



Investigations and Audits Group

Date: March 16, 2018
To: All Medicare Advantage and Part D Plan Sponsors
From: Mark Majestic, Director
Re: Opioid Potentiators

In response to recent inquiries and as part of the Centers for Medicare & Medicaid Services' (CMS) continuing efforts to combat the ongoing opioid epidemic, we are providing Medicare plan sponsors with an educational memorandum regarding drugs that can be utilized in conjunction with opioids to potentiate the opiate effect. This information may be utilized to enhance plan sponsor efforts to protect the health and safety of Medicare beneficiaries as well as combat the misuse and abuse of opioids.

Opioid potentiators are drugs, herbs, or chemicals that are utilized to intensify the effects of the opioid. While there are many methods by which opioid effects can be intensified illicitly (such as rectal administration, snorting or crushing tablets, evaporating liquid opioids, mixing liquid opioids with sodium bicarbonate, consuming grapefruit or orange juice, etc.), this memorandum is intended to convey most medications that are utilized as opioid potentiators. The information below is not intended to provide a full and complete list of all potential opioid potentiators. However, it is an educational tool to enhance plan sponsor efforts to combat the misuse and abuse of opioids.

Central Nervous System (CNS) Depressants

On August 31, 2016, the Food and Drug Administration (FDA) issued a safety announcement warning of the dangers of utilizing opioids in conjunction with CNS depressants.ⁱ The FDA cited that the combination of opioids with CNS depressants has resulted in serious side effects, including slowed or difficult breathing, overdoses, and deaths. The FDA found that CNS depressants were contributory to death in many cases where opioid analgesics were also implicated.

The FDA further required a Boxed Warning, their strongest type of warning, on the dangers of these combinations to the drug labeling of all prescription opioid pain medicines, prescription opioid cough medicines, and benzodiazepines.ⁱⁱ The FDA did, however, later clarify that medications for the treatment of opioid addiction, such as buprenorphine, buprenorphine/naloxone, and methadone, should not be withheld in patients also taking CNS depressant medications as the risks of untreated opioid addiction outweighed the risks of these combinations.ⁱⁱⁱ

CNS depressants are often misused or abused in conjunction with opioid analgesics as they are purported to enhance the euphoric effects. It is unclear whether these reinforcing euphoric effects are additive or synergistic when done in combination. Below is a list of some of the common CNS depressants that may be utilized as opioid potentiators.

Benzodiazepines

Benzodiazepines are Schedule IV controlled substances, and as such carry a risk of misuse or abuse on their own. Over 30% of opioid overdoses also include benzodiazepines. Both opioids and benzodiazepines sedate users, suppress breathing, and impair cognitive functions.^{iv} In addition to the FDA Boxed Warning, the Centers for Disease Control and Prevention (CDC) issued the *Guideline for Prescribing Opioids for Chronic Pain* in 2016 that recommend clinicians avoid prescribing benzodiazepines concurrently with opioids whenever possible in the management of chronic non-cancer pain.^v

Muscle Relaxants

Muscle relaxants (such as tizanidine, cyclobenzaprine, baclofen, chlorzoxazone, carisoprodol, etc.) can have potential harmful effects when utilized concurrently with opioids. These drugs are commonly utilized with many painful conditions in which muscle spasticity is involved. However, muscle relaxants have CNS depressant effects and increase the risk for respiratory depression, coma, and death when combined with opioids.

Carisoprodol is currently the only central muscle relaxant that is a controlled substance, and as such carries a risk of misuse or abuse on its own. This Schedule IV controlled substance is frequently combined with benzodiazepines and opioids for a heroin-like high. This combination has several street names, including “Trio” and “Houston Cocktail.” The combination of carisoprodol in conjunction with opioids and benzodiazepines can have even greater respiratory depression resulting in greater potential for patient harm.^{vi}

Barbiturates

Barbiturates are Schedule IV controlled substance, and as such carry a risk of misuse or abuse on their own. Barbiturates are CNS depressants which are most frequently used in seizure disorders. Although these drugs are less common than benzodiazepines, concurrent use with opioid analgesics may be of concern due to the potential CNS depressant effects. These CNS depressant effects can increase the risk for respiratory depression, coma, and death when combined with opioids.

Benzodiazepine-Like Hypnotics

This class of medications contains non-benzodiazepine hypnotics such as zolpidem, zaleplon, and eszopiclone. These medications are Schedule IV controlled substances and, as such, carry a risk of misuse or abuse on their own. As CNS depressants, this class of medications can increase the risk for respiratory depression, coma, and death when combined with opioids.^{vii}

Gabapentinoids

The gabapentinoids (pregabalin and gabapentin) are a class of medications which have multiple indications, including the management of pain. Pregabalin is a Schedule V controlled substance,

and as such carries a risk of misuse or abuse on its own. Gabapentin is not classified as a controlled substance by the Drug Enforcement Administration (DEA); however, certain states have included this drug in their list of controlled substances. Gabapentinoids are CNS depressants and increase the risk for respiratory depression, coma, and death when combined with opioids.^{viii ix}

Antihistamines

Antihistamines, such as promethazine, have misuse potential among patients utilizing opioids. Promethazine and codeine cough syrup, in combination with soda or juice, have a history of abuse and is referred to as “lean,” “purple drank”, or “sizzurp.”^x As CNS depressants, the effects of these drugs can increase the risk for respiratory depression, coma, and death when combined with opioids.

Antipsychotics

Antipsychotic medications, such as quetiapine, have a history of misuse and abuse due to their sedating effects. As CNS depressants the effects of these drugs can increase the risk for respiratory depression, coma, and death when combined with opioids.^{xi}

Pharmacokinetic Enhancers

Pharmacokinetic enhancers are used to boost the effectiveness of another drug. When the two drugs are given together, the pharmacokinetic enhancer interferes with the metabolism of the other drug, which allows the targeted drug to remain in the body longer and at a higher concentration. While this principle has clinical utility in many settings, it can be abused to potentiate the effects of opioids. Below is a list of some of the common pharmacokinetic enhancers that may be utilized as opioid potentiators.

HIV Drugs

Many HIV medications are strong inhibitors of the cytochrome P450 enzymes, specifically the CYP3A4. This inhibition of CYP3A4 leads to a subsequent increase in the serum concentration of the opioid due to its decreased metabolism. Ritonavir, atazanavir, indinavir, and cobicistat are a few examples of these drugs.^{xii}

Antifungals

Certain antifungal agents such as itraconazole, ketoconazole, and posaconazole are strong inhibitors of cytochrome P450 enzymes. This inhibition leads to a subsequent increase in the serum concentration of the opioid due to its decreased metabolism.

Antibiotics

Certain antibiotics such as clarithromycin are strong inhibitors of cytochrome P450 enzymes. This inhibition leads to a subsequent increase in the serum concentration of the opioid due to its decreased metabolism.

Other Potentiators

Stimulants

Stimulants, which include Schedule II prescription drugs such as dextroamphetamine and methylphenidate, are prescribed for only a few health conditions, including attention-deficit hyperactivity disorder (ADHD), narcolepsy, and treatment-resistant depression.^{xiii} Stimulants are used with opioids in combinations to combat fatigue and sedation caused by high daily doses of opioids.^{xiv} There are also pain specialists that utilize stimulants to increase the analgesic effect of opioids, although this combination is not commonly prescribed due to the high abuse potential of combining opioids and stimulants.^{xv}

Summary

It is important to note in any investigation by a Medicare sponsor that none of the listed drugs and examples are totally contraindicated in beneficiaries and are often utilized for true medical purposes. Verification of medical records, diagnoses, and provider-beneficiary relationships are an essential part of determining if a combination of a specific drug(s) and opioid are for illicit purposes. Patterns of high doses, duplicative regimens or drugs, lack of appropriate medical diagnoses, or repeated early refills of any of these drugs in combination with opioids may warrant further investigation.

CMS is aware that some patterns of prescribing or dispensing potentially abusive combinations may occur due to lack of knowledge and poor prescribing patterns. In these cases, the sponsor or the Quality Improvement Organization (QIO) may work with the providers to improve patient care and safety for the Medicare beneficiaries. If potential fraud or illicit use of opioid potentiators is suspected, please notify the National Benefit Integrity Medicare Drug Integrity Contractor (NBI MEDIC) at 1-877-7SafeRx (1-877-772-3379).

ⁱ FDA Drug Safety Communication: FDA warns about serious risks and death when combining opioid pain or cough medicines with benzodiazepines; requires its strongest warning. <https://www.fda.gov/Drugs/DrugSafety/ucm518473.htm>. Published on 8/31/2016. (Accessed on 2/19/2018).

ⁱⁱ Ibid.

ⁱⁱⁱ FDA Drug Safety Communication: FDA urges caution about withholding opioid addiction medications from patients taking benzodiazepines or CNS depressants: careful medication management can reduce risks. <https://www.fda.gov/Drugs/DrugSafety/ucm575307.htm> Published on 9/20/2017. (Accessed on 2/19/2018).

^{iv} Benzodiazepines and Opioids. National Institute on Drug Abuse. <https://www.drugabuse.gov/drugs-abuse/opioids/benzodiazepines-opioids>. Revised September 2017. (Accessed on 2/16/2018).

^v CDC Guideline for Prescribing Opioids for Chronic Pain – United States, 2016. Recommendations and Reports, 2016. 65(1); 1-49. <https://www.cdc.gov/mmwr/volumes/65/rr/rr6501e1.htm>. (Accessed on 2/19/2018).

^{vi} Carisoprodol (Soma®). Drug Enforcement Administration. March 2014. https://www.deadiversion.usdoj.gov/drug_chem_info/carisoprodol/carisoprodol.pdf. (Accessed on 2/16/2018).

^{vii} Dahlman D, Abrahamsson T, Kral AH, et al. Nonmedical Use of Antihistaminergic Anxiolytics and Other Prescription Drugs among Persons with Opioid Dependence. *Journal of Addiction*. Volume 2016, Article ID 9298571. <https://www.hindawi.com/journals/jad/2016/9298571/>. (Accessed on 2/16/2018).

^{viii} Schifano F. Misuse and Abuse of Pregabalin and Gabapentin: Cause for Concern? *CNS Drugs*. 2014;28(6):491-496.

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- ^{ix} Smith RV, Havens JR, and Walsh SL. Gabapentin Misuse, Abuse, and Diversion: a Systematic Review. *Addiction*. 2016 Jul; 111(7):1160-1174. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5573873/>. (Accessed on 2/18/2018).
- ^x Resurgence in Abuse of “Purple Drank”. U.S. Department of Justice. February 15, 2011. <https://www.justice.gov/archive/ndic/pubs43/43924/sw0008p.pdf>. (Accessed on 2/16/2018).
- ^{xi} Sansone RA and Sansone LA. Is Seroquel Developing an Illicit Reputation for Misuse/Abuse? *Psychiatry*. 2010; 7(1):13-16. <https://www.ncbi.nlm.nih.gov/pubmed/20386631> (Accessed on 2/18/2018).
- ^{xii} Database of Antiretroviral Drug Interactions. *HIV InSite*. University of California San Francisco. <http://arv.ucsf.edu/InSite?page=ar-00-02>. (Accessed on 2/16/2018).
- ^{xiii} Stimulants. Misuse of Prescription Drugs. National Institute on Drug Abuse. January 2018. <https://www.drugabuse.gov/publications/research-reports/misuse-prescription-drugs/which-classes-prescription-drugs-are-commonly-misused>. (Accessed on 2/16/2018).
- ^{xiv} Corey PJ, Heck AM, and Weathermon RA. Amphetamines to Counteract Opioid-Induced Sedation. *Annals of Pharmacotherapy*. 1999; 33(12):1362-1366.
- ^{xv} Dalal S and Melzack R. Potentiation of Opioid Analgesia by Psychostimulant Drugs: a Review. *Journal of Pain and Symptom Management*. 1998;16(4)245-253.