Safety, Tolerability, and Clinical Effect of Low-Dose Buprenorphine for Treatment-Resistant Depression in Midlife and Older Adults

Jordan F. Karp, MD; Meryl A. Butters, PhD; Amy E. Begley, MA; Mark D. Miller, MD; Eric J. Lenze, MD; Daniel M. Blumberger, MD; Benoit H. Mulsant, MD; and Charles F. Reynolds III, MD

ABSTRACT

Objective: To describe the clinical effect and safety of low-dose buprenorphine, a κ-opioid receptor antagonist, for treatment-resistant depression (TRD) in midlife and older adults.

Method: In an 8-week open-label study, buprenorphine was prescribed for 15 adults aged 50 years or older with TRD, diagnosed with the Structured Clinical Interview for *DSM-IV*, between June 2010 and June 2011. The titrated dose of buprenorphine ranged from 0.2–1.6 mg/d. We assessed clinical change in depression, anxiety, sleep, positive and negative affect, and quality of life. The Montgomery-Asberg Depression Rating scale (MADRS) served as the main outcome measure. Tolerability was assessed by documenting side effects and change in vital signs, weight, and cognitive function. Clinical response durability was assessed 8 weeks after discontinuation of buprenorphine.

Results: The mean dose of buprenorphine was 0.4 mg/d (mean maximum dose = 0.7 mg/d). The mean depression score (MADRS) at baseline was 27.0 (SD = 7.3) and at week 8 was 9.5 (SD = 9.5). A sharp decline in depression severity occurred during the first 3 weeks of exposure (mean change = −15.0 [SD = 7.9]). Depression-specific items measuring pessimism and sadness indicated improvement during exposure, supporting a true antidepressant effect. Treatment-emergent side effects (in particular, nausea and constipation) were not sustained, vital signs and weight remained stable, and executive function and learning improved from pretreatment to posttreatment.

Conclusion: Low-dose buprenorphine may be a novel-mechanism medication that provides a rapid and sustained improvement for older adults with TRD. Placebo-controlled trials of longer duration are required to assess efficacy, safety, and physiologic and psychological effects of extended exposure to this medication.

Trial Registration: ClinicalTrials.gov identifier: NCT01071538

J Clin Psychiatry 2014;75(8):e785–e793

Submitted: *August 8, 2013; accepted January 14, 2014 (doi:10.4088/JCP.13m08725).*
Corresponding author: *Jordan F. Karp, MD, WPIC, 3811 O'Hara St, Pittsburgh, PA 15213 (karpjf@upmc.edu).*

Conventional treatment of major depressive disorder (MDD) to complete remission often takes many months and may be associated with persistent depressive symptoms, elevated risk of suicide, dropping out of care, and worsening medical comorbidities. Over 50% of midlife and older adults with depression fail to respond to traditional antidepressants.[1,2] Treatment-resistant depression (TRD)—syndromal depression that does not respond to standard monoaminergic medications such as selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs)—often presents a therapeutic dilemma, given the lack of evidence-based alternative pharmacotherapies to traditional monoaminergic antidepressants.[3] When monoaminergic agents are ineffective at eliciting a full response for older patients with TRD, augmentation pharmacotherapy using medications with a unique mechanism of action and rapid onset may offer relief.

Modulation of the opiate system may be a novel treatment approach for TRD. It is established that opiate receptor subtypes modulate regulation of serotonin in the mammalian midbrain, raphe, and forebrain.[4] Indeed, the periaqueductal gray matter, an area rich in opiate receptors, receives projections from the amygdala, frontal cortex, and locus ceruleus, suggesting reciprocal modulation of the opiate and monoaminergic systems.[5] Owing to the observed euphoric, tranquilizing, and antianxiety actions of opioids, a functional deficiency of endogenous opioids has been postulated to underlie the pathogenesis of endogenous depression. This is supported by observations of mood improvement in midlife patients treated with cyclazocine (a mixed agonist/antagonist opioid),[6] β-endorphin infusions,[7] and a synthetic enkephalin analog.[8]

Buprenorphine is a partial agonist at μ-opiate receptors and an antagonist of κ-opiate receptors, and it also displays affinity for δ-opiate receptors. Buprenorphine has a favorable safety profile with low risk of respiratory depression, and the pharmacokinetics are not affected by advanced age or renal dysfunction, supporting its use in both midlife and older adults with TRD. The combination of μ-agonism and κ-antagonism produces less dysphoria than methadone,[9] and animal studies suggest that κ-antagonism may exert antidepressant effects.[10] Buprenorphine may also interact with serotonergic systems and the hypothalamic-pituitary-adrenal axis.[11] Rapid improvement in mood has been observed in both younger non–opioid-abusing patients with TRD[12] and opioid-dependent patients treated with buprenorphine.[13] Of particular relevance for TRD, especially in older adults in which cognitive impairment is often comorbid with depression,[14] is that the effects of buprenorphine on cognition may be minimal.[15,16] The unique mechanism of action, potential for early effect, and acceptable safety profile make buprenorphine an intriguing molecule to test in older adults with TRD. In this proof-of-concept, unblinded clinical

Clinical Points

- Low-dose buprenorphine is an intriguing option for some patients with treatment-resistant depression.
- Clinical improvement may be observed early during treatment.

trial, we describe the clinical effect, safety, and tolerability of low-dose buprenorphine for TRD in older adults.

METHOD

Participants

Five subjects were recruited from an ongoing study of depression in adults 60 years or older (MH083660; ClinicalTrials.gov identifier NCT00892047). In that study, participants received unblinded treatment with venlafaxine extended release, with daily doses up to 300 mg, for 12 weeks.[17] Nonresponders (defined as Montgomery-Asberg Depression Rating Scale [MADRS][18] score ≥ 10) to this regimen were declared treatment resistant and offered participation in this 8-week buprenorphine pilot study. We define these subjects as treatment resistant because of the serotonergic and noradrenergic pharmacodynamic activity of venlafaxine at this higher dosing range and the rigor with which participants were monitored and adherence maintained.[17] The mean Antidepressant Treatment History Form (ATHF)[19] score for these 5 participants prior to exposure to venlafaxine was 3.6 (SD = 0.55; median = 4), indicating that they had received at least 1 rigorous trial of an antidepressant prior to exposure to the high-dose venlafaxine.

Entrance criteria were subsequently expanded to include retrospectively defined TRD: community-dwelling subjects 50 years or older who had not responded to at least 2 different antidepressants, prescribed at a US Food and Drug Administration (FDA)–approved therapeutic dose, each for at least 6 weeks. Similar to the initial 5 subjects, all 10 of these additional subjects met Structured Clinical Interview for *DSM-IV* (SCID)[20] criteria for MDD, recurrent or single episode, and had a MADRS score ≥ 15 at baseline. Recruitment occurred between June 2010 and June 2011.

All participants also met the following entry criteria: (1) not using strong or moderate cytochrome P450 3A4 inhibitors, (2) agreed to discontinue use of all opioids and alcohol, and (3) agreed to discontinue benzodiazepines other than the equivalent of lorazepam 2 mg/d that had been stably prescribed for at least 2 weeks. Subjects could not have (1) lung disease requiring supplemental oxygen other than continuous positive airway pressure for obstructive sleep apnea; (2) estimated creatinine clearance < 30 mL/min; (3) hepatic impairment (aspartate aminotransferase or alanine aminotransferase > 1.5 times upper limit of normal); (4) dementia, as defined by Mini-Mental State Examination (MMSE)[21] score < 24 and clinical evidence of dementia; (5) lifetime diagnosis of bipolar or psychotic spectrum disorder; (6) abuse of or dependence on alcohol or other substance within the past 3 months as determined by SCID; (7) lifetime history of opioid abuse or dependence (to avoid precipitating relapse); or (8) high risk for suicide. All subjects were deemed medically stable by history and physical examination prior to entering the study.

Subjects were assessed in person weekly. All participants provided written informed consent. This project was approved and monitored by both the University of Pittsburgh Institutional Review Board and the FDA (IND 107,835). The study was registered with ClinicalTrials.gov (identifier: NCT01071538).

Assessments

Diagnostic and medical. We used the SCID[20] to assess current and lifetime depression and other psychiatric disorders. Our group has maintained high interrater reliability with formalized training and a weekly multidisciplinary consensus conference at which final diagnoses are adjudicated.[22] We used the MMSE to screen for cognitive impairment. The quality of antidepressant pharmacotherapy for this episode of depression was quantified with the ATHF.[19]

Clinical. The MADRS was designed to assess treatment-sensitive change in MDD and served as the main outcome measure for this study. We administered the MADRS using a published structured interview[23] and maintained an intraclass correlation coefficient [ICC] of 0.99 among 12 raters with backgrounds ranging from bachelor's degree to geriatric psychiatrist. The anxiety subscale of the Brief Symptom Inventory (BSI-anxiety) is a validated self-report scale derived from the Symptom Checklist 90-Revised with strong construct validity, internal consistency, and test-retest reliability.[24] We have reported that the BSI-anxiety has good internal consistency in older subjects with MDD (Cronbach $\alpha = 0.84$).[25] The Positive and Negative Affect Scales were used to assess emotional valence. These scales have high internal consistency, are largely uncorrelated, and are stable over a 2-month time period.[26] The 21-item Scale for Suicide Ideation[27] has been shown to predict completed suicide[28] and has moderately high internal consistency, with Cronbach alphas ranging from 0.84 to 0.89, and good interrater reliability.[27,29] At every visit, 5 screening questions from the Scale for Suicide Ideation were asked after the MADRS. If participants screened positive on any of these questions, the full Scale for Suicide Ideation was administered, and appropriate clinical action was implemented to assure participant safety. Weekly assessments were conducted at week 0 (pretreatment) up to week 8 (termination).

Cognitive assessments. We assessed attention, psychomotor speed, executive function, and learning and memory, cognitive domains that may be affected by opioids.[30] Before the first observed dose and at termination, we used 2 computerized tasks with repeatable conditions: a choice reaction time task and a congruous vs incongruous conditions reaction time task, which have been described in detail elsewhere.[31]

The variables that we examined from each task include (1) accuracy (a basic measure of attention), (2) response time (a measure of psychomotor speed), and (3) a ratio comparing reaction time on the incongruous trials with that on the choice (which was neutral) reaction time task, which reflects inhibition (an executive function). We assessed memory with the Hopkins Verbal Learning Test-Revised (HVLT-R) at the same timepoints, using alternate versions. The HVLT-R probes learning and memory, providing an evaluation of the learning process and the amount of information that is both acquired and retained.[32]

Tolerability, safety, and cognition. The Udvalg for Kliniske Undersogelser (UKU) Side Effect Rating Scale[33] was used to capture specific side effects putatively related to buprenorphine. At our geriatric depression research center, we have yearly retraining in the use of this scale. At our last reliability testing, the ICC was 0.91. General burden of side effects was assessed with the Frequency, Intensity, and Burden of Side Effects Rating (FIBSER) scale.[34] The MADRS and FIBSER scores were used to guide the weekly dose of buprenorphine (see Dosing Schedule and Response Criteria).

Sitting and standing blood pressure, heart rate, and weight were assessed at every visit. Orthostasis was defined as a systolic blood pressure drop of at least 20 mm Hg or an increase in heart rate of at least 10 bpm.[35]

Quality of life and sleep. We used the Medical Outcomes Study Short Form-36 (SF-36)[36,37] to assess health-related quality of life. The SF-36 provides an assessment of overall physical and mental quality of life and 8 individual subscales: general health, physical functioning, mental health, vitality, pain, social functioning, role limitations due to physical health, and role limitations due to emotional health. Sleep quality was assessed with the Pittsburgh Sleep Quality Index (PSQI).[38] A global PSQI score > 5 distinguishes good from poor sleepers. The SF-36 and PSQI were administered monthly.

Follow-up. We used the Clinical Opiate Withdrawal Scale (COWS)[39] to monitor for signs and symptoms of withdrawal during the 2 weeks of discontinuation of buprenorphine. The MADRS was repeated at week 16 (8 weeks after discontinuation of buprenorphine).

Dosing Schedule and Response Criteria

Buprenorphine was administered in 0.2-mg sublingual tablets. The first dose was administered under supervision, and subjects were reassessed 60 minutes later to assure they were not sedated or nauseated prior to leaving the clinic. For the first week, subjects took 0.2 mg/d, usually in the morning. Weekly dosing was guided by severity of depressive symptoms (MADRS) and buprenorphine-associated side effects.

Dosing was guided by MADRS and FIBSER scores. If the MADRS score was ≤ 10, the dose was unchanged. If the MADRS score was > 10 and the FIBSER score was ≤ 7, the dose was increased by 0.2 mg/d. If the MADRS score was > 10 and the FIBSER score was > 7, the dose was unchanged. Response was defined as MADRS score ≤ 10. A score of 5 to 7 on the FIBSER[34] triggered additional assessment of side effects and required justification for increasing the dose, while a score of > 7 signaled no increase in dose. At the end of 8 weeks, buprenorphine was discontinued by decreasing the dose about 20% every 2–3 days.

Statistical Analysis

Baseline demographic variables and clinical differences of participants were summarized using mean (standard deviation) for continuous variables and n (%) for categorical measures. Safety, side effects, cognitive function, and clinical measures were examined over time. Clinically meaningful definitions of safety and side effects were established, and the numbers and percentages of subjects meeting the criteria are reported. Graphs show group mean data superimposed on the individual trajectories for each subject. Preintervention-to-postintervention changes in cognitive function were tested using Wilcoxon signed rank exact test.

RESULTS

Fifteen subjects entered the study, of whom 13 provided 8 weeks of complete data in the analyses reported here. One subject stopped taking the medication at week 3 due to reported "constipation and bloating." One subject was withdrawn from participation because of worsening chronic suicidal ideation that was related to an exacerbation of psychosocial stressors. Baseline descriptors of the sample are included in Table 1. The mean daily dose was 0.40 mg (SD = 0.21; median = 0.40 mg; range, 0.12–0.83 mg), with a mean maximum daily dose of 0.69 mg (SD = 0.37; median = 0.60 mg; range, 0.20–1.40 mg).

Clinical Effect

Depression. Figure 1 shows the change in depression. The mean depression score (MADRS) at baseline was 27.0 (SD = 7.3; median = 25; range, 18–42; n = 15) and at week 8 was 9.5 (SD = 9.5; median = 7; range, 0–33; n = 13). There was a sharp decline in depression severity during the first 3 weeks of exposure (mean change = −15.0 [SD = 7.9; median = −16; range, −25 to 2; n = 14]). To explore whether this improvement was specific to core depressive symptoms, we plotted MADRS items measuring pessimistic thoughts and reported sadness. The trajectories for these 2 items match the trajectory for the total MADRS score (Figure 1) and represent depression-specific clinical improvements. Response, defined as MADRS score ≤ 10 at any week, was observed for 10 of 15 participants (66.7%; 95% CI, 38.7%–87.0%). Response at the end of 8 weeks was observed for 8 of 13 participants (61.5%; 95% CI, 32.3%–84.9%).

Discontinuation and follow-up. We used the COWS during the 4 weeks of buprenorphine discontinuation. None of the subjects experienced clinically significant withdrawal symptoms. The mean score on the COWS during discontinuation was 1.9 (SD = 1.3; median = 1.6; range, 0.3–4.3; n = 12), indicating clinically insignificant symptoms of withdrawal. Participants were contacted at week 16 (usually by telephone) to assess the durability of the antidepressant

Table 1. Baseline Descriptors of the Sample (N = 15)

	Total Group (N = 15)	Augmentation (n = 13)	Monotherapy (n = 2)[a]
Age, y			55.7 (A)/69.2 (B)
Mean (SD)	60.7 (5.6)	60.4 (5.3)	
Range	51.1–69.2	51.1–69.2	
Female, n (%)	8 (53.3)	7 (53.85)	1 (50.0)
Caucasian, n (%)	15 (100)	13 (100)	2 (100)
Medical Outcomes Study Short Form-36[b]			
Mental component score			24.6 (A)
Mean (SD)	27.7 (8.2)	28.1 (8.6)	
Range		14.6–42.6	
Physical component score			32.7 (A)
Mean (SD)	41.5 (9.4)	42.5 (9.4)	
Range		31.9–56.8	
Mini-Mental State Examination/30[c]			29.0 (B)
Mean (SD)	28.5 (1.8)	28.5 (1.9)	
Range		24–30	
Pittsburgh Sleep Quality Index			17 (A)/10 (B)
Mean (SD)	9.9 (3.5)	9.4 (3.2)	
Range		5–15	
Duration of current episode, wk			2,626 (A)/3,502 (B)
Mean (SD)/median	987.9 (1,125.5)/572	668.5 (785.5)/260	
Range	6–3,502	6–2,264	
History of substance abuse or dependence, n			
Alcohol	4	2	2
Cocaine	1	1	0
Alcohol, cannabis, cocaine	1	1	0
Antidepressant Treatment History Form[d]			3 (B)
Mean (SD)	3.7 (0.5)	3.8 (0.5)	
Range		3–4	
Montgomery-Asberg Depression Rating Scale			42 (A)/23 (B)
Mean (SD)	27.0 (7.3)	26.2 (6.4)	
Range		18–37	
Scale for Suicide Ideation			10 (A)
Mean (SD)	3.7 (6.6)	3.2 (6.6)	
Range		0–21	
Positive and Negative Affect Scale			
Negative right now			12 (A)/28 (B)
Mean (SD)	21.1 (8.2)	21.3 (8.2)	
Range		13–37	
Positive right now			12 (A)/16 (B)
Mean (SD)	21.5 (8.6)	22.7 (8.7)	
Range		10–40	
Brief Symptom Inventory—anxiety subscale			1.7 (A)/1.5 (B)
Mean (SD)	1.1 (0.7)	1.1 (0.7)	
Range		0–2.7	
UKU Side Effect Rating Scale			18 (A)/10 (B)
Mean (SD)	12.0 (3.8)	11.7 (3.7)	
Range		5–16	

[a](A) and (B) used to differentiate between the 2 subjects in the monotherapy group.
[b]Total group, n = 10; augmentation group, n = 9.
[c]Total group, n = 12; augmentation group, n = 11.
[d]Total group, n = 13; augmentation group, n = 12.

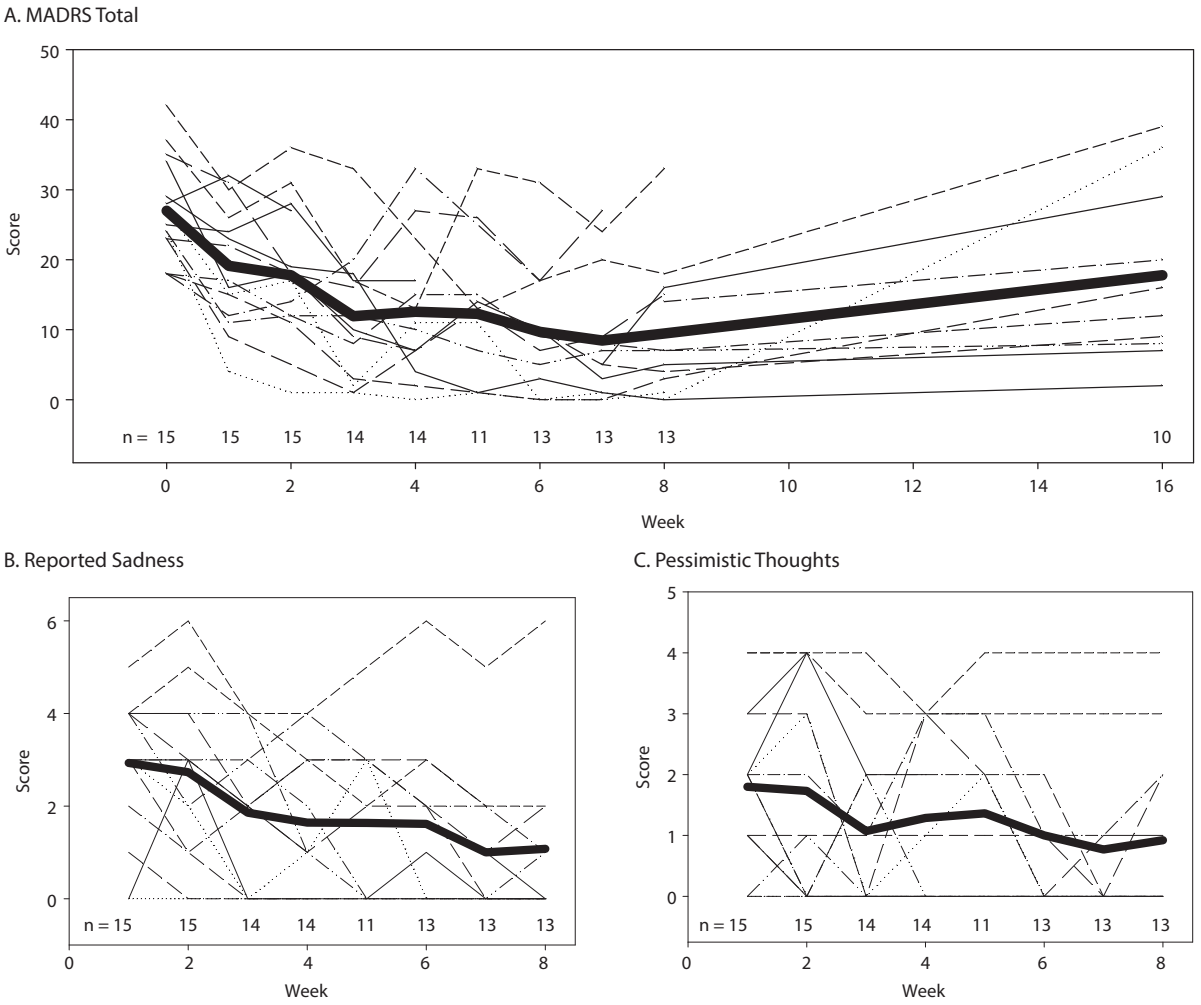
effect. Of note, 3 of the participants were continuing to take low-dose buprenorphine, obtained from their psychiatrists, after the first 8 weeks. The mean MADRS score (excluding those who continued to take buprenorphine) at week 16 was 17.8 (SD = 12.9; median = 14; range, 2–39; n = 10).

Cognitive Function

Neuropsychological assessment. On the choice reaction time task, mean accuracy (which was at or near the test ceiling) and mean reaction time did not significantly change over the 8-week trial. On the congruous versus incongruous reaction time task, mean accuracy did not significantly change over the 8-week trial, but mean reaction time improved (ie, reaction time became faster) on both the congruous and incongruous conditions, suggesting improvement in psychomotor speed. The ratio of incongruous to congruous choice reaction time revealed a trend for improvement across the 2 timepoints (baseline = 1.38 [SD = 0.23, median = 1.36] vs week 8 = 1.15 [SD = 0.23, median = 1.25]; Wilcoxon signed rank exact $P = .10$), suggesting improvement in the ability to inhibit automatic responses in favor of more effortful responses (Table 2).

HVLT-R. We observed improvements in all 4 HVLT-R measures (trials 1–3 [learning], trial 4 [delayed recall]), percentage of words learned that were retained over 20-minute delay (delayed recall), and recognition discriminability index (percentage of all words correctly recognized after 20-minute delay) (Table 2).

Figure 1. Individual Subject Trajectories for MADRS Total Score, Reported Sadness, and Pessimistic Thoughts[a]



[a]Bold lines indicate group mean trajectories. Total MADRS graph shows telephone assessment of depression symptoms at week 16 done to assess durability of the antidepressant effect.
Abbreviation: MADRS = Montgomery-Asberg Depression Rating Scale.

Other Outcomes

Figure 2 illustrates change in positive and negative affect, anxiety, sleep, and the mental and physical components of the SF-36. The general trend for all of these outcomes was in the direction of positive response, except for the physical component subscale of the SF-36, which was flat.

Safety and Tolerability

Vital signs and weight. There were no sustained elevations for either systolic or diastolic blood pressure across the 8 weeks of the study. This was observed for both sitting and standing blood pressure. Three subjects experienced a greater than 20-point increase in systolic blood pressure at 1 assessment point during the project. Weight was stable. There were inconsistent changes in weight: 4 of 15 subjects (26.7%) experienced a 5% decrease in weight, and 1 of 15 (6.7%) experienced a 5% increase in weight.

Side effects. A 2-point or greater change for the nausea and constipation items on the UKU Side Effect Rating Scale may be considered clinically significant. Five of the 15 participants had a ≥ 2-point increase on the nausea item. Of these 5 subjects, the mean number of weeks with a higher level of reported nausea was 1.6 (SD = 0.89; median = 1.0). Eight of the participants experienced a ≥ 2-point increase on the constipation item. The mean number of weeks with a higher level of reported constipation was 1.3 (SD = 0.49; median = 1.0).

DISCUSSION

We observed improvement in depression within the first week of starting buprenorphine. This is consistent with another small open-label trial in younger adults using buprenorphine for TRD in which much of the clinical improvement was observed by the end of week 1.[12] The improvement was sustained during exposure to buprenorphine. However, once buprenorphine was discontinued and subjects were reassessed at week 16, the mean MADRS score increased to 17.8, suggesting that the antidepressant benefits of low-dose buprenorphine may require long-term dosing to be sustained.

Table 2. Neuropsychological Changes Between Baseline and Week 8

Measure	Baseline		Week 8		Cohen *D* for Change
	Mean (SD)	Median	Mean (SD)	Median	
Choice reaction time task—accuracy, %	98.1 (5.5)	100	99.4 (1.1)	100	0.33
Choice reaction time task—reaction time, ms	545.1 (174.9)	501.3	555.6 (210.9)	488.9	0.16
Congruous task—accuracy, %	93.6 (16.10)	100	99.7 (0.83)	100	0.33
Congruous task—reaction time, ms	649.7 (182.5)	630.4	562.5 (140.2)	530.65	1.10*
Incongruous task—accuracy, %	89.6 (17.2)	97.5	98.9 (1.82)	100	0.39
Incongruous task—reaction time, ms	709.5 (233.4)	655.7	601.1 (131.2)	596.9	1.00*
HVLT trials 1–3	23.9 (5.5)	23.5	24.8 (5.1)	25.0	0.12
HVLT trial 4	8.3 (2.6)	8.0	9.4 (2.1)	10.0	0.31
HVLT percent retained	88.8 (13.3)	90.9	96.3 (14.6)	95.8	0.32
HVLT recognition discriminability index	10.4 (1.7)	10.5	10.8 (1.6)	11.0	0.05

*$P < .05$.
Abbreviation: HVLT = Hopkins Verbal Learning Test.

Executive function (as represented by inhibition or by impulse control), psychomotor speed, and memory for new information, cognitive domains of particular concern during exposure to opioids, did not worsen during exposure to low-dose buprenorphine. Effective treatment of depression has been shown to improve cognitive function in studies of both midlife and late-life adults.[40] Opioids may worsen cognitive function,[41] but in patients who were not opioid-naive, buprenorphine has been shown to have a neutral effect on cognition.[16] It is a limitation that we do not have psychiatrically normal or opioid-naive control participants with which to compare the repeated testing results, but the lack of slowed (and potentially improved) psychomotor speed, inhibition, and memory suggests that low-dose buprenorphine in this sample of midlife and older adults did not worsen, and may potentially improve, cognitive function.

The results from this pilot project also suggest that low-dose buprenorphine may be safe and well tolerated in midlife and older adults with TRD. The effects on vital signs and weight were not clinically actionable. This is in contrast to work by Johnson et al,[35] who described clinically significant orthostasis among older adults receiving higher-dose venlafaxine. Monoamine oxidase inhibitors, a reasonable and often effective choice for TRD, are frequently associated with increased heart rate and orthostasis.[42,43]

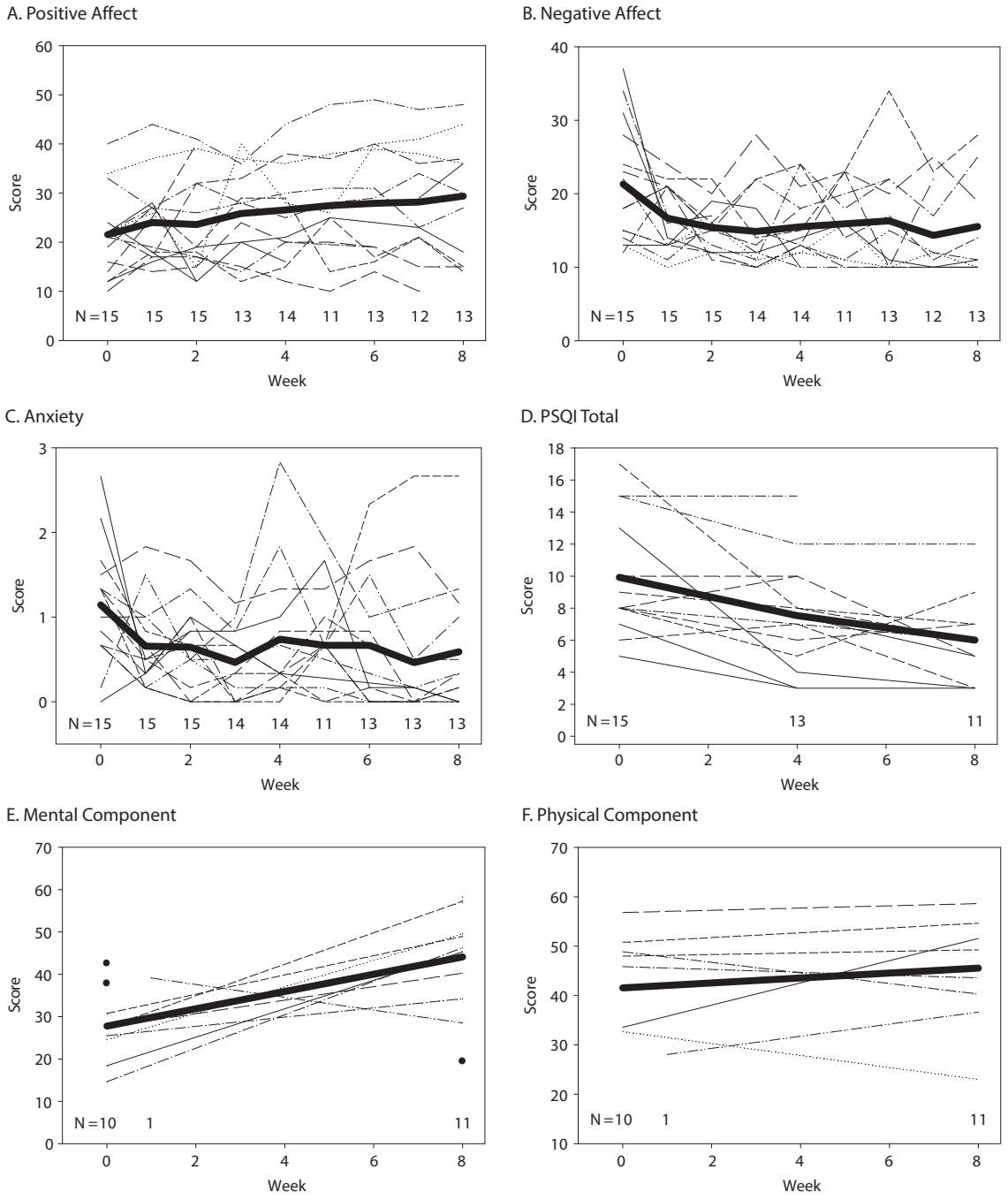
To our knowledge, there are no reports about the effect on weight of chronic administration of opioids in humans. In this study, we did not observe weight gain. This observation is relevant for patient acceptability of antidepressant pharmacotherapy. In a large population-based study with a mean follow-up of 4.8 years, depressed users of antidepressants gained 1.8 times as much as depressed individuals who did not receive antidepressant pharmacotherapy.[44] While it is unclear whether the weight gain was due to depression response and improved appetite or a medication side effect, we observed improvement in depression without increase in weight.

Constipation and nausea are among the most common opioid side effects. Buprenorphine was well tolerated, with relatively minimal effects on these gastrointestinal symptoms. In contrast, 23.4% of patients taking duloxetine, an SNRI, experienced nausea, and 10.1% experienced constipation.[45] Hu and colleagues[46] studied 401 depressed patients prescribed an SSRI: following 75–105 days of treatment, 86% of patients reported 1 or more side effects, while 55% reported at least 1 side effect they considered bothersome. In the report by Hu et al, while most side effects appeared during the first 2 weeks of treatment, the majority of patients continued to experience side effects up to 15 weeks later. Indeed, up to 32% of patients continued to complain of nausea 3 months after starting treatment.

A concern with the use of buprenorphine for TRD is the risk of physiologic dependence. However, in this pilot study, we did not observe clinically significant physiologic or psychological withdrawal when buprenorphine was tapered. This may be a result of the (1) relatively low dose used in the study, (2) brief 8-week duration of the trial, (3) exclusion of participants with a history of opioid dependence, (4) relatively long taper schedule, or (5) partial μ-agonist pharmacodynamics of buprenorphine. Patients treated with FDA-approved antidepressants with relatively short half-lives such as venlafaxine and paroxetine often experience an uncomfortable withdrawal syndrome consistent with physiologic "dependence" on the medication.[47] The risks of untreated TRD, which include the development of psychiatric and substance misuse comorbidity, psychosocial and economic decline, worsened medical comorbidity and early mortality, and suicide, should be taken into account when considering the risk/benefit ratio of a novel treatment. Indeed, when compared to interventions such as electroconvulsive therapy, vagal nerve stimulation, and deep brain stimulation, buprenorphine use in properly selected patients may be considered to have relatively minimal risks. Further research with buprenorphine or similarly acting agents, prescribed for longer duration and at higher doses, is needed to better evaluate safety and ease of discontinuation.

The off-label use of buprenorphine for indications such as pain or depression does not require the currently required waiver from the Center for Substance Abuse Treatment (a component of the Substance Abuse and Mental Health Services Administration). Off-label prescribing does require, however, a valid registration to prescribe a Schedule III controlled substance. Given the lack of placebo-controlled trials indicating the efficacy of buprenorphine for TRD, the authors do not advocate the use of this medication in routine

Figure 2. Individual Subject Trajectories for Positive and Negative Affect, Anxiety, Sleep, and the SF-36 Mental and Physical Components[a]



[a]Bold lines indicate group mean trajectories. Circle symbol indicates subject had only 1 observation.
Abbreviations: PSQI = Pittsburgh Sleep Quality Index, SF-36 = Medical Outcomes Study Short Form-36.

clinical care. That being said, there are patients suffering from TRD who may benefit from a carefully administered trial of this medication. Although we are still learning about the clinical use of buprenorphine for these challenging patients, suggested best practice procedures include, but are not limited to, (1) appropriately screening candidates to minimize the risk of diversion or relapse of an opioid misuse disorder, (2) writing the off-label indication on the prescription (such as "for depression, off-label use"), (3) maintaining meticulous records of all prescriptions, (4) requiring patients use only 1 pharmacy, and (5) obtaining regular urine drug screens to minimize the risk of diversion.

In summary, our study supports the further development of buprenorphine as a novel-mechanism treatment for TRD in midlife and older adults. The findings are limited by the open-label design of the study, which was necessary

given the paucity of safety and efficacy data for low-dose buprenorphine, especially in a sample enriched with older individuals. The lack of ethnic diversity also needs to be remedied in future studies. The next steps in our development of buprenorphine as a novel therapeutic for TRD include a proof-of-concept randomized clinical trial in which we further refine dosing strategies; examine response, safety, and tolerability; and pilot biomarkers of response. We also plan to probe the mechanisms of action of buprenorphine using the imaging, pharmacogenetic, and physiologic tools of modern clinical neuroscience.

Author affiliations: Department of Psychiatry, Western Psychiatric Institute and Clinic (Drs Karp and Reynolds); Department of Psychiatry, University of Pittsburgh School of Medicine (Drs Butters, Miller, and Mulsant and Ms Begley); Department of Behavioral and Community Health Sciences, Graduate School of Public Health, University of Pittsburgh (Dr Reynolds), Pittsburgh, Pennsylvania; Department of Psychiatry, Washington University, St Louis, Missouri (Dr Lenze); and Centre for Addiction and Mental Health and Department of Psychiatry, University of Toronto, Toronto, Ontario, Canada (Drs Blumberger and Mulsant).

Potential conflicts of interest: **Dr Karp** receives medication supplies from Reckitt Benckiser and Pfizer for investigator-initiated trials. **Dr Butters** has served as a consultant for GlaxoSmithKline. **Dr Lenze** has received research support from Forest, Johnson & Johnson, Roche, and Lundbeck, as well as (medications only) Pfizer, Corcept, and Bristol-Myers Squibb. **Dr Blumberger** received research funding from a Canadian Institutes of Health Research Industry Partnered (Brainsway Ltd.) operating grant, the Campbell Family Research Institute, and the Temerty Centre for Therapeutic Brain Intervention. **Dr Mulsant** has received financial support during the past 36 months from the National Institute of Mental Health and the Canadian Institutes for Health Research and pharmaceutical supplies from Bristol-Myers Squibb, Eli Lilly, and Pfizer for his National Institutes of Health (NIH)–sponsored research. Dr Mulsant has also received reimbursement for travel expenses from Roche and owns stock in General Electric. **Dr Reynolds** has received pharmaceutical support for NIH-sponsored research studies from Bristol-Myers Squibb, Forest, Pfizer, and Eli Lilly; has received grants from NIH, Patient Centered Outcomes Research Institute, Commonwealth of Pennsylvania, John A. Hartford Foundation, National Palliative Care Research Center, University of Pittsburgh Medical Center Endowment in Geriatric Psychiatry, and American Foundation for Suicide Prevention; and has served on the American Association for Geriatric Psychiatry editorial review board. Dr Reynolds has received an honorarium as a speaker from MedScape/WebMD and is the coinventor (licensed intellectual property) of Psychometric Analysis of the Pittsburgh Sleep Quality Index, and his NIH-funded research is supported by the following grants: P60 MD000207, P30 MH090333, UL1RR024153, UL1TR000005. **Ms Begley** and **Dr Miller** report no potential conflict of interest.

Funding/support: Supported in part by National Institutes of Health grants AG033575 (Dr Karp), P30 MH090330 (Dr Reynolds), MH083660 (Drs Reynolds, Lenze, and Mulsant), MH072947 (Dr Butters), and KL2 RR024154 (Steven Reis, MD) and the Brain and Behavior Research Foundation (formerly known as NARSAD) (Dr Karp). Reckitt Benckiser provided medication supplies for this investigator-initiated trial.

Role of the sponsor: Reckitt Benckiser was not involved in any aspect of the design or conduct of this clinical trial. The authors are grateful for their support.

Disclaimer: The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Center for Research Resources or the National Institutes of Health.

REFERENCES

1. Dew MA, Whyte EM, Lenze EJ, et al. Recovery from major depression in older adults receiving augmentation of antidepressant pharmacotherapy. *Am J Psychiatry*. 2007;164(6):892–899.
2. Rush AJ, Trivedi M, Fava M. Depression, IV: STAR*D treatment trial for depression. *Am J Psychiatry*. 2003;160(2):237.
3. Thase M, Rush A. Treatment resistant depression. In: Bloom F, Kupfer D, eds. *Psychopharmacology: The Fourth Generation of Progress*. New York, NY: Lippincott, Williams, and Wilkins; 1995.
4. Tao R, Auerbach SB. Opioid receptor subtypes differentially modulate serotonin efflux in the rat central nervous system. *J Pharmacol Exp Ther*. 2002;303(2):549–556.
5. Hache G, Coudore F, Gardier A, et al. Monoaminergic antidepressants in the relief of pain: potential therapeutic utility of triple reuptake inhibitors (TRIs). *Pharmaceuticals (Ott)*. 2011;4(12):285–342.
6. Fink M, Simeon J, Itil TM, et al. Clinical antidepressant activity of cyclazocine—a narcotic antagonist. *Clin Pharmacol Ther*. 1970;11(1):41–48.
7. Gerner RH, Catlin DH, Gorelick DA, et al. Beta-endorphin: intravenous infusion causes behavioral change in psychiatric inpatients. *Arch Gen Psychiatry*. 1980;37(6):642–647.
8. Ruther E, Jungkunz G, Nedopil N. Clinical effects of the synthetic analogue of methionine enkephalin FK 33-824. Presented at: 3rd World Congress of Biological Psychiatry; June 28–July 3, 1981; Stockholm, Sweden.
9. Tenore PL. Psychotherapeutic benefits of opioid agonist therapy. *J Addict Dis*. 2008;27(3):49–65.
10. Mague SD, Pliakas AM, Todtenkopf MS, et al. Antidepressant-like effects of kappa-opioid receptor antagonists in the forced swim test in rats. *J Pharmacol Exp Ther*. 2003;305(1):323–330.
11. Sbrenna S, Marti M, Morari M, et al. Modulation of 5-hydroxytryptamine efflux from rat cortical synaptosomes by opioids and nociceptin. *Br J Pharmacol*. 2000;130(2):425–433.
12. Bodkin JA, Zornberg GL, Lukas SE, et al. Buprenorphine treatment of refractory depression. *J Clin Psychopharmacol*. 1995;15(1):49–57.
13. Kosten TR, Morgan C, Kosten TA. Depressive symptoms during buprenorphine treatment of opioid abusers. *J Subst Abuse Treat*. 1990;7(1):51–54.
14. Butters MA, Whyte EM, Nebes RD, et al. The nature and determinants of neuropsychological functioning in late-life depression. *Arch Gen Psychiatry*. 2004;61(6):587–595.
15. Soyka M, Lieb M, Kagerer S, et al. Cognitive functioning during methadone and buprenorphine treatment: results of a randomized clinical trial. *J Clin Psychopharmacol*. 2008;28(6):699–703.
16. Dagtekin O, Gerbershagen HJ, Wagner W, et al. Assessing cognitive and psychomotor performance under long-term treatment with transdermal buprenorphine in chronic noncancer pain patients. *Anesth Analg*. 2007;105(5):1442–1448.
17. Blier P, Saint-André E, Hébert C, et al. Effects of different doses of venlafaxine on serotonin and norepinephrine reuptake in healthy volunteers. *Int J Neuropsychopharmacol*. 2007;10(1):41–50.
18. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry*. 1979;134(4):382–389.
19. Oquendo MA, Baca-Garcia E, Kartachov A, et al. A computer algorithm for calculating the adequacy of antidepressant treatment in unipolar and bipolar depression. *J Clin Psychiatry*. 2003;64(7):825–833.
20. First M, Spitzer R, Gibbon M, et al. *Structured Clinical Interview for DSM-IV Axis I Disorders (SCID)*. Washington, DC: American Psychiatric Press; 1997.
21. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975;12(3):189–198.
22. Mulsant B, Sweet R, Rifai A, et al. The use of the Hamilton Rating Scale for Depression in elderly patients with cognitive impairment and physical illness. *Am J Geriatr Psychiatry*. 1994;2(3):220–229.
23. Williams J, Kobak K, eds. Improving inter-rater reliability in clinical trials: development and validation of a Structured Interview Guide for the Montgomery-Asberg Depression Rating Scale (SIGMA). Presented at: International Society for CNS Clinical Trials and Methodology 3rd Annual Scientific Congress; 2007; Washington, DC.
24. Derogatis L. *Brief Symptom Inventory (BSI): Administration, Scoring, and Procedures Manual*. 3rd ed. Minneapolis, MN: National Computer Systems; 1993.
25. Andreescu C, Lenze EJ, Dew MA, et al. Effect of comorbid anxiety on treatment response and relapse risk in late-life depression: controlled study. *Br J Psychiatry*. 2007;190(4):344–349.
26. Watson D, Clark LA, Tellegen A. Development and validation of brief measures of positive and negative affect: the PANAS scales. *J Pers Soc Psychol*. 1988;54(6):1063–1070.
27. Beck AT, Kovacs M, Weissman A. Assessment of suicidal intention: the Scale for Suicide Ideation. *J Consult Clin Psychol*. 1979;47(2):343–352.
28. Beck AT, Brown GK, Steer RA, et al. Suicide ideation at its worst point: a predictor of eventual suicide in psychiatric outpatients. *Suicide Life Threat Behav*. 1999;29(1):1–9.
29. Beck AT, Brown GK, Steer RA. Psychometric characteristics of the Scale for Suicide Ideation with psychiatric outpatients. *Behav Res Ther*. 1997;35(11):1039–1046.
30. Rapeli P, Fabritius C, Kalska H, et al. Cognitive functioning in opioid-dependent patients treated with buprenorphine, methadone, and other

psychoactive medications: stability and correlates. *BMC Clin Pharmacol*. 2011;11(1):13.
31. Jennings JR, Mendelson DN, Redfern MS, et al. Detecting age differences in resistance to perceptual and motor interference. *Exp Aging Res*. 2011;37(2):179–197.
32. Shapiro AM, Benedict RH, Schretlen D, et al. Construct and concurrent validity of the Hopkins Verbal Learning Test-Revised. *Clin Neuropsychol*. 1999;13(3):348–358.
33. Lingjaerde O, Ahlfors UG, Bech P, et al. The UKU Side Effect Rating Scale: a new comprehensive rating scale for psychotropic drugs and a cross-sectional study of side effects in neuroleptic-treated patients. *Acta Psychiatr Scand Suppl*. 1987;76(s334):1–100.
34. Wisniewski SR, Rush AJ, Balasubramani GK, et al; TARD Investigators. Self-rated global measure of the frequency, intensity, and burden of side effects. *J Psychiatr Pract*. 2006;12(2):71–79.
35. Johnson EM, Whyte E, Mulsant BH, et al. Cardiovascular changes associated with venlafaxine in the treatment of late-life depression. *Am J Geriatr Psychiatry*. 2006;14(9):796–802.
36. Ware J, Gandek, B, the IQOLA project group. The SF-36 Health Survey: development and use in mental health research and IQOLA project. *Int J Ment Health*. 1994;23(2):49–73.
37. Dombrovski AY, Lenze EJ, Dew MA, et al. Maintenance treatment for old-age depression preserves health-related quality of life: a randomized, controlled trial of paroxetine and interpersonal psychotherapy. *J Am Geriatr Soc*. 2007;55(9):1325–1332.
38. Buysse DJ, Reynolds CF 3rd, Monk TH, et al. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res*. 1989;28(2):193–213.
39. Wesson DR, Ling W. The Clinical Opiate Withdrawal Scale (COWS). *J Psychoactive Drugs*. 2003;35(2):253–259.
40. Raskin J, Wiltse CG, Siegal A, et al. Efficacy of duloxetine on cognition, depression, and pain in elderly patients with major depressive disorder: an 8-week, double-blind, placebo-controlled trial. *Am J Psychiatry*. 2007;164(6):900–909.
41. Chapman SL, Byas-Smith MG, Reed BA. Effects of intermediate- and long-term use of opioids on cognition in patients with chronic pain. *Clin J Pain*. 2002;18(suppl):S83–S90.
42. Golwyn DH, Sevlie CP. Monoamine oxidase inhibitor hypertensive crisis headache and orthostatic hypotension. *J Clin Psychopharmacol*. 1993;13(1):77–78.
43. Tulen JHM, Volkers AC, van den Broek WW, et al. Sustained effects of phenelzine and tranylcypromine on orthostatic challenge in antidepressant-refractory depression. *J Clin Psychopharmacol*. 2006;26(5):542–544.
44. Kivimäki M, Hamer M, Batty GD, et al. Antidepressant medication use, weight gain, and risk of type 2 diabetes: a population-based study. *Diabetes Care*. 2010;33(12):2611–2616.
45. Brunton S, Wang F, Edwards SB, et al. Profile of adverse events with duloxetine treatment: a pooled analysis of placebo-controlled studies. *Drug Saf*. 2010;33(5):393–407.
46. Hu XH, Bull SA, Hunkeler EM, et al. Incidence and duration of side effects and those rated as bothersome with selective serotonin reuptake inhibitor treatment for depression: patient report versus physician estimate. *J Clin Psychiatry*. 2004;65(7):959–965.
47. Schatzberg AF, Haddad P, Kaplan EM, et al; Discontinuation Consensus Panel. Serotonin reuptake inhibitor discontinuation syndrome: a hypothetical definition. *J Clin Psychiatry*. 1997;58(suppl 7):5–10.