Pharmacologic management of anxiety and affective lability during recovery from Guillain-Barré syndrome: some preliminary observations

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Abstract: Psychiatric symptoms in Guillain-Barré syndrome (GBS) can include anxiety and affective lability, which require treatment to improve functional outcomes. Three cases in which modest doses of selective serotonin reuptake inhibitors (SSRIs), alone or in combination with anticonvulsants, reduced symptoms of anxiety and affective lability during acute rehabilitation of GBS are presented. These agents were both more effective and better tolerated than benzodiazepines and appeared to facilitate engagement in rehabilitation therapies, including psychotherapy. Further investigation of the pharmacotherapy of neuropsychiatric disturbances in this population using prospective, blinded, placebo-controlled methods is recommended.

Keywords: Guillain-Barré, anxiety, affective lability, serotonin, neuropsychiatry

Introduction

Guillain-Barré syndrome (GBS) is an immune-mediated inflammatory disorder of the peripheral nervous system that produces rapidly progressive demyelination and axonal loss. Clinical hallmarks of this syndrome include symmetric progressive flaccid muscle paresis, areflexia, ataxia, dysautonomia, and respiratory insufficiency in the presence of an increased cerebrospinal fluid protein content, as well as electromyography studies demonstrating evolving demyelination (Asbury et al 1978).

Psychiatric symptoms are common among persons with GBS and tend to develop during the period of acute care (deJager and Sluiter 1991). These may include emotional disturbances, feelings of hopelessness, and demoralization. Weiss et al (2002) studied psychiatric symptom frequencies among 49 severely compromised GBS patients during their intensive care unit (ICU) stay using a semi-structured interview and ongoing psychiatric examination. Psychiatric symptoms in this group included anxiety (82%), depressive symptoms (67%), brief reactive psychosis (25%), and hopelessness (20%). Such symptoms occurred independently, in combination, or as features of a subacute confusional state. At the conclusion of ICU care, 35% of GBS patients continue to experience long-lasting distress, and 18% experience continued anxiety (Weiss et al 2002).

Ventilator dependence has been associated with the development of psychiatric symptoms in this context (Weiss et al 2002), but is neither necessary nor a sufficient explanation for their development. Psychological reaction to an acute and disabling illness is a likely contributor. However, the rates of psychiatric symptoms reported by Weiss et al (2002) exceed those among patients with similarly acute and disabling medical and neurological conditions (Eisendrath et al 1983). It is possible that the

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pathophysiologic process producing the acute peripheral demyelination of GBS may also affect central nervous system structures involved in the genesis of these symptoms, but there is a lack of evidence at present to support that hypothesis.

Regardless of etiology, these symptoms are clinically significant, functionally disabling, and require treatment to reduce psychiatric morbidity and improve functional outcome in this population. Pain management, effective communication, assistive devices, and treatment with antidepressants may be helpful in the management of psychiatric symptoms during recovery from GBS (Hund et al 1993). Other studies have suggested that supportive therapy (Hund et al 1993), cognitive behavioral therapy (Dattilio and Castaldo 2001), and early education for patients and their families (Dattilio 2002; Merkies et al 2002) may be helpful; however, little is known about the role of pharmacotherapy in the management of psychiatric symptoms during recovery from GBS. This paper adds another dimension of treatment, which has not previously been reported. It presents the effects of modest doses of selective serotonin reuptake inhibitors (SSRIs), alone or in combination with other psychotropic agents and with supportive psychotherapy, among three patients with neuropsychiatric disturbances during their acute rehabilitation following GBS.

Cases

All patients were evaluated in a community inpatient acute rehabilitation hospital following medical hospitalization for GBS. Primary diagnoses of GBS were confirmed using clinical criteria described by Asbury et al (1978). Shortly after rehabilitation admission, each patient was referred for neuropsychiatric evaluation and management of severe anxiety and affective lability, which was interfering with recovery. Patients were followed by the neuropsychiatry service throughout this hospitalization. Neurobehavioral testing included the Folstein Mini-Mental State Examination (Folstein et al 1975) and The Frontal Assessment Battery (Dubois et al 2000). Additional information regarding neuropsychiatric status was obtained through staff and the patients' family members. Two of the patients received low-dose benzodiazepines during either their acute or rehabilitation hospitalization as prescribed by their primary treating physicians. Psychoeducation, supportive psychotherapy, and other therapies (relaxation and visualization) were also provided to the patients during the course of acute rehabilitation.

Case 1

Patient 1 is a 56-year-old female diagnosed with GBS one week after onset of rapidly progressive total body weakness. At the time of onset of this illness she was described as "mildly depressed". During her acute care hospitalization, she received treatment with intravenous IgG but did not require mechanical ventilation. As her muscle weakness and mobility impairments progressed, she developed severe episodic anxiety, affective lability, and agitation. After medical stabilization her mood was euthymic, but she continued to experience paroxysms of anxiety, affective lability (brief episodes of intense crying that did not reflect her baseline mood state), and agitation. These symptoms continued after admission to the rehabilitation hospital. Additionally, the patient was described as increasingly demanding of staff and family, particularly when in the midst of an anxious or affectively labile episode. These symptoms became sufficiently severe to interfere with her participation in therapies and nursing care and prompted neuropsychiatric consultation.

The patient reported short-lived episodes of anxiety, which did not meet DSM-IV criteria for panic attacks. She also experienced brief and involuntary episodes of crying provoked by trivial or modestly sentimental stimuli (described here as affective lability), despite an interepisodic euthymic mood. During these episodes of anxiety and affective lability she could become agitated, but she did not demonstrate agitation otherwise. Additional symptoms included insomnia, mildly impaired concentration, and mild executive dysfunction. Medications on admission included gabapentin 1800 mg daily, trazodone 100 mg at bedtime, and acetaminophen/hydrocodone 5/500, averaging two to three tablets daily.

The patient's history included a self-reported "depressive and anxiety disorder". However, the interview and examination did not provide evidence to support a DSM-IV criteria-based diagnosis of any such mood or anxiety disorder either in the past or at the time of consultation, but were instead most consistent with dysregulation of affect as described by Arciniegas and Topkoff (2000).

Escitalopram 10 mg daily was initiated. Within two days of starting treatment with escitalopram, she reported decreased anxiety. Concurrently the rehabilitation staff reported a decrease in the number and intensity of crying spells, improved frustration tolerance, and less agitation. By day three of treatment with escitalopram, the staff and patient reported a marked reduction in anxiety as well as improvement in sleep and energy. She still demonstrated

demanding and impatient behavior at times, but to a lesser degree. Five days after initiating treatment with escitalopram, acetaminophen/hydrocodone was discontinued and gabapentin was increased to 2400 mg daily. Following discontinuation of acetaminophen/hydrocodone, she was noted to be more anxious – especially around issues of pain – more fearful, and more affectively labile. Accordingly, two days thereafter her dose of escitalopram was increased to 20 mg daily. Two days after increasing her escitalopram, the frequency and intensity of paroxysmal anxiety and affective lability decreased. The patient reported both improved hope regarding her recovery and a reduced experience of pain. These improvements continued during the next two weeks, by which time she reported her paroxysms of anxiety and affective lability had ceased. Staff and family corroborated the patient's report. She was discharged home on escitalopram 20 mg, gabapentin 2400 mg daily, and trazodone 100 mg at bedtime as needed.

Case 2

Patient 2 is a 64-year-old female with no previous psychiatric history who was diagnosed with GBS two weeks after onset of generalized weakness. During her acute course she required ventilator support and underwent plasma exchange. Records from the acute care hospital described the development of "anxiety and depression" shortly after admission. Whilst in acute care, she was started on alprazolam 0.25 mg twice daily and sertraline 75 mg daily for these symptoms. She was also treated with acetaminophen/propoxyphene N-100 every four hours for pain. Two months after onset of GBS, she was admitted for neurorehabilitation. During the first four weeks of this admission she continued to experience anxiety and emotional disturbances that interfered with her participation in rehabilitation therapies. Neuropsychiatric consultation was requested by the team to evaluate and recommend treatment for these symptoms.

She reported daily crying spells of a few minutes duration that were under voluntary control and not bothersome to her. She denied current symptoms of depression, and a DSM-IV criteria-based interview suggested that she had not experienced a depressive episode prior to or since the onset of her GBS. Accordingly, her crying spells were regarded as being consistent with mild affective lability following GBS. She reported episodic anxiety and pain that persisted despite current treatments. Her anxiety was most strongly related to her fear of falling during transfers and therapies, and also to her fear that she might not recover fully from GBS. Although problematic, these symptoms did not meet the DSM-IV criteria for panic disorder. She reported modest improvement in her anxiety and affective symptoms following initiation of sertraline, but she did not endorse significant anxiolysis from alprazolam. However, she and the rehabilitation team observed rebound anxiety that temporally coincided with the predicted "off-period" following each alprazolam administration. The patient did, however, report modest improvement in her anxiety and affective symptoms following initiation of sertraline. Cognitive examination revealed mild cognitive impairment, including problems with attention, spontaneous recall, and orientation. Her history did not support a period of hypoxia or other causes of her cognitive complaints. It was suspected that her mild cognitive complaints were attributable to her treatment with alprazolam and acetaminophen/propoxyphene, and they were reduced. Treatment with sertraline 75 mg daily alone was recommended, and the patient was engaged in symptom-targeted psychotherapy to learn more effect strategies for managing her anxiety.

Within two days of reducing her alprazolam, the frequency and severity of her affectively labile and anxious episodes decreased. There was no evidence of benzodiazepine withdrawal, and reducing alprazolam and acetaminophen/propoxyphene effected improvements in orientation and attention both objectively and subjectively. Sertraline monotherapy afforded adequate control of her anxiety and affective symptoms during the remainder of her three-month course of inpatient rehabilitation, and she was discharged home on 75 mg daily.

Case 3

Patient 3 is a 66-year-old female who presented to the emergency department with generalized and progressive weakness one month after a gastrointestinal viral illness. She was hospitalized and required ventilatory support one day after admission. Intravenous IgG was used with no significant change in her condition. She had no previous history of psychiatric diagnosis or treatment, but she and her family described her as a "lifetime worrier". She was noted to be anxious and affectively labile during her acute hospitalization. She was treated with diazepam, lorazepam, alprazolam, temazepam, gabapentin, and buproprion at varying doses and administration schedules as well as citalopram up to 40 mg daily during that period. Notably, the dose of citalopram was quickly titrated to 40 mg daily. That dose escalation coincided temporally with worsening

of her anxiety and affective lability. She was subsequently extubated and admitted to acute rehabilitation after an eight-week stay in acute care. All agents except gabapentin 900 mg daily and citalopram 40 mg daily were discontinued on admission to rehabilitation. Neuropsychiatric consultation was requested on day two of her rehabilitation hospital admission to evaluate her continued and functionally impairing episodic anxiety and affective lability, and to recommend pharmacotherapy.

On examination, she endorsed brief and intense episodes of fear and helplessness, anticipatory and generalized anxiety, frequent crying spells, and impaired concentration. These symptoms did not meet DSM-IV criteria for panic disorder or panic attacks. Given the reported worsening of her symptoms in response to rapid escalation of citalopram dosing, this medication was decreased to 20 mg daily. Treatment with alprazolam was restarted by her primary team at 0.5 mg three times daily initially for the treatment of her anxiety. Two days after decreasing her citalopram, the patient, her family, and the hospital staff reported substantial reductions in the patient's episodic and interepisodic anxiety symptoms as well as reduced affective lability. Acetaminophen/hydrocodone 5/500 one to two tablets twice daily was initiated by the primary team nine days after admission because of exacerbation of pain related to osteoarthritis. This was gradually tapered to one pill three times daily as needed by time of discharge. Because of the patient's concern regarding impaired concentration, alprazolam was gradually discontinued over the following two weeks with no evidence of benzodiazepine withdrawal syndrome. The patient reported improvement in concentration and problem solving. Although infrequent and mild episodic anxiety and crying spells persisted, neither she nor the rehabilitation staff felt these symptoms interfered with her treatment. Over the subsequent three weeks, her anxiety abated and she experienced only two mild and brief episodes of affective lability. She was discharged home on citalopram 20 mg and gabapentin 600 mg daily.

Discussion

Among these patients, functionally impairing anxiety and affective lability developed shortly after the onset of GBS. These symptoms required pharmacologic intervention, and their initial treatment during the acute care period using combinations of SSRIs, gabapentin, trazodone, benzodiazepines, and opiates met with variable response. Treatment with the latter two classes of medication was associated with symptoms of cognitive impairment, prompting concern for their potentially adverse effects on recovery. Cessation of benzodiazepines and opiates in these patients was associated with improvements in arousal, selective and sustained attention, working memory, recall, and problem solving. Each of these patients demonstrated substantial improvements in anxiety, affective lability, and functional performance during treatment with modest doses of SSRIs, alone or in combination with gabapentin. These treatments afforded benefits on these symptoms sufficient to prompt the patients, their families, and the rehabilitation staff to request their continued use at the time of discharge from acute rehabilitation.

The observation of improved anxiety and affective lability, as well as the absence of significant adverse effects (for example impaired cognition) with modest doses of sertraline, escitalopram, and citalopram in the context of recovery from GBS is consistent with the reported effects of these agents on such symptoms among persons with other neurological conditions (Arciniegas and Topkoff 2000; Davies et al 2001). Also consistent with those reports is the relatively rapid response of these symptoms to appropriate dosing of these SSRIs, with substantial improvements occurring within the first 3–7 days of such treatment. These observations suggest that SSRIs may be useful for the treatment of anxiety and affective lability in this context as well. However, it is important to note that two of these three patients also received concurrent treatment with gabapentin (600–2400 mg daily). As such, it is possible that the combination of modest doses of SSRIs and gabapentin was operative in the symptom reductions observed in these patients.

The validity and generalizability of treatment effects described herein suffer all of the limitations inherent to an uncontrolled, open-label, observational, retrospective review of a small case series. Without the benefit of a placebo control or no-treatment comparison group, it is not possible to differentiate the apparent effects of the pharmacologic interventions described herein from the effects of spontaneous recovery, placebo-response, and combined pharmacological and psychotherapeutic treatment. The descriptive nature of this small case series leaves the magnitude of the cognitive, emotional, behavioral, and physical benefits provided by these medications uncertain. The retrospective nature of this review carries the inevitable biased towards the reporting of positive treatment outcomes. However, these three cases represent a consecutive series

of patients with GBS in acute rehabilitation requiring neuropsychiatric consultations for the evaluation and treatment of anxiety and affective lability, and no other cases were omitted from this series. Finally, the case series includes only three patients; whether similar benefits during treatment with modest doses of SSRIs, alone or in combination with gabapentin, would be observed consistently in a larger series of patients with these neuropsychiatric symptoms during recovery from GBS remains uncertain.

Nonetheless, these observations suggest that persons with anxiety and affective lability during recovery from GBS may benefit from judiciously applied pharmacotherapy, and that modest doses of SSRIs, alone or in combination with gabapentin, may be both more effective and better tolerated than benzodiazepines, opiates, or combinations of all of these agents. Further investigation of these hypotheses using prospective, blinded, placebo-controlled, and standardized assessment methods is needed to determine optimal treatment strategies for neuropsychiatric symptoms in this population.

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