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Buprenorphine for Prescription Opioid Addiction in a Patient With Depression and Alcohol Dependence

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Case Presentation

"Ms. B" is a 28-year-old woman with a 4-year history of illicit prescription opioid use by the oral and nasal routes. She began by occasionally sharing pills with friends at parties, then progressed to 1–2 pills a day and steadily increased to an average of 250–350 mg of oxycodone or its equivalent per day but sometimes taking up to 450 mg a day. She sporadically inhaled heroin but denied injecting it, and she was consuming 5–9 drinks (mixed or straight vodka) 6–7 nights per week. She had attended community college for a year but did not graduate, and she was working in a medical office. She obtained opioids by buying them "on the street," by "doctor shopping" using a vague complaint of back injury with severe pain, or by forging prescriptions, carefully rotating the pharmacies where she filled them to avoid raising pharmacists' suspicions. She debated with herself about quitting because she felt that her life was "ruined and going nowhere," and she sought treatment because she became frightened after nearly getting caught stealing prescription pads at work. She also reported feeling sad, with crying spells and feelings of hopelessness and self-deprecation, but without suicidal ideation.

Ms. B was addicted to prescription opioids and alcohol and was also depressed; although she acknowledged an opioid problem, she did not initially acknowledge her alcohol problem. The main reason she sought treatment was the anxiety she experienced after nearly getting caught stealing prescription pads. Her acute anxiety was situational, but it was unclear whether her long-standing depression was substance induced or an independent disorder.

Ms. B had heard about buprenorphine from friends, and she agreed to office-based treatment with counseling and pharmacotherapy with a buprenorphine-naloxone preparation. She was started on a daily dose of 8 mg/2 mg, which was increased to 12 mg/3 mg on day 2, to 16 mg/4 mg on day 4, and then, in gradual increments, to 24 mg/6 mg by the third week, at which point she reported that opioid cravings and withdrawal were suppressed for the entire day. She experienced mild alcohol withdrawal shortly after treatment began, with tremulousness and tachycardia that resolved with 200 mg of chlordiazepoxide in divided doses over 2 days. Psychosocial treatment included intensive outpatient group counseling

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three times a week, individual therapy with a social worker, medication management by an addiction psychiatrist, and encouragement to participate in Narcotics Anonymous (NA).

She was strongly motivated to stop opioids and quickly reduced her use from daily to twice weekly and from many to 1–2 pills a day, and by the fourth week she stopped use altogether. She was ambivalent about abstaining from alcohol, and her belief in her ability to drink in moderation fluctuated; she continued binging with 4–5 drinks at a time, 2–4 nights per week. Therapy focused on encouragement and praise for progress and feedback that highlighted her problematic alcohol and opioid use and the discrepancies between her intentions and her actual behaviors. After 8 weeks, Ms. B was persuaded that she could not limit her drinking, and she stopped altogether and committed to total abstinence.

Ms. B's depressive symptoms continued, and by the second week she agreed to a trial of sertraline. Her initial intention was to take buprenorphine-naloxone for brief detoxification; she expressed disdain for the possibility of becoming dependent on it as a mere "substitute." But as her opioid use stopped and her depressive symptoms improved, she became more comfortable with continuing buprenorphine-naloxone for an indefinite period and agreed to defer any decision about tapering until she felt "strong enough." She continued buprenorphine-naloxone, and after 3 months of intensive outpatient group therapy, she stepped down to one group and individual counseling session per week and monthly physician visits.

Around month 4, Ms. B stopped attending group therapy, expressing financial difficulties and the feeling that she no longer needed it. Around month 5, citing personal incompatibility, she stopped seeing her therapist and declined to increase the frequency of physician visits, which was offered as a replacement. At month 6, she began a relationship with a man she met at an NA meeting and began complaining of anorgasmia from sertraline. The sertraline dosage was decreased from 200 to 150 mg/day, and while the anorgasmia improved, depressive symptoms returned despite having maintained opioid and alcohol abstinence. The sertraline dosage was restored to 200 mg, but her depression did not improve, and she was switched to escitalopram, which produced only modest improvement. Augmentation with lithium was tried but stopped after a few doses because it made her feel "weird."

Ms. B's stressors continued, among them mounting financial difficulties and romantic disappointment when her new boyfriend relapsed to heavy drinking and it took a month for her to break off the relationship. A friend invited her to a party at which she relapsed to drinking, and she soon stopped taking buprenorphine-naloxone and relapsed to opioid use as well. After 2 weeks of intermittent binging on alcohol and prescription opioids, she presented at an urgently scheduled visit saying that she had not been taking her medications, had again stopped using opioids and alcohol for 3 days, was miserable, and wanted to get "back on track." She was restarted on buprenorphine-naloxone and sertraline; the sertraline was titrated to 300 mg/day, and risperidone, 0.5 mg h.s., was added. With ongoing encouragement, she agreed to reengage in NA, and after a few weeks she started with a new therapist. She maintained abstinence and remission from depression for 6 months.

Prescription Opioid Use Disorders

Nonmedical use of prescription opioids is a growing problem in the United States. One study (1, 2) found that lifetime use of nonmedical opioids was 5%, constituting 20% of all drug use (2). Another (3) showed that approximately 1.7 million Americans had a past-year prescription opioid use disorder, second only to cannabis use disorder. Sources of prescription opioids include home medicine cabinets; diversion by patients with real or faked pain; "doctor shopping"; illegal diversion from physicians or pharmacists; forged

prescriptions; thefts from homes, pharmacies, distributors, or manufacturers; drug dealers; and the Internet (4). The patient described in this case obtained drugs from several of these sources.

Opioid Dependence Treatments

Opioid dependence typically has a chronic, relapsing course (5, 6) that can be interrupted by medication-assisted therapy using naltrexone, methadone, or buprenorphine. Adherence to naltrexone treatment has been poor except in highly motivated patients who are often under strong external pressure (7), but this situation may be changing with the introduction of extended-release formulations (8, 9), such as a once-monthly injectable formulation (Vivitrol) that has been approved by the U.S. Food and Drug Administration for preventing relapse to opioid addiction (10). Methadone has been the mainstay of treatment in the United States and most other countries.

Buprenorphine is a schedule III medication with partial μ-opioid agonist effects. It binds very tightly to receptors, such that it will displace full agonists. Sublingual tablets are available with buprenorphine alone or with buprenorphine and naloxone in a 4:1 combination. Tablets take 3–6 minutes to dissolve and do not work if swallowed, because of first-pass metabolism. The combination product was developed to reduce abuse since naloxone precipitates withdrawal if injected by someone addicted to a full agonist. This strategy appears to be working fairly well (11-14), but not for persons abusing only buprenorphine.

As a partial agonist, buprenorphine has a plateau effect such that for most patients, increasing the dosage beyond 16 mg/day increases the duration but not the magnitude of its effects (15). This property appears to markedly reduce its overdose risk (16, 17). Buprenorphine dissociates more slowly from μ-opioid receptors than do full agonists, resulting in a less severe withdrawal (18). However, this property does not seem to reduce relapse rates following detoxification (6). Buprenorphine can be prescribed by any physician qualified through specialty certification in addiction medicine or addiction psychiatry or completion of at least 8 hours in an approved certification course (19). The availability of buprenorphine outside the highly controlled methadone system has expanded treatment options for opioid-dependent persons (20), and the buprenorphine-naloxone combination has been increasingly adopted, with high levels of satisfaction and with positive outcomes (21, 22).

It is important to administer the first dose of buprenorphine only when the patient is in moderate to severe withdrawal, to avoid precipitating withdrawal. A common starting dose is 4–8 mg, and if this is well tolerated, the usual practice is to make successive 4-mg increases to maintenance levels of 16–32 mg/day over the next 1–14 days. The most conservative approach is to require daily visits for dose adjustments during the first 3–5 days, although some clinicians successfully educate patients to manage their own induction at home (23, 24). For ongoing treatment, the most common approach is to gradually spread out visits with increasing prescription supplies, with a maximum interval of 1 month.

Comorbid Disorders

Although Ms. B's main problem was prescription opioids, she was also depressed and alcohol dependent—common problems in persons with substance use disorders (1). It is often difficult to know whether mood symptoms are substance induced or an independent disorder; however, both problems increase the risk of relapse. Substance-induced depression typically clears with abstinence, carries less relapse risk than depression that is independent of the substance use disorder, and is less likely to require additional ongoing psychiatric

treatment (25, 26). DSM-IV-TR guidelines suggest a diagnosis of an independent disorder rather than substance-induced dependence if symptoms persist for more than 4 weeks before the onset of substance use or during 1 month or more of remission or are disproportionate to agonist or withdrawal effects of the substance(s). The timing of treatment initiation is a matter of judgment and, to some degree, of the time available to decide. Ms. B was an outpatient, so decisions about antidepressant treatment had to be made sooner rather than later.

Buprenorphine is compatible with most psychiatric medications. However, a handful of deaths have been linked to concurrent abuse of benzodiazepines (17, 27, 28). This has led to concern about buprenorphine use in patients abusing benzodiazepines or taking them for anxiety disorders or alcohol detoxification. Because overdose deaths have generally been associated with injection of high doses of buprenorphine and benzodiazepines, the risk-benefit ratio of clinically appropriate doses in medically supervised detoxification from alcohol or benzodiazepines is probably favorable, but careful monitoring is recommended.

There are a few case reports of elevated liver enzymes associated with buprenorphine, but its role is unclear. Periodic monitoring of liver enzymes is advisable in patients with clinically significant liver disease but is not needed otherwise. Compared to methadone, buprenorphine has few clinically significant interactions with antiretroviral medications (29) and is less likely to prolong QTc intervals (30-32). In pregnant patients, use of the buprenorphineonly product is recommended because of uncertainty about the effects of naloxone on the fetus.

Addressing Ambivalence

The combination of positive reinforcement (reward craving, pleasure, “high”) and negative reinforcement (relief craving, reduction of withdrawal or distress) typically results in ambivalence about stopping substance use. Ms. B demonstrated these elements in her debating with herself about stopping opioid use, not initially acknowledging her alcohol problem, and not seeking treatment until she became frightened after almost getting caught stealing prescription pads. Approaches such as motivational interviewing are usually preferable to aggressive confrontation. They can be used successfully, as was done in this case, to address ambivalence by emphasizing goals salient to the patient rather than to the therapist, highlighting discrepancies between goals and behaviors, providing a menu of change options with the patient responsible for the choice, and using an empathetic style.

Treatment Components and Duration

Counseling, psychotherapy, and urine testing are essential components of treatment and increase the impact of pharmacotherapy for many patients. Office-based opioid treatment providers often refer their patients to substance abuse counselors, social workers, psychologists, or nurses for counseling, but physicians also can provide counseling as a component of medication management. Many clinicians recommend weekly urine testing early in treatment, expecting that patients will have some ongoing use, which can be addressed using prescription interval as a contingency to encourage an improving trajectory to abstinence.

As with methadone, high relapse rates have been seen after dosage tapering in buprenorphine studies (6, 19) and longer treatment duration has been associated with better outcomes (33). Early reports of outcomes in general medical settings have been favorable, with retention in buprenorphine treatment ranging from 40% to 70% at 6 months (34-36) and 38% to 52% at 18–24 months (33, 37).

Many patients want to transition off buprenorphine-naloxone as soon as possible and ask about treatment duration at the outset, often because of concerns about becoming "dependent" on medication. One way to address such concerns is to avoid the sometimes-charged term "maintenance" and encourage "extended stabilization" until opioid and other drug use stops before discussing tapering. Another strategy is to emphasize a "functional clock," asking patients to plan on continuing medication until they have not only stopped drug use but also accomplished important goals in the domains of work, school, family, or criminal justice system involvement. After discontinuation of medication, practitioners often recommend continuing involvement in counseling and/or 12-step groups and encourage patients to restart buprenorphine promptly in the event of a relapse.

Pros and Cons of Office-Based Treatment

In contrast to methadone, which is typically administered daily or nearly daily at fixed sites with limited dosing times, buprenorphine can be prescribed flexibly by any qualified provider and in office settings. The advantages offered by these factors include availability, confidentiality, and ease of access—all likely contributors to the finding that office-based opioid treatment using buprenorphine has attracted patients who needed treatment but had never previously received it (38). Office-based treatment also provides the opportunity to integrate addiction treatment into mainstream health care, shift away from an acute care model to one that is "disease management" oriented, and accelerate a broader adoption of pharmacotherapies into broader addiction treatment.

The more intensive counseling and psychiatric services that were important to Ms. B may not have been available with office-based opioid treatment in a primary care setting. A potential disadvantage of office-based treatment is that some patients may respond only to the structured restrictiveness of a methadone program or preferentially respond to the stronger μ-opioid effects that are possible with methadone (35). Diversion is another potential problem in office-based treatment because there are fewer restrictions on take-home medication. Urine drug screening is one way to check for diversion, but not all tests identify buprenorphine, so it is important to use a kit or lab that does.

Conclusions

Buprenorphine is an effective treatment for opioid dependence when used as directed, and if diverted or abused, it carries less risk of overdose than methadone or other full agonists. The combination product is recommended (except during pregnancy) because it appears to have lower abuse liability than the monotherapy product. It can be prescribed in specialized addiction treatment programs or through office-based treatment by certified physicians in any medical practice, including addiction medicine, psychiatry, and primary care. It may not work as well as methadone for some patients, but it has made agonist treatment more accessible to patients who needed it but were unwilling or unable to participate. It may assist with engaging patients in an array of ongoing complementary treatments. The case presented here reviews its use to treat a patient who was addicted to prescription opioids and alcohol, had comorbid depression, was ambivalent about stopping alcohol use, and felt demoralized by interpersonal problems. The treatment course was not always smooth, but through coordinated pharmacological and psychosocial interventions over several months, the case of Ms. B depicts characteristic positive outcomes. Buprenorphine as part of a comprehensive medication-assisted recovery approach—combined, for example, with counseling, treatment of additional nonopioid substance use disorders, and treatment of comorbid psychiatric illness—provides an important tool for relapse prevention and should be a mainstay of the standard repertoire for treating opioid dependence.

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References

1. Wu LT, Woody GE, Yang C, Blazer DG. Subtypes of nonmedical opioid users: results from the National Epidemiologic Survey on Alcohol and Related Conditions. Drug Alcohol Depend. 2010; 112:69–80. [PubMed: 20580168]
2. Wu LT, Woody GE, Yang C, Blazer DG. How do prescription opioid users differ from users of heroin or other drugs in psychopathology: results from the National Epidemiologic Survey on Alcohol and Related Conditions. J Addict Med. 2011; 5:28–35. [PubMed: 21532972]
3. Substance Abuse and Mental Health Services Administration: Results from the 2008 National Survey on Drug Use and Health: National Findings. Substance Abuse and Mental Health Services Administration, Office of Applied Studies; Rockville, Md: 2009.
4. Inciardi JA, Surratt HL, Cicero TJ, Kurtz SP, Martin SS, Parrino MW. The “black box” of prescription drug diversion. J Addict Dis. 2009; 28:332–347. [PubMed: 20155603]
5. McLellan T, Lewis DC, O’Brien CP, Kleber HD. Drug dependence: a chronic mental illness: implications for treatment, insurance, and outcomes evaluation. JAMA. 2000; 284:1689–1695. [PubMed: 11015800]
6. Ling W, Hillhouse M, Domier C, Doraimani G, Hunter J, Thomas C, Jenkins J, Hasson A, Annon J, Saxon A, Selzer J, Boverman J, Bilangi R. Buprenorphine tapering schedule and illicit opioid use. Addiction. 2009; 104:256–265. [PubMed: 19149822]
7. Cornish JW, Metzger D, Woody GE, Wilson D, McLellan T, Vandergrift BV, O’Brien CP. Naltrexone pharmacotherapy for opioid dependent federal probationers. J Subst Abuse Treat. 1997; 14:529–534. [PubMed: 9437624]
8. Comer SD, Sullivan MA, Yu E, Rothenberg JL, Kleber HD, Kampman K, Dackis C, O’Brien CP. Injectable, sustained-release naltrexone for the treatment of opioid dependence: a randomized, placebo-controlled trial. Arch Gen Psychiatry. 2006; 63:210–218. [PubMed: 16461865]
9. Hulse GK, Morris N, Arnold-Reed D, Tait RJ. Improving clinical outcomes in treating heroin dependence: randomized, controlled trial of oral or implant naltrexone. Arch Gen Psychiatry. 2009; 10:1108–1115. [PubMed: 19805701]
10. Fishman M, Winstanley E, Curran E, Garrett S, Subramaniam G. Treatment of opioid dependence in adolescents and young adults with extended release naltrexone: preliminary case-series and feasibility. Addiction. 2010; 105:1669–1676. [PubMed: 20626723]
11. Comer SD, Collins ED, Fischman MW. Intravenous buprenorphine self-administration by detoxified heroin abusers. J Pharmacol Exp Ther. 2002; 301:266–276. [PubMed: 11907183]
12. Alho H, Sinclair D, Vuori E, Holopainen A. Abuse liability of buprenorphine-naloxone tablets in untreated IV drug users. Drug Alcohol Depend. 2007; 88:75–78. [PubMed: 17055191]
13. Bruce RD, Govindasamy S, Sylla L, Kamarulzaman A, Altice FL. Lack of reduction in buprenorphine injection after introduction of co-formulated buprenorphine/naloxone to the Malaysian market. Am J Drug Alcohol Abuse. 2009; 1:1–5.
14. Mammen K, Bell J. The clinical efficacy and abuse potential of combination buprenorphine-naloxone in the treatment of opioid dependence. Expert Opin Pharmacother. 2009; 10:2537–2544. [PubMed: 19708849]
15. Walsh SL, Preston KL, Stitzer ML, Cone EJ, Bigelow GE. Clinical pharmacology of buprenorphine: ceiling effects at high doses. Clin Pharmacol Ther. 1994; 55:569–580. [PubMed: 8181201]
16. Bell JR, Butler B, Lawrance A, Batey R, Salmelainen P. Comparing overdose mortality associated with methadone and buprenorphine treatment. Drug Alcohol Depend. 2009; 104:73–77. [PubMed: 19443138]
17. Kintz P. Deaths involving buprenorphine: a compendium of French cases. Forensic Sci Int. 2001; 121:65–69. [PubMed: 11516889]

18. National Institute on Drug Abuse: Buprenorphine: An Alternative Treatment for Opioid Dependence (Research Monograph 121). National Institute on Drug Abuse; Rockville, Md: 1992.
19. Fiellin DA, Pantalon MV, Chawarski MC, Moore BA, Sullivan LE, O'Connor PG, Schottenfeld RS. Counseling plus buprenorphine-naloxone maintenance treatment in primary care. N Engl J Med. 2006; 355:365–374. [PubMed: 16870915]
20. Gunderson EW, Fiellin DA. Office-based maintenance treatment of opioid dependence: how does it compare with traditional approaches? CNS Drugs. 2008; 22:99–111. [PubMed: 18193922]
21. Barry DT, Moore BA, Pantalon MV, Chawarski MC, Sullivan LE, O'Connor PG, Schottenfeld RS, Fiellin DA. Patient satisfaction with primary care office-based buprenorphine/naloxone treatment. J Gen Intern Med. 2007; 22:242–256. [PubMed: 17356993]
22. Soeffing JM, Martin LD, Fingerhood MI, Jasinski DR, Rastegar DA. Buprenorphine maintenance treatment in a primary care setting: outcomes at 1 year. J Subst Abuse Treat. 2009; 37:426–430. [PubMed: 19553061]
23. Gunderson EW, Wang X-Q, Fiellin DA, Bryan B, Levin FR. Unobserved versus observed office buprenorphine/naloxone induction: a pilot randomized clinical trial. Addict Behav. 2010; 5:537–540. [PubMed: 20106601]
24. Sohler NL, Li X, Kunins HV, Sacajiu G, Giovanniello A, Whitley S, Cunningham CO. Homeversus office-based buprenorphine inductions for opioid-dependent patients. J Subst Abuse Treat. 2010; 38:153–159. [PubMed: 19801178]
25. Hasin D, Liu X-H, Nunes E, McCloud S, Samet S, Endicott J. Effects of major depression on remission and relapse of substance dependence. Arch Gen Psychiatry. 2002; 59:375–380. [PubMed: 11926938]
26. Aharonovich E, Liu X, Nunes E, Hasin DS. Suicide attempts in substance abusers: effects of major depression in relation to substance use disorders. Am J Psychiatry. 2002; 159:1600–1602. [PubMed: 12202286]
27. Reynaud M, Petit G, Potard D, Courty P. Six deaths linked to concomitant use of buprenorphine and benzodiazepines. Addiction. 1998; 93:1385–1392. [PubMed: 9926544]
28. Kintz P. A new series of 13 buprenorphine-related deaths. Clin Biochem. 2002; 35:513–516. [PubMed: 12493578]
29. McCance-Katz EF, Moody DE, Morse GD, Ma Q, Rainey PM. Lack of clinically significant drug interactions between nevirapine and buprenorphine. Am J Addict. 2010; 19:30–37. [PubMed: 20132119]
30. Krantz MJ, Lowery CM, Martell BA, Gourevitch MN, Arnsten JH. Effects of methadone on QT-interval dispersion. Pharmacotherapy. 2005; 25:1523–1529. [PubMed: 16232014]
31. Krantz MJ, Martin J, Stimmel B, Mehta D, Haigney MC. QTc interval screening in methadone treatment. Ann Intern Med. 2009; 150:387–395. [PubMed: 19153406]
32. Wedam EF, Bigelow GE, Johnson RE, Nuzzo PA, Haigney MC. QT-interval effects of methadone, levomethadyl, and buprenorphine in a randomized trial. Arch Intern Med. 2007; 167:2469–2475. [PubMed: 18071169]
33. Woody GE, Poole S, Subramaniam G, Dugosh K, Bogenschutz M, Abbot P, Patkar A, Publicker M, McCain K, Potter JS, Forman R, Vetter V, McNicholas L, Blaine J, Lynch KG, Fudala P. Extended vs short-term buprenorphine-naloxone for treatment of opioid addicted youth: a randomized trial. JAMA. 2008; 300:2002–2011.
34. Parran TV, Adelman CA, Merkin B, Pagano ME, Defranco R, Ionescu RA, Mace AG. Long-term outcomes of office-based buprenorphine/naloxone maintenance therapy. Drug Alcohol Depend. 2010; 106:56–60. [PubMed: 19717249]
35. Stotts AL, Dodrill CL, Kosten TR. Opioid dependence treatment: options in pharmacotherapy. Expert Opin Pharmacother. 2009; 10:1727–1740. [PubMed: 19538000]
36. Stein MD, Cioe P, Friedmann PD. Buprenorphine retention in primary care. J Gen Intern Med. 2005; 20:1038–1041. [PubMed: 16307630]
37. Fiellin DA, Moore BA, Sullivan LE, Becker WC, Pantalon MV, Chawarski MC, Barry DT, O'Connor PG, Schottenfeld RS. Longterm treatment with buprenorphine/naloxone in primary care: results at 2–5 years. Am J Addict. 2008; 17:116–120. [PubMed: 18393054]

38. Sullivan LE, Chawarski M, O'Connor PG, Schottenfeld RS, Fiellin DA. The practice of office-based buprenorphine treatment of opioid dependence: is it associated with new patients entering into treatment? Drug Alcohol Depend. 2005; 79:113–116. [PubMed: 15943950]