



PCSS Guidance

Topic: Management of Psychiatric Medications in Patients Receiving Buprenorphine/Naloxone

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Guideline Coverage:

This topic is also addressed in Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction (TIP 40), pages 18-22 and 75-76. http://buprenorphine.samhsa.gov/Bup_Guidelines.pdf and in Methadone-Assisted Treatment for Opioid Addiction in Opioid Treatment Programs (TIP 43), page 36-42.

Clinical Question:

How do I manage medications for co-occurring psychiatric disorders in a patient receiving buprenorphine/naloxone (bup/nx) for the treatment of opioid dependence?

Background:

Among opiate-dependent patients the lifetime prevalence of affective disorders has been reported to be 85.4% in women and 70.0% in men (Rounsaville, 1982), with a current prevalence of major depression of 15.8% (Brunner, 1997). The lifetime prevalence of anxiety disorders was reported to be 13.2% in women and 24.5% in men (Rounsaville, 1982). Post-traumatic stress disorder (PTSD) is also common, though patients may deny a PTSD history until they feel confident in their treating clinician. Villagomez (1995) reported a lifetime prevalence of PTSD of 20% in women and 11% in men.

There are few data on the prevalence of co-occurring psychiatric conditions among patients entering office-based treatment with buprenorphine, and unfortunately there is little research literature available to guide the treatment of patients with these co-occurring psychiatric conditions. Savant et al. (2013) found that major depression was the most prevalent mood disorder (19% current, 24% past) among patients seeking primary care office-based buprenorphine/naloxone. A minority of patients met criteria for current dysthymia (6%), past mania (1%), or past hypomania (2%). The literature on the treatment of these conditions in methadone maintenance patients is sparse, but it offers the most likely relevant clinical guidance. In a placebo-controlled trial, Nunes (1998) showed an improvement in depression in methadone maintenance patients treated with imipramine. Kosten reported a poor outcome in a study that treated depressed opioid-dependent patients with the combination of desipramine and buprenorphine and recommended against using this combination (2004). There have been mixed, but generally negative results with the use of selective serotonin reuptake inhibitors (SSRI's) in this population (Petrakis, 1998). Some success has been reported with sertraline in depressed methadone patients (Hamilton, 2000; Carpenter, 2004). A recent meta-analysis (Pani et al. 2010) found low evidence supporting the clinical use of antidepressants for the treatment of depression among patients treated with opioid agonists. This finding was recently replicated in a second meta-analysis. Among patients with major depression or dysthymia in methadone maintenance treatment, no difference in depressive outcomes was found, regardless of whether patients were on medication or placebo (Pedrelli et al. 2011).

In the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC waves 1,2), lifetime non-medical prescription opioid use was found to be associated with any anxiety disorder and generalized anxiety disorder (GAD in wave 2; Martins et al. 2012) While it is common clinical practice to prescribe

SSRIs and other antidepressants to treat anxiety disorders in patients maintained on methadone and buprenorphine, there is even less research available to guide the management of anxiety disorders in this population. Yet buprenorphine-maintained patients are frequently diagnosed with anxiety (23-42%), and benzodiazepine prescriptions are filled at high rates (47-56%) in this population (Mark et al, 2013). Buspirone, a partial 5HT1A receptor agonist which has low abuse liability and does not induce tolerance, has not been demonstrated to be effective in treating anxiety disorders in methadone patients (McRae, 2004). Short-acting benzodiazepines are generally avoided because of both abuse and toxicity problems (Borron, 2002). However, there is one study that described the successful use of the long-acting benzodiazepine, clonazepam, for maintenance treatment of anxiety disorders in methadone patients with a history of benzodiazepine abuse (Bleich, 2002). Current guidelines recommend against prescribing buprenorphine in patients with uncontrolled use of benzodiazepines due to overdoses noted with combined buprenorphine and benzodiazepines in Europe (Kintz, 2001; Obadia, 2001; Boyd, 2003).

Buprenorphine, like methadone and LAAM, is metabolized chiefly by the cytochrome P450 3A4 system. This presents the potential for clinically significant interactions with several classes of medications commonly prescribed in the treatment population. The following lists include those medications that may theoretically affect buprenorphine levels. (See also PCSS-MAT Clinical Guidance, "Clinically Relevant Drug Interactions: Buprenorphine or Methadone with Other Frequently Prescribed Drugs.")

3A4 Inhibitors: These drugs may raise buprenorphine levels: e.g. fluoxetine (Prozac), fluvoxamine (Luvox), nefazodone (Serzone), cimetidine (Tagamet). antiretrovirals (e.g. delavirdine)

3A4 Substrates: These drugs may raise buprenorphine levels: e.g. trazodone (Desyrel), alprazolam (Xanax), diazepam (Valium), buspirone (Buspar), Zolpidem (Ambien), caffeine, haloperidol (Haldol), pimozide (Orap), erythromycin, nifedipine, oral contraceptives

3A4 Inducers: These drugs may lower buprenorphine levels e.g. carbamazepine. phenobarbital, phenytoin, barbiturates, primidone. St. John's Wort, rifampin, efavirenz, nevirapine

A more complete list of inhibitors, inducers and substrates is available at www.drug-interactions.com and TIP 40, page 21. There is minimal specific information available about the actual clinical impact of combinations of buprenorphine and many of these medications, though some studies are underway. Pharmacokinetic interactions identified between buprenorphine and antiretroviral medications have not been correlated with serious adverse events to date. Because of the high affinity of buprenorphine for the mu-opioid receptor and the long duration of binding at the receptor, it seems relatively unlikely that any specific interaction would occur during the course of buprenorphine treatment. Unlike the experience with both methadone and LAAM, where dose adjustments or medication changes are frequently required because of drug-drug interactions, most clinicians have not encountered clinically significant problems using bup/nx in combination with other drugs metabolized by the P450 3A4 system.

General Principles:

Inform patient of your knowledge of the pharmacotherapy options for treating various psychiatric disorders and of the drug-drug interactions involving buprenorphine, and provide reassurance that his or her addiction will not be an obstacle to the treatment of any co-occurring psychiatric disorders. Include the patient in the decision-making process to allay anxiety about relapse. Offer addiction counseling as needed.

Recommendations:

Level of evidence: **Low - expert opinion/clinical experience**

For patients receiving bup/nx who require pharmacotherapy of a co-occurring psychiatric disorder, the following steps are recommended:

1. Patients should be screened for co-occurring psychiatric disorders during the initial evaluation for buprenorphine treatment. Patients who present any immediate risks to themselves or others should be referred for specialty care and /or inpatient treatment

2. After two to three week stabilization on buprenorphine, any psychiatric symptomatology should be reassessed. Depressive syndromes are common at the time of admission to buprenorphine treatment and anxiety symptoms may be caused by opiate withdrawal. Substance-induced psychiatric disorders will clear within 1 to 2 weeks, once the patient is stabilized on buprenorphine.
3. Any psychiatric symptoms that continue for more than 30 days after the termination of illicit drug use suggest the presence of an independent psychiatric disorder. If the diagnosis is confirmed, treatment should be initiated. In situations where a pre-existing psychiatric disorder is well documented, treatment can begin immediately after buprenorphine treatment is initiated.
4. Because of the lack of evidence-based studies on the efficacy of pharmacotherapy of co-occurring psychiatric disorders in buprenorphine patients, clinicians should rely on the general recommendations for opioid-dependent patients. Evidence suggests efficacy for doxepin, imipramine, and desipramine in depressed methadone patients, although the use of desipramine in patients receiving buprenorphine has not been successful; there is less consistent evidence to support the use of the SSRI's though general clinical experience supports the use of all of the newer antidepressants in this population. Benzodiazepines should be used with caution in buprenorphine-treated patients.

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PCSS Guidances use the following levels of evidence*:

High = Further research is very unlikely to change our confidence in the estimate of effect

Moderate = Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low = Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low = Any estimate of effect is very uncertain.

Type of evidence:

Randomised trial = **high**

Observational study = **low**

Any other evidence = **very low**

* Grading quality of evidence and strength of recommendations

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