Patients Receiving Benzodiazepines, in Combination with Opioid Analgesics, May Suffer from Respiratory Compromise and Death

A position statement by the Physician-Patient Alliance for Health & Safety (May 2018)

In the hospital setting, unmonitored use of opioids can lead to dangerous sedation, respiratory compromise, and death. The Joint Commission in its Sentinel Event #49, "Safe use of opioids in hospitals" cautioned:

> *While opioid use is generally safe for most patients, opioid analgesics may be associated with adverse effects, the most serious effect being respiratory depression, which is generally preceded by sedation.*

Opioids are the most prescribed class of medication in hospitals, leading it to be one of the most common class of medication to cause adverse patient events.

One of the commonly overlooked complications to safe opioid administration is failing to account for the additive sedation effects of non-opioid medication. In recognition of these dangers, in August 2016, the FDA issued its strongest warning about combined use of opioids and benzodiazepines (and issued another caution more recently on September 20, 2017, saying:

> *After an extensive review of the latest scientific evidence, the U.S. Food and Drug Administration announced today that it is requiring class-wide changes to drug labeling, including patient information, to help inform health care providers and patients of the serious risks associated with the combined use of certain opioid medications and a class of central nervous system (CNS) depressant drugs called benzodiazepines.*

> *Among the changes, the FDA is requiring boxed warnings – the FDA's strongest warning – and patient-focused Medication Guides for prescription opioid analgesics, opioid-containing cough products, and benzodiazepines – nearly 400 products in total – with information about the serious risks associated with using these medications at the same time. Risks include extreme sleepiness, respiratory depression, coma and death.*

Robert Califf, M.D., who was then FDA Commissioner, emphasized the need for caution:

> *"It is nothing short of a public health crisis when you see a substantial increase of avoidable overdose and death related to two widely used drug classes being taken together," said "We implore health care professionals to heed these new warnings and more carefully and thoroughly evaluate, on a patient-by-patient basis, whether the benefits of using opioids and benzodiazepines – or CNS depressants more generally – together outweigh these serious risks."*

Health Canada has also issued a warning about benzodiazepines:

> *"Benzodiazepines belong to the sedative-hypnotic-anxiolytic class of drugs, which are used to decrease agitation and anxiety, and help with sleep. When used properly, they can help. But when abused, they can cause addiction, overdose and death."*

It is common for patients to receive multiple medications during their hospital stay. Some patients arrive to the hospital with an existing baseline of home medication for other conditions. Accordingly, when patients are admitted to hospital, it is essential for clinicians to "recognize and understand syndromes of intoxication, overdose and withdrawal for common substances of abuse including ETOH, opioids, cocaine, THC, benzodiazepines, and over-the-counter (OTC) or prescription drugs."

In hospital, some patients are placed on a complex, multimodal analgesic regimen to help avoid opioid escalation. To keep these patients safe, the first step is to be aware of the sedating potential of the different medication classes; patients receiving these combinations need to be placed on a more aggressive monitoring plan, preferably with continuous electronic monitoring by pulse oximetry to measure oxygenation and capnography to measure the adequacy of ventilation.

One of the most dangerous classes of medication to interact with opioids are benzodiazepines. Benzodiazepines are an extremely common class of medication, which includes alprazolam, lorazepam, clonazepam, diazepam, temazepam and midazolam. Many patients enter the hospital taking benzodiazepines to treat conditions such as anxiety, muscle spasms, and sleep disorders; if they're already habituated to the drug, patients need to stay on them during their stay to avoid withdrawal. Already a mild respiratory inhibitor alone, benzodiazepines have a synergistic interaction with opioids, multiplying the risking of respiratory depression, which if not recognized can lead to respiratory arrest and death..

Benzodiazepines are not the only class of medications that can interact poorly with opioids. Anticonvulsants, muscle relaxants, antidepressants, antipsychotics, pain adjuvants, antihistamines, and antiemetic medications all significantly increase the risk of opioid-related respiratory depression.

Here are some recommendations contained in the Society of Hospital Medicine guide "Reducing Adverse Drug Events related to Opioids Implementation Guide" (known as the RADEO Guide:

Mechanism	Drugs or Condition	Consequence
Competition for cytochrome enzymes	Nifedipine	Variable
Pharmacodynamic interaction	Benzodiazepines, barbiturates, other opioids and other CNS depressants	Increased respiratory depression and sedation
Increase plasma level of AAG a_1 acid glycoprotein (acute reactant protein)	Stress reactions, cancer, opioid addiction and concurrent administration of amitriptyline	Inadequate analgesia or withdrawal
Changes in gastric pH or activity of P-glycoprotein	Verapamil, quinidine	May increase methadone absorption
Potentiation of QT prolongation	Fluoroquinolones, macrolides, tricyclic antidepressants, citalopram, ondansetron	May precipitate torsades de point

**This is not an exhaustive table. Different medications induce or inhibit specific cytochrome enzyme subtypes. There is tremendous inter-individual variability in the cytochrome P450 activity. For simplicity, the drugs are grouped according to the overall effects on the whole cytochrome enzyme system rather than a specific enzyme subtype.[52], [53]*

The above chart is by no means exhaustive, but can serve as a useful reminder when caring for a patient taking or being administered some commonly used drugs.

In a recent interview regarding the Society of Hospital Medicine comprehensive guide, "Reducing Adverse Drug Events Related to Opioids" (otherwise known as the RADEO guide), the lead author, Thomas W. Frederickson MD, FACP, SFHM, MBA, emphasized the sedation risk from the additive effects of non-opioid medications must be recognized by all clinicians when administering opioids to their patients:

> *The biggest risk are the benzodiazepines, and the reason that the benzodiazepines pose a risk are really two.*
>
> *First is they're very common. Many patients come into the hospital taking benzodiazepines. They're commonly used for anxiety and other conditions as well. So, patients, who are already on benzodiazepines, habituated benzodiazepines, need to continue that medication in the hospital.*

> *So, when you have an additive effect, or even more than an additive effect of adding an opioid medication to control pain, the sedating effects of the benzodiazepines, as well as the opioids, can be more than additive; and this really is a situation that requires an increased level of caution for providers and policies in place that include more heightened monitoring and such to avoid untoward events.*

In order to avoid respiratory compromise and death, there must be significant caution and monitoring of patients receiving benzodiazepines and other sedatives, particularly when received in combination with opioids.

To help prevent respiratory compromise and death in patients receiving an opioid analgesic and a benzodiazepine or other sedative, the Physician-Patient Alliance for Health & Safety recommends:

- When a patient is admitted to hospital, it is essential for clinicians to recognize and understand the syndromes of respiratory compromise.
- During hospitalization, patients, who receive an opioid analgesic and a benzodiazepine or other sedative, be placed on a more aggressive monitoring plan, preferably with continuous electronic monitoring by pulse oximetry to measure oxygenation and capnography to measure the adequacy of ventilation.

This Position Statement is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Always seek the advice of your physician or other qualified health provider with any questions you may have regarding a medical condition, the use of benzodiazepines, and opioids.