Clinical Update: September 2022

COMPLEXITIES OF RISK ASSESSMENT: OPIOIDS, DRUG INTERACTIONS, & DESIGNER BENZODIAZEPINES

As the number of fatal and non-fatal overdoses continues to rise, we should question why this is occurring. One frequent cause of death in drug overdose is from central nervous system (CNS) depression.[1] When illicit or prescription substances cause CNS depression, there can be a decrease in oxygen that is delivered to the brain. This results in a phenomenon known as hypoxia, which can lead to debilitating short- and long-term effects, such as brain damage or putting the individual into a comatose state. CNS depression is often a consequence of an alteration in neurotransmitter activity within the brain. Most CNS depressants increase the action of the inhibitory neurotransmitter, gamma-aminobutyric acid (GABA).[2] Agents commonly associated with CNS depression include opioids, gabapentinoids, benzodiazepines, barbiturates, alcohol, nonbenzodiazepines indicated for insomnia, tricyclic antidepressants, typical antipsychotics, and skeletal muscle relaxants.[3,4] Ongoing monitoring for drug interactions is crucial as concomitant use of multiple CNS depressants may result in oversedation. Some symptoms to recognize when an overdose occurs include loss of concentration, confusion, reduced heart rate, reduced blood pressure and slowed breathing.[2] Certain drug classes that are commonly misused, can cause CNS depression and may lead to an overdose death.

Commonly prescribed medications such as opioids and benzodiazepines can be classified as CNS depressants.[3] Opioids are Mu-receptor agonists and are associated with notable nervous system effects including a depressed level of consciousness. Common prescription opioids include hydrocodone, oxycodone, morphine, hydromorphone, and fentanyl. The use of opioids with skeletal muscle relaxants may allow for opioid sparing but could enhance CNS depression.[4] GABA analogs including gabapentin and pregabalin, produce CNS depression as they are structurally similar to the inhibitory neurotransmitter, GABA.[3] Recent reports have found gabapentin overdoses have increased in individuals suffering from opioid use disorders.[5] Benzodiazepines and barbiturates, such as phenobarbital, cause sedation by slowing action potential propagation in the central nervous system.[3] Examples of commonly used benzodiazepines include alprazolam, diazepam, and lorazepam. Ethanol causes sedation via the facilitation of GABA receptors and inhibition of glutamate, an excitatory neurotransmitter. Nonbenzodiazepine sedatives, also known as “Z-drugs”, treat insomnia and cause sedation through agonist activity at GABA receptors in the brain. Z-drugs include zolpidem, eszopiclone, and zaleplon. In addition, tricyclic antidepressants and first-generation antipsychotics in particular have anticholinergic properties that contribute to CNS depression. The FDA warns that patients taking medication assisted treatment (MAT) for opioid addiction, such as methadone and buprenorphine, are also at a potential risk of CNS depression and other hazardous outcomes if the patient combines these medications with other CNS depressants.[6]

Benzodiazepines are commonly prescribed in the United States, for a variety of indications.[7] With increased prescribing, it is important for practitioners to be aware of what other substances their patients are consuming. For instance, patients may consume prescription and designer benzodiazepines. Designer benzodiazepines are illicitly manufactured in clandestine laboratories and, as a result, there are limited clinical studies on a quantifiable potency. Unfortunately, due to the variability in illicit manufacturing, these designer benzodiazepines may possess less than or greater effects when compared to prescription benzodiazepines and may lead to increased mortality.[8,9,10] Many are aware of

the risks of CNS depression when opioids and benzodiazepines are co-ingested, but any medication that affects the patient's opioid or GABA receptors may produce this effect. In particular, designer drugs can have a profound effect on the patient. Identification of any designer drug affords providers the opportunity to discuss the unpredictability of the illicit drug supply and possibly result in more effective harm reduction strategies. One recent trend observed is the cutting of xylazine in fentanyl.[11] This is particularly dangerous because, while xylazine has CNS depressant activity, it is not an opioid, so it does not likely respond to naloxone reversal.

In the following patient case below, multiple potential drug-drug interactions are identified. The interaction between bupropion and oxycodone is important as bupropion inhibits the cytochrome P450 (CYP450) liver enzyme CYP2D6, which metabolizes oxycodone to oxymorphone, a more active metabolite.[12] This interaction may cause the patient to not achieve expected analgesic effects, and result in taking more oxycodone than prescribed to relieve their pain. If adherence to bupropion therapy is a concern, or if the bupropion is transitioned to another therapy without CYP2D6 inhibition, there is a resultant increase in oxycodone effect despite no change in dosage. A distinct gabapentin and oxycodone interaction also may contribute to CNS depression in this patient.[13] While these two pairs of drug interactions are deemed moderate risk, both can contribute to CNS depression. As seen below, the final report indicated the presence of alpha-hydroxyetizolam, a metabolite of the designer benzodiazepine etizolam. The presence of etizolam should be given further consideration as it may also contribute to CNS depression.

Medication Compliance

Drug and/or Metabolites	Result Interpretation	Result	Comment
Gabapentin	COMPLIANT	59 mcg/mL	Test result is consistent and expected with prescribed drug.
Oxycodone	COMPLIANT	>4350 ng/mL	Test result is consistent and expected with prescribed drug.
Designer Benzodiazepines	PRESENT	POSITIVE	Test results indicate use of a non-prescribed drug. Based on limited scientific information, the detection period for designer benzodiazepines in urine by LC/MS/MS should be no more than 10 days from last use.

Drug-Drug Interaction (DDI)

Potential Interaction Detected		Interaction Severity	Interaction Description
Bupropion (Wellbutrin)	Oxycodone	MODERATE	The concurrent administration of benzhydrocodone, hydrocodone or oxycodone and a strong inhibitor of CYP2D6 may result in decreased efficacy of hydrocodone or oxycodone. Parent and metabolite concentrations of hydrocodone or oxycodone may be altered.(2)
Gabapentin	Oxycodone	MODERATE	Concurrent use of opioids may result in elevated levels of and toxicity from gabapentin and pregabalin, including profound sedation, respiratory depression, coma, and/or death.(1-4)

Citations in interaction descriptions can be provided as needed. DDI disclaimers can be found at https://www.aegislabs.com/about-ddi. Please contact Clinical Scientists at 1-877-552-3232 for more information.

Test(s) Requested Contents

Tested For	Result	Laboratory Result
Buprenorphine	NONE DETECTED	
Tramadol	NONE DETECTED	
Alcohol Metabolites		
Ethyl Glucuronide	NONE DETECTED	
Ethyl Sulfate	NONE DETECTED	
Synthetic Stimulants	NONE DETECTED	
Naloxone	NONE DETECTED	
Amphetamines	NONE DETECTED	
Barbiturates	NONE DETECTED	
Designer Benzodiazepines		
alpha-Hydroxyetizolam	**POSITIVE**	
Benzodiazepines	NONE DETECTED	
Synthetic Cannabinoids	NONE DETECTED	
Cyclobenzaprine	NONE DETECTED	
Gabapentin		
Gabapentin	**POSITIVE**	59 mcg/mL
Cocaine Metabolite	NONE DETECTED	

Inappropriate polypharmacy is the unnecessary or excessive prescribing, or over-prescribing of medications.[14] This inappropriate prescribing puts the patient at increased risk of potential drug-drug interactions (DDIs), which can occur between medications, foods, and supplements. Possible adverse effects can include falls, cognitive impairment, and effects on a disease state, where a medication prescribed for one purpose worsens or causes another. Drug interactions can be pharmacokinetic in nature, some of which involve the alteration of CYP450 enzyme metabolism. Interactions can range from mild to severe and are often preventable. The severity and mechanism responsible are important to identify when determining how to best manage the interaction as they may lead to unwanted adverse events and/or therapeutic alterations. For example, the addition of a CYP3A4 inducer such as carbamazepine to buprenorphine therapy could lead to decreased efficacy of buprenorphine, the onset of withdrawal syndrome, and potentially increase the patient's risk of non-medical opioid use.[15]

It is important that providers are aware of what their patients are taking. Research has shown that the combination of prescription and illicit CNS depressants, such as designer benzodiazepines, have led to increased mortality.[8] One initial approach is identifying potential drugs of abuse that patients may be taking. From there, one can hypothesize potential harmful effects and risks they may then experience. Aegis strives to provide practitioners the clarity needed to facilitate improved care for patients with substance and mental health disorders.

NOTICE: The information above is intended as a resource for health care providers. Providers should use their independent medical judgment based on the clinical needs of the patient when making determinations of who to test, what medications to test, testing frequency, and the type of testing to conduct.

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