Management of Insomnia and Anxiety in Myasthenia Gravis

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Myasthenia gravis is a neuroimmunological disorder leading to skeletal muscle weakness. Common symptoms of the disease, such as anxiety, depression, and insomnia, can cause significant distress in patients. Unfortunately, selecting an appropriate medication for treatment of psychiatric comorbidities can prove to be challenging for providers given the unique pharmacologic constraints that myasthenia gravis presents. The authors present the following clinical vignette and accompanying discussion in an attempt to highlight the special considerations that must be taken into account when treating anxiety and insomnia in patients with myasthenia gravis, as well as to provide an overview of available medication options through the lens of existing constraints.

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CLINICAL VIGNETTE

The patient is a 31-year-old woman with a history of myasthenia gravis and reported anxiety, depression, attention deficit hyperactivity disorder, posttraumatic stress disorder (PTSD), and polysubstance abuse who presented to the neurology service as a transfer from an outside hospital in myasthenic crisis, likely precipitated by drug use and sleep deprivation. Her initial presenting symptoms of weakness, shortness of breath, dysphagia, and muscle spasms had improved significantly with intravenous immunoglobulin and solumedrol; however, the primary team was concerned that persistent anxiety and insomnia were preventing a full recovery. They had attempted to treat these symptoms with trazodone and zolpidem, without success. The psychiatric consultation liaison service was consulted to provide medication recommendations.

On interview, the patient reported that while she typically slept about 10 hours per night outside of the hospital, she had been unable to sleep at all since admission to the outside hospital one week ago. She described feeling exhausted, irritable, and extremely anxious as a result. She reported that while her current mood was "terrible" from lack of sleep, she felt that her depression was well controlled as an outpatient on bupropion 300 mg. She denied experiencing nightmares or flashbacks. She reported that she had briefly taken doxazosin for difficulty sleeping while at an inpatient drug rehab facility in the past; this had provided full relief of symptoms at the time. She otherwise denied any history of sleep problems or sleep medications. She had never had a sleep study. Hemoglobin was within normal range.

She reported that she had been taking alprazolam for anxiety for 11 years, and felt that her symptoms were well controlled on this before hospitalization. She had been detoxed with lorazepam before transfer to our facility. Despite this, she described symptoms consistent with prior episodes of withdrawal, including restlessness and heart palpitations. There was no evidence of psychomotor agitation on exam, and vital signs demonstrated only mild, intermittent elevations in heart rate and blood pressure. She had no tremors, hallucinations, or cognitive dysfunction.

From the initial assessment, it was difficult to determine whether the patient's symptoms of anxiety and insomnia were secondary to benzodiazepine withdrawal, a primary anxiety disorder, or PTSD. Because there was no clear benzodiazepine withdrawal presentation and the patient had a history of positive response to doxazosin, she was started on a trial of prazosin 1 mg at bedtime. The following morning, she reported significant improvement in sleep and mood. She was able to be discharged on this regimen after medical stabilization and reported continued adherence at the time of outpatient follow up per records.

DISCUSSION

Myasthenia gravis is a neuroimmunological disorder most often associated with autoantibodies formed against the nicotinic acetylcholinergic receptors at the neuromuscular junction, leading to skeletal muscle weakness (1). The disease can be a source of significant psychosocial distress for patients, with symptoms of anxiety, depression, and insomnia representing fairly common complaints (2). Such symptoms have been

shown to negatively influence quality of life in myasthenic patients; thus, effective treatment is particularly important (3).

Psychiatric Comorbidities in Myasthenia Gravis

Psychiatric comorbidities are quite common in patients with myasthenia gravis, particularly mood and anxiety disorders (4). In fact, some studies have suggested that the point prevalence may be as high as 45% for anxiety (2, 3) and 58% for depression (2, 4). However, other studies have indicated a prevalence of overall psychiatric comorbidity closer to 30%, which is similar to that of the general population (5). They suggest that higher figures may be better attributed to psychological reactions to more severe courses of myasthenia than to true co-occurring psychiatric disorders (5). Case reports in which psychopathologic complaints have remitted with effective treatment of somatic myasthenic symptomatology appear to support this theory (6), as do existing data that have demonstrated an association between disease severity and higher scores on depression and anxiety rating scales (4). The exact relationship between myasthenia gravis and psychiatric comorbidity remains an area for further study.

Symptoms of anxiety and depression have been shown to have a significant effect on health-related quality of life in patients with myasthenia gravis (3), highlighting the importance of effective diagnosis and treatment. Interestingly, psychiatric consultation liaison requests for patients with neuroimmunological diseases have been noted to be relatively rare (4). At present, the existing body of literature on pharmacotherapy for psychiatric comorbidities in myasthenia gravis is quite limited (7). This creates a challenge for providers in selecting appropriate treatment modalities, especially when combined with the unique pharmacologic constraints associated with the disease itself.

Sleep Disorders in Myasthenia Gravis

Existing literature on the prevalence of sleep disorders in myasthenic patients is inconsistent (8). Although some studies demonstrate associations with restless legs syndrome, poor sleep quality, and sleep disordered breathing, others do not; thus, further research is needed (8). Interestingly, although the prevalence of insomnia in the general population has been reported to be as high as 74%, the prevalence in myasthenia gravis was reported in one study to be only 39% (2, 9).

Pharmacologic Considerations in Myasthenia Gravis and Overview of Common Sleep Medications and Anxiolytics

For succinctness, the following sections are focused on discussing the adverse effects that are of particular relevance to patients with myasthenia gravis. In other words, adverse effects that are no more applicable to myasthenic patients than to the general population (e.g., diarrhea) are not addressed. For further details on medications for treating insomnia and acute anxiety in patients with myasthenia gravis, see Table 1.

Benzodiazepines. Although benzodiazepines possess highly effective anxiolytic properties, they also have the potential to produce respiratory depression in susceptible individuals (10). Myasthenic patients are included in this group, given their increased risk for respiratory muscle weakness and resulting distress. A recent case report described a patient with myasthenia gravis who developed ptosis and respiratory distress after receiving a dose of a benzodiazepine for insomnia (11). Benzodiazepines are generally considered to be contraindicated in patients with the disease; they would not have been an appropriate choice for our patient, given her resolving episode of myasthenic crisis (and history of substance abuse) (12). However, it is interesting to consider that our patient had reportedly been taking benzodiazepines for 11 years as an outpatient, which suggests that the risks posed may be somewhat lower in the setting of stable disease.

Z drugs. Z drugs, to include zaleplon, eszopiclone, and zolpidem, are nonbenzodiazepine hypnotic agents that are frequently used for short-term treatment of insomnia. They are contraindicated in patients with myasthenia gravis, given reports of zolpidem causing respiratory insufficiency in patients with preexisting respiratory impairments (13, 14).

Antihistamines. H_1-receptor antagonists, such as diphenhydramine, doxylamine, and hydroxyzine, are frequently used for their sedative properties. Although this class of drugs is known for causing acetylcholine receptor (AChR) antagonism, it is important to note that these drugs display selectivity for the muscarinic AChR, not the nicotinic AChR (15). In other words, while they may cause antimuscarinic effects (e.g., dry mouth, blurry vision, constipation, urinary retention, drowsiness), they should not theoretically produce antinicotinic effects (e.g., neuromuscular blockade or skeletal muscle weakness) the latter would be particularly problematic in myasthenia gravis (16). However, in one case it was reported that cetirizine appeared to trigger an episode of diplopia, dysphagia, and facial weakness in a patient with a history of myasthenia gravis previously in complete stable remission; the mechanism by which this likely occurred is unclear but may be related to the anticholinergic properties of the disease (17).

Although antihistamines are not generally contraindicated in myasthenia gravis, providers may wish to exercise caution in light of reports such as this one. They may also consider educating patients about this potential risk, given the widespread presence of antihistaminergic agents in over-the-counter medications. Providers who feel that the use of a drug from this class is clinically warranted may wish to consider an agent with a lower risk of anticholinergic effects; hydroxyzine and its analogs have very low affinities for the AChR compared with other agents such as

TABLE 1. Common medications for treating insomnia and acute anxiety in patients with myasthenia gravis

Drug	Reported effects
Alpha-1 blockers	Orthostatic hypotension
Antihistamines	Case reports of triggering decompensation in myasthenia gravis
Benzodiazepines	Generally contraindicated; potential to cause respiratory depression in patients with preexisting respiratory impairments
Gabapentin	Case reports of triggering decompensation and unmasking previously undiagnosed myasthenia gravis
Melatonin	Well tolerated; no known adverse effects of particular concern to myasthenic patients
Mirtazapine	Myasthenia observed in <1% of patients in premarketing evaluation, but no existing case reports of triggering decompensation
Quetiapine	Case reports of various atypical antipsychotics triggering decompensation in myasthenia gravis; orthostatic hypotension
Ramelteon	Respiratory effects in patients with preexisting respiratory impairments not definitively known
Suvorexant	Respiratory effects in patients with preexisting respiratory impairments not definitively known
Trazodone	Orthostatic hypotension
Tricyclic antidepressants	Theoretical risk of neuromuscular blockade demonstrated in vitro; does not appear to be replicated in vivo (no reports of triggering decompensation)
Z drugs	Potential to cause respiratory insufficiency in patients with preexisting respiratory impairments
Herbal supplements	Lack of high-quality literature on the safety of unregulated supplements; caution should be advised

diphenhydramine (13). In general, however, antihistamines would not be the most appropriate first choice for treating anxiety and insomnia, given that safer and more effective alternatives are available (18).

Alpha-1 blockers. Alpha-1 blockers, such as prazosin and doxazosin, are sympatholytics used for treating anxiety and PTSD. The greatest area for concern with this drug class in regard to myasthenia gravis is their potential to cause autonomic adverse effects, such as lightheadedness and orthostatic hypotension. This is problematic, as autonomic dysfunction is a known issue in myasthenia gravis (19). Varying degrees of autonomic dysfunction have been reported, to include symptoms ranging from gastroparesis and orthostatic hypotension to panautonomic failure (20). Impaired cholinergic transmission and increased latency of parasympathetic responsiveness have been proposed as the likely explanation for autonomic dysfunction in myasthenia gravis (19).

It has been reported that symptoms of autonomic dysfunction may be aggravated during periods of stress—for example, during myasthenic crisis (21). This could be extrapolated to suggest that perhaps myasthenic patients may be at a greater risk for orthostatic hypotension due to A1-blockers during crisis if autonomic dysregulation exists at baseline as the result of the myasthenic disease process. It is thus necessary for providers to weigh the risks versus the benefits.

Given that our patient had successfully been treated with an alpha-1 blocker for insomnia and anxiety in the past, we decided that a trial of prazosin might be appropriate. It is noteworthy that although our patient experienced some mild tachycardia, this symptom has been notably absent in reported cases of autonomic dysfunction in myasthenia gravis (19). Because her current symptoms were not otherwise suggestive of autonomic dysfunction and she was undergoing continuous vital sign monitoring, we determined that the level of risk was acceptable. For our patient, prazosin proved to be successful in providing relief of symptoms without adverse effects.

Suvorexant. Suvorexant is an orexin receptor antagonist first approved for use in the United States in 2014 for the treatment of insomnia (22). It has been generally well tolerated, with mild to moderate somnolence as the most common adverse effect (23). Although no effects on respiratory function were observed in healthy nonelderly subjects, effects on respiratory function could not be excluded in patients with compromised respiratory function (specifically, chronic obstructive pulmonary disease and sleep apnea) (22). Providers may thus wish to exercise caution in prescribing this medication in myasthenia gravis, particularly in the setting of unstable disease, pending further research on these effects.

Ramelteon. Ramelteon is a melatonin receptor agonist approved for the treatment of insomnia. Although it has been generally well tolerated, respiratory effects cannot be definitively known from existing studies (24). There were no respiratory depressant effects noted with a single 16-mg dose in mild to severe chronic obstructive pulmonary disease or mild to moderate obstructive sleep apnea (24). Until more definitive information is available, particularly pertaining to the potential for respiratory effects in myasthenia gravis, providers may wish to exercise caution when prescribing in myasthenic populations.

Gabapentin. Gabapentin is sometimes used off-label for treatment of anxiety and insomnia. There have been cases reported of this medication both unmasking myasthenia gravis in previously undiagnosed patients and inducing decompensation in known myasthenic patients; however, the mechanism by which this may occur is currently unclear (25, 26). Recent literature considers gabapentin to be contraindicated in myasthenia gravis (27).

Quetiapine. Quetiapine is an atypical antipsychotic that can be used at a low dose as an off-label treatment for insomnia; however, the complete list of adverse effects is quite extensive (28). There have been a number of case reports in which quetiapine, as well as other antipsychotics (to include olanzapine and risperidone), have led to an aggravation of myasthenic symptoms, pointing to their anticholinergic properties as a potential mechanism (11). Quetiapine also has the potential to cause orthostatic hypotension; the implications for myasthenia gravis have been discussed previously. In consideration of these factors, the use of quetiapine should be cautioned in patients with the disease.

Tricyclic antidepressants (TCAs). TCAs such as doxepin, amitriptyline, and nortriptyline have been used at low doses for the treatment of anxiety and insomnia (18). Although they possess anticholinergic properties (particularly amitriptyline), they do not pose a risk for producing muscle weakness given their muscarinic receptor selectivity (29). In experimental settings, they have been noted to interfere with neuromuscular transmission via pre- and postsynaptic membrane stabilization (30). Because patients with myasthenia gravis have less nicotinic AChR available for neurotransmission, they are at a higher risk for neuromuscular blockade and resulting disease exacerbation (30). However, this effect does not appear to be replicated in vivo. To our knowledge, there are no reported cases of TCAs triggering decompensation in patients with myasthenia gravis; thus, the risk remains a theoretical one. Although TCAs are not contraindicated in the disease, providers may still choose to exercise caution in prescribing.

Trazodone. Trazodone is a serotonin antagonist and reuptake inhibitor that is used off-label to treat insomnia. Case reports indicate that it has been used successfully in this role for patients with myasthenia gravis (31). It is noteworthy that trazodone can cause orthostatic hypotension given its alpha-1 blocking properties, and implications for myasthenia gravis have been discussed previously (32). It appears to be a fairly safe option for patients with the disease; unfortunately for our patient, it did not provide relief of symptoms.

Mirtazapine. Mirtazapine is an atypical antidepressant that has been used off-label for insomnia and anxiety given its sedating properties as an H_1 receptor blocker (18, 33). During premarketing evaluation, myasthenia was observed as a frequent adverse event, but this represented <1% of patients, and did not imply causality (34). To our knowledge, there are no reports in the existing literature of mirtazapine triggering decompensation in myasthenia gravis. The use of this medication does not appear to be of particular concern for our patient population based on current information.

Melatonin. Melatonin is available as an over-the-counter sleep aid. Existing literature does not appear to demonstrate a consistent pattern of adverse effects; reports consist of a range of fairly benign symptoms (35). As the reported adverse effects are not of special concern with respect to myasthenia gravis, it is likely a fairly safe agent in this patient population.

Herbal supplements. A number of herbal supplements, such as valerian root and 5-hydroxytryptophan (5-HTP), are marketed as over-the-counter sleep aids. Unfortunately, because these supplements are unregulated by the Food and Drug Administration, the content of available preparations is potentially variable. There is also a lack of high-quality literature examining the overall safety of these supplements.

Although the currently reported adverse effects and drug interactions for valerian and 5-HTP do not appear to be of specific concern in myasthenia gravis (36, 37), further research in this area would be needed to determine their safety in this patient population. As always, providers should educate patients regarding the risks of unregulated supplements and encourage them to exercise caution if they are considering these agents.

Pharmacologic Interactions With Existing Medication Regimens

When selecting an agent to add to a patient's existing medication regimen, it is important to consider any interactions that may result. Thus, a brief review of the most common medication classes used in the treatment of myasthenia gravis is warranted.

Anticholinesterase agents, such as pyridostigmine bromide and neostigmine, are frequently used for symptomatic relief in myasthenia gravis (38, 39). Providers should keep in mind that agents with anticholinergic properties, such as antihistamines, TCAs, and trazodone, can decrease the procholinergic effects of this medication class. Though not a drug interaction, it is also worth noting here that neostigmine may cause insomnia, though infrequently (39).

Chronic immunosuppressants are commonly used for the long-term management of myasthenia gravis and present a number of considerations relevant to this discussion. Prednisone, cyclosporine, and tacrolimus are all metabolized by the CYP3A4 enzyme; thus, clinicians should keep in mind the potential for interactions when prescribing with other medications that interact with this enzyme, especially inducers and inhibitors (40–42). Although none of the psychiatric medications discussed in previous sections are noted to cause interactions with these immunosuppressants, providers should assess them on an individual basis before prescribing.

Prednisone also has the potential to cause behavioral and mood changes, ranging from insomnia to psychosis, as well as to exacerbate existing psychiatric conditions (40). A similar range of psychiatric adverse effects along with varying degrees of neurotoxicity have been described with tacrolimus therapy in transplant patients (42, 43). It is unclear whether these adverse effects are applicable to

myasthenic patients, as formal studies in this nontransplant population are lacking; however, clinicians may wish to keep them in mind pending further research. Tacrolimus may also prolong the QT interval; thus, providers should exercise caution in adding additional agents with QT prolonging effects, such as quetiapine (42). Fortunately, for many of the other commonly used chronic immunosuppressants such as azathioprine, mycophenolate mofetil, rituximab, and cyclophosphamide, no significant drug interactions with the medications discussed in previous sections or any psychiatric adverse effects have been described (44–47).

The two treatment modalities used in myasthenia gravis for rapid immunotherapy include plasmapheresis and intravenous immunoglobulin. Although plasmapheresis can lead to inadvertent removal of current medications from the patient's system, the effects of the procedure on the psychiatric medications discussed in previous sections require further study (48). No relevant interactions or psychiatric adverse effects have been described for intravenous immunoglobulin (49).

CONCLUSIONS

As the patient in our vignette was still recovering from an episode of myasthenic crisis, we wanted to be particularly cautious about selecting a medication for treating her symptoms of anxiety and insomnia. Trazodone, though relatively safe in myasthenia gravis, had already been tried without success. Benzodiazepines and z drugs were relatively contraindicated, given their potential to cause respiratory insufficiency. Gabapentin was also contraindicated, given its potential to aggravate myasthenic symptomatology. As antihistamines and quetiapine have sometimes been reported to trigger decompensation, they were also avoided, although they are generally not contraindicated in myasthenia gravis. Ramelteon and suvorexant require further investigation with regard to the potential for respiratory depression in susceptible patients, and thus these agents were also avoided. Alpha-1 blockers, TCAs, mirtazapine, and melatonin were all considered to be fairly safe with respect to the disease. Given a history of prior success with an A1-blocker, we attempted a trial of prazosin with good relief of symptoms.

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