Key Words: buprenorphine, substance-withdrawal, psychosis, mania, two-hit hypothesis

New-Onset Psychotic Symptoms Following Abrupt Buprenorphine/ Naloxone Discontinuation in a Female Patient with Bipolar Disorder: A Case Report

By Yezhe Lin, Alexander D. Zhang, Ching-Fang Sun, Justin B. White, Ansi Qi, Jessica A. Farrell, Robert L. Trestman, Rachel K. Martin, Anita S. Kablinger

ABSTRACT *~ Buprenorphine and naloxone (Suboxone) is a combination medication-assisted treatment (MAT) for opioid use disorder. MAT withdrawal-induced psychosis is a rare clinical presentation. To our best knowledge, only three reports have summarized the characteristic manifestations of buprenorphine withdrawal psychosis, yet all of them were male. In this case report, we present a 41-year-old female patient with bipolar disorder and comorbid substance use disorder who developed new-onset psychosis and relapse of manic symptoms following abrupt discontinuation of Suboxone. Manic and psychotic symptoms remitted after a short-term hospitalization with the treatment of an antipsychotic and a mood stabilizer. In addition to discussing this case presentation and treatment approach, we review existing literature and discuss possible underlying mechanisms to enhance understanding of this clinical phenomenon.* Psychopharmacology Bulletin. *2022;52(3):72–80.*

Background

The prevalence of opioid misuse and abuse has escalated rapidly in the United States, with an estimated 2.4 million Americans currently suffering from opioid use disorder.[1] Buprenorphine/naloxone (Suboxone) is considered the first-line treatment in the management of opioid use disorder. Buprenorphine is the therapeutic agent in this combination to treat opioid dependence; naloxone is

Lin, MD, Sun, MD, White, MD, Farrell, MD, Trestman, MD, Martin, MD, Kablinger, MD, Department of Psychiatry and Behavioral Science, Carilion Clinic-Virginia Tech Carilion School of Medicine, Roanoke, VA, USA; Virginia Tech Carilion School of Medicine, Roanoke, VA, USA. Zhang, BA, Virginia Tech Carilion School of Medicine, Roanoke, VA, USA. Qi, MD, Department of Medical Psychology, Shanghai General Hospital, Shanghai Jiao Tong University, Shanghai, China.

Dr. Anita S. Kablinger, Dr. Yezhe Lin, Carilion Clinic Psychiatry & Behavioral Medicine – Roanoke 2017 S Jefferson St 2nd Floor, Roanoke, VA. Tel: (540) 589 - 6631; (540) 750 5425. Email: ASKablinger@carilionclinic.org; ylin@carilionclinic.org

included to minimize potential abuse. This combination reduces abuse compared to buprenorphine alone through the mechanism of opioid receptor antagonism.[2] Sublingual bioavailability of naloxone has been estimated only to be about 10%.[3] Buprenorphine works primarily as a partial mu-agonist and kappa-antagonist[4] and is also reported to have possible effects on mood[5,6] and psychosis.[7] Three previous case reports illustrate that abrupt discontinuation of buprenorphine can lead to withdrawal-induced psychosis (Table 1).[8–10] However, no female case has been reported. Here we present the fourth case of buprenorphine withdrawal-induced psychosis in a female patient with a history of bipolar disorder.

Case History

Mrs. T is a 41-year-old, married, unemployed female with a past psychiatric history of bipolar I disorder, generalized anxiety disorder, panic disorder, and polysubstance abuse (alcohol, cocaine, heroin, methamphetamine, nicotine). She started Suboxone treatment two years prior to the current presentation at a dose of 12–3 mg daily for one year and then decreased to 8–2 mg per day for maintenance. The patient had good adherence to suboxone treatment until two months ago. She denied current substance misuse. Her family history is significant for her father with alcohol use disorder and mother with substance abuse and depression.

Observing manic and psychotic symptoms, the patient's family encouraged her to seek help for almost two months. The patient eventually presented to the emergency department upon recommendation by an outpatient psychiatrist. A workup, including basic metabolic panel, blood counts, urinalysis, EKG, and urine drug screen, was unremarkable. After medical clearance, she was admitted to the acute psychiatric inpatient unit due to manic and psychotic symptoms.

Symptomatology

During the initial interview, Mrs. T made bizarre statements, such as her report of having a hammer under her seat. She also endorsed a decreased need for sleep (3 hours per night). The patient appeared skeptical when asked about psychotic symptoms and adamantly denied auditory and visual hallucinations but stated, "I am hearing what I need to hear. I mean, I have seen some things, but I was meant to see those things." Young Mania Rating Scale (YMRS)[11,12] score upon admission was 22 (positive for mania).

TABLE 1

Summary of Case Reports of Acute Psychosis Following Buprenorphine/Opiate Withdrawal

ID	Authors, Year	Patient Description and Withdrawal Symptoms	Past Psychiatric History	Medical Comorbidities or Previous Substance Use	Family History	Course and Treatment Response
1	Navkhare et al. (2017)[8]	A 40-year-old male developed delusions of reference and persecution, and visual hallucinations after abrupt discontinuation of buprenorphine 16 mg daily	None	Opiates	None	Trial of olanzapine with partial improvement. Symptoms remitted within two days after resuming buprenorphine 2 mg daily.
2	Weibel et al. (2012)[9]	A 37-year-old male developed paranoid delusions and auditory hallucinations two weeks following abrupt withdrawal of buprenorphine 8mg daily.	LSD-induced hallucinations	Heroin Marijuana	Not Reported	Initially started on risperidone, titrated to 8 mg daily without complete remission; then resumed buprenorphine 8 mg daily and symptoms remitted five days later.

(*Continued*)

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Summary of Case Reports of Acute Psychosis Following Buprenorphine/Opiate Withdrawal

ID	Authors, Year	Patient Description and Withdrawal Symptoms	Past Psychiatric History	Medical Comorbidities or Previous Substance Use	Family History	Course and Treatment Response
3	Karila et al. (2008)[10]	A 32-year-old male developed paranoid ideation and visual and auditory hallucinations following buprenorphine taper from 6 mg daily.	Unspecified psychotic disorder	Heroin Benzodiazepines Buprenorphine Misuse (12–24 mg/day intranasal) Cocaine	Not Reported	After tapering buprenorphine by 2 mg, the patient developed opioid withdrawal symptoms (anxiety, myalgia, sleep disturbance). After an additional 2 mg decrease, the patient experienced visual and auditory hallucinations, paranoid ideation, alternating phases of agitation, and prostration. Treated initially with loxapine 200 mg/day with partial improvement and then buprenorphine 6 mg/day added. Symptoms remitted within one day of buprenorphine resumption.

On examination, the patient was a well-groomed middle-aged woman appearing stated age. Her posture and gait were normal. While overall cooperative, she was anxious and guarded. She held intermittent eye contact. She had pressured speech with normal volume and was oriented to time, place, and situation. Her attention was sustained, and she illustrated the ability to recall autobiographical and historical information. Her mood was described as mixed, both euphoric and sad. Collateral information from her partner revealed her ideas of reference, paranoia, and auditory and visual hallucination. The partner reported the manic and psychotic symptoms started after abrupt discontinuation of Suboxone treatment two months ago. Due to limited psychiatric access in a rural setting, she did not receive any intervention. Her partner noted pressured speech, decreased need for sleep, increased goal-directed behavior, and delusions of reference. She squandered valuable items, gave away money, and drove hundreds of miles to look for specific license plates, and street signs that she believed were significant dates for her family, such as her daughter's birthday. She also endorsed false beliefs that she had outstanding warrants and asked for a divorce from her happily married partner. Her partner also reported that Mrs. T developed religious preoccupation and excessively focused on reading religious texts (which is incongruent with her cultural background). She also endorsed vague paranoid ideation (skeptical about questions during the interview) and auditory hallucinations (telling her husband, "They are telling me this…" "They are doing that…"). Her symptoms caused significant distress to her family. The partner was aware of previous manic symptoms in the context of heroin and methamphetamine relapse, but the psychotic symptoms were novel in the past 13 years since they married. Both the patient and husband denied substance misuse in the past two years. She had several past psychotropic trials, including venlafaxine, paroxetine, escitalopram, bupropion, perphenazine, ziprasidone, quetiapine, lurasidone, risperidone, gabapentin, valproate, and atomoxetine. She had a questionable adherence to her previous trials with intermittent substance use. Her last trial was quetiapine which was discontinued five months before admission.

Diagnosis

Admitting diagnoses: substance-induced psychotic disorder and substance-induced mood disorder.

Historical confirmed diagnoses: bipolar I disorder, generalized anxiety disorder, panic disorder, alcohol use disorder, stimulant use disorder (cocaine, methamphetamine), opioid use disorder (heroin), and nicotine use disorder.

Treatment

On admission, she was initiated on lamotrigine 25 mg nightly and ziprasidone 40 mg twice daily. Lamotrigine was later changed from night to morning dosing, and ziprasidone was cross-tapered to paliperidone due to reported side effects of dizziness. Paliperidone was titrated to 9 mg every night. After seven days of hospitalization, her manic symptoms and psychotic symptoms remitted (YMRS scored 9). She was subsequently discharged with outpatient follow-up.

Discussion

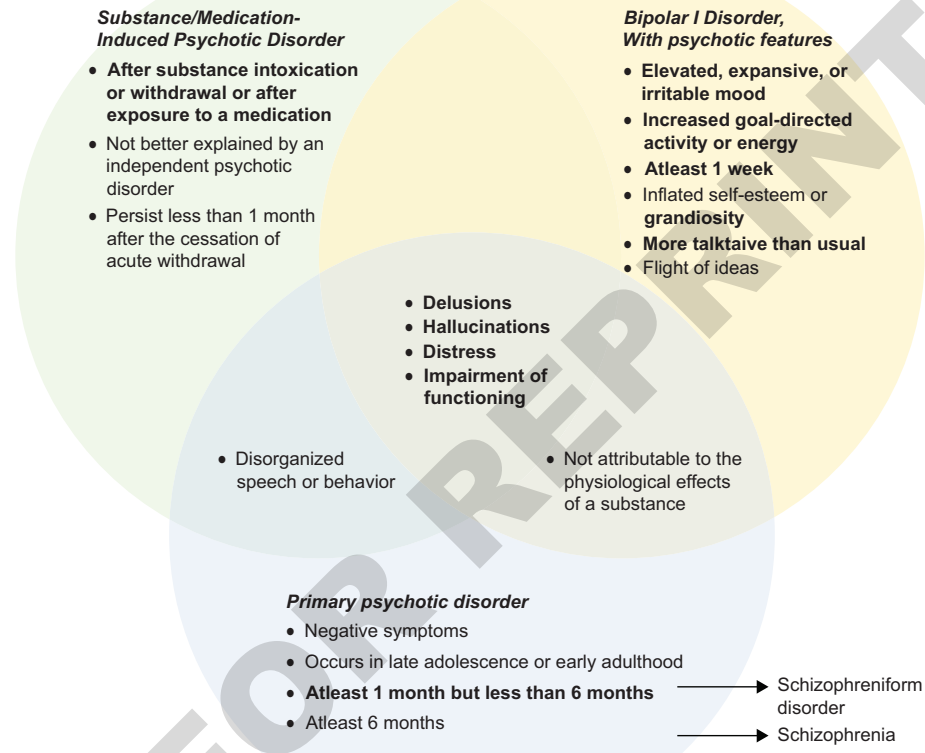
We present a case of new-onset psychotic symptoms in a 41-year-old female with a history of bipolar disorder following abrupt buprenorphine discontinuation with no prior psychosis or family history of psychotic disorders. To our knowledge, this is the first case involving a female patient with buprenorphine withdrawal-induced mania and psychosis. Along with three other case reports (Table 1), the most common psychotic symptoms following abrupt buprenorphine discontinuation are auditory hallucinations, paranoid ideation, and delusions of reference. A combination of manic-like symptoms, visual/auditory hallucinations, and delusions of reference that started after abrupt discontinuation of Suboxone 2-months prior suggests the diagnosis of buprenorphine-withdrawal induced psychosis in this patient. Figure 1 illustrates the differential diagnoses for this case, including substance-induced psychotic disorder, bipolar disorder with psychotic features, and primary psychotic disorder.

We considered buprenorphine-withdrawal-induced psychosis the most likely diagnosis due to the timeline and constellation of symptoms. These symptoms immediately after buprenorphine discontinuation with unremarkable urine drug screen strongly suggest an underlying etiology of substance withdrawal rather than intoxication. It is unusual for symptoms of substance-induced psychosis to last more than a month, and her presentation is inconsistent with opiate withdrawal (nausea, vomiting, watery discharge, diarrhea, etc.).[13] Her abrupt discontinuation of Suboxone likely precipitated psychosis. Our decision not to resume Suboxone was due to patient preference; she expressed fear of potential dependence given her substance use history and endorsed good treatment response to paliperidone and lamotrigine.

New-onset psychotic symptoms were less likely to represent a primary psychotic disorder considering her age and no history of psychosis.[14] meanwhile, the patient's history, interview, and collateral also suggest a possible manic episode and psychotic symptoms.

FIGURE 1

Differential Diagnoses Among Substance-Induced Psychotic Disorder, Bipolar Disorder with Psychotic Features, and Primary Psychotic Disorder. (Positive symptoms were in Bold)



Several predisposing factors could contribute to this case of Suboxone withdrawal-induced psychosis: early adverse life events, substance use history, unemployment, and nonadherence. Her clinical presentation, as explained by the diathesis-stress model ("two-hit" model), postulates schizophrenia can be the result of a neuro-biologic vulnerability interacting with an environmental stressor,[15,16] could have placed her at a higher risk of mania and psychosis. Thus, the coincidence of abrupt stopping of her Suboxone regimen and newly emerged psychosis on top of her manic episode indicates this newly-onset psychosis was likely related to Suboxone withdrawal. Additionally, prolonged mania and specific psychotic symptoms may also be the characteristic manifestations of buprenorphine withdrawal-induced psychiatric disorders.

Several potential mechanisms could account for her acute psychosis. Abrupt discontinuation of antipsychotics can provoke super-sensitivity psychosis even in patients without a previous history of psychosis.[15] However, this is unlikely with our patient as the psychotic symptoms appeared 3-months after the discontinuation of quetiapine and only emerged after the abrupt discontinuation of Suboxone. Buprenorphine has an antipsychotic effect through antagonism at the kappa-receptor.[17] The antipsychotic action was lost when she abruptly discontinued the medication.

This case highlights that buprenorphine withdrawal can induce psychosis in conjunction with prior case studies. Prescribers should be aware of the potential risk of psychotic symptoms with Suboxone discontinuation. ✤

Limitations

We did not perform any neuroimaging tests as the patient did not present with focal neurological deficits. Suboxone was not resumed due to patient preference, and therefore, unable to assess if resumption resulted in symptom remission.

Ethical Declaration

Informed consent was obtained from the patient and her caregiver (husband).

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