

Catatonia and Delirium in polypharmacy including baclofen and botulinum toxin injection: Case Report and literature review

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Abstract

It is not uncommon for patients to have symptoms that overlap with catatonia and delirium, or atypical presentations of either syndrome. Baclofen toxicity and withdrawal has been associated with adverse neuropsychiatric symptoms. We describe a case of a 32-year-old woman with catatonia and delirium in the setting of chronic disability, polypharmacy including baclofen and recent botulinum toxin injection. The patient was successfully treated with lorazepam, risperidone and valproate. She received botulinum toxin again and tolerated it well, and she is no longer taking baclofen. Botulinum toxin injection exacerbating the psychiatric side effects of baclofen needs to be considered.

Introduction

Catatonia is a neuropsychiatric syndrome characterized by abnormalities in mental status and motor function. It is usually diagnosed by the presence of at least 2 of the 14 items on the Bush-Francis Catatonia Scale (BFCS) (Table 1) or by the DSM-V criteria, the presence of at least 3 of 12 items (Table 2). While catatonia is usually associated with withdrawal and psychomotor retardation, it may also present with agitation. The exact mechanism of catatonia is not known and it has been associated with multiple medical and psychiatric illnesses. It may have physical consequences including complications of immobility such as pulmonary emboli and pressure ulcers in the retarded subtype, and may itself be fatal, particularly in the agitated subtype. One of the distinguishing characteristics of catatonia is its reversibility with administration of benzodiazepines, achieving cure rates in some studies upwards of 90% (Table 1 and 2) [1]. While multiple medical illnesses have been associated with catatonia, it has been found to affect 9-17% of psychiatric patients [2]. Of these psychiatric cases of catatonia, mood disorders are implicated in 46% and schizophrenia in 20% [3].

Medications have been documented to cause catatonia. While there have been a few case reports of baclofen toxicity causing catatonia and experimental studies have indicated that it can cause catatonia in rats [4], a literature search did not find any case reports of baclofen withdrawal as a primary cause of catatonia.

We describe a case of a 32 year old woman with catatonia in the setting of chronic disability, polypharmacy including baclofen and recent botulinum toxin injection.

Case Report

Medical history

Ms. K is a 32 year old white female with a complex past medical history, which included seizures, dextrocardia, fibromyalgia, Klippel-Feil syndrome, scoliosis, migraines, torticollis, obesity and severe sleep apnea. Her psychiatric history included depression and a suicide attempt by medication overdose more than ten years earlier. Known family medical history included a parent with bipolar disorder, as well as other relatives with schizophrenia and dementia.

Patient was reported to be speaking incoherently at home. Her parents brought her to the emergency department. Vitals on admission were stable: BP 114/51, T 98, RR 15, Pulse 88, oxygen saturation 97%. The ED physicians found her to be alert and oriented to self only and she spoke in fragmented, nonsensical sentences (“I loved the s--- in the lion. The socks crawled then the wall did that in the water”). Physical exam was normal, with no neurological deficits appreciated. She was admitted to the General Medicine service, with the differential diagnosis of an adverse drug reaction, overdose or toxicity, vs. psychiatric disease vs. somatization.

Approximately a week before admission, Ms. K’s psychiatrist prescribed lisdexamfetamine to encourage alertness and weight loss. Two days before admission, Ms. S had a routine outpatient visit with neurology, where 280 Units of botulinum toxin injection were injected for torticollis. The following day, her behavior was normal, per her family.

She saw multiple medical providers at multiple facilities for her medical problems, including a pulmonologist and neurologist at our institution, and a primary care physician, pain

Table 1. Bush-Francis Catatonia Scale.

Hyperactivity	Stereotypy
Immobility	Mannerisms
Mutism	Verbigeration
Staring	Rigidity
Posturing, catalepsy	Negativism
Grimacing	Waxy flexibility
Echopraxia, echolalia	Withdrawal

Table 2. DSM-V catatonia criteria.

Catalepsy	Mutism	Stereotypy
Waxy flexibility	Negativism	Grimacing
Stupor	Posturing	Echolalia
Agitation	Mannerisms	Echopraxia

specialist and psychiatrist and therapist at outside hospitals. Of note, she was taking 19 different medications from different physicians, which she filled both from her local drugstore and through a mail order pharmacy in another state (**Table 3**).

According to past medical records, she had a history of aphasia caused by amitriptyline and was seen in our emergency department two years earlier for a seizure, which was suspected to be secondary to bupropion.

Social history

Ms. K lived at home with her parents. In the past, she attended some college and previously worked as a sales associate. Due to her chronic medical problems, she had not worked for three years. Her parents did not allow her to drive due to her use of opioid pain medications and described her as too indecisive to shop alone. For several years, she had developed a nocturnal sleep cycle: waking around 5pm and sleeping until around 5am.

However, Ms. K enjoyed an active social life online and over the phone with friends and family and managed her own medications. She was not known to use alcohol, tobacco or illicit drugs.

Before admission, Ms. K had experienced several disputes with different family members and experienced the loss of sentimental keepsakes, which may have contributed to stress and depressed mood.

Initial Lab Results

Complete blood count

WBC 8.0 k/ul, RBC 4.65 m/ul Hgb 13.4 g/dL, HCT 39.9%, MCV 85.7 fl, Plt 271 k/ul. **PT/INR:** PT 11.7 sec, INR 1.0. **aPTT:** 30.1 sec. **EtOH:** Not detected. **Liver function panel:** Albumin 3.8 g/dL, Total Protein 6.7 g/dL, ALP 101 IU/L, ALT 70 IU/L*, AST 74 IU/L* , T Bili 1.5 mg/dL *, Direct Bili 0.6 mg/dL*, Phosphate: 2.4 mg/dL *, Mg: 2.1 mg/dL, **Osmolality:** 289 MOsm/K , **Basic metabolic panel:** Na 138 mmol/L, K 4.8 mmol/L* Cl 102 mmol/L ,CO₂ 17 mmol/L (L), Anion gap 19 (H), BUN 11, Cr 0.78 (*specimen hemolyzed).

Creatine kinase

CK 107 IU/L, **Lactate:** 1.3 mmol/L, **Blood culture:** No growth after 5 days, **Blood gases:** pH 7.43, PCO₂ 40 mm Hg,

PO₂ 72 mm Hg (L), **Troponin:** 0.0 ng/mL

Urine drug screen

UDS negative for amphetamines, barbiturates, benzos, cannabinoids, cocaine, PCP

Positive for opiates. **Acetaminophen:** <10 ug/mL. **Salicylates:** <4 mg/dL, **Urinalysis:** Yellow, clear, pH 7.0, SG 1.017, **Protein 1+ (H)**, Blood neg, Glucose neg, Ketones mod, Bili neg, UBG <2.0 Nitrite neg, WBC neg, 8 RBC/hpf, 5 hyaline casts/hpf

Hospital Course

Neurology was consulted and suspected an intoxicated state and initially recommended a CT of the head and neck to rule out ischemia. Toxicology was consulted. The family did not suspect an overdose. Toxicology recommended holding baclofen, pregabalin, duloxetine, opioid pain medications and zolpidem, as those drugs could have contributed to her altered mental status. All of Ms. K’ home medications were held. Urine Drug Screen was negative for illicit drugs. Neurology recommended a psychiatric consultation and an MRI of the head, although Ms. K was unable to cooperate. When the psychiatry team assessed Ms. K on Day 3, she was not alert or oriented to person, place or time, spoke only meaningless, incoherent single words and could not maintain eye contact. She was able to follow some simple commands but otherwise uncooperative with the interview. No psychomotor agitation or retardation was observed. Patient denied intentional overdose or suicide attempt. She denied suicidal ideations.

Delirium from polypharmacy was the initial diagnosis and psychiatry recommended continuing workup of medical causes of altered mental status. Ms. K was noted to have urinary retention which was treated with catheterization and tamsulosin. Her EEG was normal. An EKG detected possible atrial flutter, although a follow-up echocardiogram was normal. She was maintained on IV fluids and toxicology recommended 100 mg pyridoxine IV per day. On Day 6, the hospitalist caring for Ms. K noted dyskinesia, dilated pupils, tachycardia (highest HR 112) and hyperreflexia, and serotonin syndrome was considered. Ms. K was noted to be speaking nonsensically and did not cooperate with questions. She was unable to recognize a pen or watch. She was noted to have a tic of clicking her mouth repetitively. Medical workup had thus far had been inconclusive. Serotonin syndrome was ruled out as there was no myoclonus. Neuroleptic malignant syndrome (NMS) was ruled out as there was no rigidity and there was no evidence patient had been taking antipsychotics. We considered catatonia as a differential diagnosis, based on her stereotyped movements, nonsensical speech patterns and expansive mood, and she received a 1 mg IV lorazepam trial. After the dose, Ms. K appeared calmer with decreased mouth clicking and was able to recognize the pen and watch.

Encouraged, we started lorazepam 1 mg PO twice daily. Because delirium secondary to polypharmacy was also in the differential, we decided to start with a lower dose of lorazepam

Table 3: Reported outpatient medications.

Morphine, extended release 30mg q 8 hr	Albuterol MDI	Codeine 10 mg/Acetaminophen 325 mg 1 tab qhh	Benadryl **
Clotrimazole-betamethasone cream BID PRN	Propranolol 10 mg q12 hr	“Energy shots”**	Fluticasone nasal spray
Zolpidem 5 mg qd PRN	Duloxetine 60 mg BID	Tylenol	Levonorgestrel-ethinyl estradiol (Quasense)
Pantoprazole 40 mg qd	Modafinil 400 mg BID	Lisdexamfetamine 30 mg and 40 mg	Meloxicam 15 mg qd
Pregabalin 300 mg BID	Baclofen 20 mg TID	Naloxegol 25 mg qd	

**Closed bottle

(1 mg BID) than the usual high dose lorazepam typically given for catatonia (2-2.5 mg up to six times per day) [5]. On Day 8, Ms. K was agitated at night, continued her clicking tic, and started repetitively waving her arms. She was able to complete the MRI, although it showed no acute changes. The Mini Mental Status Exam (MMSE) was 9: Ms. K was able to read, speak and follow some commands, but her speech was largely fragmented, now with echolalia.

We reviewed patient’s home medications. She had missed 3 doses of baclofen in the 3 days before admission. The prescribed dose was 20 mg three times daily. Ms. K’ nighttime agitation worsened, and on Day 9, her MMSE score decreased to 6 which again lead to concern of worsening delirium. Her mental status exam was significant for a constricted affect, word salad speech, and a short attention span. A family member reported that her whole body shook overnight. Due to her history of severe sleep apnea, we held the lorazepam until she could be restarted on a BIPAP. We also suspected that patient’s presentation could be baclofen withdrawal, and after discussion with neurology, re-started baclofen 5 mg twice daily. A video EEG completed on Day 10 was unremarkable. When we held the lorazepam, there was a dramatic worsening of mental status and increased catatonic symptoms. She was uncooperative with the MSE, and demonstrated far more severe echolalia, echopraxia, abnormal posturing, agitation and continued motor tics. This led to a stronger suspicion of catatonia, and we started titrating the lorazepam even though there were concerns of sepsis and delirium. We restarted her on lorazepam 1 mg PO twice daily. On Day 11, her white cell count rose to 16 and she complained of dysuria. General Medicine started 500 mg ciprofloxacin twice daily for a suspected urinary tract infection. We increased lorazepam to 1 mg three times daily and continued baclofen 5mg bid.

Ms. K was more confused on Day 12. She ran screaming into the ward at night due to command auditory hallucinations, and a family member observed her trying to feed someone who was not present. Although she remained verbal, the content was nonsensical, and she was not oriented to self, time or place. (She identified herself with a friend’s name, identified her sister with their father’s name, stated that the year was in the 1990s, and that she was at home). Her MMSE was 4. Grimacing, twitching, stereotyped waving of one arm were observed. We recommended increasing lorazepam to 1 mg IV every 6 hours, with an additional 1 mg IV every 6 hours for agitation, and

titrated up the dose of baclofen to 5 mg in the morning and 10 mg in the evening. Her medical condition had also worsened. A urine culture identified *Klebsiella pneumoniae*. Ciprofloxacin was discontinued and replaced with cefepime, due to concern about the potential neuropsychiatric effects of fluoroquinolones. Her white cell count went up to 17.5 and her lactate to 4.4. The ICU was consulted and recommended a 2 L fluid bolus. Sepsis from catatonia was considered and we continued to give lorazepam.

Lab Results Day 10

Urinalysis: Yellow, hazy, pH 6.0, SG 1.013, protein negative, blood negative, glucose negative, ketones negative, bilirubin negative, UBG <2.0, nitrite positive, WBC large; 2 RBC/hpf, 96 WBC, hpf, many bacteria, Urine culture: >10,000 colonies *Klebsiella pneumoniae*/mL,

Day 12

CBC: WBC 17.5 k/uL

Blood cultures: NG after 5 days

Day 12 to 13:

Lactate: 4.4 mM/L (at 0745)

Lactate: 2.8 mM/L (at 1830, after two fluid boluses at 1115 and 1521)

Lactate: 4.4 mM/L

Day 13 CBC

WBC 13.4 k/uL

Ms. K’ urinary tract infection improved by Day 13. We continued to increase the baclofen to 10 mg twice daily because baclofen withdrawal was considered at that time. Ms. K became psychotic and violent on Day 14, and physically attacked a family member. She was observed gesturing, blinking and grimacing. She received total 7 mg lorazepam on day 14 and eye movement and echolalia decreased partially. As the urinary tract infection continued to improve, the primary team switched her from IV cefepime to PO sulfamethoxazole trimethoprim. We increased lorazepam to 2 mg IV every 6 hours, with 1 mg IV every 6 hours as needed for agitation, added risperidone 0.5 mg daily and divalproex sodium 250 mg twice daily. As the increased dose of baclofen had not improved her mental status and may have worsened catatonia, we stopped baclofen.

The new psychiatric regimen decreased Ms. K' agitated behavior. From day 18 to 25, patient made progress. We planned a lorazepam taper and communicated it with her outside psychiatrist: 1.5 mg every 4 hours for 2 days, 1 mg every 4 hours for 2 days, 0.5 mg every 4 hours for 2 days, 0.5 mg every 6 hours for 2 days, 1 mg twice daily for 1 week and 1 mg at night for 3 months. During the entire stay, she received Lorazepam 143mg total.

Ms. K' mental status and medical condition remained stable on the lower dose of lorazepam for the next few days, and she was discharged home to family on Day 25, an appointment with her psychiatrist scheduled for the next day. Two months after discharge, Ms. K is seeing a psychiatrist every six weeks, a therapist every other week and a trauma specialist every week. The latter is a new addition to her team. She finds this team helpful. Per her outpatient neurologist, she continues to have chronic torticollis, with limited range of motion and neck pain. She received 280 units of botulinum toxin again and tolerated it well. Her medications include cyclobenzaprine, valproate, risperidone, low dose lorazepam, pregabalin and propranolol. She is no longer taking duloxetine, lisdexamfetamine, modafinil and baclofen.

Discussion

Literature review

It is not uncommon for patients to have symptoms that overlap with catatonia and delirium, or atypical presentations of either syndrome. Fink describes four subtypes of catatonia: retarded, excited, oneiroid and malignant [6]. Delirium also has hypoactive, hyperactive and mixed presentations [7]. Wilson et al. [8] point out that the DSM-V diagnostic criteria do not permit co-diagnosis of catatonia and delirium in many cases, particularly if catatonia is secondary to a medical illness. However, in their study of 136 ICU patients, 31% had symptoms of catatonia and delirium. On the other hand, antipsychotics have been associated with catatonia [9]. We were presented with this challenge in our patient management: lorazepam worsening delirium versus risperidone worsening catatonia. However, the MMSE score improved after continuous use of lorazepam in addition to risperidone. Studies are needed to see the effect of continual lorazepam use in patients presenting with delirium and catatonia combined.

A recent case report written by Meyen et al. [10] illustrated the challenges of managing a patient with catatonia and delirium [10]. Regarding catatonia treatment, Meyen et al recommended investigating and aggressively treating potential medical causes of catatonia and delirium. In a systematic review of catatonia treatment [11], benzodiazepines, particularly lorazepam, were found to be the most widely reported treatment and the studies examined reported response rates of 66-100%. ECT may be used for catatonia resistant to benzodiazepines, with response rates between 59-100%, although higher frequency may be associated with a higher risk of adverse effects. Finally, there

is some evidence that valproate may be helpful for agitation, particularly in patients that do not respond to benzodiazepines or ECT [12].

Our differential for altered mental status in Ms. K included catatonia and delirium. Given the long record of adverse psychiatric reactions to baclofen use or withdrawal, we strongly suspected it as a potential etiology. From our examination of Ms. K' home medications, we were able to confirm that she missed at least 2-3 doses of baclofen. Additionally, Ms. K exhibited multiple psychiatric symptoms consistent with baclofen withdrawal, including disorientation, confabulations, auditory and visual hallucinations, and agitation. Her poor attention span, which was consistent throughout her admission, was suggestive of delirium. However, she also exhibited several signs of catatonia throughout her admission, including echopraxia, echolalia, grimacing, negativism, mutism, staring, stereotypy, verbigeration, impulsivity and combativeness.

We were particularly interested in baclofen, as baclofen toxicity and withdrawal have been associated with psychiatric syndromes [13-18]. We initially suspected baclofen withdrawal as a causal factor for patient's catatonia as our patient has missed three doses of baclofen. Given that restarting baclofen did not resolve our patient's altered mental status and instead likely worsened her catatonia, we then suspected baclofen itself may have been a causal factor for catatonia. The three doses that she missed were during a period of three days and her usual dose was 20 mg baclofen TID. Patient did not improve when baclofen was restarted, which is the usual course with baclofen withdrawal syndromes.

Baclofen is an anti-spasmodic that acts as an agonist to GABA-b receptors. Baclofen withdrawal has been associated with adverse neuropsychiatric symptoms, including confusion [19], psychosis [20], delirium [21], and hallucinations and delusions [22] since the 1970s. In case reports, restarting baclofen generally helps to improve the patient's mental status [23,24]. To our knowledge, no case report has ever associated baclofen withdrawal with catatonia.

In a 1999 case report of catatonia attributed to benzodiazepine withdrawal, baclofen cessation was suggested as a contributor [25]. In this case report, the authors describe a possible interaction between GABA-A and GABA-B activity, as benzodiazepine withdrawal can lead to a decline in GABA-A agonist activity. This decline was purported to be further exacerbated by a decrease in GABA-B activity from baclofen withdrawal, thus causing an overall imbalance in GABA receptors and resulting catatonia. Furthermore, repetitive transcranial magnetic stimulation (rTMS) has been studied as a potential treatment for catatonia by stimulating GABA-B receptors. Baclofen has been demonstrated to enhance the effect of rTMS in catatonia, likely by increasing GABA-B agonism [26]. This observation further supports the possibility that baclofen withdrawal can worsen catatonia via an abrupt decrease in GABA-B activity, as in our patient. However, re-starting baclofen only worsened

the symptoms.

Interestingly, baclofen toxicity has also been implicated as a cause of hallucinations and psychosis [27], confusion [28] and depression [29]. A few case reports have attributed catatonia to baclofen intoxication and use, and it has been documented to cause catatonia in rats [30]. This catatonia was observed to be reversible by the administration of homotaurine and delta-amino-n valeric acid, which are two GABA-B receptor antagonists, indicating that excessive GABA-B activity could induce catatonia. In addition, two case reports have described two patients presenting with baclofen-induced catatonia [31,32]. In the first case, the catatonia began after the patient increased his dose of baclofen, and resolved after the baclofen dosage was titrated back down. In the second case, the patient presented with a baclofen overdose and subsequent psychosis with catatonia, which resolved with a trial of lorazepam. In our case, baclofen toxicity was certainly a possibility given our patient's unclear medical history, and would support the findings in these previous cases.

We have considered other factors that may have contributed to Ms. K' catatonic state. She started lisdexamfetamine about a week before the admission. There are a few case reports of both acute and chronic use of amphetamines causing catatonia [33]. Ms. K had also received a botulinum toxin injection two days earlier. A literature search in the PubMed database for "botulinum" and "catatonia" and "botox" and "catatonia" turned up zero results. Furthermore, a few months after discharge, she received a botulinum toxin injection uneventfully; however at the time she was also no longer taking Baclofen. In our case, our patient had a botulinum toxin injection two days before admission. While botulinum toxin has been shown to have numerous adverse effects, the reported symptoms, such as muscle weakness, myalgias and anticholinergics adverse effects [34] are peripheral in nature, with no reports of psychiatric central nervous system side effect of botulinum toxin. The safety of botulinum toxin after several reports of adverse effects is being reviewed by the US Food and Drug Administration (FDA) suggestive that the toxin had spread in the body [35]. Furthermore, a previous study has shown that botulinum toxin has the potential to enter the brainstems of rats, even when injected peripherally [36].

Botulinum toxins cause synergistic or additive peripheral toxicity with skeletal muscle relaxants including difficulty with swallowing, speaking, breathing or walking [37]. However, it is possible that synergy exists between baclofen and botulinum toxin, with botulinum toxin potentiating the central adverse effects of baclofen. Baclofen primarily acts by GABA-B agonism, while botulinum toxin acts by preventing acetylcholine release at neuromuscular junctions. It is possible that there is an interaction between GABA-B receptor overactivity and acetylcholine depletion. Ultimately, studies are needed to demonstrate if botulinum toxin injections could potentiate the psychiatric effects of baclofen in patients. It is more important

because botulinum toxin injections are given commonly by different levels of practitioners apart from physicians.

The consistent course of lorazepam dramatically improved patient's symptoms, supporting a diagnosis of catatonia primarily. In our patient, cause for catatonia likely is multifactorial including polypharmacy and our patient's baclofen prescription. Any interaction between botulinum toxin injection and baclofen and possibility of botulinum toxin injection exacerbating the psychiatric side effects of baclofen needs to be considered. The diagnosis was complicated by the patient's polypharmacy, prescribed by multiple providers in different health systems and filled by two pharmacies, as well as underlying depression and a urinary tract infection. The patient was successfully treated with lorazepam, risperidone and valproate. In the two months since discharge, Ms. K has done well with a simplified medication regimen (notably she has not restarted baclofen) and close mental health follow-up as she is currently in the care of three mental health professionals.

Declaration

The authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article.

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