U.S. Food and Drug Administration
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Drug Safety Communications

FDA urges caution about withholding opioid addiction medications from patients taking benzodiazepines or CNS depressants: careful medication management can reduce risks

This provides updated information to the FDA Drug Safety Communication: FDA warns about serious risks and death when combining opioid pain or cough medicines with benzodiazepines; requires its strongest warning issued on August 31, 2016.

Safety Announcement

[9-20-2017] Based on our additional review, the U.S. Food and Drug Administration (FDA) is advising that the opioid addiction medications buprenorphine and methadone should not be withheld from patients taking benzodiazepines or other drugs that depress the central nervous system (CNS). The combined use of these drugs increases the risk of serious side effects; however, the harm caused by untreated opioid addiction can outweigh these risks. Careful medication management by health care professionals can reduce these risks. We are requiring this information to be added to the buprenorphine and methadone drug labels along with detailed recommendations for minimizing the use of medication-assisted treatment (MAT) drugs and benzodiazepines together.

Buprenorphine and methadone help people reduce or stop their abuse of opioids, including prescription pain medications and heroin. Methadone and buprenorphine have been shown to be effective in reducing the negative health effects and deaths associated with opioid addiction and dependency.[1] These medications are often used in combination with counseling and behavioral therapies, and patients can be treated with them indefinitely. Buprenorphine and methadone work by acting on the same parts of the brain as the opioid that the patient is addicted to. The patient taking the medication as directed generally does not feel high, and withdrawal does not occur. Buprenorphine and methadone also help reduce cravings[2] (see Table 1. List of Buprenorphine and Methadone MAT Drugs).

Many patients with opioid dependence may also use benzodiazepines or other CNS depressants, either under a health care professional's direction or illicitly. Although there are serious risks with combining these medicines, excluding patients from MAT or discharging patients from treatment because of use of benzodiazepines or CNS depressants is not likely to stop them from using these drugs together. Instead, the combined use may continue outside the treatment setting, which could result in more severe outcomes.

Health care professionals should take several actions and precautions and develop a treatment plan when buprenorphine or methadone is used in combination with benzodiazepines or other CNS depressants. These include:

- Educating patients about the serious risks of combined use, including overdose and death, that can occur with CNS depressants even when used as prescribed, as well as when used illicitly.
- Developing strategies to manage the use of prescribed or illicit benzodiazepines or other CNS depressants when starting MAT.
- Tapering the benzodiazepine or CNS depressant to discontinuation if possible.
- Verifying the diagnosis if a patient is receiving prescribed benzodiazepines or other CNS depressants for anxiety or insomnia, and considering other treatment options for these conditions.
- Recognizing that patients may require MAT medications indefinitely and their use should continue for as long as patients are benefiting and their use contributes to the intended treatment goals.
- Coordinating care to ensure other prescribers are aware of the patient's buprenorphine or methadone treatment.
- Monitoring for illicit drug use, including urine or blood screening.

Patients taking MAT drugs should continue to take these medicines as prescribed. Do not stop taking other prescribed medicines without first talking to your health care professional. Before starting any new medicines, tell your health care professional that you are taking MAT. Do not take non-prescribed benzodiazepines or other sedatives (See Table 2. List of Benzodiazepines and Other CNS Depressants) or use alcohol when taking MAT because the combined use increases the possibility of harm, including overdose and death.

In August 2016, we issued a Drug Safety Communication warning about the combined use of opioid-containing pain or cough medicines with benzodiazepines or other CNS depressants. We said at that time that we would continue to evaluate the evidence regarding combined use of benzodiazepines or other CNS depressants with MAT drugs.

Our subsequent review of a published study[3] and other drug use data showed that buprenorphine and benzodiazepines frequently have been prescribed for the same patient, often by the same prescriber, and these drugs are usually dispensed by the same pharmacy. An epidemiological study from Sweden found that receiving MAT with benzodiazepines or other CNS depressants such as drugs to treat insomnia appears to increase the risk of death.[4] Based on this information, for the methadone products, information about the interaction with benzodiazepines and other CNS depressants will be added to an existing *Boxed Warning* about the risks of slowed or difficult breathing and death. Expanded guidance will be added to the *Warnings and Precautions* section on how to manage patients in methadone treatment in Opioid Treatment Programs (OTPs) who are also taking CNS depressants. For the buprenorphine products, an existing statement in the *Warnings and Precautions* section will be expanded and revised to provide more detailed guidance on managing patients in buprenorphine treatment who are also taking CNS depressants.

We urge patients and health care professionals to report side effects involving buprenorphine, methadone, or other medicines to the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of the page.

Table 1. List of Buprenorphine and Methadone MAT Drugs

Generic Name	Brand Name(s)
buprenorphine	Subutex, Probuphine
buprenorphine/naloxone	Bunavail, Suboxone, Zubsolv
methadone	Diskets, Dolophine, Methadose

Table 2. List of Benzodiazepines and Other CNS Depressants[*]

Generic Name	Brand Name(s)
Benzodiazepines	
alprazolam	Xanax, Xanax XR
chlordiazepoxide	Librium, Librax
clobazam	Onfi
clonazepam	Klonopin
clorazepate	Gen-Xene, Tranxene
diazepam	Diastat, Diastat Acudial, Valium
estazolam	No brand name currently marketed
flurazepam	No brand name currently marketed
lorazepam	Ativan
oxazepam	No brand name currently marketed
quazepam	Doral
temazepam	Restoril
triazolam	Halcion
Other Sleep (Non-Benzodiazepine Hypnotic) Drugs and Tranquilizers	
butabarbital sodium	Butisol
eszopiclone	Lunesta
pentobarbital	Nembutal
ramelteon	Rozerem
secobarbital sodium	Seconal sodium
suvorexant	Belsomra
zaleplon	Sonata
zolpidem	Ambien, Ambien CR, Edluar, Intermezzo, Zolpimist
Muscle Relaxants	
baclofen	Gablofen, Lioresal
carisoprodol	Soma, Soma Compound, Soma Compound w/ codeine
chlorzoxazone	No brand name currently marketed
cyclobenzaprine	Amrix

dantrolene	Dantrium, Revonto, Ryanodex
metaxalone	Skelaxin
methocarbamol	Robaxin, Robaxin-750
orphenadrine	No brand name currently marketed
tizanidine	Zanaflex
Antipsychotics	
aripiprazole	Abilify, Abilify Maintena, Aristada
asenapine	Saphris
cariprazine	Vraylar
chlorpromazine	No brand name currently marketed
clozapine	Clozaril, Fazaclo ODT, Versacloz
fluphenazine	No brand name currently marketed
haloperidol	Haldol
iloperidone	Fanapt
loxapine	Adasuve
lurasidone	Latuda
molindone	No brand name currently marketed
olanzapine	Symbyax, Zyprexa, Zyprexa Relprevv, Zyprexa Zydis
paliperidone	Invega, Invega Sustenna, Invega Trinza
perphenazine	No brand name currently marketed
pimavanserin	Nuplazid
quetiapine	Seroquel, Seroquel XR
risperidone	Risperdal, Risperdal Consta
thioridazine	No brand name currently marketed
thiothixene	Navane
trifluoperazine	No brand name currently marketed
ziprasidone	Geodon

*This is not a comprehensive list.

Facts about Buprenorphine and Methadone

- Medicines containing buprenorphine or methadone as the active ingredient are FDA-approved to treat opioid addiction and dependency. These medicines are called medication-assisted treatment (MAT), and they are often used along with counseling and behavioral therapies to treat opioid addiction.
- Patients may require treatment with MAT medicines indefinitely.
- MAT medicines have been shown to be effective in reducing the negative health effects and deaths associated with opioid addiction and dependency.[1] Patients receiving MAT cut their risk of death from all causes in half.
- Buprenorphine and methadone relieve the withdrawal symptoms and psychological cravings experienced by patients addicted to opioids.[5]
- Methadone to treat opioid addiction is dispensed only at specially licensed treatment centers.

- Methadone is marketed under the brand names Diskets, Dolophine, and Methadose, and also as generics. Methadone is available as a tablet, liquid, and wafer.
- A physician must complete training in order to be qualified to prescribe or dispense buprenorphine to treat addiction.[6] Buprenorphine is dispensed by retail pharmacies and sometimes at opioid treatment centers.
- Buprenorphine, either alone or in combination with other medicines, is marketed under the brand names Bunavail, Probuphine, Suboxone, and Zubsolv, and also as generics. Buprenorphine is available as a tablet dissolved under the tongue, as a film dissolved under the tongue, as a film dissolved on the inside of the cheek, and as an implant inserted into the upper arm.
- Common side effects of buprenorphine and methadone include nausea, vomiting, constipation, muscle aches and cramps, and sleep problems.

Additional Information for Patients

- If you are taking buprenorphine or methadone to treat opioid addiction or dependence (referred to as medication-assisted treatment or MAT), take care when combining these drugs with benzodiazepines or other sedatives to treat anxiety or insomnia. Taking both of these types of medicines can result in serious side effects, including overdose and death. These serious side effects result because buprenorphine, methadone, and benzodiazepines all impact (depress) the central nervous system (CNS). The CNS controls most of the functions of the body, including breathing.
- Combining the MAT medications buprenorphine or methadone with alcohol, or other prescription or illicit opioids such as heroin also increases these serious side effects.
- It is important to continue taking your buprenorphine or methadone as prescribed. Do not stop without first talking with your health care professional. Also do not stop or start any prescribed medicines without first talking to your health care professional.
- Always inform all your health care professionals about all the drugs you are taking, including prescription and over-the-counter (OTC) medicines, and other substances such as alcohol. It is helpful to keep a list of all your current medicines in your wallet or another location where the list is easily retrieved. You can fill out and print a copy of My Medicine Record.
- It is important to lock up your medicines and to dispose of them properly to keep them from being taken accidentally by children or falling into the wrong hands.
- Talk to your health care professional if you have any questions or concerns about buprenorphine, methadone, or other medicines you are taking.
- Read the patient Medication Guide or patient information leaflet that comes with your filled prescription(s).
- Report side effects from buprenorphine, methadone, or other medicines to the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of this page.

Additional Information for Health Care Professionals

- The medication assisted treatment (MAT) drugs for opioid use disorder buprenorphine or methadone should not be categorically denied to patients taking benzodiazepines or other central nervous system (CNS) depressants.
- Although concomitant use of buprenorphine or methadone with benzodiazepines or other CNS depressants increases the risk of adverse reactions, including overdose and death, creating barriers to MAT can pose an even greater risk of morbidity and mortality due to the opioid use disorder.
- As a routine part of orientation to buprenorphine or methadone treatment, educate patients about the risks of concomitant use of benzodiazepines, sedatives, other prescribed opioid analgesics, alcohol, and illicit drugs.
- Develop strategies to manage use of prescribed or illicit benzodiazepines or other CNS depressants at initiation of buprenorphine or methadone treatment, or if it emerges as a concern during treatment. Adjustments to induction procedures and additional monitoring may be required.
- Current evidence does not support dose limitations or arbitrary caps of buprenorphine or methadone as a strategy to address benzodiazepine or other CNS depressant use in MAT-treated patients. However, if a patient is sedated at the time of buprenorphine or methadone dosing, a health care professional should evaluate the cause of sedation. Omitting or decreasing the dose of buprenorphine or methadone may be appropriate.
- Cessation of benzodiazepines or other CNS depressants is preferred in most cases of concomitant use with MAT medicines. In some cases, monitoring at a higher level of care for tapering may be appropriate. In others, gradually tapering off a prescribed benzodiazepine or other CNS depressant or decreasing to the lowest effective dose is appropriate.
- For patients receiving buprenorphine or methadone treatment, benzodiazepines are not the treatment of choice for anxiety or insomnia. Before co-prescribing benzodiazepines, ensure that patients are appropriately diagnosed and consider other medicines and nonpharmacologic treatments to address anxiety or insomnia.
- Recognize that patients may require MAT medications indefinitely, and their use should continue for as long as patients are benefiting and their use contributes to the intended treatment goals.
- Ensure that other health care professionals prescribing benzodiazepines or other CNS depressants are aware of the patient's methadone or buprenorphine treatment and coordinate care to minimize the risks associated with concomitant use. Take measures to confirm that patients are taking their medicines as prescribed and are not supplementing with illicit drugs. Toxicology screening should test for use of prescribed and illicit benzodiazepines or other CNS depressants.
- Report adverse events involving buprenorphine, methadone, or other medicines to the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of this page.

Data Summary

We conducted a drug utilization analysis of concomitant use of benzodiazepines with buprenorphine products being used for medication-assisted treatment (MAT), using the Prescription Behavior Surveillance System's (PBSS) data from 1/1/2013 to 12/31/2013. The PBSS includes de-identified, longitudinal data from eight participating state prescription drug monitoring programs: California, Ohio, Louisiana, Kentucky, West Virginia, Idaho, Maine, and Delaware.

Of 190,907 patients prescribed at least 7 consecutive days of buprenorphine therapy, 17.7 percent had at least one overlapping benzodiazepine prescription period of 7 or more days, and another 2.5 percent had at least one overlapping prescription period of less than 7 days. The median length of overlap in therapy across the eight states ranged from 29 to 41 days. The overlapping benzodiazepine and buprenorphine treatments were commonly prescribed by the same prescriber (ranging from 33.1 percent to 65.2 percent across the eight states) and dispensed by the same pharmacy (from 71.5 percent to 93.3 percent). PBSS data capture prescriptions filled for any payment source (e.g., cash, public insurance); however, prescriptions filled outside of the participating PBSS states may not have been captured, resulting in an underestimate of the number of patients who had concomitant buprenorphine and benzodiazepine prescriptions.

We also reviewed the published medical literature. Using prescription data from the Veterans Health Administration for fiscal year 2010, Park et al.[3] noted that patients receiving MAT (n=5,409 for methadone; n=5,690 for buprenorphine) were commonly dispensed a benzodiazepine prescription. The median percent of patients who received concomitant methadone or buprenorphine prescriptions was 13.3 percent and 20.2 percent across multiple U.S. regions, respectively. These results from the Veterans Health Administration may not be generalizable to the entire U.S. population, but the finding of frequent overlapping prescriptions for benzodiazepines and buprenorphine was similar to findings from PBSS 2013 data described above.

Abrahamsson et al.[4] analyzed data from a nationwide cohort of Swedish residents 18-50 years old who were dispensed methadone- or buprenorphine-based MAT between July 1, 2005 and December 31, 2012. Within the cohort of patients prescribed MAT, the authors compared the risk of fatal overdose, non-overdose-related mortality, and all-cause mortality during therapy episodes of prescribed CNS depressants to periods of time without CNS depressant therapy. CNS depressants included benzodiazepines (diazepam, oxazepam, lorazepam, alprazolam, nitrazepam, flunitrazepam, triazolam, midazolam, and clonazepam) and three non-benzodiazepine hypnotic drugs (zopiclone, zolpidem, and zaleplon). Of 4,501 patients in the MAT cohort, 32.4 percent filled a prescription for a benzodiazepine and 40.8 percent filled a prescription for one of three non-benzodiazepine hypnotic drugs. During periods of cotreatment with MAT and benzodiazepines, there was an elevated risk of non-overdose-related and all-cause mortality, although the associations were not considered statistically significant (Table 3). During periods of cotreatment with MAT and the non-benzodiazepine hypnotic drugs, there was an elevated risk of fatal overdose, non-overdose mortality, and all-cause mortality, but the

associations were considered statistically significant only for fatal overdose and all-cause mortality. The hazard ratios for the non-benzodiazepine hypnotic drugs and benzodiazepines are not directly comparable because the authors did not adjust for the indication for use of these drugs. The authors estimated periods of active MAT based on prescription fill date and assumptions about how long MAT typically lasts, so periods of active MAT during follow-up may have been misclassified. Periods of active MAT may have also been missed if patients in the cohort received in-clinic MAT during follow-up. In addition, while the authors attempted to adjust for time periods when patients were using more than one concomitant CNS depressant, it is not clear whether the adjustment was sufficient to isolate the effects of a single CNS depressant when used concomitantly with MAT. Further, the authors' adjustments for sex, age, and time-dependent variables representing previous nonfatal overdose, psychiatric inpatient treatment, and suicide attempt, may not have been sufficient to control for the greater severity of comorbid psychiatric conditions likely during periods of concomitant use of CNS depressant drugs. Other potential confounders, including socioeconomic status, were not available in this data source.

Table 3. Risk of Death Associated with Periods of Concomitant Therapy with MAT and Benzodiazepines or Non-benzodiazepine Hypnotic Drugs in Sweden, July 2005-December 2012*

	Adjusted Hazard Ratio (95% Confidence Interval)		
	Overdose Mortality	**Non-overdose Mortality**	**All-cause Mortality**
Benzodiazepine Treatment	1.05 (0.51-2.15)	1.74 (1.00-3.01)	1.44 (0.93-2.23)
Non-benzodiazepine Hypnotic Drug Treatment	2.34 (1.37-3.99)	1.25 (0.71-2.20)	1.66 (1.12-2.45)

*The table is based on the paper by Abrahamsson et al.[4] Benzodiazepines included in the study were diazepam, oxazepam, lorazepam, alprazolam, nitrazepam, flunitrazepam, triazolam, midazolam, and clonazepam. The non-benzodiazepine hypnotic drugs included in the study were zopiclone, zolpidem, and zaleplon.

A study by Warner et al.[7] examined trends in drug overdose deaths from 2010 through 2014 using data from the National Vital Statistics System, which aggregates nationwide death certificate data. In 2014, 3,495 drug overdose deaths involved methadone, and other CNS depressant drugs were frequently involved in those deaths (Table 4). The benzodiazepines alprazolam and diazepam were the first and fifth most frequently involved concomitant drugs.

New FDA analyses using the same data source found 322 drug overdose deaths in 2014 that involved buprenorphine. Concomitant use of CNS depressant drugs was also frequently observed in deaths involving buprenorphine. Alprazolam, clonazepam, and diazepam were the most frequently involved concomitant drugs at death. Although the absolute number of methadone-involved deaths in 2014 was ten times the number of deaths involving buprenorphine, the data source did not have information to adjust for confounding or differences in drug utilization between methadone and buprenorphine. Therefore, we could not assess whether the risk of overdose death with concomitant CNS

depressant drugs differed between methadone and buprenorphine. A limitation is that the quality of data extracted from death certificates depends on the level of detail provided by medical certifiers, which can vary by jurisdictions and over time. We also do not know whether the drugs were being used to treat pain or opioid use disorder, just that they were involved in the death.

Table 4: Most Frequent Concomitant Drugs for Drug Overdose Deaths Involving Selected Opioids: United States, 2014

Referent Drug	Number of Deaths Involving Referent Drug	Number (%) Deaths Involving Both Referent Drug and Concomitant Drug				
		Most Frequent Drug	Second Frequent Drug	Third Frequent Drug	Fourth Frequent Drug	Fifth Frequent Drug
buprenorphine	322	alprazolam 106 (32.9%)	clonazepam 56 (17.4%)	diazepam 36 (11.2%)	heroin 36 (11.2%)	fentanyl 32 (9.9%)
methadone	3,495	alprazolam 634 (18.1%)	oxycodone 352 (10.1%)	cocaine 337 (9.6%)	heroin 314 (9%)	diazepam 232 (6.6%)

Selected results using National Center for Health Statistics (NCHS), National Vital Statistics System. Mortality files linked with death certificate literal text, constructed for analysis on October 6, 2016.

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