	%
Anti-anxiety (*n* = 34)	16	**45.7**	14	**36.8**	5	**33.3**	17	**41.5**	16	**45.7**	9	**50.0**
SSRI (*n* = 23)	11	**31.4**	12	**31.6**	7	**46.7**	15	**36.6**	14	**40.0**	8	**44.4**
Mixed Neurotransmitter Reuptake Inhibitors (*n* = 4)	2	**5.7**	3	**7.9**	4	**4.2**	2	**4.9**	1	**2.9**	1	**5.6**
Tricyclics (*n* = 3)	1	**2.9**	1	**2.6**	0	**0.0**	3	**7.3**	3	**8.6**	0	**0.0**
Anti-psychotics (*n* = 7)	3	**8.6**	2	**5.3**	1	**6.7**	5	**12.2**	4	**11.4**	3	**16.7**
Mood Stabilizers (*n* = 5)	2	**5.7**	3	**7.9**	1	**6.7**	3	**7.3**	4	**11.4**	0	**0.0**
Any Medication (*n* = 54)	25	**71.4**	25	**65.8**	12	**80.0**	29	**70.7**	27	**27.9**	15	**83.3**

Medication Class, cont.	Probable psychiatric diagnosis based on MINI							
	Obsessive-compulsive disorder (*n* = 20)		Post-traumatic stress disorder (*n* = 45)		Eating disorder (*n* = 8)		Generalized anxiety disorder (*n* = 39)	
	n	%	n	%	n	%	n	%
Anti-anxiety	9	**45.0**	17	**37.8**	4	**50.0**	17	**43.6**
SSRI	9	**45.0**	9	**20.0**	4	**50.0**	14	**35.9**
Mixed Neurotransmitter Reuptake Inhibitors	3	**15.0**	1	**2.2**	1	**12.5**	3	**7.7**
Tricyclics	2	**10.0**	2	**4.4**	0	**0.0**	3	**7.7**
Anti-psychotics	2	**10.0**	4	**8.9**	1	**12.5**	3	**7.7**
Mood stabilizers	2	**10.0**	3	**6.7**	0	**0.0**	4	**10.3**
Any medication	15	**75.0**	25	**55.6**	6	**75.0**	29	**74.7**

[1] Anti-anxiety: buspirone, clonazepam, diazepam, hydroxyzine, lormetazepam, midazolam, oxazepam, passedan tropfen (Austria), Zolpidem; SSRI (Selective Serotonin Reuptake Inhibitors): citalopram, escitalopram oxalate, fluoxetine, paroxetine, sertraline; Mixed Neurotransmitter Reuptake Inhibitors: buproprion; Tricyclic Antidepressants: doxepin; Anti-psychotics: olanzapine, quetiapine fumarate, trazadone Mood Stabilizers: lamotrigine, lithium carbonate.