

Combined Abuse of Clonidine and Amitriptyline in a Patient on Buprenorphine Maintenance Treatment

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Buprenorphine/naloxone maintenance therapy is often prescribed in primary care to treat opioid dependence. Previous reports have described concomitant abuse of opioids and clonidine. In this case, a primary care patient on buprenorphine/naloxone maintenance therapy demonstrating altered mental status, hallucinations, falls, and rebound hypertension was found to be concomitantly abusing clonidine and amitriptyline, which share metabolic pathways with buprenorphine. Clinicians should be aware of patients' combining amitriptyline, clonidine, and gabapentin with buprenorphine to achieve a mood altering state, avoid co-prescribing them if possible, and maintain communication with pharmacies and other providers when they are prescribed.

Key Words: antidepressive agents, "buprenorphine" [MeSH], clonidine, naloxone, "receptors, opioid" [MeSH], tricyclic

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Buprenorphine/naloxone is Food and Drug Administration-approved for the treatment of opioid dependence in primary care (Fudala et al., 2003; Yokell et al., 2011). Buprenorphine is a partial μ -opioid receptor agonist and κ -opioid receptor antagonist with a ceiling effect, which reduces both abuse potential and accidental respiratory depression (Walsh et al., 1994). Naloxone is an opioid receptor antagonist, which causes withdrawal effects if used intravenously by opioid-dependent patients. Buprenorphine/naloxone is used for medication-assisted therapy for opioid dependence, with naloxone included to reduce abuse potential (Lobmaier et al., 2010). Nonetheless, there are increasing reports of emergency department visits by patients taking buprenorphine/naloxone

(Yokell et al., 2011), with this number growing as the number of patients on buprenorphine maintenance increases (Center for Substance Abuse Research, 2013).

Clonidine is a centrally acting α_2 -selective adrenergic receptor agonist used to treat hypertension and to control or prevent withdrawal in patients with opioid and alcohol use disorders. Case reports describe abuse of clonidine alone or in combination with methadone, codeine, or heroin (Schaut and Schnoll, 1983; Sharma and Newton, 1995; Dennison, 2001). Clonidine reportedly boosts and extends the opioid-related "high" and reduces the amount of psychoactive drug needed (Schaut and Schnoll, 1983; Sharma and Newton, 1995; Beuger et al., 1998). Clonidine may be easier to acquire than some other drugs of abuse due to limited awareness of its abuse potential and low cost (Schaut and Schnoll, 1983; Beuger et al., 1998).

Amitriptyline is a tricyclic antidepressant used to treat depression, anxiety, and insomnia. Abuse alone or in combination with methadone has been described by individuals seeking euphoric effects (Cohen et al., 1978; Prahlow and Landrum, 2005).

A July 2013 MEDLINE search found no reports of the effects of combined use of clonidine, buprenorphine/naloxone, and amitriptyline. We report a case of abuse of clonidine and amitriptyline in a patient on buprenorphine maintenance treatment.

CASE REPORT

A 60-year-old white female presented to a primary care clinic in February 2011 after opioid detoxification, requesting buprenorphine/naloxone therapy for opioid dependence. Medical history included hypertension, depression, insomnia, headaches, chronic kidney disease (serum creatinine 1.85 mg/dL), and 35 years of abusing various substances, including cocaine, methamphetamine, and, most recently, oxycodone and hydromorphone. Chronic medications included metoprolol 50 mg twice daily and clonidine 0.2 mg twice daily for hypertension and amitriptyline 100 mg at bedtime for depression. Blood pressure (BP) was 169/104 mm Hg and urine drug screen (UDS) was positive for barbiturates prescribed during detoxification. Opioid withdrawal score was 1. After adding lisinopril 10 mg daily for blood pressure control and appropriate induction onto buprenorphine/naloxone, the patient was stabilized on sublingual buprenorphine/naloxone two 8/2 mg strips per day. In light of the patient's chronic headache pain and the fact that buprenorphine's duration of action as an analgesic is relatively short (6–9 hours) (Center

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for Substance Abuse Treatment, 2004), the dose was divided and administered twice daily, rather than as a single daily dose, as recommended for patients with opioid dependence alone (Center for Substance Abuse Treatment, 2004). Subsequently, the patient complained of continuing craving and headache pain, and the dose was increased to 8 mg/2 mg 3 times daily. She committed to attend 12-step meetings. At follow-up in April, her UDS showed only buprenorphine. Blood pressure was 128/78 mm Hg.

In May, she was hospitalized for headache, nausea, vomiting, hypertensive urgency (BP 182/102 mm Hg), and acute renal insufficiency (creatinine 1.85 mg/dL). Urine drug screen was not performed. She was managed with clonidine and labetalol and discharged after 36 hours (BP 153/96 mm Hg and creatinine 1.25 mg/dL). Buprenorphine/naloxone was continued.

In June, the patient's daughter reported that the patient was experiencing altered mental status with hallucinations; she suspected ongoing medication abuse. The patient was taken to a detoxification unit but left against medical advice. Owing to suspicion of possible relapse to prescription drug abuse, the primary care staff called 4 local pharmacies and confirmed that she had received 690 tablets of clonidine 0.2 mg within 33 days. After requests for further clonidine refills were refused, patient returned to the office June 27, where she refused inpatient treatment, agreed to stop using clonidine, and received prescriptions for diltiazem, lisinopril, hydrochlorothiazide, and buprenorphine/naloxone.

In July, the daughter called reporting the patient, who lived alone, had been evaluated at a local emergency department after taking high doses of "some medication," passing out, and hitting her head. The primary care team again contacted local pharmacies and found that, in addition to her buprenorphine/naloxone, she had obtained 810 tablets of clonidine 0.2 mg and 180 tablets of amitriptyline 100 mg over the previous 7 weeks, all using prescriptions from the primary care office. She returned to the office in August, presenting with severe headache, hypertensive urgency (BP 174/109 mm Hg), and acute renal insufficiency (creatinine 2.08). She was hospitalized and stabilized. Urine drug screen was negative for opioids or other illicit drugs (buprenorphine testing was not performed). During psychiatric evaluation, she admitted that she was "addicted to clonidine," claiming it was the only drug that controlled her BP and denying that it gave her a high. At no point did she admit to running out of clonidine. Magnetic resonance imaging showed cerebral and cerebellar atrophy, areas of encephalomalacia, and lacunar infarcts. She again refused substance abuse inpatient treatment and was discharged on metoprolol, lisinopril/hydrochlorothiazide, and buprenorphine/naloxone. She missed her posthospital office visit and was subsequently lost to follow-up.

DISCUSSION

Increased buprenorphine prescribing and rising numbers of buprenorphine-related emergency department visits highlight the need for practitioners to recognize the potential for use of buprenorphine/naloxone in combination with other drugs to achieve a mood-altering state. High levels of concomitant abuse of clonidine and opioids, particularly

methadone, have been reported in some US regions (Beuger et al., 1998; Dennison, 2001). When combined with review of her pharmacy records, this patient's recurrent bouts of rebound hypertension and renal insufficiency suggest abuse of clonidine (followed by abrupt discontinuation) during buprenorphine maintenance, whereas periodic hallucinations suggest concomitant amitriptyline abuse as well (Prahlow and Landrum, 2005). Her fall may have been caused by hypotension, which can result from taking high doses of clonidine, or dizziness, a reported side effect of buprenorphine (Center for Substance Abuse Treatment, 2004). All available evidence suggests that she was taking buprenorphine/naloxone as prescribed, although the dose administered is at the upper end of current prescribing guidelines and has been associated with some untoward effects, including diversion (Walsh, 2011). Although evidence for abuse of buprenorphine/naloxone is not clear, the patient seems to have combined several pharmaceuticals with mood-altering properties to create a kind of "medication cocktail," which resulted in recurrent impairment. An online review of conversations from drug forums and pharmacist blogs in July 2013 found numerous references to individuals seeking "highs" by combining buprenorphine/naloxone with clonidine or gabapentin. Clonidine, amitriptyline, and gabapentin are all commonly prescribed medications in primary care, where most buprenorphine/naloxone is prescribed. Many primary care providers may not be aware of their abuse potential. Unlike alcohol and benzodiazepines, which may also be combined with buprenorphine to achieve a mood-altering state, these medications would not be detected on blood or urine toxicology screens. This patient's declining renal function and abnormal magnetic resonance imaging point to the potentially serious complications of uncontrolled and rebound hypertension, which are frequent in patients who abuse clonidine.

This case report points to several potential areas for future study. What is the prevalence of concomitant use of these medications in patients on buprenorphine maintenance and what are their effects on treatment outcomes? The metabolic pathways of these medications also suggest 1 or more possible mechanisms for the observed interaction that warrant further exploration. Both buprenorphine and clonidine are metabolized by CYP450-3A4 and 3A5 systems (Claessens et al., 2010; Brown et al., 2011; Colson et al., 2012), buprenorphine and amitriptyline are metabolized by CYP450-2C9 system (Olesen and Linnet, 1997), and amitriptyline and clonidine are metabolized by CYP450-2D6 system (Olesen and Linnet, 1997). Could 1 or more of these interactions increase serum levels or prolong the half-life of some of the medications involved? If so, what is the impact on creation or enhancement of a mood-altering state?

Pharmacists and physicians should be aware of the potential for abuse of clonidine, amitriptyline, and possibly gabapentin in patients on buprenorphine maintenance and should seek to avoid using these medications in combination with buprenorphine whenever possible. Consideration should also be given to including this information in packaging information for buprenorphine products and in buprenorphine education programs such as Providers' Clinical Support System for Medication Assisted Treatment, an excellent source of

up-to-date information on buprenorphine therapy (PCSSMAT, 2014). If these medications are used in combination, special instructions should be included to prevent early or repeated refills, and communication among all medical providers and pharmacists is essential. Patients who use these substances concomitantly to achieve a mood-altering effect should be referred for more intensive substance abuse treatment rather than office-based buprenorphine.

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