STATE OF MARYLAND

DHMH

Maryland Department of Health and Mental Hygiene
201 W. Preston Street • Baltimore, Maryland 21201
Martin O'Malley, Governor – Anthony G. Brown, Lt. Governor – Joshua M. Sharfstein, M.D., Secretary

June 11, 2014

Dear Colleague,

As the nation's drug overdose epidemic continues to peak, we would like to share some critical information with you on the potentially lethal combination of benzodiazepines and opioids. Please carefully read the attached document prepared by the University of Maryland School of Pharmacy.

A great resource for access to prescription data and safer management your patients' use of controlled substances is the Maryland Prescription Drug Monitoring Program, otherwise known as the PDMP. This free service can inform you whether your patients are receiving medications from other sources. We strongly recommend that all clinicians prescribing opioid medications regularly query the PDMP. Please visit the following website for more information and to register: http://adaa.dhmh.maryland.gov/PDMP/SitePages/Home.aspx

Thank you for your attention to this matter.

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Lethal Mixtures – Benzodiazepines and Opioids, including Buprenorphine

Prepared at the Request of the DHMH Behavioral Health Administration
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Drug overdose has been steadily increasing and is now the leading cause of death by injury in the US (1). In 2010, 75% percent of prescription overdoses involved opioid analgesics (2). When benzodiazepines are combined with opioids, patients may experience reduced oxygen saturation and respiratory depression along with an increased risk of mortality (3).

SAMHSA's May 2014 Drug Abuse Warning Network (DAWN) Report notes that emergency department visits involving alprazolam have doubled from 2005 to 2010 and then remained stable in 2011 (10). The majority (81%) of these emergency department visits involved the nonmedical use of alprazolam in combination with another drug. Narcotic pain relievers were the most commonly cited second drug accounting for 32% of cases with alprazolam and 57% of cases with alprazolam and 2 or more drugs. This concurrent use or abuse of alprazolam and narcotics puts patients at significant risk of fatal overdose(10). Physicians should consider the following in managing patients prescribed opioids (including buprenorphine) on a chronic basis (11):

1. Whenever possible, benzodiazepines should be avoided in patients who are regularly maintained on opioids. When benzodiazepines are required, they should only be used on a short term basis.
2. Regular urine screens, which assess for natural and semi-synthetic opioids, should be monitored. Positive screens should be verified with a confirmation test, such as gas chromatography mass spectrometry (GCMS).
3. The Maryland Prescription Drug Monitoring Program (PDMP) data should be reviewed for any patient prescribed a controlled substance, particularly opioids or benzodiazepines. When a discrepancy is identified, the discovering physician should make notification to other prescribers.

4. Written treatment agreements should be utilized to clarify treatment expectations and to specifically educate about the risk for overdose including when opioids and benzodiazepines are combined.

Buprenorphine is rarely associated with overdose death. However, care must be taken with benzodiazepines in combination with buprenorphine. Buprenorphine is a partial opioid agonist that is generally considered safer than full agonists in overdose. When combined with benzodiazepines, buprenorphine's natural ceiling effect for toxicity may be diminished, resulting in significant respiratory depression (4, 5). Patients are at greatest risk for serious toxicity and death when buprenorphine is used in high doses, injected, or combined with sedatives such as benzodiazepines (6, 7). One study found that benzodiazepines were associated with 82% of fatal buprenorphine poisonings (8). The exact mechanism for increased respiratory toxicity is unclear, but it appears to be more pharmacodynamic than pharmacokinetic (5). Buprenorphine and benzodiazepines affect respiration by several different mechanisms. Benzodiazepines increase upper airway resistance, while opioids reduce central and peripheral respiratory drive (5, 7).

While naloxone is the treatment of choice for opioid overdose, buprenorphine overdoses may not be responsive to this standard agent. If a patient does not respond to a naloxone dose of 4 mg, it is unlikely that they will respond to higher doses. In these cases, the focus of care should switch to supportive treatment (9). Because of buprenorphine's long half-life, patients may require continuous infusion as opposed to bolus administration and should be closely monitored (9). When buprenorphine is combined with benzodiazepines, the benzodiazepine antagonist flumazenil can be effective in reversing respiratory depression (7).

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