A life of drugs and 'downtime'

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Unrelenting depression and opioid addiction have destroyed Mr. B's career and marriage. Numerous medications have not improved either condition. What would you try next?

CASE Near-fatal combination

Inpatient psychiatry refers Mr. B, age 50, to our outpatient psychiatry clinic. Two weeks earlier, he tried to kill himself by sitting on a stepladder, tying a noose around his neck, and consuming large amounts of quetiapine, trazodone, and vodka. His wife found him unconscious on the floor with facial abrasions, empty pill bottles, and the noose lying next to him.

Emergency medical personnel brought Mr. B to the ER. His total Glasgow Coma Scale score of 3 indicated he was comatose. Pulse was 65 bpm (low-normal), and blood alcohol level was 106 mg/dL, suggesting he had ingested hazardous amounts of vodka. Quetiapine and trazodone blood levels were not measured.

Gastric lavage was unsuccessful because the orogastric tube became curled in the distal esophagus. Mr. B was successfully intubated and admitted to the intensive care unit. After 2 days, he was medically stable and regained consciousness, though he was delirious. He was transferred to inpatient psychiatry, where the attending psychiatrist diagnosed major depression and alcohol abuse disorder.

Before presentation, Mr. B had been taking venlafaxine, 75 mg/d, and mirtazapine, 30 mg at bedtime. His previous outpatient psychiatrist had added methylphenidate, 40 mg/d, to augment the antidepressants—which were not alleviating his depression—and the attending continued all 3 medications. Prior trials of sertraline, bupropion, trazodone, quetiapine, and aripiprazole were ineffective.

By the time Mr. B is transferred to us, his suicidal thoughts have remitted but he is still notably depressed. He is anergic, feels hopeless about the future, has markedly diminished self-worth, feels excessively guilty over past actions, is socially withdrawn, and shows a blunted, depressed affect. He also complains of insomnia despite taking mirtazapine at bedtime.

HISTORY Depression and drugs

Mr. B says he has felt depressed on and off since his teens, and his current episode has been continuously severe for 1½ years. He began abusing alcohol and benzodiazepines during this episode but says he has been clean and sober for 2 weeks. He tried to kill himself 2 other times over 6 months by overdosing on alprazolam and was hospitalized after both attempts. He has no history of mania or psychosis.

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Mr. B also abused opioids. In college, he was prescribed codeine for back pain after a sports injury. He experienced profound relief from depression after his first dose and soon began abusing codeine and other opioids for mood effects, including diphenoxylate/atropine and "cough syrup." He says he has never used heroin.

Twenty years of illicit opioid use destroyed Mr. B's occupational and social functioning, leaving him unable to work in his chosen field. During that period, he was frequently unemployed, socially isolated, and unable to sustain romantic relationships.

At age 40, Mr. B entered a methadone program, began working steadily, and got married. Five years later, he tapered off methadone and to our knowledge remained continuously opioid-free until presentation. Mr. B's depression persisted while using opioids and worsened after stopping methadone. He also completed an 8-week residential substance abuse treatment program several months before presentation.

HISTORY Family problems

Mr. B says he was emotionally abused as a child and described his father as excessively rageful. He says he entered a highly skilled profession to please his father but did not enjoy it and has not worked in the field since his early 30s. He has been unemployed for 1 year because his depression makes him feel "unworthy" to work.

The patient's marriage of 10 years has been riddled with conflict. His depression, substance abuse, suicidality, and unemployment have fueled his wife's resentment and anger.

What is perpetuating Mr. B's depression?

a) psychosocial stressors including marital conflict, unemployment, and a troubled youth
b) recent alcohol abuse
c) prolonged opioid withdrawal
d) genetic endogenous opioid system abnormalities
e) all of the above

The authors' observations

Mr. B's depression is challenging because of its severity and many possible causes and perpetuating factors. In addition to acute psychological stress and recent alcohol and benzodiazepine abuse, he has endured long-term opioid addiction. Although he had stayed opioid-free for 5 years, his past addiction contributed to his depression.

Whether Mr. B's depression or opioid dependence came first is unclear. Either way, past opioid dependence can worsen depression prognosis.[1] Opioid dependence might cause a withdrawal state that lasts years after acute withdrawal has subsided, although some researchers dispute this concept.[2] According to Gold et al,[3] long-term opioid use can cause endogenous opioid system derangements and depression after exogenous opioid use has ceased.

Depression is difficult to diagnose unambiguously in patients who have been using alcohol or anxiolytics because these CNS depressants' effects might mimic depression. Patients whose symptoms suggest dual disorders commonly alternate between traditional psychiatric interventions and chemical dependence treatment.

As with Mr. B, a patient who abstains from 1 substance might start abusing another. This "replacement" is part of an "addiction interaction" theory that recognizes multiple substance and/or behavioral addictions in a patient.[4] "Replacement" addiction indicates that substance abuse therapy is not adequately addressing some issues.

Coordinating concurrent depression and substance abuse treatment is critical. Although Mr. B's ongoing psychosocial stress was addressed to varying degrees,

Would you prescribe buprenorphine for treatment-resistant depression?

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Clinical Point

If a patient 'replaces' 1 addiction with another, watch for issues missed in substance abuse treatment

Clinical Point

Buprenorphine has no additional opioid effect beyond a certain dosage, so it has a lower abuse potential than heroin or methadone

endogenous opioid system derangements and/or prolonged opioid withdrawal may have been missed.

TREATMENT Medication change

We discontinue methylphenidate because it is causing anxiety while leaving Mr. B's depression unabated. Also, methylphenidate can be addictive.

Over several weeks, we titrate venlafaxine to 300 mg/d and continue mirtazapine, 30 mg at bedtime. We start weekly individual psychotherapy and encourage Mr. B to regularly attend Alcoholics Anonymous (AA) meetings, which he had been attending intermittently for years.

After 1 month, Mr. B's depression improves marginally, but his depressed mood, anergia, and flat affect persist. He has not relapsed into alcohol or benzodiazepine dependence but reports occasional cravings for opioids and longs for the profound antidepressant effect they once gave him.

How would you treat Mr. B's depression at this point?

a) switch daytime antidepressants
b) try an opioid with an antidepressant effect, such as buprenorphine
c) try electroconvulsive therapy (ECT)

The authors' observations

Sublingual buprenorphine is not FDA-approved to treat depression, although several small studies have described its antidepressant efficacy.[5-7] How exogenous opioids reduce depressive symptoms is unknown, although some researchers believe that endogenous opioids:

- work with the mesolimbic dopaminergic system to mediate pleasure and reward
- modulate the mesolimbic system
- or have the same attenuating effect on both psychic and physical pain.

The endogenous opioid system includes several classes of opioid peptides and receptors, including mu and kappa receptors.[8] Mu receptors mediate opioid effects such as euphoria, respiratory depression, miosis, constipation, and physical withdrawal. Because buprenorphine is a partial mu agonist, it has no additional opioid effect beyond the patient's maximum tolerable dosage.[9] Buprenorphine thus has a lower abuse potential, causes less severe physical withdrawal, and is much safer in overdose than the full mu receptor agonists heroin or methadone.[9,10]

Box 1

How to obtain a DEA waiver for outpatient buprenorphine use

The Drug Enforcement Administration (DEA) requires physicians to obtain a waiver to use buprenorphine to treat opioid dependence in outpatients. This waiver exempts outpatient practitioners from the DEA requirement that only specially licensed opioid treatment programs—such as methadone clinics—can dispense opioid medications.

To obtain the waiver, a physician must:

- show competency to use buprenorphine—usually by completing an 8-hour training course
- certify that he/she can conveniently refer patients for psychosocial treatment.

To receive DEA-approved buprenorphine training, in person or online, contact:

- American Society of Addiction Medicine. (888) 362-6784, www.asam.org/BuprenorphineCME.html
- American Academy of Addiction Psychiatry. (401) 524-3076, www.aaap.org/buprenorphine/buprenorphine.htm
- American Psychiatric Association. (703) 907-7300, www.psych.org/edu/bup_training.cfm
- American Osteopathic Academy of Addiction Medicine. (800) 621-1773, ext. 8163, www.aoaam.org.

For information on obtaining the waiver, visit www.buprenorphine.samhsa.gov.

Buprenorphine also is a kappa receptor antagonist, which might explain its antidepressant efficacy.[11] Whereas full mu agonism mediates euphoria, kappa receptor agonism results in dysphoria. By contrast, kappa receptor antagonism might cause a more stable, noneuphoric antidepressant effect.

Based on Mr. B's clinical status, we ask him to consider sublingual buprenorphine/naloxone to treat depression and prevent relapse to opioid addiction.

Is Mr. B a suitable candidate for buprenorphine therapy

a) yes
b) no

The authors' observations

Mr. B's opioid addiction history and type of depression support buprenorphine augmentation. Whereas switching antidepressants or starting ECT would address only his persistent depression, buprenorphine also would target his opioid craving.

Numerous conventional psychotropics have not alleviated Mr. B's depression, and changing antidepressants might nullify his small gains over the past month. We might consider ECT if buprenorphine does not reduce his depression.

Doctors need to obtain a waiver from the Drug Enforcement Administration (DEA) before using buprenorphine to treat opioid dependence—its approved indication (***Box 1***). This waiver is not necessary for off-label buprenorphine use. We needed the DEA waiver for Mr. B because we were using buprenorphine to treat opioid relapse prevention as well as depression. To prescribe buprenorphine without a DEA waiver, document that you are using the drug only for the off-label purpose.

Buprenorphine risks

Overdose. Buprenorphine can be abused by grinding and dissolving tablets, then injecting them intravenously. Doing this while under the influence of benzodiazepines or other sedatives can cause respiratory depression, leading to coma or death.

Combination buprenorphine/naloxone carries a much lower risk of IV overdose than buprenorphine alone because naloxone blocks mu opioid receptors. This formulation was created specifically to prevent buprenorphine misuse. Because naloxone is metabolized hepatically, it is not pharmacologically active when taken orally and will not block buprenorphine's effect when buprenorphine/naloxone is taken as prescribed.

Physical dependence and withdrawal. Long-term buprenorphine use can cause physical dependence. Abrupt discontinuation or excessively high doses can precipitate withdrawal. How withdrawal is precipitated is unclear, although some believe the drug displaces itself from mu receptors when doses are too high. Myalgia, headache, abdominal discomfort, rhinorrhea, anxiety, and irritability are common buprenorphine withdrawal symptoms. The dosage at which the drug precipitates withdrawal varies with each patient's tolerance for opioids.

When stopping buprenorphine therapy, taper the medication gradually to minimize withdrawal discomfort and relapse risk. Start tapering by 2 mg per month, then taper more rapidly or slowly based on the patient's subjective experience.

TREATMENT An opioid option

After discussing the risks and benefits with Mr. B and his wife, we add buprenorphine/naloxone, 8 mg/d, then increase it to 16 mg/d the next day. He tolerates the medication, and within 1 week his anergia disappears and he feels more motivated and productive. He reports no euphoria from buprenorphine but says it decreases his craving for alcohol, benzodiazepines, and opioids.

continued

Clinical Point

When stopping buprenorphine, start tapering by 2 mg per month, then taper more rapidly or slowly based on patient response

Clinical Point

Buprenorphine's benefit in severe depression might outweigh its potential for physical dependence in some cases

Box 2

Treating comorbid depression and substance abuse? Remember these 8 steps

1. **Address** depression and substance abuse concurrently
2. **Communicate regularly** with other providers about progress on depression and substance abuse issues
3. **Recommend** and support involvement in 12-step programs such as AA
4. **Use medications** for both depression—such as antidepressants—and relapse prevention—such as naltrexone, acamprosate, or buprenorphine/naloxone
5. **Explore family history** of addiction and how this affected the patient developmentally. Find out if depression and substance abuse had common causes; this helps the patient realize that he/she did not become depressed or addicted by choice
6. **Ask about** and discuss multiple addictions that were not initially reported
7. **Help the patient express,** tolerate, and experience difficult feelings rather than avoid them
8. **Empathize** with the patient; express understanding that factors out of the patient's control caused depression and addiction

Six months after presentation, Mr. B has not considered suicide, abused alcohol or drugs, or required psychiatric hospitalization. His depression is much improved, though intermittent depressed mood and affect and low self-esteem persist.

We continue buprenorphine/naloxone, 16 mg/d, and mirtazapine, 30 mg at bedtime, and reduce venlafaxine to 225 mg/d to mitigate sexual side effects. During weekly individual psychotherapy, we target Mr. B's marital conflict and low self-esteem, and instruct him on overcoming life obstacles such as unemployment. He is looking for work and attends AA approximately 5 times a week.

The authors' observations

Considering the tumultuousness of Mr. B's life, his willingness to enter psychotherapy and address underlying issues is significant. Adding buprenorphine to his antidepressant regimen helped stabilize his mood and make psychotherapy possible.

Psychotropics have not induced total remission of Mr. B's depression, which is multifactorial and requires multimodal treatment. Still, we consider buprenorphine therapy at least partially successful—he has gone 6 months without attempting suicide or requiring psychiatric hospitalization.

Some clinicians consider buprenorphine's potential for physical dependence a drawback to depression therapy. Physical dependence on a psychotropic does not necessarily outweigh its benefit in severe depression. Indeed, patients with depression can experience discontinuation symptoms from selective serotonin reuptake inhibitors and withdrawal from benzodiazepines.[2,12]

FOLLOW-UP 'Bup' stigma

Mr. B feels stigmatized about buprenorphine use, partly because his wife shames him for his history of addiction and views buprenorphine as a constant reminder of his "failures."

Mrs. B's dysfunctional attitude leaves Mr. B too ashamed to tell his fellow AA members that he takes buprenorphine. His inability to share these feelings also diminishes his sense of belonging in the 12-step fellowship. Even so, he feels that buprenorphine has helped him tremendously and wants to continue taking it.

During psychotherapy, we address Mr. B's buprenorphine-related stigma and pervasive shame stemming from his history of mental illness, addiction, inability to work in his chosen field, and past employment failures. We encourage him to overcome his shame by pointing out his strengths—such as the skills he can offer potential employers—and by emphasizing that he did not choose to become depressed and addicted.

The authors' observations

Most patients addicted to opiates feel much less stigmatized by buprenorphine therapy than by methadone. Patients who feel shame while taking buprenorphine usually are reacting to past opioid addiction rather than current therapy. Mr. B's buprenorphine-related shame stems from his personality structure.

Shame, however, could create negative expectations of buprenorphine therapy, and can lower some patients' self-esteem to the point that they feel they do not deserve to get better. Some patients stop buprenorphine prematurely because they believe they have beaten the addiction, but this often leads to relapse to the previous opioid of choice.

Help patients work through the shame of past addiction and encourage them to view buprenorphine therapy as a positive step toward recovery (***Box 2***). As mental health professionals, we must not collude with society to shame people with past chemical addiction. Creatively yet responsibly broadening our perspective toward psychiatric intervention can help patients such as Mr. B receive optimal treatment.

Although members of a 12-step group might harbor an idiosyncratic position on medications or treatment, cooperation with professionals is the program's mainstream stance. Ideally, combination pharmacotherapy, psychotherapy, and guidance for optimal use of support groups can provide a stable foundation for recovery from both psychiatric and addictive disorders.

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Related Resources

- U.S. Department of Health and Human Services, Substance Abuse and Mental Health Services Administration, Center for Substance Abuse Treatment Knowledge Application Program, Treatment Improvement Protocol Series. www.kap.samhsa.gov/products/manuals/tips/index.htm.

Drug Brand Names

Acamprosate • Campral
Alprazolam • Xanax
Aripiprazole • Abilify
Buprenorphine • Subutex
Buprenorphine/naloxone • Suboxone
Bupropion • Wellbutrin
Diphenoxylate/atropine • Lomotil
Methadone • Dolophine
Methylphenidate • Ritalin, Concerta
Mirtazapine • Remeron
Naltrexone • ReVia, Vivitrol
Quetiapine • Seroquel
Sertraline • Zoloft
Trazodone • Desyrel
Venlafaxine • Effexor

Disclosure

Dr. Roth is a speaker for Reckitt Benckiser. Drs. Eiger and Tan report no financial relationship with any company whose products are mentioned in this article or with manufacturers of competing products.

Clinical Point

Some patients feel stigmatized by addiction therapy; help patients work through this shame to promote a positive outcome

Bottom Line

Patients with depression and concurrent or past addiction require more creative therapy than nonaddicted patients, especially after first-line treatments fail. In patients with past opioid addiction, augmenting antidepressants with buprenorphine is an option to carefully consider along with robust psychosocial treatment.