Current PSYCHIATRY

CASES THAT TEST YOUR SKILLS

Mr. R hears 'whispers from terrorists' plotting an attack. He presents severely agitated with vomiting, psychosis, and paranoia. What is your diagnosis, given his history of ADHD, depression, and substance abuse?

Chemical 'warfare' in Philadelphia

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EMERGENCY PRESENTATION A rough commute

Mr. R, age 25, presented to the emergency room confused and severely agitated. That morning, his parents found him in his Philadelphia apartment covering his mouth and nose with a T-shirt to guard against imminent chemical warfare.

The day before, Mr. R had developed auditory and visual hallucinations and paranoid and persecutory delusions. That day, on his way to work, he said he had seen "terrorists releasing toxic chemicals into the air" and heard "whispers of terrorists plotting an attack on the East Coast."

Mr. R showed no suicidal or homicidal ideations. He denied significant medical or surgical history but reported that he had recently been diagnosed with depression after a "bad Ecstasy experience." For 6 months he had been taking paroxetine, 20 mg once daily, and bupropion, 150 mg once daily, for his depression.

At age 18, Mr. R was diagnosed with attention-deficit/hyperactivity disorder (ADHD) after years of struggling through school with impaired concentration. At that time, he began taking methylphenidate, 10 mg each morning, and completed 3 years of college in North Carolina. He then dropped out of college and attempted suicide twice.

After the second suicide attempt, a psychiatrist diagnosed Mr. R as having major depression. The psychiatrist discontinued methylphenidate and started bupropion, dosage unknown. After 1 year, he stopped taking the antidepressant, thinking he no longer needed it.

Last year, Mr. R moved back to Philadelphia to be closer to his parents. Shortly afterward, he began obtaining methylphenidate illegally and later starting using cocaine, marijuana, amphetamines, and 3,4-methylenedioxymethamphetamine ("Ecstasy").

At presentation, Mr. R's mood was dysphoric with bizarre affect. Eye contact was poor with easy distractibility. Speech was pressured, with full range. His thought process was grossly disorganized with tangential thinking and flight of ideas.

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His short- and long-term memory were intact; insight and judgment were limited. A Mini-Mental State Examination could not be completed because of his disorganization and distractibility.

Does Mr. R. have schizophrenia or schizoaffective disorder? Or are his symptoms related to ADHD or substance abuse?

The authors' observations

Mr. R's paranoid delusions and hallucinations may suggest schizophrenia. With his history of suicide attempts, a depressive or schizoaffective disorder may also be considered.

However, Mr. R is close with his family and has several friends. His parents say he has not been withdrawn or paranoid, and there is no known family history of mood disorder, substance abuse, or other psychiatric illness. Mr. R also has been working steadily and had worked the night before presenting to us, so schizophrenia and schizoaffective disorder are ruled out. ADHD and abuse of multiple substances could explain his behavior because overdose of stimulants and illicit drugs may produce a psychotic event.

FURTHER HISTORY The power of addiction

After more questioning, Mr. R said that he had recently started using gamma butyrolactone (GBL) in a failed attempt to build muscle. For 4 months he had been taking 3.5 oz of GBL daily—0.25 oz every 2 to 3 hours and 0.75 oz at night to help him sleep.

Within 6 hours of his most recent GBL dose (reportedly 1 oz), Mr. R developed intractable nausea, vomiting, and flatus, followed quickly by anxiety, palpitations, and generalized hand/body tremors that disturbed his sleep. Hallucinations and delusions started the next day.

At presentation, Mr. R's blood pressure was 188/92 mm Hg, his heart rate was 110 bpm, and his respiratory rate was 22 breaths per minute. Pupils were 5 mm and reactive with intact extraocular movement. A urine drug screen indicated amphetamine use.

Mr. R was tentatively diagnosed as having GBL withdrawal syndrome and was admitted for observation and treatment. The psychiatry service followed him for change in mental status and drug dependence.

Can a withdrawal syndrome reasonably account for Mr. R's symptoms?

The authors' observations

GBL is a precursor of gamma-hydroxybutyrate (GHB), a highly addictive agent that is used illicitly, typically at parties and nightclubs (*Box, page 96*). GBL is among the clinical analogues of GHB that have become popular street drugs.

GHB withdrawal syndrome has only recently been described in the literature and is virtually indistinguishable from withdrawal after cessation of GBL and other precursors. To date, 71 deaths have been attributed to GHB withdrawal.[2]

A constellation of symptoms exhibited by Mr. R point to GHB withdrawal, which should be included in the differential diagnosis of any sedative/hypnotic withdrawal *(Table 1, page 97)*.

How GHB works. GHB easily crosses the blood-brain barrier. Like other sedative/hypnotics, its depressant effects on the brain in low doses (2 to 4 grams) produce a euphoric feeling as inhibitions are

Box

GHB: To many users, a 'wonder drug'

Introduced in 1960 as an anesthetic, gamma-hydroxybutyrate (GHB) has become a notorious recreational drug. It is often called the "date rape drug" because of its intoxicating sedative effects.

Users have viewed GHB as a dietary supplement that can also enhance athletic and sexual performance, relieve depression, and induce sleep. Weightlifters have used GHB to quickly build muscle while avoiding side effects associated with anabolic steroids.

As more products containing GHB were introduced, many serious adverse events—including seizure, respiratory depression, and profound decreases in consciousness—were identified with its use and misuse. Although the Food and Drug Administration banned over-the-counter sales of GHB in 1990,[1] the agent is still widely available on the black market and over the Internet.

GHB also is marketed through its chemical precursors, specifically GBL and 1,4-butanediol. These precursors are rapidly and systemically converted to the active GHB product. GBL is hydrolyzed by a peripheral lactonase, and 1,4-butanediol is processed by alcohol dehydrogenase and aldehyde dehydrogenase—the enzymes involved in ethanol degradation.[1]

depressed. Profound coma or death result from higher doses (>4 grams).[3] Heart rate may also be slowed and CNS effects may result in myoclonus, producing seizure-like movements. Combining GHB with other drugs can increase the other agents' depressant effects, leading to confusion, amnesia, vomiting, irregular breathing, or death.[2]

A tiny increase in GHB dose can dramatically increase the symptoms and risk of overdose.[4] GHB's effects are also variable: A 1-teaspoon dose can produce the desired "high" one time and an overdose the next.

GHB and ethanol share a common mechanism of action.[5] At pharmacologic doses, GHB appears to act in part through effects on the structurally related GABA neurotransmitter or its receptors.

Not surprisingly, a withdrawal syndrome characterized by delirium and autonomic instability ensues after GHB use is abruptly stopped. By functioning as indirect GABA agonists and ultimately evoking inhibitory neurotransmission, benzodiazepines and most barbiturates may alleviate GHB withdrawal symptoms.[4] Thiamine is added to prevent Wernicke-Korsakoff syndrome, as is seen in alcohol withdrawal.[5]

GHB withdrawal. Symptoms are divided into three phases:

- **Phase 1 (acute, first 24 hours).** Presenting symptoms include anxiety, restlessness, insomnia, tremor, diaphoresis, tachycardia, and hypertension. Nausea and vomiting are variable but can be unrelenting.

While symptoms vary in severity, most prominent are agitation, restlessness, and insomnia. Some patients do not sleep for days after their last dose, and diffuse body tremors prevent them from sitting or lying still. Tachycardia and hypertension are hard to evaluate at this phase because patients present at different stages of withdrawal. Initial blood pressure readings as high as 240/130 mm Hg and heart rates of 120 bpm have been reported, however.

- **Phase 2 (days 2 through 6).** Worsening autonomic symptoms, progressive GI symptoms, and overall worsening of the withdrawal mark this tumultuous period. Patients usually present at this point—in acute distress and no longer able to self-treat.

Confusion, delirium, and florid psychosis characterize this phase. Mr. R's paranoid delusions and hallucinations are the most common form of psychosis seen in GHB withdrawal.[5] In some cases, the psychosis impairs social, occupational, and other functioning.

Table 1

Comparison of sedative-hypnotic withdrawal syndromes

Substance	Onset	Duration of severe symptoms	Autonomic instability*	Neurologic/ psychiatric symptoms	Mortality	Major mechanism inducing withdrawal state‡
GHB	<6 hours	5 to 12 days	Mild	Severe	<1%	Loss of GHB, $GABA_A$, and $GABA_B$-mediated inhibition
Benzodiazepines	1 to 3 days	5 to 9 days	Moderate	Moderate	1%	Loss of $GABA_A$-mediated inhibition
Baclofen	12 to 96 hours	8 days	Moderate	Severe	None reported	Loss of $GABA_B$-mediated inhibition
Ethanol	<6 hours	10 to 14 days	Severe	Moderate to severe	5% to 15%	Loss of $GABA_A$-mediated inhibition; disinhibition of NMDA receptors

NMDA: N-methyl D-aspartate. GHB: Gamma-hydroxybutyrate

*Marked by tachycardia, fever, hypertension, and/or diaphoresis. ‡All withdrawal states involve multifactorial processes.

Source: Reference 5

Underlying or concurrent causes of delirium must be ruled out. Patients at this stage often require physical restraint or immediate sedation to prevent injury and dangerous complications, including hyperthermia and rhabdomyolysis. Benzodiazepines are often used in high doses[1] for sedation. IV hydration and antiemetics are also treatment mainstays. Atypical antipsychotics are added ASAP to control the paranoia.

- **Phase 3 (days 7 through 13).** Symptoms usually resolve at this stage. The delirium most often clears first, followed by restored autonomic stability and GI rest. While decreased sleep and periods of psychosis persist, agitation is less severe. The patient is discharged on average after 11 days.

Intense outpatient follow-up should include individual psychotherapy, substance abuse counseling, and drug therapy. Highly addictive medications should be avoided because of the patient's substance abuse history.

Did Mr. R accurately report the amount of GBL he had taken? How should GBL and GHB blood levels be measured, given the agents' rapid absorption rates?

The authors' observations

As with most drugs of abuse, high doses over time contribute to severe GHB withdrawal syndrome. GHB doses taken before withdrawal are up to 10 times greater than those taken in typical recreational use.[5]

However, quantifying GHB levels with standard urine drug screens is nearly impossible because:

- the agent is absorbed within 20 to 60 minutes
- only 2% to 5% of the agent is eliminated in the urine.

GHB—which comes in powder, tablet, and liquid form and is usually dissolved in water before use—often is mixed with other drugs or alcohol. Varying preparations and use with multiple substances can produce inconsistent GHB levels and decrease sensitivity and specificity in routine drug screening. GHB abusers also report the amount ingested in "capfuls," ounces, and teaspoons, making accurate quantification harder still.[2]

Though infrequently used because of feasibility and cost, gas chromatography and infrared spectroscopy of a urine specimen are the only known methods for determining GHB levels. Chronic GHB use, negative polypharmacy history, and negative urine and blood analysis for alcohol, benzodiazepines, sedative-hypnotics, or other substances usually confirm GHB withdrawal diagnosis.[1]

TREATMENT 'Bad' medicine

In the ER, Mr. R was given two 1-mg doses of lorazepam IV 1 hour apart. After 1 hour, his vital signs improved slightly (heart rate: 100/min; blood pressure: 165/99 mm Hg). Thiamine and folate were also started. Mr. R's severe agitation and paranoia persisted, so three more 2-mg doses of lorazepam IV were given at 4-hour intervals.

Within 2 days, Mr. R was transferred to the voluntary inpatient psychiatric unit. His nausea, vomiting, and autonomic instability resolved, but his delirium and psychosis persisted. Quetiapine, 100 mg bid, was started to address his psychosis, and bupropion, 150 mg once daily, was restarted to manage his previously diagnosed depression. Three days after starting bupropion, Mr. R's mood improved based on patient reports and Clinical Global Impression scores (6 at baseline, 2 at discharge), but his persecutory delusions persisted, causing mild anxiety.

The next day, Mr. R's auditory and visual hallucinations had ceased, his preoccupation with terrorists began to subside, and his concentration, sleep, and appetite were improving. By day 6 of hospitalization, he still complained of mild tremors and anxiety, but his persecutory delusions resolved.

After 9 days, Mr. R was discharged. Autonomic stability was achieved and his delirium had mostly resolved. Outpatient drug rehabilitation and psychiatric services were arranged.

As of this writing, Mr. R had not sought outpatient treatment. His current medical status is unknown.

Related resources

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- Project GHB. www.projectghb.org

DRUG BRAND NAMES

Bupropion • Wellbutrin
Lorazepam • Ativan
Methylphenidate • Ritalin, Concerta
Paroxetine • Paxil
Quetiapine • Seroquel

DISCLOSURE

The authors report no financial relationship with any company whose products are mentioned in this article, or with manufacturers of competing products.

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