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Pharmacotherapy for Treatment of Cognitive and Neuropsychiatric Symptoms After mTBI

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Abstract

Cognitive and neuropsychiatric symptoms are extremely common following mild traumatic brain injury (TBI), also known as concussion. Although most patients will recovery rapidly, a significant minority go on to experience persistent symptoms. There are currently no FDA approved medications for treatment of cognitive and neuropsychiatric problems in the context of mild TBI, yet a number of agents are prescribed "off-label" for these complaints. Rigorous trials are lacking, but there are a number of open-label studies, and some small randomized controlled trials that support the safety and possible efficacy of pharmacotherapies in this population. Clinical trials conducted in samples with more severe brain injuries can also serve as a guide. A number of agents are reviewed. There is the most support in the literature for the neurostimulant methylphenidate for treatment of mild TBI-related cognitive dysfunction, and the selective serotonin reuptake inhibitor, sertraline, for the treatment of post-injury depression. There is clearly a need for more well-designed studies to guide clinicians in selecting the appropriate medication and dose. Without clear guidance from the literature, a cautious approach of starting low and titrating slowly is recommended.

Introduction

Traumatic brain injury (TBI) is a major public health problem with approximately 1.7 million TBIs occurring annually in the US. The vast majority of these injuries fall into the category of mild TBI or concussion.[1] Although most individuals with concussion or mild TBI recovery rapidly, within days or weeks of sustaining their injuries, a significant minority of cases will go on to experience persistent symptoms that interfere with their productivity and quality of life. Cognitive and neuropsychiatric complaints are among the most troubling symptoms that persist after mTBI. There is evidence that behavioral and pharmacotherapeutic treatments may be effective in treating these problems, however,

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rigorous clinical trials are lacking. Although there are currently no FDA approved medications for acute and persistent post-concussion symptoms, agents that are commonly used to treat cognitive and neuropsychiatric problems are used “off-label” to manage these issues in the context of mTBI. This paper reviews the research literature that supports the safety and efficacy of a number of medications for treating cognitive and neuropsychiatric problems in patients with mTBI. Considerations for treating the neuropsychiatric consequences of mTBI are also discussed.

Cognitive complaints following mTBI include mental fogginess, difficulties with attention and concentration, and memory problems. Subjective complaints in these areas in the immediate aftermath of injury are common, and approximately 10–33% of patients continue to report these problems as long as three months after injury.[2] Studies of neuropsychological recovery of mTBI show objective evidence of cognitive dysfunction in the acute post-injury period.[3] Meta-analyses suggest that objective deficits remit in most patients by three months post-injury, however, a subset of individuals may continue to show chronic evidence of cognitive dysfunction.[4] Neuropsychiatric symptoms, such as depression, anxiety, and irritability are also common following mTBI (see Table 1 for a summary of cognitive and neuropsychiatric symptoms of mTBI). These symptoms are troubling on their own, and also appear to be influential in the maintenance of persistent dysfunction following mTBI.[5] Hence, effective treatment of neuropsychiatric dysfunction following mTBI is critical for good recovery.

Causes of cognitive and neuropsychiatric complaints after mTBI

A TBI occurs when the brain undergoes rapid acceleration and deceleration forces as a result of physical trauma. Although cortical contusions and subcortical lesions are sometimes present in moderate to severe TBIs, these features are typically absent in mTBI. Direct mechanical injury to axons can lead to a distributed pattern of neuronal injury referred to as diffuse axonal injury (DAI). DAI is the result of rapid deformation of axons, which damage the axonal cytoskeleton[6,7] and can directly disrupt axonal transport. DAI is the most common pathological feature of TBI, and there is evidence of DAI even at the lowest level of severity.

Cognitive and neuropsychiatric symptoms, may arise directly from disruption to the neural circuits that underlie cognitive function and neuropsychiatric regulation. Complex cognitive and emotional functions rely on the dynamic interplay of multiple brain regions. Hence, axonal injury, and the resultant degradation of white matter connections, decreases the efficiency of information transfer. Dependent on the extent and distribution of damage, multiple sensory, motor, emotional, and cognitive systems can be affected. Complex functions involving the integration of information from multiple brain regions may be the most vulnerable to inefficiencies. Evidence in support of DAI as the anatomical substrate underlying slowed processing speed and executive dysfunction comes from multiple neuroimaging studies employing diffusion tensor imaging (DTI) (e.g.[8,9]). Some evidence suggests that DAI may underlie neuropsychiatric dysfunction and other persistent complaints. One study found that mTBI patients with persistent symptoms, which included neuropsychiatric and cognitive complaints, showed higher mean diffusivity values on DTI as

compared to both uninjured controls and fully recovered mTBI patients, evident in multiple white matter tracts.[10]

Most pharmacological interventions to address problems after mTBI target the common neurotransmitter systems that may be disrupted by brain injury. Dopamine is a neurotransmitter that has important roles in motor and cognitive function. Dopamine excess can lead to neuropsychiatric problems such as psychosis, anxiety and impulse control disorders. Dopamine levels are also directly correlated with arousal.[11] Dopamine plays an important role in many aspects of higher cognition and behavior, primarily through the mesocorticolimbic and niagro-striatal pathways. Damage to these pathways Can therefore lead to problems seen frequently after TBI including: memory[12] and neuropsychiatric disorders.[13]

The cholinergic system is perhaps best known for its role in memory, with Alzheimer disease being the prototypical disorder. This system involves a number of structures that have important cognitive roles including the striatum, limbic system and hippocampus. In addition to memory, the cholinergic system is important in attention, arousal and executive function.[14]

Serotonergic pathways are concentrated in the brainstem but do project more diffusely to several structures that are known to have important roles in mood, cognition, sleep and behavior including the hippocampus, prefrontal cortex, forebrain and limbic system.[15] The raphe nucleus is a major source of serotonin production in the brain. There are a number of serotonin receptor subtypes, with different roles and responses to medications.

The noradrenergic system is also important for regulation of several cognitive and neurobehavioral activities. The most important site for synthesis of norepinephrine from dopamine is in the locus coeruleus. Pathways ascend to a number of areas important for cognition and neurobehavioral regulation including the amygdala, hippocampus, striatum and cerebral cortex.[16]

When treating cognitive and neuropsychiatric symptoms in the context of mTBI, providers should be aware that these symptoms are not always, or even frequently, the direct result of brain trauma. For instance, it is important to highlight that cognitive and neuropsychiatric consequences of mTBI may be secondary effects of other post-concussion symptoms. Multiple brain injury symptoms are known to lead to distress and interfere with cognition. For instance, headache, hyperacusis, fatigue, and sleep disturbance are all associated with cognitive and emotional symptoms in non-brain injured populations. Furthermore, there is a potentially reciprocal relationship between cognitive deficits and emotional dysfunction—wherein, cognitive problems may cause frustration and distress; in turn, depression and anxiety can interfere with focus and sustained attention. Evidence for the bi-directional causality between these phenomena comes from studies demonstrating that pharmacotherapeutic treatment for one issue may lead to improvement in the other. Fann and colleagues noted improvement in neuropsychological test performance after treatment with an antidepressant (sertraline) in depressed mTBI patients.[17] Another study by Lee and colleagues found that depressed mild-moderate TBI patients treated with methylphenidate

demonstrated significant improvements in depression, in addition to cognition and alertness.[18]

Furthermore, many concussion symptoms, including the neuropsychiatric and cognitive complaints, have a relatively high base-rate in the absence of brain injury. For example, a cross-sectional observational study examined self-reported post-concussion symptoms in a large sample of high school athletes with no concussion in the past 6 months found that 19% of boys and 28% of girls reported a symptom burden that was consistent with a diagnosis of postconcussion syndrome, with pre-existing conditions associated with higher symptom reporting.[19] Hence, providers should be aware that elevated symptoms may reflect premorbid patient characteristics. Certain characteristics may predispose some individuals to prolonged symptoms after concussion that may lead to initiation of pharmacological intervention. Patient or family history may provide information on pre-morbid conditions or risk factors for the development of neuropsychiatric diagnoses. Many symptoms that may be labeled as “post-concussive” are also seen with depression, such as fatigue, irritability and slowing of cognitive function. A history of anxiety and depression has been linked to the development of post-concussive symptoms.[20] Additionally, maladaptive responses may emerge over time, leading to the establishment of “sick” behaviors (e.g. avoidance, overt displays of distress, etc.) and loss of “well” behaviors (participation in normal activities).

Pharmacotherapy for cognitive symptoms following mTBI

Much of what we know about pharmacological interventions to enhance cognition after TBI comes from studies that have examined moderate and severe brain injury populations. There is some caution that needs to be taken when extrapolating these findings to persons with mild TBI. Among the medications utilized to hasten or improve recovery after mild TBI, the neurostimulants have been studied to the greatest extent. Methylphenidate is a mixed dopaminergic and noradrenergic medication that has been used to treat both patients with TBI as well as those with other diagnoses with related clinical presentations such as attention deficit disorder. Johansson (2014) examined the efficacy of methylphenidate on a group of 29 (28 mild and one moderate) persons with TBI.[21] The patients were divided into three groups. Each group received 4 weeks of no treatment, low dose methylphenidate (5mg daily escalating to 5mg tid) and high dose methylphenidate (20mg daily escalating to 20 mg tid), but the order in which patients received none, low or high doses was altered for each group. Testing was done on the final day of each 4-week block. There was a significant decrease in mental fatigue (as measured by the Mental Fatigue Scale (MFS)), and this was dose-dependent. Additionally, there were mild adverse effects that resolved with discontinuation of the medication in 4 of the 29 patients. In a similar study with 51 persons (47 with mild TBI and 4 with moderate TBI), with a mean of several years post-injury, a dose-dependent improvement in fatigue (MFS) and cognitive processing speed (digit symbol coding) were noted along with improvements in the vitality and social functioning components of the SF-36.[22] Both of these studies lacked a placebo-control group.

Methylphenidate for treatment of post-concussion cognitive problems has been evaluated in a small randomized, double-blind placebo-controlled trial. Thirty-two patients with clinically significant cognitive complaints and a history of mTBI, PTSD, or both conditions,

were randomized to receive treatment with galantamine (12 mg bid), methylphenidate (20 mg bid) or matching placebo for 12 weeks. Methylphenidate (20mg bid) was associated with an improvement in cognitive complaints (Post morbid Cognitive Scale of the Ruff Neurobehavioral Inventory (RNBI)) and attention (Digit symbol test).[23] Improvements compared to placebo were also noted in post concussive symptoms (Rivermead Post Concussive Symptoms Questionnaire) and posttraumatic stress symptoms (Posttraumatic Stress Disorder Checklist (PCL-S)). This result is promising, but the authors note that results should be confirmed in a larger trial.

One small study has examined the efficacy of amantadine, a medication that increases dopamine release and decreases its uptake.[24] It is also a weak NMDA receptor antagonist.[25] In this retrospective case-controlled study, 25 adolescents who sustained sports-related concussions and had not recovered (based on symptoms and computerized cognitive testing) after approximately 21 days of rest were recruited. They were prescribed amantadine 100mg twice a day for 3–4 weeks. This group was compared with a retrospective cohort of patients matched by age, sex and concussion history, treated conservatively (i.e. rest, no pharmacological interventions) at the same clinic prior to the start of the amantadine protocol. Pre-treatment cognitive function and post-concussion symptoms were measured using ImPACT. Post-treatment ImPACT testing was repeated at approximately 40–50 days post-injury. Statistically greater improvement was noted for verbal memory, reaction time and patient-reported symptoms in the treatment group compared with the control group although both groups demonstrated statistically significant improvement in all domains tested. However, it should be noted that the treatment group was more impaired than the control group for symptom score, and verbal and visual memory, and post-treatment scores were similar for both groups.

As mentioned previously, the acetylcholinesterase inhibitor galantamine has also been studied regarding effects on aiding recovery after mild TBI (and/or posttraumatic stress disorder) in a small randomized placebo-controlled trial. Although galantamine had no effect on cognitive symptom scores of the RNBI (the primary outcome measure), participants in the galantamine group demonstrated a statistically significant improvement in episodic memory.[23] This finding is consistent with the known role of acetylcholine (Ach) in memory and the efficacy of medications that boost Ach to alter the progression of Alzheimer disease.[26] The potential role of acetylcholinesterase inhibitors to enhance cognition after more severe TBI has also been supported in the literature.[27]

Higher quality studies do provide some support for the use of medications to enhance cognitive recovery after moderate to severe TBI. For example, several randomized, placebo-controlled studies have demonstrated that methylphenidate can enhance recovery of certain aspects of cognition after TBI.[28,29] Amantadine has also been shown in a randomized, double blind, placebo-controlled trial to benefit patients with severe TBI.[30] The extent to which these findings may translate to individuals with mTBI should be evaluated in future research. See Table 2 for a summary of medications used to treat cognitive symptoms of mTBI.

Pharmacotherapy for neuropsychiatric symptoms following mTBI

There is a strong rationale for treating neuropsychiatric symptoms after mTBI, as successful treatment may result in improvements in other symptom domains. Selective serotonin reuptake inhibitors (SSRIs) to treat depression after TBI have received the most attention in the research literature. Fann and colleagues examined sertraline as a treatment for depression in a group of 16 participants within 3 to 24 months of mild TBI, in an 8-week non-randomized, single blind placebo run-in trial. All participants received one capsule of an inert placebo every morning during the first week of the trial. The Hamilton Depression Rating Scale (HAM-D) was the primary outcome measure. No participants in the trial met the criteria for "placebo responder" during the placebo run-in phase, by exhibiting a decrease in HAM-D score by 50% or more, or total HAM-D score below 10. All patients then went on to receive an 8-week single-blind course of sertraline, which started at 25 mg every morning, and was titrated up to 200 mg per day over the course of the study, depending on tolerability. The effectiveness of sertraline was supported by a high rate of treatment response, 87% of participants, as determined by a 50% drop on the HAM-D from baseline to week 8. Over half of participants (67%) met criteria for remission, as defined by a final HAM-D of 7 or less.[31] These patients also demonstrated statistically significant improvement on neuropsychological tests, particularly in the domains of psychomotor processing speed, efficiency, flexible thinking, and recent memory ability.[32]

A larger double blind randomized controlled trial also evaluated sertraline as a treatment for major depressive disorder (MDD) in the context of TBI, in a 52-participant convenience sample.[33] Participants in this 10-week trial included those with mild (35.5%), moderate (38.7%), and severe TBI (25.8%), with concurrent diagnosis of MDD. Using the same protocol as Fann and colleagues (2000), participants were started on 25 mg/ day of sertraline, and the dose was gradually increase to 100 mg/day as tolerated. Both the placebo and sertraline groups demonstrated significant improvements in depression over the course of the trial. Among treatment completers, there were more responders (50% drop on the HAM-D from baseline to week 10, or final HAM-D score of 10 or less) in the sertraline condition, as compared to the control condition (59% versus 32%). Hence, the results of this trial show a relatively modest benefit of sertraline over placebo on post-TBI depression. These findings diverge somewhat from Fann et al., 2000, which suggested a greater benefit for sertraline. A couple of factors may account for this discrepancy. The one-week placebo lead-in design may have underestimated the placebo effect in Fann et al.'s (2000) study. Also, it is possible that sertraline is most effective as a treatment of depression in patients with mTBI, an effect which may have been obscured in Ashman et al.'s (2009) more heterogenous sample with regard to injury severity.

More support for both sertraline and methylphenidate for treatment of post-TBI depression comes from a randomized placebo-controlled trial compared sertraline, methylphenidate, and placebo in 30 participants with mild-moderate TBI and MDD. Participants were assigned to receive either methylphenidate (20 mg/day), sertraline (100 mg/day), or inert placebo for a 4-week trial. Both the sertraline and methylphenidate groups demonstrated improvement in HAM-D scores, relative placebo. There were no differences between the

two treatment groups with regards to depression outcomes, however, the methylphenidate group reported greater improvements in cognition and alertness.[18]

Another SSRI, citalopram, has also been evaluated as a treatment for depression after TBI. Participants with mild to moderate TBI and MDD were enrolled in an open label study of 20–60 mg/day of citalopram. Treatment response and remission were defined as they had been in other studies.[31,33] At 6 weeks, 54 subjects were assessed using the HAM-D, and 27.7% of participants had responded, with a 24.1% remission rate. At 10-weeks 26 subjects were assessed with HAM-D, and at this time point 46.2% of the sample had responded with 26.9% in remission.[34] The authors concluded that this response rate was lower than what had been reported in other studies of pharmacotherapy for post-TBI depression, but noted that they are consistent with results of the largest effectiveness trial of citalopram for general out-patients with major depression in the absence of TBI.

The efficacy and tolerability of other antidepressants, including the serotonin-norepinephrine reuptake inhibitors, bupropion, and the monoamine oxidase inhibitors (MAOIs) in TBI are not well established. Some have cautioned against using MAOIs in persons with TBI, for concerns that individuals with cognitive and behavioral impairments may have difficulty adhering to dietary restrictions recommended with these medications.[35] This may be less of a concern in persons with mild TBI, who tend to have less severe cognitive deficits. Caution should also be used with regard to bupropion, which can lower seizure threshold.[35]

Anxiety is also common after TBI and related to cognitive disability and satisfaction with life,[36] yet it has received relatively less attention than depression. There is very limited quality evidence for the treatment of anxiety disorders in the context of TBI. One case report, a retrospective study of venlafaxine in the treatment of compulsions, showed a significant effect of venlafaxine at 150 mg/day.[37] Benzodiazepines are not recommended for long-term use because TBI patients may be more susceptible to their potential adverse reactions and they may actually cause a paradoxical agitation in these patients.[38] SSRIs may have efficacy for treatment of anxiety in the context of TBI, and have been recommended.[39]

There is fairly minimal literature that is specific to the management of other mood disorders after mTBI. However, problems such as lability and irritability are not uncommon and are part of the ICD-10 criteria for the diagnosis of PCS. As previously discussed, patients with persistent neuropsychiatric symptoms may also have pre-morbid related diagnoses (whether identified as such or not). It is therefore reasonable to consider pharmacological management based on clinical presentation and existing literature from the general TBI and pertinent psychiatric populations. Mood stabilizing medications such as valproic acid, carbamazepine and lamotrigine can be considered for patients with significant irritability or lability, or those with a personal or family history of bipolar affective disorder. See Table 2 for a summary of medications used to treat neuropsychiatric symptoms of mTBI.

Discussion

Cognitive and neuropsychiatric symptoms are very common after mild TBI. “Watchful waiting” is often an appropriate clinical strategy, given the propensity for symptoms to

resolve relatively quickly without intervention. However, for those cases in which symptoms persist and interfere with day-to-day functioning, interventions, including pharmacological treatment, should be considered. Pharmacotherapy for cognitive and neuropsychiatric symptoms should always be prescribed within the context of education and reassurance regarding TBI and recovery expectations, and referral to psychotherapy as appropriate.[40] Furthermore, a careful review of patient history (prior educational problems or accommodations, prior mood disturbances or interventions for same) is critical for differential diagnosis and informing risk for persisting symptoms. Attention to and proper management of other troubling symptoms (e.g., headache, vestibular dysfunction, hyperacusis) are also recommended, as improvements in these symptoms may have benefits for mood and cognition.

Although the focus of this review is on pharmacological management, in the authors' opinion, it is seldom appropriate to treat post-concussion symptoms with medications alone. This is especially true for symptoms that are persist into the chronic post-injury phase. A number of studies have described the interplay of neurological and psychological factors after concussion.[41,42] Given the complexity of the pathophysiology of these symptoms (biological, psychological, social, litigation, pre-existing health, to name a few), a comprehensive, holistic treatment plan is essential. When provided acutely, cognitive behavioral therapy (CBT) may help prevent progression to PCS,[43] and CBT has also been shown to have some benefit for post-concussion syndrome.[44] A comprehensive treatment plan should include interventions to address individual problems identified as contributing to the post-concussive symptomatology. It is likely that non-pharmacological interventions will be utilized, and the treatment plan will typically need to be modified in subsequent evaluations. On the other hand, given the evidence that psychiatric illness (both pre-injury and post-injury) is associated with prolonged symptoms after mTBI, earlier initiation of pharmacological intervention for these conditions may be warranted.[45]

Despite the lack of controlled studies that support the use of medications to enhance recovery after mild TBI, it is perhaps surprising that clinicians are prescribing these medications with some frequency.[46] It is somewhat reassuring that several studies (in both mild and moderate to severe TBI) have published information regarding safety, with relatively low rates of adverse events being reported with the use of methylphenidate and amantadine.[22,23,30] However, there is no direct information to guide clinicians regarding dosing of medications. Accordingly, it is recommended to start low and titrate slowly as there is evidence from studies of more severely injured persons that brain injury may increase susceptibility to the side effects of many psychotropic medications.[5] Additionally, it may not be appropriate to base dosing on an uninjured population, as TBI may lead to loss of integrity of the blood-brain barrier, increasing medication permeability and possibly potency. Depending on the comfort level of the individual clinician, referral to other specialists (e.g., psychiatrist) for specific or more complicated neuropsychiatric problems may be considered.

Given the current interest in the management of concussions and willingness of physicians to prescribe medications to improve recovery, it is also surprising that a recent search of clinicaltrials.gov did not yield any trials related to the pharmacological management of

cognitive deficits and neuropsychiatric symptoms after concussion. Clearly there is a need for more well-designed studies to guide clinicians in their management of prolonged cognitive and neuropsychiatric symptoms after mTBI. However, there are formidable logistical challenges in conducting large-scale clinical trials in this population. For example, a Department of Defense funded study planned to enroll 160 participants with mild TBI, PTSD, or both, across 7 recruitment sites, but was terminated due to recruitment difficulties after enrolling only 32 subjects.[23] The most frequent reasons for study exclusion were co-morbid medical conditions and failure to reach a minimum symptom threshold. These are common challenges. Studies that recruit mild TBI patients from acute referral sources (e.g. emergency department or acute sports concussion management) will access a large number of cases, the vast majority of which will recover spontaneously within a relatively brief time frame, and hence, be inappropriate for clinical trials. By contrast, chronic mild TBI patients with persistent symptoms may have comorbidities and/or poorly documented injuries. Furthermore, chronic patients present to a wide spectrum of clinical services—including specialty clinics, neurology, neurorehabilitation, and primary care—posing a challenge for recruitment into research. The development of neuroimaging and serum biomarkers to facilitate early identification of patients with greatest risk of persistent dysfunction may help stratify patients into appropriate treatment studies. These advances, along with the growing awareness of persistent deficits after concussion, promise to lay the groundwork for future rigorous trials of pharmacotherapies for treatment of cognitive and neuropsychiatric symptoms of mild TBI.

Summary

Cognitive and neuropyschiatric problems are common after mTBI. In the majority of cases, these symptoms will resolve in a relatively short period of time and will not require pharmacological intervention. In recalcitrant cases, it may be appropriate to consider a trial of a medication (as part of a more comprehensive treatment plan) to help facilitate recovery. However, there is very limited information to guide clinicians regarding basic decisions such as choice of drug(s), timing of initiation of medications and dosing. More research is clearly needed to answer these fundamental questions.

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Table 1.

Cognitive & Neuropsychiatric symptoms of mTBI

Cognitive Symptoms	**Neuropsychiatric Symptoms**
Mental fogginess	Depression
Attention/ Concentration	Anxiety
Processing Speed	Irritability
Executive Function	Emotional lability

Table 2.

Medications discussed regarding potential use to manage symptoms after mild TBI

Medication	Mechanism of action	Usual dosages (adult)	Relevant side effects	References
methylphenidate	Norepinephrine and dopamine reuptake inhibition	5–20 mg, 2–3 times/day	Tachycardia, hypertension, anxiety, loss of appetite, dizziness, palpitations, nausea	18,19,21
amantadine	Direct and indirect dopaminergic stimulation; weak NMDA receptor antagonist	100–200 mg, 2 times/day	Nausea, dizziness, headache, dry mouth, blurred vision, nervousness	22
galantamine	Acetylcholinesterase inhibitor; nicotinic acetylcholine receptor agonist	4–8 mg, 2 times/day	Nausea, vomiting, diarrhea, dizziness, drowsiness, loss of appetite	21
donepezil	Acetylcholinesterase inhibitor	5–10 mg daily	Nausea, vomiting, diarrhea, dizziness, loss of appetite	25
sertraline	Serotonin reuptake inhibitor	50–200 mg daily	Nausea, dizziness, drowsiness, loss of appetite, trouble sleeping	17,18,29,30,31
citalopram	Serotonin reuptake inhibitor	20–40 mg daily	Nausea, dry mouth, loss of appetite, drowsiness	32
buproprion	Norepinephrine and dopamine reuptake inhibitor	200–300 mg daily	Nausea, dry mouth, headache, dizziness, blurred vision, seizures	34,35
venlafaxime	Norepinephrine and serotonin reuptake inhibitor	75–225 mg daily, divided into 2 or 3 doses	Nausea, drowsiness, dizziness, trouble sleeping, nervousness	37