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Discontinuation of Antidepressants During Attempts to Conceive:

A Pilot Trial of Cognitive Behavioral Therapy for the Prevention of Recurrent Depression

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Abstract

Background—Many women discontinue antidepressants (ADs) when trying to conceive, although risk of depressive relapse is high. We examined the feasibility and potential clinical effect of cognitive behavioral therapy for the prevention of recurrence (CBT-PR) for women with a history of recurrent major depressive disorder (MDD) who planned to discontinue maintenance AD treatment for pregnancy.

Methods—This was an open preliminary study of CBT-PR in women (N = 12) planning or early in pregnancy with remitted MDD on maintenance ADs with a plan to discontinue ADs for pregnancy. Participants received 12 sessions of CBT-PR during the acute phase and optional monthly booster sessions during follow-up. Participants were assessed monthly during the acute phase and then twice additionally during follow-up by an independent rater using mood scales (depression module of the Mini-International Neuropsychiatric Interview and Montgomery-Åsberg Depression Rating Scale); pregnancy status was also assessed.

Results—Over the 24 weeks of the trial, 75% (n = 9) of participants did not restart ADs and did not relapse to depression. Of the 3 who reintroduced AD, 2 experienced a depressive relapse, whereas one did not meet full criteria for MDD. Adherence to the intervention was very good with all participants completing all therapy sessions and assessments.

Conclusions—Cognitive behavioral therapy for the prevention of recurrence seems feasible and may provide protection for women with recurrent depression on ADs who discontinue their medication while trying to conceive. The extent to which euthymia is sustainable with CBT-PR requires further study; the results of which may broaden treatment choices for women in anticipation of and during pregnancy.

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Keywords

CBT; depression; pregnancy; antidepressants; behavior therapy

Major depressive disorder (MDD) is a debilitating illness that affects approximately 20% of reproductive-age women.^{1,2} Despite the lack of supporting data, pregnancy has historically been considered protective against both the emergence and recurrence of depressive symptoms. Contrary to this belief, both epidemiological and prospective data suggest that pregnancy may be a time of great risk for both recurrence and new-onset depression. Existing epidemiological studies^{1,3} conducted in pregnant adult women reveal prevalence rates of moderate to severe depressive symptoms ranging from 6.9% to 20%. The risks of untreated depression during pregnancy are significant and may include poor maternal nutrition; inadequate weight gain; poor prenatal care; the use of cigarettes, alcohol, or other substances^{4,5}; and an increased risk for postpartum depression.⁶ Thus, it is particularly critical to effectively manage symptoms of depression during pregnancy.

For women with remitted MDD who discontinue antidepressant (AD) medication to avoid fetal drug exposure, the risk of depressive relapse is high.^{7,8} Discontinuation of maintenance AD treatment is associated with high relapse rates^{9–11} in nonpregnant samples, and this has also been observed in pregnant women.¹ Health care providers and patients must weigh the risks and benefits of AD continuation or discontinuation while considering maternal mental health and the effects of fetal medication exposure on a variety of perinatal obstetrical outcomes.

Data on AD effects on the fetus are vast and reflect a wide range of findings. Many reports of adverse effects of fetal exposure to AD are challenging to interpret given the difficulty in delineating the contribution of potential effects of medication exposure on 1 hand and the effects of untreated or partially treated mood and anxiety disorders on the other. Many large studies have shown that there is no significant difference in the risk of congenital malformations with selective serotonin reuptake inhibitor use in pregnancy compared with that in nonexposed controls.^{12,13} Other studies demonstrate that selective serotonin reuptake inhibitor use is linked to adverse perinatal outcomes including increased newborn complications such as neonatal jitteriness, tachypnea, cyanosis and tremulousness, and subsequent special nursery care.^{14–18} Although some reports regarding AD use in pregnancy, such as an increased risk of autism, attention-deficit/hyperactivity disorder, and a negative impact upon neurobehavioral development, have been controversial,^{19–21} they have been highly publicized by the media, which may increase the number of women who may elect to discontinue ADs during pregnancy.

Data from a large-scale, multisite study found no association between the decision to discontinue medication during pregnancy and duration of illness, the number of previous MDD episodes, or the frequency of comorbid psychiatric illness.⁷ Therefore, women with severe MDD are substantially represented among those who are likely to discontinue medication for pregnancy. Medication discontinuation has been associated with a relapse rate of 68% (50% of which occurred during the first trimester) compared with the 26% risk for women who continued maintenance AD medication treatment; rates of medication

discontinuation may be even higher in community treatment settings than in the tertiary care setting studied in this sample. The growing concern around AD use during pregnancy and the data on women's decisions to discontinue their AD compel the scientific community to seek alternative treatments for depression during pregnancy.

Cognitive behavioral therapy (CBT) is a psychosocial treatment that is empirically supported for the treatment of a variety of mood and anxiety disorders. Several large meta-analyses have demonstrated that CBT is an effective treatment of depression and possibly as effective as pharmacotherapy in managing mild to moderate unipolar depression.^{22–24} Cognitive behavioral therapy has also been examined in the context of depressive relapse and recurrence with some success; generally, these studies suggest that CBT-based therapies confer benefit against depressive relapse/recurrence.^{25–30} Recently, 1 study demonstrated that CBT was successful in preventing perinatal depression among women with a history of depression.³¹

Despite the recent attention on psychotherapy for treating depression and the potential for adverse events associated with the use of ADs during pregnancy, there has been no formal examination of the effectiveness of CBT in preventing recurrence in the high-risk population of women with a history of MDD who elect to discontinue AD use during attempts to conceive. The goals of this preliminary study were to examine the preliminary feasibility and potential clinical effect of CBT for the prevention of depressive recurrence in a sample of adult women with a history of MDD who articulated a wish to discontinue AD in anticipation of efforts to become pregnant.

METHODS

Participants

Participants were accessioned via clinical or research contact with the Massachusetts General Hospital (MGH) Center for Women's Mental Health in Boston, MA, or via a referral from another health care provider within the community. Participants were eligible for participation if they (1) were aged 18 years or older, (2) were planning pregnancy or in the first trimester of pregnancy, (3) independently decided to discontinue their AD, (4) were on treatment with a stable dosage of an AD for at least 4 weeks at the time of the first visit, (5) met stable depression remission criteria for at least 6 months and received a score of less than or equal to 9 on the Hamilton Rating Scale for Depression (HRSD), (6) and had a history of a unipolar MDD. Women were ineligible for the study if they (1) demonstrated significant risk for self-harm or harm to others; (2) had psychotic symptoms; (3) met criteria for a primary diagnosis of schizophrenia, bipolar disorder, active eating disorder, dementia, delirium, or other cognitive disorder according to the Mini-International Neuropsychiatric Interview (MINI); (4) had an active substance and or alcohol abuse disorder within 6 months before study entry; (5) were currently using a mood stabilizer, antipsychotic, or antiepileptic; (6) received CBT or interpersonal therapy within the last year; or (7) had recently been diagnosed with a medical disorder that could mimic depressive symptoms (eg, hypothyroidism).

Assessments

Mini-International Neuropsychiatric Interview—The MINI³² is a valid structured diagnostic tool that assesses Axis I and II disorders in accordance with the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, symptom criteria. The MINI was used to establish baseline diagnoses for each participant, and the major depressive episode module was used to ascertain whether or not participants experienced a depressive relapse.

Montgomery-Åsberg Depression Rating Scale—The Montgomery-Åsberg Depression Rating Scale (MADRS)³³ is a 10-item, semistructured assessment designed to measure depression severity and maximize sensitivity to change from treatments. The MADRS was used to establish a more comprehensive rating of depression severity than would be obtained by self-report.

Quality of Life Satisfaction Questionnaire—The Quality of Life Satisfaction Questionnaire (QLESQ) short form³⁴ asks individuals to rate their satisfaction with 13 domains of life, satisfaction with their overall well-being, and overall satisfaction with life on a scale of 1 to 5, whereby 1 represents feeling “not at all or never” satisfied, and 5 represents feeling “frequently or all the time” satisfied. A raw score for the short form is determined by calculating the sum of all items. Raw scores are then converted to a percentage score, whereby 0 equals the least amount of satisfaction, and 100 is the greatest level of satisfaction.

Clinical Global Impression Scale—Two Clinical Global Impression (CGI) ratings³⁵ were used. The first, severity of illness, is an assessment of the patient's current state. The second, global improvement, is an assessment of the participant's improvement from baseline. The CGI severity scores range from 1 (“not ill”) to 7 (“among the most extremely ill”), and the global improvement scale ranges from 1 (“very much improved”) to 7 (“very much worse”).

Hamilton Rating Scale for Depression—17-Item Version—The HRSD is the most widely studied instrument for depression, and its reliability and validity are high.³⁶ The HRSD was used to determine study eligibility only, and participants who achieved a score of 9 or more were excluded from study participation.

Design

All study procedures were approved by the institutional review board of Partners HealthCare/MGH. After a study investigator (MD or PhD) trained in all study procedures described the study to the participants, written informed consent was obtained. The study included 2 phases: an acute phase and a follow-up phase (Fig. 1). For the acute treatment phase, visits included a baseline assessment, 12 sessions of CBT, and bimonthly independent assessments. Assessments monitored both the participant's depressive symptoms using the MINI and the MADRS. Data on reproductive status (eg, trying to conceive, currently pregnant), medications, and fertility treatments (if any) were also collected. Participants could complete up to 3 optional monthly CBT booster sessions (with an additional 2 independent assessments) over the follow-up phase. Although participants were enrolled in

the trial for a period of 1 year, the analyses presented here represent data collected up to 24 weeks of participation. All assessments were performed by a research assistant or trained study clinicians. The research assistants were trained by the study psychologist on how to conduct and assess psychiatric interviews and questionnaires. Assessments were scripted, and training included mock interviews and assessments. The study end point for relapse was defined as meeting the criteria for a current depressive episode according to the MINI or AD treatment reinitiation, even in the absence of meeting criteria for a full depressive episode. In the event of relapse, participants were given the opportunity to continue to receive CBT from the study therapist until a referral for therapy outside the study could be secured.

Drug taper schedules were determined at the baseline visit by participants in collaboration with staff physicians of the MGH Center for Women's Mental Health; taper schedules were determined based on what was clinically appropriate for the medication and the preference of the participant. Typically, doses of medication were tapered at a rate of approximately 25% per week.

Cognitive behavioral therapy sessions were conducted by a PhD level psychologist specifically trained in CBT. The CBT therapy used for this study followed the general principles of CBT with an emphasis on identifying and modifying maladaptive patterns of thinking and behavior that may trigger or expose vulnerabilities for depression, particularly in the context of trying to conceive.³⁷ The acute phase included 6 modules that focused on the following topics: presentation of the CBT model for depression, motivational interviewing, relaxation strategies, activity scheduling, cognitive restructuring, problem solving, and assertiveness. For quality assurance, all sessions were audiotaped.

Data Analyses

Descriptive statistics were conducted to characterize the sample and to describe treatment outcome. Descriptive data on differences between those who relapsed versus those who remained euthymic are also provided.

RESULTS

Characteristics of the Sample

In total, 15 women were screened from July 2009 to June 2011, and 12 participants were enrolled. Three of the screened participants were ineligible for the study because of failure to establish MDD as the primary Axis I diagnosis; 2 of these participants had subsyndromal depression and never met criteria for MDD or minor depressive disorder, whereas the other one had general anxiety disorder as her primary diagnosis. One participant had already stopped her AD 3 weeks before enrollment but was included in the study because she remained euthymic. Of note, 1 participant decided not to attempt pregnancy after completing the acute phase of treatment because of the dissolution of her marriage. Her data are included for the acute phase (when she was planning pregnancy) but are not included for the follow-up phase.

Demographic data for the sample are provided in Table 1. The mean (SD) for age was 34 (3.96) years. Participants had a median of 3 past episodes of major depression (range, 1–15)

and a median of 1 failed attempt at AD discontinuation (range, 0–3). The mean (SD) for MADRS score at baseline for the entire sample at baseline was 5.72 (4.8). Antidepressants being tapered included bupropion (n = 3), sertraline (n = 5), fluoxetine (n = 2), and citalopram (n = 2). The mean (SD) for the length of AD taper was 4.3 (2.53) weeks (range, 1–9 weeks).

Description of Treatment Outcome

During the acute phase, 2 participants experienced a relapse of major depression, and an additional participant reinitiated AD treatment although not meeting full criteria for a major depressive episode. No additional participants relapsed during the booster phase (24 weeks). The mean (SD) for MADRS score at baseline among the participants who relapsed was 9.67 (8.08) and 4.78 (2.64) for the participants who did not relapse or reinitiate AD treatment. The mean CGI severity of illness score for the entire sample was 1.17 (normal) at baseline. Participants who relapsed had a mean (SD) for MADRS score of 15.33 (1.15) and a mean (SD) for CGI score of 3.33 (1.15, mildly ill) at the time of relapse; participants who remained euthymic up to 24 weeks had a mean (SD) for MADRS score of 8.33 (5.61) at the end of the acute phase and 5.5 (5.7) at 24 weeks. At the end of the acute phase, participants who did not relapse had a mean (SD) for CGI severity score of 1.8 (0.83, borderline ill) and 1.15 (0.38, normal) at 24 weeks. Summary data on individual participants, including reproductive status of participants, are provided in Tables 2 and 3.

With respect to quality of life, participants that remained euthymic had a mean (SD) for QLESQ score of 72.44 (12.1), and those who later relapsed had a mean (SD) for QLESQ score of 72.66 (10.33) at baseline. Participants who relapsed had a mean (SD) for QLESQ score of 61.6 (5.75) at the time of relapse; participants who remained euthymic up to 24 weeks had a mean (SD) for general QLESQ score of 62.94 (15.5) at the end of the acute phase and 76.87 (4.78) at 24 weeks.

Illness Characteristics of Relapsers Versus Nonrelapsers

The time to relapse (from the end of AD taper) for the 2 participants who relapsed was 5 weeks and 10 weeks. The participant who reinitiated AD treatment in the absence of a mood episode did so 1 week after completing her AD taper. The mean (SD) for the number of past episodes of major depression for the participants who relapsed or reinitiated AD was 4.1 (1.4) as compared with 4.7 (4.1) for the nonrelapse group. The mean (SD) for the number of past failed attempts to discontinue AD treatment for the participants who relapsed or reinitiated AD treatment was 0 (0) and 1.22 (0.83) for the euthymic group.

Feasibility

Feasibility was operationalized as the number of sessions attended and assessments completed during participation. Of the 9 participants who did not relapse, all participants completed 12 sessions of CBT during the acute phase (within a period of 16 weeks), all optional booster sessions and all study assessments. The 3 participants who met relapse criteria also completed all relevant sessions and assessments until their study end point. As noted previously, participants who relapsed continued meeting with the study therapist until a referral for psychotherapy outside the study could be secured.

DISCUSSION

In this study, the feasibility and potential clinical effect of using CBT to prevent depressive recurrence were evaluated across a small sample of euthymic women on maintenance AD treatment who wished to discontinue their AD given a plan to begin efforts to conceive. All participants completed the full course of treatment, including all sessions (including optional booster sessions) and scheduled assessments, and 75% of participants ($n = 9$) did not relapse after the discontinuation of AD and completion of 12 sessions of CBT for the prevention of recurrence (CBT-PR). Two participants experienced a depressive relapse, and 1 participant restarted ADs without meeting full criteria for a major depressive episode during the acute phase of treatment. No additional participants relapsed through 24 weeks. These findings are consistent with other studies documenting success using CBT to prevent depressive recurrence,^{25–30} although none have attempted to do so in this particular special population.

Although significance testing could not be completed because of the small sample size, there were some apparent differences between those participants who did and did not relapse. First, the average baseline MADRS score for the group that relapsed was higher than the nonrelapse group and fell in the lower end of the “mildly depressed”³³ scoring category for the MADRS (mildly depressed score range is 7–19). Although participants were excluded from the trial if they met the criteria for a depressive episode, higher scores at baseline may represent subsyndromal illness among the participants who eventually relapsed and may be indicative of which women are least likely to tolerate AD discontinuation even when receiving CBT, to which they are adherent. Of note, there was also a slight increase in MADRS scores among those who did not relapse at the end of the acute phase, although this increase was generally resolved at 24 weeks. A similar trend was observed with quality of life, whereby quality of life scores decreased among the nonrelapsers at the end of the acute phase but increased again by 24 weeks. The average score at 24 weeks was higher than at baseline and was still higher than the mean score among a healthy community population.³⁸ The slight worsening of quality of life scores and increase of depressive symptoms may be an artifact of the end of weekly treatment and worry about transitioning into booster sessions while being in various stages of their reproductive goals. Preferences on the number of treatment sessions among this population should be investigated further.

Of note, the 2 participants who relapsed had a documented history of infertility. One participant had recently completed an infertility treatment cycle and was pregnant, whereas the other participant was between treatment cycles at the time of relapse. The participant who reinitiated medication without meeting criteria for a depressive episode had yet to conceive. There is an extensive literature exploring relationships among infertility diagnosis, infertility treatment, and stress.^{39,40} Although the sample size and study design preclude us from drawing conclusions about this observed relationship, women with infertility or difficulty conceiving may be especially vulnerable to depressive recurrence and, as a result, may require more intensive monitoring and intervention. More study is needed regarding risk factors for depressive relapse among women going through infertility treatment.

The current study has several limitations worth noting. The nonrandomized design and small sample size do not allow for conclusions around the causality of treatment effects. In

addition, because of the preliminary nature of this study, a control group was not used. However, naturalistic control data are available for women who discontinue ADs for pregnancy. As previously reported, in a large observational study, approximately 68% of women who discontinued AD treatment for pregnancy relapsed to a depressive episode.⁵ The generalizability of the results is further limited by the sample's homogeneity with respect to certain sociodemographic variables, including race, ethnicity, and level of educational attainment. In addition, most participants had prior experience with psychotherapy; the lasting effects of which may have contributed to their well-being. However, conducting a trial of this kind seems feasible, and preliminary findings suggest that CBT-PR is worthy of further investigation.

CONCLUSIONS

In summary, this was a successful proof of concept study, and CBT-PR may be an effective method of preventing relapse or recurrence of major depression among women who discontinue ADs proximate to attempts to conceive or during pregnancy. It is yet to be determined how long euthymia can be sustained after CBT discontinuation. Further research is needed to characterize women who are able to successfully discontinue AD treatment and sustain euthymia both during the immediate administration of the behavioral intervention and after CBT is discontinued, including women of diverse socioeconomic strata and women with psychiatric comorbidities. Larger scale studies are warranted to increase the breadth of treatment options available to women who have a history of depression and wish to conceive.

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FIGURE 1.
Study timeline.

TABLE 1**Baseline Demographic and Clinical Characteristics of Participants**

Characteristics	
Race, n (%)	
White	11 (91.7)
Asian	1 (8.3)
Ethnicity, n (%)	
Non-Hispanic	11 (91.7)
Hispanic	1 (8.3)
Marital status, n (%)	
Married	12 (100)
Single	0 (0)
Education, n (%)	
Bachelors	1 (8.3)
Some graduate	1 (8.3)
Masters	7 (58.3)
Doctoral	3 (25)
Living children, n (%)	
0	10 (83.3)
1	2 (16.7)
Current infertility treatment, n (%)	
Yes	3 (25)
No	9 (75)
History of miscarriage, n (%)	
0	10 (83.3)
1	1 (8.3)
2	1 (8.3)
History of previous psychotherapy, n (%)	
Yes	11 (91.7)
No	1 (8.3)
Medication, n (%)	
Fluoxetine	2 (16.7)
Sertraline	5 (41.7)
Bupropion	3 (25)
Citalopram	2 (16.7)
Diagnosis, n (%)	
Major unipolar depression	11 (91.7)
Minor unipolar depression	1 (8.3)
Age, mean (SD), y	34 (3.96)
No. ADs tried, mean (SD)	2.33 (1.6)
No. times ADs were discontinued, mean (SD)	1 (0.89)
No. depressive episodes in the last year, mean (SD)	1.1 (1.14)

Characteristics	
Time since last episode, mean (SD), y	9.13 (11.3)
Recurrence of depression after discontinuation, median (range)	1 (0–3)
Lifetime depression	4.3 (1–15)

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TABLE 2

Course of Depressive Symptoms From Baseline to End Point in Subjects Who Relapsed

Participant	MADRS at Baseline	MADRS at Relapse Visit	Time From AD Discontinuation to Relapse/Reinitiation, wk	Reproductive Status At the End of the Acute Phase
A	19	16	10	Pregnant
B	5	14	5	Not pregnant
C *	5	16	1.5	Not pregnant

* Decided to reinitiate treatment without meeting criteria for relapse according to the MINI.

TABLE 3

Course of Depressive Symptoms From Baseline to End Point in Subjects Who Remained Euthymic

Participant	MADRS at Baseline	MADRS at Visit 12 wk	MADRS at 24 wk	Reproductive Status at the End of 24 wk in Study
D	5	19	11	Not pregnant
E	5	4	3	Pregnant
F [*]	5	11	8	Pregnant
G	2	10	2	Pregnant
H	0	3	0	Pregnant
I	4	4	13	Not pregnant
J	9	13	16	Pregnant
K	6	9	4	Pregnant
L	7	2	0	Pregnant

* Already pregnant at baseline interview.