Delirium Associated With Baclofen Withdrawal: A Review of Common Presentations and Management Strategies

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The authors reviewed 23 published cases of psychiatric symptoms in association with baclofen withdrawal. Delirium, and not other functional psychiatric conditions, arose secondarily from abrupt baclofen cessation. Vulnerability to baclofen-withdrawal delirium appeared to be greater in individuals who received chronic baclofen therapy. Baclofen-withdrawal delirium can be difficult to distinguish from delirium of other etiologies, and unrecognized and inadequately treated baclofen-withdrawal delirium is associated with significant morbidity and mortality. Complete resolution of delirium symptoms was possible with reinstatement of baclofen. The clinical management of patients experiencing baclofen-withdrawal delirium includes supportive interventions to reduce complications of delirium until symptoms resolve.

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Muscle relaxants are employed by medical practitioners to alleviate the pain and physical discomfort associated with muscle spasm. Baclofen, a β-4-chlorophenol derivative of γ-aminobutyric acid (GABA) has demonstrated particular antispasmodic utility. Agonism at the GABA\(_B1\) receptor is implicated in the drug’s production of inhibition of spinal reflexes that reduce muscle spasm and pain. Baclofen has become widely used for patients with spinal cord injury, multiple sclerosis, and cerebral injuries resulting in spasticity.\(^1\)\(^2\) Baclofen was initially introduced as an orally administered agent. However, orally administered baclofen may be ineffective in as many as 25%–35% of cases, because the oral doses required to achieve sufficient central GABA agonism necessary to induce skeletal muscle relaxation in those cases may be prohibitively high.\(^3\) In the mid-1980s, intrathecal baclofen administration was introduced. This method allows achievement of sufficiently high CSF levels of the medication, without incurring the adverse effects of substantially higher oral doses.

This article addresses a clinically significant consequence of abrupt baclofen withdrawal that was previously underreported in the psychiatric literature. The literature includes several case reports of abrupt-onset psychosis, mood disturbances, and behavioral disturbances arising from abrupt cessation of baclofen use. We suggest that these symptoms can be better conceptualized in the context of delirium. The cause of delirium in these cases can be elusive, but if the delirium is not addressed properly, it is a life-threatening.\(^4\)\(^5\) The psychiatrist who recognizes the possibility of delirium arising from baclofen withdrawal can render effective and expeditious treatment to reduce potential consequences of significant morbidity and mortality associated with baclofen withdrawal, in addition to securing the patient’s comfort by reducing muscular spasticity.

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METHOD

Case reports and case series reporting psychiatric symptoms associated with baclofen withdrawal were identified by a search of English-language articles through MEDLINE and PsycINFO and a review of the bibliography of each that was retrieved. MEDLINE was searched from 1966 through January 2004 by using the following search terms: baclofen, depression, bipolar disorder, anxiety, psychosis, and delirium. PsycINFO was searched from 1972 through January 2004; the terms baclofen, major depression, depression, bipolar disorder, anxiety, anxiety disorders, and psychosis were employed.

The individual cases were categorized by type of psychiatric symptoms, duration of baclofen treatment, temporal relationship of psychiatric symptoms to baclofen cessation, longitudinal course, and past psychiatric history. Although most of the cases were derived from nonpsychiatry journals, the cases were examined for consistency with a diagnosis of delirium or other psychiatric disorder.

Documents and articles that lacked descriptions of specific cases were not included in this review. Articles reporting physical effects associated with abrupt baclofen cessation (e.g., hyperthermia, spasticity, hyper- or hypotension, tachycardia, seizures) without commensurate descriptions of cognitive, emotional, or psychiatric symptoms were also eliminated.7–9

RESULTS

We identified 23 reported cases of psychiatric disturbances associated with baclofen withdrawal.4,10–27 Eighteen cases involved patients treated with oral baclofen,10–12,14,15,17,18,20,21,23–27 and five involved patients treated with baclofen through intrathecal infusion.4,13,16,19,22 A chi-square analysis testing the hypothesis of equal frequencies of expected cases of baclofen-associated psychiatric disturbances among orally and intrathecally treated patients revealed statistically significant differences in observed frequencies ($\chi^2 = 6.26$, df = 1, p < 0.03). Data on the doses employed, treatment duration, and latency until onset of withdrawal are provided in Table 1. Seven cases involved female patients, and 16 involved male patients; but no statistically significant gender differences in the frequency of psychiatric disturbances were found ($\chi^2 = 2.78$, df = 1, p > 0.05). The mean age of the patients was 42.7 years (SD = 15.8).

Psychiatric symptoms associated with baclofen withdrawal included auditory hallucinations (N = 7, 30.4%),12,14,17,24,25 visual hallucinations (N = 13, 56.5%),12–15,17,18,20,21,23,25 tactile hallucinations (N = 1, 4.3%),24 delusions (N = 4, 17.4%),10,15,24,27 confusion (N = 11, 47.8%),4,10,11,13,16,18,19,22,23,25 agitation (N = 13, 56.5%),4,10,13–16,18,20,22,24,27 disorientation (N = 4, 17.4%),10,13,14,17,23 fluctuation of consciousness (N = 2, 8.7%),13,22 insomnia (N = 4, 17.4%),4,10,13,17,23 anxiety (N = 3, 13.0%),23,24 depersonalization (N = 1, 4.3%),23 and formal thought disorder (N = 1, 4.3%).15

Treatment approaches consisted of reinstatement of baclofen alone in 10 cases (43.5%),12,15,17,21–23,25–27 Other treatment approaches included reinstatement of baclofen in combination with other agents, such as haloperidol or other antipsychotics (N = 4, 17.4%),10,14,20,24 benzodiazepines (N = 6, 26.1%),4,13,14,18,19,23 and anticonvulsants (N = 1, 4.3%).25 In some cases, baclofen was not reinstated, but the patients were treated with other agents, including dantrolene (N = 1, 4.3%)6 or benzodiazepines (N = 1, 4.3%).11 The time to complete resolution of psychiatric symptoms after treatment was 42.9 hours, with a range of 4 to 72 hours.4,10,12–15,17,18,20–27

In four cases (17.4%), a history of a preexisting psychiatric disorder was reported. Prior psychiatric disorders included depression,12 schizophrenia,16 atypical personality disorder,14 and a remote alcohol abuse history.24

DISCUSSION

This retrospective review is limited by the lack of a uniform approach to the assessment and description of delirium in the original reports, most of which were published in the literature of fields other than psychiatry. Several reports described varied psychiatric symptoms, such as "hallucinations" or "manic psychosis,"10,14,17 resulting from baclofen withdrawal without noting that such dramatic behavior changes can occur in the context of delirium. In none of the cases reviewed here were the reported psychiatric symptoms consistent with a psychiatric disorder or an exacerbation of a preexisting psychiatric illness,12,14,24,27

In all of the cases, fluctuation of consciousness, inattention, memory impairments, and/or perceptual disturbances emerged abruptly in association with the cessation of baclofen. The psychiatric symptoms emerged in the context of disturbed physical parameters, including tachycardia, autonomic changes, seizures, and spasticity. Other etiologies for the delirium (e.g., substance withdrawal and infectious, metabolic, or other CNS events) were eliminated. Furthermore, in the cases reviewed here, the delirium did not appear to arise secondarily from some other process that was the immediate result of baclofen withdrawal (e.g., from rhab-
domyolysis or postictal confusion). Last, the delirium abated rapidly, usually after restoration of baclofen, without any residual symptoms. It is interesting to note that, in one case, a reattempt at abrupt cessation of baclofen after stabilization resulted in reemergence of the delirium.\textsuperscript{17}

The mechanism of action of baclofen as an antispasmodic is unclear. At high doses, baclofen is thought to stimulate presynaptic GABA receptors, hyperpolarizing the neuronal membranes and thereby inhibiting polysynaptic pathways that lead to muscle spasticity.\textsuperscript{1} The neurological symptoms encountered with abrupt withdrawal from baclofen include rebound muscle spasticity and tremors. In some cases, the resultant muscle rigidity is so severe that severe rhabdomyolysis results, in a pattern that mimics neuroleptic malignant syndrome.\textsuperscript{26,28}

Similarly, neuropsychiatric effects of abrupt baclofen withdrawal are thought to invoke the GABA system as well. Baclofen, like GABA, inhibits CNS pathways involving monoamine neurotransmitter systems. Some researchers have suggested that this inhibition is indirect and that substance P is involved as an intermediate neurotransmitter.\textsuperscript{15,29} With continued use of baclofen, continuous inhibition of monoamine neurotransmitter systems leads to emergence of supersensitive dopamine and noradrenergic receptors. Sudden withdrawal of baclofen would cause a disinhibition of previously suppressed monoamine pathways, that is, a release of norepinephrine and dopamine onto supersensitized receptors, leading to autonomic arousal (e.g., tachycardia, hypertension, agitation, restlessness) and delusions, hallucinations, and delirium.\textsuperscript{20,30}

Factors influencing vulnerability to baclofen-withdrawal delirium include duration of exposure to the medication and the abruptness of baclofen cessation. In this review, delirium arose in individuals who had a minimum of 5 months of exposure to baclofen.\textsuperscript{14,20} The minimum duration of baclofen therapy needed before cessation produces significant withdrawal is unknown; however, it has been suggested that delirium is unlikely if cessation occurs after only 1–2 months of exposure.\textsuperscript{25}

Further, the abruptness of baclofen cessation appears to affect the risk of withdrawal-induced delirium. This relationship is consistent with the fact that baclofen has a short half-life of approximately 3–4 hours. In the cases reviewed here, withdrawal symptoms emerged within 2 days of interruption of baclofen therapy. For patients who experienced intrathecal pump malfunction, there was a precipitous decline in CSF baclofen levels and the symptoms of delirium emerged rapidly, within 12–24 hours.\textsuperscript{13,16,22} On the other hand, cessation of oral baclofen tended to produce withdrawal symptoms at relatively slower rates and with greater variability in the latency to onset (i.e., up to 4 days postcessation).\textsuperscript{27} Coexisting medical conditions and coadministered medications may also influence the rate at which baclofen is metabolized and, therefore, may alter the rate of decline of the agent.

In most cases, baclofen was ceased abruptly because the patient chose to discontinue the medication, because of the need to suspend administration of oral medications preoperatively, or because of intrathecal pump malfunction. In one case, a patient hospitalized for a reason unrelated to the condition for which baclofen was prescribed experienced withdrawal because the prescribed baclofen was not included in the admission orders.\textsuperscript{12} In two cases, an attempt was made to taper the dose of baclofen, but even this reduction was too rapid and precipitated withdrawal.\textsuperscript{18,25} Generally, it is recommended that discontinuation of baclofen occur by means of tapering over 1–2 weeks.\textsuperscript{14} In one case, when the baclofen was reinstated and tapered gradually, the patient tolerated the process well without any reoccurrence of withdrawal symptoms.\textsuperscript{17}

Most of the patients who experienced withdrawal delirium had been treated with oral baclofen. One can only

<table>
<thead>
<tr>
<th>Variable</th>
<th>Oral (N = 18)</th>
<th>Intrathecal (N = 5)</th>
<th>Total (N = 23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baclofen dose</td>
<td>Mean</td>
<td>Range</td>
<td>Mean</td>
</tr>
<tr>
<td>Duration of treatment before discontinuation (months)\textsuperscript{a}</td>
<td>70.3 mg/day</td>
<td>10–160 mg/day</td>
<td>547 µg/day</td>
</tr>
<tr>
<td>Latency until onset of withdrawal symptoms\textsuperscript{a}</td>
<td>23</td>
<td>5–60</td>
<td>19.3</td>
</tr>
<tr>
<td></td>
<td>1–4 days</td>
<td>12–24 hours</td>
<td>14–24</td>
</tr>
</tbody>
</table>

\textsuperscript{a}References 10–12, 14, 15, 17, 18, 20, 21, 23–27.

\textsuperscript{b}References 4, 13, 16, 19, 22.
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speculate about how the route of administration influences withdrawal vulnerability. Patients treated with intrathecal baclofen (or their caretakers) may seek medical attention soon after the pump alarm signals a reduction in the pump reservoir or a defect in the apparatus and may, therefore, be less apt to develop the full gamut of withdrawal symptoms, including delirium. In contrast, patients who cease taking oral baclofen may not seek medical attention until withdrawal symptoms, including delirium, become marked.10,12,15,23,24,26,27 This difference highlights the importance of medication adherence and ongoing collaboration between patient and physician. Patients may need to be educated about the importance of maintaining consistency in dosing and of undertaking discontinuation of baclofen only after consultation with a physician in order to avoid dangerous sequelae.

Given the wide range of prewithdrawal baclofen doses, vulnerability to withdrawal does not appear to be dose dependent. Similarly, gender does not appear to influence withdrawal vulnerability. As for age, all of the cases reviewed here involved adult or elderly patients, the youngest patient was age 18 years.25 We identified a few published reports describing children who experienced intrathecal pump failures and developed severe physiological reactions in response to abrupt baclofen cessation, including autonomic dysfunction, hyperpyrexia, and spasticity.7,8,28 However, these cases were not included in this review because they lacked descriptions of concurrent cognitive and/or psychiatric withdrawal symptoms. Moreover, children for whom baclofen is prescribed may have severe conditions and may be more likely to receive intrathecal than oral therapy. As noted previously, intrathecal administration of baclofen may carry with it certain safeguards that mobilize medical intervention and prevent the development of a severe withdrawal and delirium.

Clinical Management

Abrupt mental status changes arising in a patient with history of chronic muscle spasticity should prompt consideration of baclofen withdrawal. If orally administered baclofen had been employed, the clinician should ascertain the dose and determine whether the medication has been recently discontinued and over what time period it was discontinued. The literature suggests that readministration of baclofen leads to rapid resolution of delirium induced by baclofen withdrawal. If discontinuation of baclofen is deemed necessary, it may be accomplished by means of gradual taper over the ensuing weeks.

For patients who had been receiving intrathecal baclofen before experiencing discontinuation of baclofen because of pump malfunction, resumption of baclofen in oral form may not mitigate withdrawal delirium. Prohibitively high oral doses could be required to reach the CSF levels of baclofen that had been achieved before intrathecal baclofen therapy was interrupted.31 In addition, the intrathecal route of administration is often used because previous therapy with oral baclofen failed.13 Nonetheless, resumption of oral baclofen may be an expedient measure.32 If it is unsuccessful, administration of a bolus intrathecal dose of baclofen can alleviate symptoms of spasticity and curb neuropsychiatric disturbances that arise from abruptly low CSF levels.32 In addition, such measures would allow sufficient time to address the problems associated with pump failure, such as insufficient amounts of baclofen in the pump reservoir, battery failure, pump failure, catheter disconnection from the pump, disruptions in the catheter (kinking, leakage, obstruction), and displacement of the catheter from the intended intrathecal space.4,33 Some of these problems may be easily rectified (e.g., restoring volumes of baclofen in the pump reservoir19), whereas other interventions may require surgical exploration and repair. It may be necessary to contact the intrathecal pump manufacturer for help with difficult-to-resolve problems.34

Other supportive interventions are likely to be required to reduce the complications of delirium until symptoms resolve. For example, use of antipyretics may be warranted.34 If resumption of baclofen fails to remit spasticity, use of dantrolene or other antispasmodics and/or benzodiazepines may be helpful.4,16 In addition, benzodiazepines and/or anticonvulsants may suppress or attenuate withdrawal seizures.3,14,12,14,18,19,24 Antipsychotic medications may be required to control hallucinations and psychomotor restlessness and to prevent the possibility of inadvertent self-harm.10,14,24 However, in light of concerns about risk of seizures, caution should be exercised in using antipsychotic medications; concomitant benzodiazepine use may mitigate this risk. The aforementioned supplemental agents are not required for long periods, as withdrawal symptoms are time limited, especially if the baclofen is resumed.

Patients should be monitored for significant morbidity (e.g., aspiration). In patients with severe spasticity and/or an elevation in the creatinine kinase level, renal function should be monitored by means of urinalysis, urine myoglobin measures, and serum measures of urea nitrogen and creatinine. Intravenous hydration and prudent use of diuretics may be required to prevent renal failure. Serial monitoring of serum creatinine kinase activity may help in gauging the efficacy of treatment interventions.32

As with other conditions resulting in delirium, abrupt


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baclofen discontinuation carries with it the risk of death. Withdrawal of intrathecal baclofen has resulted in six deaths reported to the U.S. Food and Drug Administration, \textsuperscript{5,6} and has resulted in the inclusion of a black-box warning on labels pertaining to intrathecal baclofen use. This warning has not been applied to oral baclofen.

Summary

Baclofen, which generally has few side effects, has become one of the most widely prescribed muscle relaxants. It offers certain advantages over other antispasmodics, including its availability for oral or intrathecal administration. Delirium is associated with abrupt baclofen discontinuation, although the precise mechanism by which delirium develops has not yet been elucidated. The cause of delirium associated with baclofen discontinuation can be elusive, because the symptoms mimic those of other conditions, including neuroleptic malignant syndrome and alcohol or benzodiazepine withdrawal. By ascertaining that a patient’s delirium is induced by baclofen withdrawal, the consultation-liaison psychiatrist may facilitate effective treatment and optimize the patient’s care.

References