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CONCURRENT USE OF MUSCLE RELAXANTS AND/OR HYPNOTICS WITH OPIOIDS: RESPIRATORY DEPRESSION RISK AND RETROSPECTIVE UTILIZATION REVIEW

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CONTENTS

LIST OF FIGURES

LIST OF TABLES

ABBREVIATIONS

AEs	adverse events
aHR	adjusted hazard ratio
aOR	adjusted odds ratio
ASCO	American Society of Clinical Oncology
ASH	American Society of Hematology
ASIPP	American Society of Interventional Pain Physicians
BBW	black box warning
BZD	benzodiazepine
CDC	Centers for Disease Control and Prevention
CI	confidence interval
COPD	chronic obstructive pulmonary disease
CNS	central nervous system
CNSd	central nervous system depressant or depression
CS	controlled substance
CSA	central sleep apnea
DDI	drug-drug interaction
DoD	Department of Defense
DSC	drug safety communication
ER	extended release
FDA	United States Food and Drug Administration
FFS	(Utah Medicaid) Fee-for-Service
GABA	gamma-aminobutyric acid
HR	hazard ratio
IR	immediate release
LA	long-acting
MA	meta-analysis
MME	morphine milligram equivalents
MOR	μ opioid receptor
MR	(skeletal) muscle relaxant
MRA	Melatonin receptor agonist
NBRA	non-benzodiazepine, benzodiazepine receptor agonists (also called ‘Z drugs’)
NCCN	National Comprehensive Cancer Network
NMDA	N-methyl-D-aspartic acid
OD	overdose
OR	odds ratio
ORA	orexin receptor antagonist
OSA	obstructive sleep apnea
OUD	opioid use disorder
PD	pharmacodynamic
PK	pharmacokinetic
POD	percentage of overlapping days
PTSD	post-traumatic stress disorder

RCT	randomized controlled trial
RD	respiratory depression
REMS	Risk Evaluation and Mitigation Strategy
SCD	sickle cell disease
SD	standard deviation
SH	sedative-hypnotic
SNRI	serotonin-norepinephrine reuptake inhibitor
SR	systematic review
SUD	substance use disorder
TCA	tricyclic antidepressant
US	United States (of America)
VA	Veterans Affairs

1.0 INTRODUCTION

Opioids are natural, semi-synthetic, or synthetic compounds that agonize central and peripheral opioid receptors. They are primarily prescribed for the treatment of moderate-to-severe acute or chronic pain.[1,2] By directly depressing signals from the central respiratory control center and other mechanisms, opioids can impair respiration, potentially leading to respiratory depression (ie, hypoventilation with inadequate exchange of gases in the lungs).[3-5] Respiratory depression (RD) is often, but not always, preceded by increased sedation.[3,6] Opioid-related mortality is primarily attributed to overdoses (ODs) caused by RD.[6] Fatal and non-fatal opioid ODs occur at an estimated incidence of 1.3 and 3.2 out of 1000 people with chronic pain prescribed opioids, respectively. The incidence of opioid OD increases among people with other risk factors for RD or OD, including the co-prescription of other central nervous system (CNS) depressants, among other factors (eg, active substance use disorder [SUD]).[7]

Today, the US Centers for Disease Control and Prevention (CDC) recognizes 3 distinct phases of the opioid crisis: phase I, starting in the 1990s, was attributed to increase deaths from prescription opioids, which plateaued or slightly increased between 2010 and 2021; phase 2 starting in 2010 was attributed to a rise in deaths from heroin; and phase 3, starting in 2013, was attributed to increase deaths from synthetic opioids, including prescribed or illicitly obtained fentanyl.[8]

Owing to the risk of misuse and death from opioids, many policies have been implemented over the past decade to promote their judicious and safe use.[9] The 2016 CDC guideline on opioids for chronic pain widely influenced clinician prescribing patterns, and the adoption of opioid-related institutional or regulatory policies.[6,9] The 2016 CDC guideline included a recommendation to avoid prescribing benzodiazepines (BZDs) and opioids concurrently; it was also recommended to weigh the risks versus benefits of using other CNS depressants (eg, muscle relaxants [MRs] or hypnotics) with opioids.[10] Also in 2016, the US Food and Drug Administration (FDA) required opioid analgesics and cough products to carry a black box warning (BBW) for the risk of RD and death when used in combination with BZDs or CNS depressants, which was primarily based on observational evidence of increased risk in combination with BZDs.[11]

Since 2010, the average number of opioid prescriptions and average prescribed opioid dose has declined, while the number of opioid OD deaths increased.[6] Thus, authors of the 2023 American Society of Interventional Pain Physicians (ASIPP) guideline described that "It is crucial to realize and report that all opioid overdose deaths are not related to prescription opioid overdose deaths and the illicit opioid epidemic is not a prescription drug epidemic" (page S35). ASIPP and experts expressed that a fourth wave of the opioid crisis is ongoing since the start of the COVID-19 epidemic, driven by the increased availability of illicit opioids, misuse of stimulants (eg, methamphetamine and cocaine) and increased barriers to other pain treatments including interventional techniques, among other factors.[6,9] While the risks of misuse, RD, and OD warrant the judicious prescribing of opioids, there is evidence that some policies unintentionally contributed to patient harm.[6,9] For example, tapering the opioid dose (ie, the reduction in mean daily opioid dose by ≥ 15% within 60 days) in a cohort of adults with chronic pain on long-term opioid therapy at a daily dose ≥ 50 morphine milligram equivalents (MME) was associated with a significantly increased incidence of opioid OD and mental health crises.[12]

To support the safe use of prescription opioids in the Utah Medicaid population, the **objective** of this report is to address the risk of RD from concurrent use of opioids with non-BZD CNS depressants, specifically, non-BZD and non-barbiturate MRs and sedative-hypnotics (SH) through (1) a review of select evidence and (2) a retrospective utilization review of concurrent prescription fills for these agents among Utah Medicaid Fee-for-Service (FFS) patients. While the risks of using BZDs and opioids concurrently is often emphasized, less emphasis has been given to concurrent use of opioids with other CNS depressants despite their inclusion in FDA warnings. Our evidence review focused on information about the risks of concurrent use of these agents according to warnings and precautions from prescribing information, FDA safety communications, recent US pain-focused opioid guidelines, and select observational evidence.

2.0 METHODS

To identify information about opioid-induced RD or OD and the risks from concurrent use of CNS depressants, we focused on information from prescribing information for opioids, MRs, and SHs (see section 2.11 below and **Appendix A**); FDA safety communications about opioids (https://www.fda.gov/drugs/drug-safety-and-availability/drug-safety-communications); and guidance from recent US pain-focused guidelines. Prescribing information about CNS depression, RD, or OD were compiled from the drug compendia Lexidrug, and select package inserts available from DailyMed (https://www.fda.gov/drugs/drug-safety-and-availability/drug-safety-communications) and/or the FDA's website (https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm). For feasibility, information from package inserts was limited to representative medications for drug classes that share a similar mechanism of action (ie, opioids and subclasses of SHs). We searched for opioid-related recent (2019-2024) US guidelines on the "society guideline links" sections of UpToDate (https://www-uptodate-com) within opioid indication monographs (ie, pain, cough, diarrhea). Based on the availability of recent US guidelines and common uses for opioids, we narrowed our focus to guidelines for pain that address the risks from using opioids with CNS depressants. We also searched for guidelines at the following organizational websites applicable to the treatment of cancer or sickle cell disease (SCD), including the American Society of Clinical Oncology (ASCO), National Comprehensive Cancer Network (NCCN), and American Society of Hematology (ASH).

Based on feasibility constraints, we were unable to perform an exhaustive systematic literature search for all available observational or experimental evidence regarding the risk of RD or OD from concurrent use of opioids with MRs and/or hypnotics. Background information about drug-induced RD was gathered from reviewed guidelines, references cited by reviewed guidelines, and targeted free text searches in the bibliographic database, PubMed (https://pubmed.ncbi.nlm.nih.gov/)[*]. To supplement data from FDA safety communications and reviewed guidelines, we reviewed relevant articles cited by the FDA and guidelines and reviewed studies that were considered similar to studies cited by those sources by pubmed.ncbi.nih.gov.

[*] We searched PubMed in May 2024, using the following search string: "respiratory" + opioid (as a drug class) or the generic names of MRs or sedative-hypnotics addressed by this report.

2.1 Data Collection and Descriptive Analysis of Concomitant Use of Muscle Relaxants and/or Hypnotics with Opioids

We performed a descriptive analysis of concurrent utilization of opioids with non-BZD and non-barbiturate MRs and/or SHs among Utah Medicaid FFS patients between April 1, 2023 and March 31, 2024 (the study period).

2.1.1 Included medications

Eligible medications were mono-ingredient or combination ingredient prescription opioids, and non-BZD and non-barbiturate (except for butalbital with codeine that was included) MRs or SHs currently marketed in the US. SHs indicated for narcolepsy, and the agent chloral hydrate, which is FDA-indicated for procedural sedation and not routinely used,[13] were excluded. We also excluded buprenorphine formulations that are FDA-indicated for treatment of opioid use disorder (OUD). Refer to **Appendix A** for a list of included active ingredients or drug products.

A comprehensive list of active ingredients for opioids, MRs, and SHs was compiled by querying relevant pharmacologic categories in Lexidrug , which included "hypnotic, miscellaneous," "analgesic, opioid," "antitussive," "antidiarrheal," "skeletal muscle relaxant." Further refinement was carried out through searches of the drugs@FDA database (https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm) and FDA drug safety communications, particularly focusing on lists of CNS depressant categories.. Notably, although tizanidine is not classified as a "skeletal muscle relaxant" by Lexidrug, it was included in the MR category due to its FDA indication for spasticity and MR classification by the FDA.[11,14] Additionally, because doxepin (in 3 or 6 mg tablet form) is FDA-indicated for insomnia, it was included among reviewed SHs.[15]

2.1.2 Patient cohorts and subgroups

Eligible patients among the Utah Medicaid FFS population were identified from queries of outpatient prescriptions fills for at least 1 active ingredient of interest (see list in **Appendix A**) during the 12-month study period (April 1, 2023 and March 31, 2024). Patient cohorts and overlapping prescription subgroups are as follows:

- *Overall cohort* = Patients who filled at least 1 eligible prescription for an opioid, MR, or SH during the study period.
- *Opioid cohort* = Patients who filled at least 1 eligible prescription for an opioid (regardless of overlap with a product in another medication class).
    - *Opioid + MR subgroup* = Patients who filled at least 1 concurrent prescription (based on overlapping days' supply) for an opioid and MR.
    - *Opioid + SH subgroup* = Patients who filled at least 1 concurrent prescription (based on overlapping days' supply) for an opioid and SH.
    - *Opioid + MR + SH subgroup* = Patients who filled concurrent prescriptions (based on overlapping days' supply) for an opioid, MR, and SH.

2.1.3 Descriptive analysis

Concurrent use of opioids with MRs and/or SHs was determined based on overlapping days' supply (by at least 1 day) of one or more filled medications from the respective drug classes during the study period. To identify overlapping days' supply, we used the prescription claims data for the date of fill and the number of days' supplied. Days' supply for successive prescription fills of the same active ingredient (including different products, regardless of dosage form, of the same opioid, MR, and/or SH) were calculated by adding their days' supply together (ie, carrying over days' supply). Conversely, when prescriptions involved different active ingredients within the same drug class (eg, morphine and codeine), the days' supply was not additive. In such cases, the days' supply was calculated as the sum of the number of days between the fill date of the first drug and the fill date of the second drug, plus the days' supply of the second filled drug. Notably, for patients receiving both a long-acting (LA) and short-acting (SA) opioid, the true days' supply of the opioid regimen may have been overestimated, since the SA opioid is often meant to be taken concurrently with the LA opioid (rather than substituted for the LA opioid).

In addition to reporting the number and proportion of Utah Medicaid FFS patients who had concurrent use of opioids with MRs and/or SH, to describe the potential duration of co-use of these agents, we calculated the percentage of overlapping days (POD). For the opioid cohort and each opioid subgroup (ie, opioid + MR, opioid + SH, and opioid + MR + SH), POD was calculated as a patient-level proportion of number of overlapping prescription days out of either the total number of days of opioid supply or the total number of days of Utah Medicaid coverage (see **Table 1).**

Table 1. Calculation of Percentage of Overlapping Days (POD)

Numerator[a]	Denominator[a]
Total number of overlapping days' supply between prescriptions in different drug classes (opioid + MR, or opioid + SH, or opioid + MR + SH) during the study period[b].	1a. Total number of opioid days supplied during the study period[b]
	1b. Total number of days with Medicaid coverage during the study period[b]
• For each unique patient, POD was calculated as the proportion of the number of overlapping days (of opioid + MR, opioid + SH, or opioid + MR + SH) divided by either the total number of opioid days supplied or the total number of days of Utah Medicaid coverage during the study period. • Each POD calculation was performed for the total opioid cohort and for each subgroup with overlapping therapy of opioid + MR and/or + SH. • We expressed POD as a percentage, and calculated summary statistics (eg, mean, median).	

Abbreviations: MR, muscle relaxant; POD, percentage of overlapping days; SH, sedative-hypnotic

[a] In calculation of the numerator and denominator, we carried over days' supply for successive prescriptions with the same active ingredient; successive overlapping prescription fills for different active ingredients were not carried over.

[b] The study period was from April 1, 2023 and March 31, 2024

Within the overall cohort and subgroups, we performed descriptive statistics (eg, mean, median, standard deviation[SD]) for age, sex assigned at birth, and duration of Medicaid eligibility during the study period (based on dates reported in the Utah Medicaid database). For each overlap subgroup, we

also calculated descriptive statistics for the individual PODs. Among patients with overlapping days' supply of an opioid with a MR and/or SH, we identified the various combinations that overlapped (by active ingredient) and described those that occurred with the highest frequency.

3.0 OVERVIEW OF RESPIRATORY DEPRESSION, OPIOIDS, AND CNS DEPRESSANTS

3.1 Respiratory Depression (RD)

Respiration (ie, the exchange of oxygen [O_2] and carbon dioxide [CO_2]) requires the coordination of (1) signals from the CNS, (2) sensory input from central and/or peripheral mechanical, metabolic, and chemical receptors, and (3) the contraction and relaxation of respiratory muscles. The central respiratory center (primarily in the pons and medulla) receives signals from sensory inputs about the status of the lungs, metabolic demand, and changes in the partial pressure of O_2/CO_2. The central respiratory center responds by sending signals to the respiratory muscles to control the frequency and depth of inhalation and exhalation, frequently referred to as the "respiratory drive".[3,16] During normal respiration in a healthy individual, there is a predictable increase in the respiratory rate as the partial pressure of CO_2 increases.[3]

Impairment of one or more of factors (ie, that affect the CNS, sensory inputs, and/or respiratory muscles or tissues) can compromise respiration. **Respiratory depression (RD)** is hypoventilation that results in the inadequate exchange of gases in the lungs and can occur as a cause of neuromuscular diseases (eg, with compromised respiratory muscles), chronic lung diseases (eg, chronic obstructive lung disease [COPD]), sleep apnea), or medications, among others. Severity of RD is a continuum with symptoms ranging from mild dyspnea on exertion, to dyspnea at rest and hypersomnolence, and ultimately to delirium, cyanosis, and seizures, with a risk of sustained apnea and resultant cardiopulmonary arrest.[3] While sedation usually precedes apnea,[6] some individuals may initially present with severe symptoms (eg, apnea).[3] RD severity is impacted by the degree of factors impacting respiration.[3]

Respiration during sleep differs from respiration while awake, allowing for a greater impact of factors that can exacerbate or cause RD.[3] Particularly during rapid eye movement sleep, the volume and rate of respiration varies. In addition, the diaphragm becomes the primary muscle controlling respiration (accessory muscles are paralyzed), the upper airway narrows, and the respiratory control center is less responsive to changes in gas concentrations.[16] Perhaps for these reasons, opioid-related deaths from RD often occur during sleep.[6]

Medications that cause or contribute to RD do so through one or more mechanisms, including directly repressing respiratory drive, impairing response to hypoxemia and/or hypercapnia, and obstructing or changing patency of the airway.[3] Deaths from opioid ODs are primarily attributed to RD with sustained apnea.[4] Examples of signs of an imminent OD from a CNS depressant (CNSd) include confusion, sedation, and slurred speech.[17] Proposed mechanisms underlying RD from opioids and CNS depressants in general is discussed in the following sections.

3.2 Opioids

Opioids are natural (eg, codeine, morphine; also called opiates), semi-synthetic (eg, oxycodone, hydrocodone, heroin), or synthetic (eg, methadone, fentanyl) compounds[1] that agonize central and peripheral opioid receptors. Therapeutically, they are primarily used to treat moderate-to-severe acute or chronic pain.[2] Opioid-induced analgesia is primarily attributed to partial or full agonism of the μ opioid receptor (MOR), although other pathways may contribute to analgesia such as inhibition of reuptake of serotonin (tramadol) and/or norepinephrine (tramadol and tapentadol), or possibly, antagonism of *N*-methyl-d-aspartate (NMDA) receptors (methadone).[2] Some opioids (as a single ingredient or in combination with other agents) are also FDA-indicated for management of cough,[18] diarrhea,[19] or opioid use disorder (OUD; ie, methadone and buprenorphine).[20] Due to the risk of addiction, misuse and abuse, all opioids are controlled substances.

There are 23 unique opioids currently available by prescription in the US (see list in **Appendix A**). Many opioids are available in combination with other products (eg, non-opioid pain medications), and as both long-acting (LA)/extended-release (ER) and short-acting/immediate release (IR) products. Available formulations vary by opioid, for example, including intravenous/injectable products, oral capsules or tablets, oral solutions, transdermal patches, rectal suppository, and buccal films.[21-27] Abuse-deterrent opioid products are available (ie, ER products: Oxycontin, hydrocodone bitartrate ER, Hysingla ER, Xtampza ER; IR product: RoxyBond), which were granted special labeling by the FDA about the lower risk of abuse after demonstrating positive outcomes (eg, reduced "drug liking" compared to the standard formulation) in clinical abuse trials.[28] Notably, some clinical situations may require concomitant treatment with both an IR and LA opioid (eg, for acute-on-chronic pain in a patient who was stabilized on LA opioids for chronic pain),[17] although general pain-focused guidelines tend to encourage caution with concomitant use of IR and ER opioids, since the combination may increase the risk of opioid OD and evidence for concomitant use of a LA opioid with an IR opioid for breakthrough pain is limited.[6,17]

Owing to the many different formulations and unique pharmacologic properties, opioids are a heterogenous class of medications. Characteristics of the opioid formulation, such as a long duration of action and/or high potency, likely plays a role in the risk of RD, as discussed in the following section.

3.2.1 Opioid-related respiratory depression

Opioids not only directly suppress the respiratory drive, but they can also attenuate several mechanisms designed to counteract impaired respiration compromised respiration.[3-5] Opioids can increase the risk of RD through at least the following 6 mechanisms, according to experts[4]:

1. Depression of central respiratory center signals for alterations in respiratory rhythm.
2. Impairment of both central and peripheral chemoreceptors, leading to diminished responsiveness to hypoxemia and hypercapnia stimuli.
3. Impairment of upper respiratory airway patency, increasing the risk of obstructive sleep apnea, aspiration-induced pneumonia, and disruptions in breathing coordination.
4. Activation of rigid skeletal muscles responsible for respiration control, particularly with certain opioids, exacerbating the ability to achieve full lung volume expansion.
5. Induction of sedation (ie, similar to the respiration mechanisms during sleep described above) – the degree of sedation correlates with the severity of RD.

6. Induction or exacerbation of sleep-disordered breathing through contributing to central or obstructive sleep apnea and disruption of specific sleep phases.

Because of individual differences in their pharmacologic and/or pharmacokinetic (PK) characteristics, certain opioids may exhibit a greater or lower potential to induce RD. For example, fentanyl may be an opioid that has a heightened propensity to induce RD owing to its high opioid receptor potency, rapid onset of effect, and higher likelihood to cause respiratory muscle rigidity, particularly following rapid administration. Fentanyl reduces the amount of air taken in by the lungs (minute ventilation) at a 70 times greater potency than morphine, induces RD faster than morphine, and accelerates the onset of hypoxia more rapidly than morphine or oxycodone.[4] Additionally, methadone was associated with a disproportionate number of opioid ODs between 1999 and 2009.[17,29] Compared to other opioids, methadone's PK/pharmacodynamic (PD) profile is complex, with a peak effect on RD occurring after the maximal analgesic effect,[17] potentially contributing to accidental OD.

Opioids that are weaker MOR agonists, or partial MOR agonists may carry a lower risk of RD. Relative to most other opioids, tramadol is a weaker MOR agonist [17]; tramadol and tapentadol also have mixed mechanisms of action (eg, inhibition of norepinephrine uptake), which might lower the risk of RD.[3] Buprenorphine is a *partial* MOR agonist, which lowers the risk for RD compared to full MOR agonists.[4] Owing to the lower risk of OD and abuse, the 2022 Veterans Affairs (VA)/ Department of Defense (DoD) pain guideline for adults weakly recommends buprenorphine first-line for individuals who have chronic pain and require daily opioid therapy. Notably, the VA/DoD guideline pointed out that fatal OD from buprenorphine is still possible when it is combined with a CNSd.[30]

Patients on long-term opioid therapy are particularly at risk for RD following an increase of an opioid dose.[4] Moreover, the RD risk may differ depending on the specific characteristics of the opioid therapy. A 2023 SR and meta-analysis (SRMA) of observational studies reported moderate-to-high quality evidence for a significant association between fatal and/or non-fatal OD and higher opioid doses (per 50 mg incremental increase), LA opioids (versus short-acting opioids), and the combination use of as-needed and scheduled opioids (versus scheduled opioids only).[7] Some patients on long-term opioid therapy develop tolerance to RD effects, yet tolerance to respiratory effects develops "…to a lesser degree than analgesic tolerance" (Bateman et al, page 11).[4] Use of opioids with other CNSd (eg, pregabalin, ethanol) can potentially reverse tolerance to RD.[4]

Naloxone hydrochloride is an opioid antagonist that is FDA-approved for emergency treatment of an opioid OD in pediatric and adult patients.[31,32] It is available as an intravenous, subcutaneous, or intramuscular injection, or nasal spray, with 3 nasal spray products (generic, Narcan, Rivive) available over-the-counter as of 2023.[33,34] Because of naloxone's short duration of action relative to most opioids, patients may require more than one dose of naloxone.[31,32] At standard single doses, naloxone may not reverse high potency opioids (eg, fentanyl) or mixed partial agonist/antagonists opioids (eg, buprenorphine); higher naloxone doses may be required for reversal of RD caused by those agents.[4,31,32] Naloxone antagonizes opioid receptors only, and thus, does not reverse RD due to non-opioid agents, which is problematic for patients with RD secondary to CNSd polypharmacy.[4]

3.3 Muscle Relaxants and Sedative-hypnotics

Non-benzodiazepine MRs, also called skeletal muscle relaxants, encompass 8 unique active ingredients (see **Appendix A**) with differing pharmacology and FDA-approved indications. While the exact mechanism of action for many MRs is unknown, most are thought to improve acute musculoskeletal pain, muscle spasms, and/or spasticity through centrally acting effects.[14,35-41] Most MRs are available as a single oral dosage form (eg, oral tablet).[42-49] Cyclobenzaprine, methocarbamol, and orphenadrine are also available as injectable formulations, and baclofen can be administered intrathecally as a continuous infusion.[42,43,47,49] Notably, oral cyclobenzaprine is available as an IR (used 3 times daily as needed) or an ER (used once daily) formulation.[47] Orphenadrine is also available as an oral tablet co-formulated with aspirin and caffeine, sharing a similar FDA indication to orphenadrine monotherapy.[50] Unlike the other reviewed MRs, carisoprodol is classified as a controlled substance (Schedule IV).[42-49]

Most MRs are FDA-indicated for *acute* (eg, 2-3 week) treatment of musculoskeletal conditions, with the exception of baclofen, dantrolene, and tizanidine, which are approved for the treatment of spasticity (possibly for longer than acute treatment).[42-49] Dantrolene is also indicated for treatment of malignant hyperthermia.[45] According to the 2022 CDC guideline for prescribing opioids, MRs are an option for acute treatment of lower back pain, possibly after first-line treatment with a non-steroidal anti-inflammatory (NSAID) medication.[17] A cross-sectional observational analysis by Soprano et al (2020) of a nationally representative US sample from 2005 to 2016 found that MRs were commonly prescribed at ambulatory visits with diagnoses of back pain or musculoskeletal conditions; the number of prescriptions for MRs doubled during this period, primarily driven by continued use rather than new prescriptions. In 2016, opioids were prescribed at only 10% of sampled national visits in contrast to being prescribed at 67.2% of office visits where MRs were continued.[51]

Non-benzodiazepine and non-barbiturate SHs encompass 9 unique active ingredients, classified into 4 drug classes: 1) non-benzodiazepine, benzodiazepine receptor agonists (NBRAs; eszopiclone, zaleplon, zolpidem); 2) melatonin receptor agonists (MRAs; ramelteon, tasimelteon); 3) orexin receptor antagonists (ORAs; daridorexant, lemborexant, suvorexant); and 4) the histamine receptor antagonist and tricyclic antidepressant (TCA), doxepin.[52-60] These agents are FDA-indicated for sleep onset and/or sleep maintenance insomnia, except for tasimelteon, which is indicated for nighttime disturbances in Smith-Magenis Syndrome or for non-24-hour sleep wake cycle disorder.[52-60] Zolpidem is available in various oral formulation including IR capsule or tablet, ER tablet, sublingual tablet, and oral solution spray; the FDA-indication for insomnia varies by zolpidem formulation.[58] All other SHs are available in a single oral formulation as a tablet or capsule.[52-57,59,60] The FDA-approved formulation of doxepin for insomnia is low-dose tablets (3 mg and 6 mg), whereas at higher doses are approved for other uses.[52]

Insomnia, defined as difficulty falling or staying asleep persisting for at least 3 months, has a prevalence ranging from about 6% to 36% among adults, depending on definition criteria used.[61] Generally, sleep disturbances (not necessarily insomnia) are highly comorbid with chronic pain. In an SRMA of observational and randomized evidence from patients with chronic non-cancer pain, the pooled prevalence of sleep disturbances was 75% and the prevalence of insomnia ranged from 59-94% across 8 studies.[62] Recent US guidelines for the treatment of chronic insomnia that address non-pharmacologic treatment in adults prefer cognitive-behavioral therapy for insomnia as first-line treatment,[63,64] although this therapy may not be accessible to or effective for all patients. The 2017 American Academy of Sleep

Medicine guideline weakly recommends treatment of adult chronic insomnia with most SHs addressed by this report (ie, suvorexant, eszopiclone, zaleplon, zolpidem, ramelteon, doxepin),[65] whereas the 2019 VA/DoD guideline only weakly recommends for treatment with NBRAs or doxepin.[64] Suvorexant and ramelteon are recommended neither for nor against by the VA/DoD guideline due to insufficient evidence at that time.[64] Chronic insomnia may require long-term pharmacotherapeutic treatment, which is an option for adult patients who fail to respond/lack access to cognitive-behavioral therapy, lack contraindications to pharmacotherapy, and who continue to benefit from the treatment during regular follow up per the American Academy of Sleep Medicine.[65]

3.3.1 Muscle relaxants and sedative-hypnotics as CNS depressants

Generally, non-opioid CNSd may cause or contribute to RD by directly acting on central respiratory drive centers and/or by altering other respiration processes, such as modifying the function of respiratory muscles.[3] Moreover, changes in respiratory processes can also occur due to the impact SH's have on a patient's level of consciousness. Sedatives that change sleep architecture could lead to impaired respiration, meaning medications that do not directly depress respiration might still adversely affect respiration indirectly through their influence on sleep processes.[66] Importantly, while subtle respiratory changes caused by a CNS depressant may not clinically affect a healthy individual, theoretically, clinically impaired respiration could occur in patients taking a medication that impairs respiratory drive like opioids and/or in patients with predisposing comorbidities.[67]

To determine whether the reviewed MRs and SHs qualify as CNSd, we reviewed prescribing information for one formulation of each MR and one formulation of a corresponding drug from each class of SHs (eg, NBRAs, ORAs) regarding the potential for sedation, RD, and interactions with opioids. This information was supplemented with drug interaction assessments from Lexidrug for opioids with each reviewed MR and SH (**Table 2**). All reviewed agents are known to have the potential to interact with opioids through depression of the CNS per Lexidrug, including doxepin, MRAs and ORAs.[68] Moreover, prescribing information for all agents alludes to sedating or CNS depressant effects (refer to **Table 2** for details).[14,15,35-41,69-71] **Overall, we infer that the magnitude of potential CNSd and/or RD effects could vary by class or medication, but that regardless, each reviewed representative MR and SH should be considered a CNS depressant.**

In the subsequent paragraphs, we highlight some differences in our impression of the potential risk for CNSd or RD with opioids when combined with various classes/agents addressed in this report. Although CNS depressants, other than BZDs, are often grouped together when considering the risk of RD in combinations with opioids (such as in FDA safety communications or opioid guidelines – see sections 4.0 and 6.1), clarifying the comparative risk for RD between medications or classes is pertinent when selecting an agent for patients requiring concomitant CNS depressant therapy. **In leu of finding clear, comparative evidence regarding the RD risk of each agent of interest, our conclusions about the comparative risk for CNSd or RD should be interpreted cautiously, as they were primarily formed on a theoretical basis and were not based upon a systematic review of the literature.**

Based on prescribing information and select expert opinion reviews,[3,5] certain agents *might* carry a comparatively higher risk of RD than other reviewed potential CNS depressants when combined with an opioid. NBRAs, carisoprodol and its metabolite meprobamate, are known to bind to the gamma-aminobutyric acid (GABA) receptor subtype A ($GABA_A$)[5,70]; this interaction may result in respiratory

impairment via the activation of $GABA_A$ receptors within the medulla.[5] Respiratory depressant activity at the $GABA_A$ receptor by these agents could theoretically be synergistic with respiratory depressant activities by opioids in the medulla.[5] According to Webster et al, NBRAs may depress respiratory drive, decrease the strength of respiratory muscles, and possibly lower resistance in the upper airways.[3] Unlike the prescribing information for other reviewed medications/classes that generally warned about the risk for interactions with other CNSd, prescribing information for zolpidem (a NBRA) includes a specific warning about the potential for RD when zolpidem is combined with an opioid.[70] Post-marketing cases of RD with zolpidem have been reported, primarily among people with pre-existing respiratory impairment or when used with an opioid. If use of zolpidem with an opioid is necessary, it is advised to use the lowest possible dose (including possibly selecting an IR zolpidem product at the lowest dose of 5 mg) for the shortest duration possible, and to monitor for RD.[70] While other NBRAs (ie, eszopiclone and zaleplon) theoretically carry a similar risk of RD to zolpidem, eszopiclone and zaleplon do not carry the same warning for RD and labeling for interactions with opioids specifically like zolpidem.[72,73] Prescribing information for carisoprodol indicates that its effects could be additive with other CNSd including opioids, but no information about dose reductions was provided.[36] Additionally, prescribing information for the ORA, suvorexant, also advised that dose reductions may be necessary if it is used with another CNS depressant, including an opioid.[69]

Expert opinion authors considered carisoprodol to carry a comparatively higher risk of RD when use with opioids, commenting that "Because other skeletal muscle relaxants do not appear to mediate their pharmacological effects through the $GABA_A$ [receptor], the likelihood of potentiation of the effects of opioids and benzodiazepines would appear to be much less likely" (Horsfall et al, page 117).[5] Baclofen, a GABA analog, primarily acts on $GABA_B$ receptors, which differ from the ionotropic $GABA_A$ receptors.[74] However, prescribing information indicated that baclofen may have additive CNS depressant effects with other medications, potentially leading to RD.[39] Product labeling for carisoprodol, methocarbamol, and tizanidine warn that fatal ODs have occurred as monotherapy or in combination with another CNSd.[14,36,37] Unlike other MRs, dantrolene is not a centrally acting MR and therefore may cause comparatively less CNS depression; nonetheless, dantrolene prescribing information noted that it can cause drowsiness, dizziness, RD, and it has the potential to interact with CNS depressants.[40]

Among the classes of non-BZD and non-barbiturate SHs, agents that do not act on GABA receptors, particularly MRAs and doxepin, *might* carry a comparatively lower risk of significant RD. The MRA, ramelteon, is highly selective for melatonin receptors that are located outside of the central respiratory drive center, and it is not considered to produce general sedative effects, according to one group of authors.[75] A single dose of ramelteon did not appreciably change respiratory sleep parameters (eg, apnea index) compared to placebo in patients with mild to moderate OSA; however, this was a very short-term trial and prescribing information for ramelteon recommends avoiding its use in patients with severe OSA due to lack of evidence.[71] The 2023 Beers list for potentially inappropriate medications in older adults excluded low-dose doxepin (<6 mg) from the list on the basis that low-dose doxepin has a comparable safety profile to placebo.[76] Yet, prescribing information for low-dose doxepin acknowledged the potential for additive CNS depressant effects with other medications, and advised avoiding its use in patients with severe sleep apnea due to the theoretical potential for RD.[15] Notably, the histamine (H_1) receptor antagonist diphenhydramine, whose pharmacology might overlap with low-dose doxepin, has been shown to alter the interaction between the hypoxic and hypercapnic respiratory drive, which could theoretically cause impairment in patients with other risk factors for RD.[67]

Table 2. Potential for CNS Depression and Interactions with Opioids, by Drug Class or Single Drug Product, per Prescribing Information and Lexidrug

Class/Medication	Information about CNS/respiratory depression and interactions with opioids from select prescribing information	Lexidrug DDI software[a, 68]
Non-benzodiazepine and non-barbiturate sedative-hypnotics (SHs)		
Non-benzodiazepine benzodiazepine receptor agonists[b] eszopiclone, zaleplon, zolpidem	Zolpidem tartrate capsules[70]: • $GABA_A$ receptor modulator, which increases GABA signaling • Labeled warning/precaution for CNS-depressant effects that may intensify when used with other CNSd, and DDI with opioids about the possibly increased risk of RD • Labeled warning/precaution for RD; sedative-hypnotics can decrease respiratory drive. Respiratory impairment has primarily been observed in patients with pre-existing respiratory impairment. • Labeled DDI with CNSd and opioids specifically, concerning the possibly increased risk of RD with opioids	• Each agent in class is considered a CNSd • Category "D" (consider therapy modification) interaction with an opioid
Melatonin receptor agonists[b] ramelteon, tasimelteon	Ramelteon[71]: • Melatonin receptor agonist with "no appreciable affinity for the GABA receptor complex or for receptors that bind neuropeptides, cytokines, serotonin, dopamine, noradrenaline, acetylcholine, and opiates" (page 11; prescribing information) • Warning/precaution for sedation that may impair a person's ability to perform activities requiring alertness. Patients are advised to avoid use with alcohol. • Respiratory parameters (eg, FEV_1, apnea index) were not impaired compared to placebo after a *single dose* given to patients with moderate-to-severe COPD and moderate-to-severe sleep apnea • Other than for alcohol, no specific labeled DDI with CNSd including opioids	• Each agent in class is considered a CNSd • Category "D" (consider therapy modification) interaction with an opioid
Orexin receptor antagonists[b] daridorexant, lemborexant, suvorexant	Suvorexant[69]: • It is believed that orexin receptor antagonists work by blocking the action of wake-promoting orexin peptides • Warning/precaution for CNSd that can impair a person's ability to perform activities requiring alertness, and the risk of additive effects when combined when another CNSd including opioids. A dose reduction of suvorexant or another CNSd is advised when it is used with another CNSd. • Warning/precaution for the lack of evidence for use in patients with severe OSA or COPD; suvorexant has the potential to compromise respiratory function in patients with OSA or COPD. • Other than as a warning/precaution, no specific labeled DDI with CNSd including opioids	• Each agent in class is considered a CNSd • Category "D" (consider therapy modification) interaction with an opioid
Tertiary amine tricyclic antidepressant doxepin	Doxepin 3 and 6 mg tablets (Silenor)[15]: • Antagonist at the histamine (H_1) receptor; sleep-promoting effects could occur through this or another unknown mechanism • Warning/precaution for CNSd effects including impairment of activities requiring alertness, and the potential for additive effects when used with other CNSd • Advised using caution for doxepin in patients with OSA and avoidance in patients with severe OSA, due to lack of evidence for use and the potential for impaired respiratory function (inferred based on the sedative-hypnotic class in general) • Respiratory depression has occurred in infants exposed to doxepin from breast milk (after use of an unknown dose of doxepin by their mother) • Labeled DDI with CNSd in general	• Considered a CNSd as a systematic agent • Category "D" (consider therapy modification) interaction with an opioid
Muscle relaxants (MRs)		
Baclofen	• Unknown exact mechanism of action, but it is known to inhibit spinal reflexes; structurally, it is a GABA analog, and it may stimulate $GABA_B$ receptors[39] • Warning/precaution for drowsiness and sedation that can be additive with other CNS depressants; such effects can cause " … sedation with tolerance, somnolence, ataxia, and respiratory and cardiovascular depression" (page 9)[39] • Labeled DDI with CNSd in general[39]	• Considered a CNSd • Category "D" (consider therapy modification) interaction with an opioid
Carisoprodol	• Centrally acting MR with the exact mechanism of action unknown; metabolite is meprobamate, which is known to be sedating[36] • Warning/precaution for sedation including impairment of activities that require alertness, and the potential for additive effects when used with other CNSd[36] • CNSd and RD have occurred with overdose, and fatal ODs have occurred as monotherapy or in combination with other CNSd[36] • Labeled DDI with CNSd in general[36]	• Considered a CNSd • Category "D" (consider therapy modification) interaction with an opioid

Abbreviations: AE, adverse event; CNS, central nervous system; CNSd, central nervous system depressant; COPD, chronic obstructive pulmonary disease; DDI, drug-drug interaction; FEV_1, forced expiratory volume in one second; GABA, gamma-aminobutyric acid; MR, muscle relaxant; MSK, musculoskeletal; OD, overdose; OSA, obstructive sleep apnea; RD, respiratory depression; TCA, tricyclic antidepressant

[a] Based upon potential interactions between each included sedative-hypnotics and MR as monotherapy and selected opioids (buprenorphine, fentanyl, hydrocodone, methadone, morphine, oxycodone) in the LexiDrug drug interactions database

[b] For medications in the same drug class, we included information from prescribing information for one representative drug from the drug class, although it is possible there are differences between drugs in the same class

Table 2. Potential for CNS Depression and Interactions with Opioids, by Drug Class or Single Drug Product, per Prescribing Information and Lexidrug

Class/Medication	Information about CNS/respiratory depression and interactions with opioids from select prescribing information	Lexidrug DDI software[a, 68]
Chlorzoxazone	• Centrally acting agent for relief of acute MSK pain; the exact mechanism of action unknown, it may act through sedation[38] • Warning for possibly additive effects with other CNSd[38] • RD can occur in an overdosage[38] • Other than the warning about use with other CNSd, no specific labeled DDI[38]	• Considered a CNSd • Category "D" (consider therapy modification) interaction with an opioid
Cyclobenzaprine	• Reduces motor activity at gamma and alpha motor neurons, possibly through actions in the CNS or spinal cord, but it " … has not been shown to be effective in muscle spasms due to central nervous system disease" (page 10). It is structurally related to tricyclic antidepressants (TCAs) and is known to have anticholinergic and sedative properties.[77] • Carries a warning for the possibility of TCA-like AE, including adverse CNS events; however, these events have tended to occur at dosages exceeding those used to treat spasms[77] • Labeled DDI with CNSd in general[77]	• Considered a CNSd • Category "D" (consider therapy modification) interaction with an opioid
Dantrolene	• Directly acts on skeletal muscle to decrease muscle contractions (possibly through preventing calcium release)[40] • Known to induce "A central nervous system effect … with drowsiness, dizziness … " and RD is a possible AE[40] • Labeled DDI with CNSd[40]	• Considered a CNSd • Category "D" (consider therapy modification) interaction with an opioid
Metaxalone	• Unknown mechanism of action; proposed to act through depression of the CNS[41] • Labeled warning/precaution for the possible risk of additive sedation when combined with other CNSd in general – advised to monitor for RD and sedation if used together[41] • Labeled DDIs with CNSd in general[41]	• Considered a CNSd • Category "D" (consider therapy modification) interaction with an opioid
Methocarbamol	• Unknown mechanism of action; it is structurally related to guaifenesin and it is proposed to act through depression of the CNS.[37] • Labeled warning for the possible risk of additive CNS depression when combined with other CNSd in general. With overdosage, deaths have occurred with monotherapy or in combination with other CNSd.[37] • Labeled DDI with CNSd in general[37]	• Considered a CNSd • Category "D" (consider therapy modification) interaction with an opioid
Orphenadrine	• Unknown mechanism of action; possesses possible analgesic effects, and known anti-cholinergic actions[35] • Labeled warning for dizziness or lightheadedness which may impair activities requiring alertness[35] • Labeled precaution for the risk of "Confusion, anxiety, and tremors … " in people who use orphenadrine with propoxyphene (an opioid)[35] • Other than the precaution for use with propoxyphene, no labeled DDI for use with CNSd[35]	• Considered a CNSd • Category "**X**" (**avoid combination**) interaction with an opioid
Tizanidine	• A centrally acting alpha$_2$ receptor agonist thought to increase inhibition of motor neurons[14] • Labeled warning/precaution for sedation that could impair activities requiring alertness, and whose effects could be additives with other CNSd; advised to monitor for sedation[14] • In overdosage, depression of the CNS, cardiac, and respiratory functions have been observed; fatal OD has been observed as monotherapy and in combination with other CNSd[14] • Labeled DDI with CNSd in general[14]	• Considered a CNSd • Category "D" (consider therapy modification) interaction with an opioid

Abbreviations: AE, adverse event; CNS, central nervous system; CNSd, central nervous system depressant; COPD, chronic obstructive pulmonary disease; DDI, drug-drug interaction; FEV_1, forced expiratory volume in one second; GABA, gamma-aminobutyric acid; MR, muscle relaxant; MSK, musculoskeletal; OD, overdose; OSA, obstructive sleep apnea; RD, respiratory depression; TCA, tricyclic antidepressant

[a] Based upon potential interactions between each included sedative-hypnotics and MR as monotherapy and selected opioids (buprenorphine, fentanyl, hydrocodone, methadone, morphine, oxycodone) in the LexiDrug drug interactions database

[b] For medications in the same drug class, we included information from prescribing information for one representative drug from the drug class, although it is possible there are differences between drugs in the same class

4.0 FDA SAFETY COMMUNICATION(S) ABOUT THE RISK OF RESPIRATORY DEPRESSION WITH OPIOIDS

The FDA publishes drug safety communications (DSCs) to disseminate new or updated drug safety considerations to patients and healthcare professionals. Since at least 2012, the FDA has released DSCs about the risk of RD and/or death associated with an opioid. Initial communication focused on the risk of RD/death in children exposed to codeine after tonsillectomy/adenoidectomy,[78] which culminated in additional boxed warnings/contraindications for codeine- and tramadol-containing products.[79] Although not released as a DSC, in 2013, the FDA required labeling changes for ER/LA opioid analgesics including adding the boxed warning for the risk of life-threatening RD,[80] that was later extended to all opioid analgesic and cough/cold products.[81]

In 2016, the FDA described the risk of RD and death associated with combined used of benzodiazepines (BZDs) and opioids, and required a boxed warning be added to all opioid products indicated for pain or cough and BZD products. **Although nearly all evidence cited by the FDA for the increased risk of RD included observational studies of patients taking opioid *analgesics* with BZDs only, the FDA decided to extend the warning to opioid cough products and other CNS depressants: "…because of similar pharmacologic properties, it is reasonable to expect similar risks with concomitant use of opioid cough medications and benzodiazepines, other CNS depressants, or alcohol" (FDA DSC, 2016).**[11] One descriptive study of prescription drugs[†] implicated in drug OD deaths cited by the FDA's 2016 DSC described that opioids were involved in 17% of OD deaths attributed to MRs (MRs were implicated in 0.1% of all pharmaceutical OD deaths); this was a numerically lower percentage than deaths involving opioids with BZDs or other CNS agents (eg, antipsychotics, antidepressants).[82] For the boxed warning about the risks of using opioids with BZDs or other CNS depressants, the FDA provided examples of CNS depressants, which included most insomnia medications/classes (doxepin was not included, despite it being FDA-approved for insomnia in 2010[83])[‡] and all MRs addressed by this report, however the FDA acknowledged that their list was not comprehensive.[11]

Table 3 summarizes safety messages from the FDA (from 2010 to present) that concerned the risk of opioid-induced OD/RD and/or risks of using opioids with CNS depressants addressed by this report. Note that DSCs communicate important safety considerations from the FDA, but they may not address all safety considerations about the use of opioids with SHs and MRs.

[†] Drug OD deaths were considered by the study authors to be most likely attributable to prescription medications based on their classification system (using certain *International Classification of Diseases, Tenth Revision (ICD-10)* codes); however, it is possible that illicit or diverted prescription drugs contributed to some of the deaths.
[‡] Other reviewed medications excluded from the list were tasimelteon and ORAs that were not FDA-approved at the time of the communication, including daridorexant and lemborexant.

Table 3. Key Messages from the FDA's Drug Safety Communications about the Risks of Respiratory Depression or Overdose from Opioids (from 2010 to May 1, 2024)

Safety communication date	Key messages	Affected drug products
April 13, 2023[81,84]	• Updated the opioids boxed warning to address the following, *among other considerations*: ○ **Risk of OD increases as the opioid dose increases.** Ensure careful dosing and titration of opioids.	ER/LA and IR opioids
	• **Reordered boxed warnings to emphasize risk of RD, and risks of using opioids with BZDs and CNSd**	ER/LA and IR opioids
	• Dosing and administration section updated to (1) encourage increasing the dose only when benefits outweigh the risks including after a failure of lower doses, and (2) recognize that RD can occur with any treatment length, although risks may be higher when starting/changing to a new dose	ER/LA opioids
	• Dosing and administration section updated to (1) advise using the lowest effective dose for the shortest length needed, and (2) recognize that RC can occur with and treatment length, although risks may be greater when starting/changing to a new dose	IR opioids
	• Encouraged prescribing naloxone to patients at increased risk of an OD, and offering/discussing naloxone with all patients prescribed an opioid ○ **Listed OD risk factors: co-use of BZD or CNSd**, diagnosis of OUD, history of an opioid OD	N/A – general DSC guidance
July 23, 2020[85]	• The FDA recommended the following about the use of naloxone to prevent death from opioid OD: ○ Discuss naloxone with all patients prescribed an opioid, including to treat pain or for OUD (methadone or buprenorphine) ○ Consider prescribing naloxone to patients at an increased risk of OD (including those factors listed by the 2023 DSC above) ○ Consider naloxone for patients in contact with others at risk for an opioid OD (eg, children in household) ○ Also consider naloxone for people not prescribed an opioid who carry an increased risk for OD (eg, history of OUD or OD)	N/A – general DSC guidance
December 19, 2019[86]	• The FDA added warnings/precautions to prescribing information regarding: gabapentinoids (ie, gabapentin or pregabalin) use has been **associated with RD in patients with another risk factor, including use with opioids or CNSd,** among others	Gabapentinoids
January 11, 2018[18] (update to April 20, 2017 DSC)	• The FDA added information about the risk of OD/death/RD (among others) to a boxed warning, consistent with opioids used for pain • Use of these products is not recommended for people <18 years old due to safety concerns including RD	Cough and cold products containing codeine or hydrocodone
September 20, 2017[20] (update to August 31, 2016 DSC)	• Added to prescribing information: **advised to not withhold evidence-based opioid-based treatments (ie, methadone, buprenorphine) for OUD from patients with OUD who are taking a CNSd** ○ Considered risks from untreated OUD outweigh the risks from taking an opioid with a CNSd	Buprenorphine and methadone products FDA-indicated for treatment of OUD
April 20, 2017[79] (update to DSCs from 2015)	• Due to the risk of RD, the FDA required the following labeling changes: ○ Added contraindication for use of codeine for cough or tramadol for pain in children < 12 years old; and tramadol for pain after tonsil/adenoid surgery among children/adolescents <18 years old ○ Added a warning for use of tramadol or codeine in adolescents 12-18 years with other risk factors for disordered breathing (eg, sleep apnea or lung disease) ○ Added warning to avoid breastfeeding while using these products	Pain or cough products containing codeine or tramadol
August 31, 2016[11]	• **Due to the risk of RD and death, the FDA required adding a boxed warning and revisions to warnings/precautions, drug interactions, and patient counseling sections of drug labeling about the risks of combining opioids with BZDs or CNSd. To mitigate the risks, the FDA advised to:** ○ Only combine these medications with opioids for pain when alternative options are not available or unsuccessful. ○ Use the lowest effective dose for the shortest duration possible ○ Avoid use of opioid cough medications in patients taking a BZD or CNSd • *Examples[a] of non-BZD and non-barbiturate CNSd given by the FDA:* ○ *Sleep drugs/tranquilizers:* eszopiclone, ramelteon, suvorexant, zaleplon, zolpidem ○ *MRs*: baclofen, carisoprodol, chlorzoxazone, cyclobenzaprine, dantrolene, metaxalone, methocarbamol, orphenadrine, tizanidine ○ Antipsychotics ○ Alcohol	Pain or cough opioid products, and BZDs
February 20, 2013[20] (update to DSC from 2012)	• Due to the risk of RD and death, the FDA added a boxed warning and contraindication for prescribing codeine to children after tonsillectomy and/or adenoidectomy	Codeine-containing products

Abbreviations: BZDs, benzodiazepines; CNSd, central nervous system depressants; DSC, drug safety communication; ER, extended release; IR, immediate release; LA, long-acting; MRs, muscle relaxants; N/A, not applicable; OD, overdose; OUD, opioid use disorder; RD, respiratory depression;

[a] The FDA did not consider this list to be comprehensive of all possible CNSd

5.0 OPIOID CLASS WARNINGS/PRECAUTIONS ABOUT RESPIRATORY DEPRESSION AND/OR RISKS OF USE WITH OTHER MEDICATIONS

For feasibility, to glean class-based warnings/precautions about the risk of opioid-induced RD or OD and concomitant use with CNS depressants, we reviewed prescribing information for a representative sample of oral or transdermal[§] prescription opioid formulations[**] (ie, IR and ER products, different types of opioids, combination products, and products indicated for analgesia, cough/cold, and diarrhea). Information about BBWs for reviewed mono-ingredient products (ie, tramadol, buprenorphine, methadone, fentanyl, oxycodone, and morphine) was supplemented with information from Lexidrug for other dosage forms with the same active ingredient. Refer to **Table 4** for contraindications and **Table 5** for labeled warnings/precautions related to the risk of RD/OD or CNS depression for the reviewed opioid products (and BBW for select other formulations with the same active ingredient per Lexidrug).

Regarding **contraindications,** all reviewed opioid products (except for opium tincture – see information about opium tincture below) are contraindicated in patients with significant RD and for use in unmonitored/settings without resuscitative equipment in patients with acute or severe bronchial asthma.[27,87-96] Some reviewed products carry additional warnings specific to the formulation or active ingredient. For example, codeine- and tramadol-containing products are contraindicated in children <12 years old and children <18 years old who are post-adenoidectomy or tonsillectomy due to the risk of RD.[27,95] Due to the risk of RD, the reviewed hydrocodone-containing product (hydrocodone and chlorpheniramine ER solution) that is indicated for treatment of cough and upper-respiratory symptoms is contraindicated in children < 6 years old.[90]

Life-threatening RD is a potential risk of all opioids, and a BBW for all reviewed opioids, except for opium tincture.[21-27,87-96] Prescribing information advised that the risk of RD is greatest when initiating or increasing an opioid dose. Overall, reviewed prescribing information highlighted several patient characteristics that increase the risk of adverse consequences from opioid-induced RD, such as compromised pulmonary function, debilitated status, or central sleep apnea (opioid-induced central sleep apnea is dose-dependent).[27,87-96] Additional factors may increase the risk of RD from specific opioids or formulations (see **Table 5**); for example, concomitant use with medications inhibiting the opioid's metabolism,[27,87-90,92,94-96] concomitant use with ethanol,[90,96] or exposure to heat (for transdermal fentanyl).[88] Labeling for reviewed ER products implied that they generally carry an increased risk of OD and death since they have longer durations of action, and therefore ultimately expose the user to more opioid.[87,89,96] Patients with cytochrome P450 2D6 ultra-rapid metabolizer phenotypes are at increased risk for RD from codeine and tramadol.[21,27,95] As a BBW, prescribing information for all reviewed opioid oral solutions advised extra caution to ensure the correct dose is used to reduce the risk of RD.[21,23,25-27,90] Prescribing information for all reviewed opioid *analgesics* advised discussing the availability of naloxone

[§§] We focused on oral or transdermal preparations because these formulations are common in outpatient settings.
[**] Reviewed prescribing information for the following products: oral morphine IR tablet and ER capsules; oxycodone IR capsules and ER tablets; oral oxycodone and acetaminophen tablets; codeine phosphate and promethazine oral solution; transdermal fentanyl; oral methadone tablets; oral tramadol IR tablets; opium tincture; buprenorphine buccal film; and hydrocodone polistirex and chlorpheniramine polistirex ER oral suspension.

with patients/caregivers, and to especially consider offering naloxone to patients at increased risk for OD (eg, people with OUD, **people who are taking a CNSd,** or who had an OD previously).[87-89,91-96]

Except for opium tincture, all reviewed opioids carry a BBW for the increased risk of sedation and RD when used in combination with CNS depressants (eg, including sedatives, hypnotics, and MRs) that can result in death.[21-27,87-96] As it was stated by the FDA in their DSC, the BBW was extended to all CNS depressants due to the pharmacologic similarities to BZDs, a class of medications that demonstrated increased risks of OD when combined with opioid analgesics in studies reviewed by the FDA. Notably, the labeled wording for managing concomitant use of an opioid with a CNS depressant differs between the reviewed prescribing information for opioid analgesics and opioid cough/cold products:

- *Opioid analgesics* prescribing information advised to "Reserve concomitant prescribing of these drugs for use in patients for whom alternative opioids are inadequate."[96] If they are used concomitantly with a CNS depressant, it is advised to (1) use the lowest necessary dose for the shortest necessary duration, (2) provide education about the risk of and monitoring for RD/sedation, and (3) consider prescribing naloxone.[87-89,91-96]
- *Opioid cough products* prescribing information advised to "Avoid use of opioid cough medications in patients taking benzodiazepines, other CNS depressants, or alcohol."[27] If such combination is unavoidable, it was also recommended to that the provider educate patients/caregivers about the risk of RD.[27,90]

The reviewed cough/cold product, codeine + promethazine, also carries a separate BBW for the risk of RD when promethazine is used in children.[27] Separate from the labeled BBW and drug interactions for use of opioids with CNS depressants, **prescribing information for all reviewed opioids except for opium tincture included a separate potential drug interaction with MRs specifically. All labeling described that "[the opioid] may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression";** provided examples of MRs were cyclobenzaprine and metaxalone.[27,87-96]

Opioids other than opium tincture also carry a BBW for the risk of developing addiction, which can lead to abuse, misuse, and OD or death.[21-27,87-96] Owing to the risk of misuse, in general, opioid analgesic prescribing information advised limiting opioids to situations in which the potential benefits outweigh the risks and there are not suitable alternatives.[87-89,91-96] The reviewed opioid cough/cold products (indicated for ≥ 18 years old) advised reserving use of these products until the etiology of the cough had been determined, and the benefits to the individual patients are considered to outweigh the risks.[27,90]

Unlike other reviewed prescription opioid products, **opium tincture** does not carry the same labeled warnings/precautions for RD. Opium tincture pre-dates federal laws requiring that prescription drugs have proven safety and efficacy, and thus, while marketing of the product is allowed by the FDA, it has never been approved by the FDA.[97] Opium tincture contains a mixture of opiates including morphine (approximately 10 mg/mL of anhydrous morphine), and it is considered effective for the treatment of diarrhea, typically at lower doses of morphine than would be used to manage pain.[19] Although opium tincture does not carry the same labeled warnings as other opioids, it still harbors the potential to induce RD and interact with CNS depressants. Prescribing information advised considering dose reductions of opium tincture when combined with other CNS depressants.[97]

Table 4. Contraindications Related to Respiratory Depression, Overdose, and/or Use with CNS Depressants for Select Oral or Transdermal Prescription Opioids[a]

Contraindication	Description	Affected product(s)[a]
Significant RD[21-27,87-96]	Contraindicated in patients with significant RD (see warnings).	All reviewed opioid products except for opium tincture[b]
Unmonitored use in patients with acute or severe bronchial asthma[21-27,87-96]	Limit use for such patients to settings with monitoring and resuscitative equipment.	All reviewed opioid products except for opium tincture[b]
Use with an MAOI[27,92,95,96]	Do not use opioids in patients taking or recently exposed (within 14 days) to an MAOI.	IR/ER morphine, codeine + promethazine, tramadol IR
Use in children <6 years old[90]	Contraindicated due to the risk of RD; deaths have occurred in the therapeutic dosage range when used by children.	Hydrocodone + chlorpheniramine
Use in children <12 years old[27,95]	Contraindicated due to the risk of RD in children, particularly following certain procedures and in children who are ultra-rapid codeine metabolizers.	Codeine + promethazine, tramadol IR
Use for pain after tonsillectomy and/or adenoidectomy in children <18 years old[27,95]	Contraindicated due to the risk of RD after these procedures in children.	Codeine + promethazine, tramadol IR
Use in children[97]	Due to lack of evidence, opium tincture is contraindicated for use by children.	Opium tincture
Use in patients without opioid tolerance, or use for short-term pain or acute post-operative pain, or for mild pain[88]	Opioid intolerant patients should not use transdermal fentanyl due to the risk of RD and death. Use is restricted to patients in whom the potential benefits are considered to outweigh the risks.	Transdermal fentanyl

Abbreviations: BBW, black box warning; CNS, central nervous system; CNSd, central nervous system depressant or depression; ER, extended release; IR, immediate release; MAOI, monoamine oxidase inhibitors; RD, respiratory depression

[a]*Due to time constraints and the similarities in the risk of RD between different opioids, our review of prescribing information and BBWs per Lexidrug was limited to select opioids, including: oral morphine IR tablet and ER capsules; oxycodone IR capsules and ER tablets; oral oxycodone and acetaminophen tablets; codeine phosphate and promethazine oral solution; transdermal fentanyl; oral methadone tablets; oral tramadol IR tablets; opium tincture; buprenorphine buccal film; and hydrocodone polistirex and chlorpheniramine polistirex ER oral suspension. Thus, this information is not comprehensive. Please refer to product-specific prescribing information for details.*

[b]*Many of these warnings are interrelated: BBW was assigned to the individual warnings emphasized in the black box of prescribing information for at least 1 product, whereas those labeled "part of a BBW" were elaborations of previously included individual BBWs.*

Table 5. Labeled Warnings/Precautions Related to Respiratory Depression, Overdose, and/or Use with CNS Depressants for Select Oral or Transdermal Prescription Opioids[a]

Warning/Precaution	Description[b]	Affected product(s)[a]
Life-threatening RD[21-27,87-96]	***BBW:*** There is a risk for serious RD, especially during dose changes (ie, initiation or escalation). Prescribing information for codeine + promethazine and hydrocodone + chlorpheniramine advised monitoring patients closely, especially within the 24-72 hours after starting therapy. Maintain recommended dosing and titration schedules. Opioids increase the risk of CSA in a dose-dependent manner; it is advised to reduce the dose in people who present with CSA. Buccal, intranasal, lozenge, or sublingual products should not be substituted for another fentanyl product due to the risk of RD. Maximal RD effects from methadone occur after maximal analgesic effects. Children who ingest hydrocodone + chlorpheniramine are particularly at risk for RD (this product is indicated for ages 18 +). • Highlighted populations with increased risk: patients with COPD or with other compromised respiratory function, who are elderly or debilitated, who have a head injury, rapid metabolizers of codeine or tramadol (see additional warnings for codeine and tramadol), who have CSA, or when used when other drugs that can induce RD (per labeling for hydrocodone + chlorpheniramine)	All reviewed opioid products except for opium tincture[b]
Increased risk in combination with CNSd[21-27,87-96]	***BBW:*** Using opioids concurrently with a CNSd (eg, BZDs, sedatives, hypnotics, anxiolytics, tranquilizers, MRs, general anesthetics, antipsychotics) increases the risks for sedation and RD, which can result in death. Use of BZDs or CNSd (in general) with an opioid analgesic should be limited to patients "…for whom alternative treatment options are inadequate."[96] If prescribed concomitantly with opioid analgesics, it is advised to (1) monitor for RD, (2) use the lowest dose for the shortest co-duration possible, and (3) consider prescribing naloxone. Avoiding using opioid-containing cough products in patients already taking a CNSd. If methadone is used to manage OUD, OUD treatment should not be denied because the patient is concomitantly using a CNSd – still CNSd co-use should be avoided, and steps should be taken to ensure the CNSd is used judiciously, including that it is used for an accurate diagnosis and that alternative options have been considered.	All reviewed opioid products except for opium tincture[b]
Risk of OD from accidental ingestion[21-27,87-96]	***BBW:*** Fatal OD can occur when an opioid is ingested accidentally. Patients using TD fentanyl should always followed recommended disposal procedures; it should not be disposed of in the trash, as this has resulted in accidental exposure and death. For methadone tablets, it is reported that accidental ingestion of just one tablet can result in death.	All reviewed opioid products except for opium tincture[b]
Serious RD risk in children and ultra-rapid codeine metabolizers[27,95]	***BBW:*** Serious RD and death has occurred in children exposed to codeine or tramadol. Children <12 years old who are ultra-rapid codeine metabolizers, who have OSA, and/or recently post tonsillectomy and/or adenoidectomy are particularly at risk (see codeine and tramadol contraindications). Codeine and tramadol products should be used cautiously (and with the lowest effective dose for the shortest duration necessary) in children 12-18 years old who have other risk factors for RD, including use of other CNSd, among others. Codeine or codeine-containing cough products are not indicated for children <18 years old because the benefits do not outweigh the risks, including potential addiction. Adults with certain CYP2D6 genotypes (*1/*1 or *1/*2) classified as *ultra-rapid* metabolizers will also rapidly convert codeine and tramadol to their active metabolites (morphine and O-desmethyl tramadol) and are at increased risk for RD – such patients should not use codeine- or tramadol-containing products.	Codeine + promethazine, tramadol
RD in children[27,90]	***BBW:*** There are case reports of promethazine (a phenothiazine antihistamine)-associated RD and death in children; risks of RD may be increased when used with other CNSd. Use of promethazine should be avoided in people with risk factors for RD, including use of CNSd, among other factors. • *Warning/precaution:* Hydrocodone + promethazine can cause fatal RD in children, and its use exposes children to the risk developing addiction, which itself may result in OD and death – use should be limited to those ages 18 and older because the benefits do not outweigh the risks in children.	Codeine + promethazine, hydrocodone + chlorpheniramine
Use with ethanol[90,96]	***BBW:*** Co-use may increase exposure to morphine and hydrocodone, possibly resulting in a fatal OD.	morphine ER capsule, hydrocodone + chlorpheniramine ER solution
Concomitant use with CYP3A4 inhibitors or inducers[88-91,94]	***BBW:*** Use of oxycodone, fentanyl, or hydrocodone with a CYP3A4 inhibitor or stopping co-use with a CYP3A4 inducer may increase exposure to oxycodone, fentanyl, or hydrocodone, potentially leading to fatal RD. Patients taking such medications with oxycodone or fentanyl should be monitored closely for decreases in oxycodone or fentanyl dose.	Oxycodone (± APAP), TD fentanyl, hydrocodone + chlorpheniramine
Concomitant use with CYP3A4 inducers or inhibitors, or CYP2D6 inhibitors[27,95]	***BBW:*** Use of codeine or tramadol with a CYP3A4 inhibitor or stopping co-use with a CYP3A4 inducer may increase exposure to codeine or tramadol, which increases exposure to their active metabolites after conversion by CP2D6 and the risk for RD. Stopping co-use of a CYP2D6 inhibitor could result in increased conversion to the active metabolites of codeine and tramadol, increasing the risk of RD. Avoid use of codeine or tramadol-containing products with CYP3A4 inhibitors or inducers, or CYP2D6 inhibitors, and monitor the patient closely if such medications are used with codeine or tramadol.	Codeine + promethazine, tramadol
Concomitant use with CYPs 3A4, 2B6, 2C19, 2C9 inhibitors or inducers, or CYP2D6 inhibitors[87]	***BBW:*** Use of methadone with inhibitors of CYPs 3A4, 2B6, 2C19, 2C9, or 2D6, or stopping co-use with inducers of CYPs 3A4, 2B6, 2C19, 2C9 can result in increased exposure to methadone, which can cause fatal RD (especially when this occurs after a stable dose of methadone is established). Dose reductions of methadone should be considered if a drug meeting these criteria is added or removed from the patient's regimen.	Methadone

Abbreviations: AE, adverse event; APAP, acetaminophen; BBW, black box warning; CO2, carbon dioxide; CNS, central nervous system; CNSd, central nervous system depressant or depression; CSA, central sleep apnea; CYP, cytochrome; ER, extended release; IR, immediate release; IV, intravenous; OD, overdose; OUD, opioid use disorder; RD, respiratory depression; TD, transdermal

[a]Due to time constraints and the similarities in the risk of RD between different opioids, our review of prescribing information and BBWs per Lexidrug was limited to select opioids including: oral morphine IR tablet and ER capsules; oxycodone IR capsules and ER tablets; oral oxycodone and acetaminophen tablets; codeine phosphate and promethazine oral solution; transdermal fentanyl; oral methadone tablets; oral tramadol IR tablets; opium tincture; buprenorphine buccal film; and hydrocodone polistirex and chlorpheniramine polistirex ER oral suspension. Thus, this information is not comprehensive. Please refer to product-specific prescribing information for details.

[b]Many of these warnings are interrelated: BBW was assigned to the individual warnings emphasized in the black box of prescribing information for at least 1 products, whereas those labeled "part of a BBW" were elaborations of previously included individual BBW.

Table 5. Labeled Warnings/Precautions Related to Respiratory Depression, Overdose, and/or Use with CNS Depressants for Select Oral or Transdermal Prescription Opioids[a]

Warning/Precaution	Description[b]	Affected product(s)[a]
Risk of medication errors[21,23-27,90]	***BBW:*** Use caution when prescribing and preparing opioid prescriptions for oral solutions due to the risk of dosing errors, which can cause unintentional, fatal OD. Accurate measuring devices should be used. • Transmucosal oral fentanyl dosage forms (buccal, intranasal, lozenge, sublingual) have very different pharmacokinetic properties from each other such that substituting the wrong product for another could result in fatal OD – these products should not be substituted for one another on a dose-by-dose basis.	Morphine oral solution, oxycodone oral solution, codeine + promethazine oral solution, transmucosal fentanyl (buccal, intranasal, lozenge, sublingual), methadone oral 1 and 2 mg/mL oral solution, tramadol oral solution, hydrocodone + chlorpheniramine solution
Heat increases TD fentanyl absorption[88]	***BBW:*** Fatal fentanyl OD has occurred through exposure of the TD system to direct external heat sources during wear. Patients should avoid such exposures. • *Warning/precaution:* Fevers theoretically could increase exposure to TD fentanyl; patients should avoid strenuous exertion that significantly increases body temperature. During fever, monitor closely for sedation and RD, and dose-reduce fentanyl as necessary.	TD fentanyl
Naloxone access[87,88,92,93,95,96]	***Part of BBW:*** Discuss the availability of naloxone with patients/caregivers and provide education about how to monitor for RD and administer naloxone. Especially consider offering naloxone to patients at an increased risk of OD (eg, people who have OUD, take another CNSd, or who have had an OD), or who associate with people at increased risk, including children.	Reviewed products containing morphine, oxycodone, TD fentanyl, methadone, tramadol IR, and buprenorphine buccal film
Do not ingest altered ER capsules/ tablets/films, or chew TD fentanyl or buprenorphine[21,22,87-89,93,96]	***Part of BBW:*** Ingestion or injection of altered (eg, crushed or chewed) ER opioid products, including methadone products, increases the risk for RD. Extracting and ingesting buprenorphine from its buccal film or TD patch increases the risk of overdose and death. Exposure of fentanyl patches to the oral mucosa can result in overdose and death.	Morphine ER, oxycodone ER, TD fentanyl, methadone, tramadol ER, buprenorphine buccal film or TD patch
Concomitant use with an MAOI[27,92,96]	*Warning/precaution:* Concurrent or recent use of an MAOI may increase the risk for morphine-related AEs including RD and is contraindicated.	Morphine, codeine + promethazine
Serious RD risk is increased in debilitated, elderly, or patients with serious respiratory impairment[27,87-97]	*Warning/precaution:* Patients with significant respiratory impairment or decreased respiratory reserve or respiratory drive are at increased risk of RD from an opioid. Serious RD is more likely to occur in elderly or debilitated patients; treat patients with non-opioids and monitor for RD regularly if opioids are used. • Codeine + promethazine and hydrocodone + promethazine labeling warned that they should not be used by patients in whom preventing a cough would interfere with their respiratory status (eg, patient with a respiratory illness and productive cough). The dose of products indicated for cough should not be increased in patients with an unresponsive cough; instead, the cough should be reevaluated. • It is advised that opium tincture be used cautiously by "the elderly, in debilitated individuals, and in patients with increased intracranial pressure, cerebral arteriosclerosis, hepatic cirrhosis or liver insufficiency, gastrointestinal hemorrhage, myxedema, emphysema, and bronchial asthma" (page 2, package insert).[97]	All reviewed opioid products
Avoid/monitor use in patients with head injuries, impaired consciousness, or in a coma[27,87-97]	*Warning/precaution:* Patients in a coma or otherwise altered consciousness (eg, increased intracranial pressure) are more susceptible to negative effects from CO_2 retention, so if opioids are used, patients should be monitored for sedation and RD. Opioids should be avoided in patients with impaired consciousness or coma. • See populations of precaution for use of opium tincture as listed above.	All reviewed opioid products
Avoid use in patients with severe hepatic or renal impairment[88,93,97]	*Warning/precaution:* Exposure to fentanyl was increased in people with cirrhosis (from study of TD fentanyl) or with elevated blood urea nitrogen levels while awaiting kidney transplant (from study of IV fentanyl). Due to the long half-life of TD fentanyl and the risk for increased exposure and RD in patients with severe renal or hepatic disease, use is not recommended; starting the dose at one-half the usual dose is advised for patients with mild-to-moderate renal or hepatic impairment. A pharmacokinetic study of buprenorphine sublingual tablets demonstrated increased exposure to buprenorphine among patients with moderate to severe hepatic impairment, which increases the risk of overdose. Monitor patients with moderate or severe hepatic impairment for symptoms of an overdose and consider a dose reduction for patients with severe impairment. • Opium tincture should be used cautiously in patients with cirrhosis or liver insufficiency.	TD fentanyl; and opium tincture or buprenorphine buccal film (for hepatic dysfunction)
Drug interactions[97]	*Precaution:* Although not necessarily specific to the risk of RD, prescribing information for opium tincture advised that potential interactions with opium according to other product information be considered when it is used. Dose reductions may be considered when opium tincture is used with another CNS depressant.	Opium tincture
Risk of increased drug exposure in cancer patients with oral mucositis[93]	*Warning/precaution:* Cancer patients with oral mucositis who receive a transmucosal formulation of buprenorphine may experience more rapid exposure to buprenorphine, increasing the risk for toxicity. Consider a dose reduction and monitoring for toxicity in at-risk patients.	Buprenorphine buccal film

Abbreviations: AE, adverse event; APAP, acetaminophen; BBW, black box warning; CO2, carbon dioxide; CNS, central nervous system; CNSd, central nervous system depressant or depression; CSA, central sleep apnea; CYP, cytochrome; ER, extended release; IR, immediate release; IV, intravenous; OD, overdose; OUD, opioid use disorder; RD, respiratory depression; TD, transdermal

[a]Due to time constraints and the similarities in the risk of RD between different opioids, our review of prescribing information and BBWs per Lexidrug was limited to select opioids including: oral morphine IR tablet and ER capsules; oxycodone IR capsules and ER tablets; oral oxycodone and acetaminophen tablets; codeine phosphate and promethazine oral solution; transdermal fentanyl; oral methadone tablets; oral tramadol IR tablets; opium tincture; buprenorphine buccal film; and hydrocodone polistirex and chlorpheniramine polistirex ER oral suspension. Thus, this information is not comprehensive. Please refer to product-specific prescribing information for details.

[b]Many of these warnings are interrelated: BBW was assigned to the individual warnings emphasized in the black box of prescribing information for at least 1 products, whereas those labeled "part of a BBW" were elaborations of previously included individual BBW.

5.1 Opioid Risk Evaluation and Mitigation Strategy (REMS) Program

Started in 2012 for ER/LA opioid *analgesics* and extended to IR opioid *analgesics* in 2018, the Risk Evaluation and Mitigation Strategy (REMS) program requires that manufacturers of opioid analgesics for outpatient use offer education programs to healthcare providers about the safe use of opioids and offer options to return opioids by mail (as of 2023).[98] Notably, the patient counseling guides for opioid analgesics provided by the REMS program advise counseling patients to avoid taking opioids with MRs and "sleep medicines" due to the risk of RD and death.[99] Buprenorphine products for the treatment of OUD and transmucosal IR fentanyl products have drug-specific REMS programs.[100] Intended to reduce the risk of OD associated with transmucosal fentanyl dosage forms, providers must certify that the intended patient is tolerant to 60 mg of morphine (or equivalent) before each prescription.[101] The fentanyl transdermal iontophoretic system (Ionsys), which is only for hospitalized patients, also has a REMS program.[24] Dsuvia (sufentanil sublingual tablet), FDA-indicated for acute pain and the only anilidopiperidine opioid other than fentanyl with non-intravenous dosage forms,[102] is only available through a REMS program. The REMS for sufentanil sublingual tablet requires that it be administered by a healthcare provider at a registered healthcare facility to mitigate the risk of RD from accidental ingestion.[103]

6.0 GUIDELINE RECOMMENDATIONS AND SELECT OBSERVATIONAL EVIDENCE

We searched for recent guidelines addressing use of opioids for treatment of pain, cough, or diarrhea, and included guidelines providing formal or informal recommendations/considerations for prevention of RD and/or concurrent use of opioids with other medications. Recommendations or guidance were extracted from 3 guidelines addressing treatment of pain and/or opioid use for pain, primarily in adults, including guidelines from the American Society of Interventional Pain Physicians (ASIPP; 2023), Centers for Disease Control and Prevention (CDC; 2022), and Department of Veterans Affairs/Department of Defense (VA/DoD; 2022). Recommendations from these guidelines were supplemented by information from select condition-specific guidelines on the treatment of cancer-related pain from the National Comprehensive Cancer Network (NCCN; 2024) and American Society of Clinical Oncology (ASCO; 2023), and sickle cell disease (SCD)-related pain from the American Society of Hematology (ASH; 2022).

Importantly, guidelines from the ASIPP, CDC, and VA/DoD emphasized that their recommendations should not be used to develop *rigid* regulatory standards. Recommendations are intended as guidance for good practices, to be used in combination with the prescriber's judgment and case-by-case considerations.[6,17,30]

Generally, treatment guidelines for non-cancer pain provided recommendations to help ensure the appropriate and safe use of opioids, including promoting practices to minimize the risk of opioid-related adverse events (AEs) such as sedation, RD, and OD. Examples of good opioid prescribing practices recommended by guidelines from the ASIPP, CDC, and VA/DoD include using the lowest effective opioid dose for the shortest duration needed, and initiating treatment with short-acting opioids in treatment-naïve patients.[6,17,30] Reviewed guidelines advised only initiating opioids if the anticipated treatment benefits outweigh the potential risks. For patients on longer-term opioid therapy, providers should

assess ongoing benefits and risks at regular intervals.[6,17] For example, the ASIPP guideline advises that providers develop care plans with ongoing monitoring for side effects and the effectiveness of treatment (ie, 30% pain reduction or improved function) to ensure that the benefits of continued opioid use outweigh the risks.[6] The VA/DoD guideline took a relatively stricter position than ASIPP and the CDC, strongly recommending against starting opioids for chronic non-cancer pain regardless of the severity/etiology/patient impact of the ongoing pain, and without providing non-opioid management strategies for other possible severe pain etiologies aside from low back pain, headache, and hip/knee osteoarthritis. The VA/DoD also recommends against long-term opioid therapy, especially in younger patients or those with a substance use disorder.[30]

Additional information about risks of using opioids with CNS depressants, other risk factors for sedation or RD, and risk mitigation strategies other than using good opioid prescribing practices is discussed below.

6.1 Concurrent Use of Opioids with Other Sedating Medications

Reviewed pain-focused guidelines recognized that concurrent of opioids with other CNS depressants increases the risk of sedation, and possibly increases the risk of RD and/or OD. The ASIPP, CDC, and VA/DoD guidelines advised using caution when combining opioids with CNS depressants in general (advising against using opioids with BZDs in most situations), and recommend limiting use to when the benefits are considered to outweigh the risks.[6,17,30] Other than BZDs, the CDC listed MRs, non-BZD sedative-hypnotics, and sedating anticonvulsants (eg, gabapentinoids) as examples of CNS depressants.[17] According to ASIPP, hypnotics or sedatives can worsen opioid-related central sleep apnea (CSA) or obstructive sleep apnea (OSA), which is particularly important because opioid-related deaths from decreased respiratory drive often occur during sleep.[6] Certain medication combinations may also increase the risk of RD by inhibiting the metabolism of opioids.[6]

Other than opioid concurrent use with BZDs or gabapentinoids,[6,17,30] guidelines cited limited empirical evidence that demonstrates an increased risk for opioid-related AEs with other classes of CNS depressants (eg, non-BZD sedatives, MRs). Notably, the VA/DoD guideline performed a systematic literature search for randomized controlled trial (RCT) or systematic review (SR) evidence about the use of opioids with other classes of CNS depressants (eg, tricyclic antidepressants [TCAs], antihistamines, MRs, NBRAs). Only one retrospective cohort study of commercially insured adults (18-64 years) with non-cancer pain who filled at least 2 opioid prescriptions was cited by the VA/DoD and CDC guidelines that demonstrated a significantly increased odds of opioid OD among patients who filled a prescription for **zolpidem,** depending on the duration of zolpidem use and presence of a co-diagnosis of anxiety and/or post-traumatic stress disorder (PTSD). Compared to patients who did not fill a zolpidem prescription, zolpidem use was associated with an increased adjusted odds of opioid OD among the following groups:

- people *without* anxiety and/or PTSD with 1-30 days of therapy (adjusted odds ratio [aOR], 1.67; 95% confidence interval [CI], 1.21 to 2.30) or 91-180 days of therapy (aOR 1.54; 95%CI 1.20 to 1.99).
- and people *with* anxiety and/or PTSD who used zolpidem for 31 to 90 days compared to patients without zolpidem and anxiety and/or PTSD (group demonstrated the highest odds of OD; aOR, 95% CI: 1.77, 1.25 – 2.51).[104]

Regardless of limited empiric evidence about the risks of using non-BZD and non-gabapentinoid CNS depressants with opioids, use of opioids with any CNS depressant was considered to have increased adverse risks by authors of the reviewed guidelines,[6,17,30] yet without empiric evidence it is not clear what the absolute risk level is or how it differs between different drug combinations. Refer to section 6.1.2 for additional observational evidence about risks of concurrent use of opioids with non-BZD SHs or MRs.

6.1.1 Sedating medications included by opioid overdose risk models

Whereas the VA/DoD guideline mentioned the availability of or use of screening tools to assess an individual's risk of opioid OD or other opioid-related harms,[30] according to the CDC guideline, "No validated, reliable way exists to predict which patients will suffer serious harm from opioid therapy" (page 5).[17] Regardless of reliability of the entire model, two screening tools mentioned by the VA/DoD guideline included CNS-active medications in their risks models, as described below:

- STORM (Stratification Tool for Opioid Risk Mitigation) is a model used by the VA to predict an individual's risk of *opioid OD or suicide*.[30,105,106] The tool populates in each provider's dashboard to highlight a patient's risk factors for poor outcomes, and to suggest risk mitigation strategies (eg, psychosocial treatment, non-opioid medications for pain, prescribing naloxone). In consultation with experts and a review of the medical literature, non-opioid sedating medications considered to increase the risk of OD or suicide were included in the model in 3 ways: (category 1) co-prescription(s) for sedative medications; (category 2) "evidence-based but sedating medications" used to treat pain or other comorbidities (ie, TCAs, serotonin-norepinephrine reuptake inhibitors [SNRIs], anticonvulsants); and (category 3) the count of number of drug classes prescribed from category 2.[105]
    - Medications included in category 1 were selected based limited on empirical evidence including predictors of suicide and observational studies addressing the combination of opioids with BZDs, and expert guidance from the 2010 VA pain guideline for medications considered to be contraindicated with opioid therapy,[††] including: BZDs, barbiturates, meprobamate, midodrine, triazolam, Z-drugs (zaleplon, zolpidem tartrate, eszopiclone), select MRs (eg, carisoprodol), and select other SHs (eg, ramelteon).[107] Without controlling for other risk factors in the final model, use of at least one of these medications in combination with any opioid was associated with an increased the odds of an OD or suicide-related event (OR of 1.4) compared to patients not prescribed that combination among a cohort of all VA patients who had an active opioid prescription in 2011.[105]
- RIOSORD (Risk Index for Overdose or Serious Opioid-Induced Respiratory Depression) is a provider-completed risk index that *predicts a patient's risk of OD or RD*, which can be used before starting opioid therapy and periodically during opioid therapy. Factors associated with opioid-related harms were identified from the medical literature, and those factors highly associated with RD or OD in a multivariate model from a retrospective case-control study of VA patients (who were primarily older

[††] The updated 2022 VA/DoD guideline on the use of opioids for chronic pain lists the following as contraindications to starting opioids for chronic pain: active (not in remission) substance use disorder (SUD), suicide risk, and use of benzodiazepines (BZDs). Yet, SUD and elevated suicidality are recognized as *relative* contraindications, in which the relative benefit for each patient's situation should be considered.

white males) were retained in the final tool. Items in the tool are weighted (assigned a score) based on the strength of association with RD or OD.[108]

- The only non-opioid medications included in the risk score were concomitant use of a BZD (4 points), or antidepressant (7 points). A maximum score is 115; in the studied population, the point estimate for the predicted probability of RD or OD for a total score ≥ 67 was 94%.[108]

6.1.2 Select additional observational evidence for risks of concurrent use of opioids and CNS depressants

We identified an SRMA of observational studies to supplement information from prescribing information, FDA guidance, and guidelines about the risk of RD and/or OD among patients who concomitantly received an opioid plus a MR or SH. Because we did not perform a formal systematic literature search for evidence, the information summarized below may be lacking other relevant studies, and therefore, should be interpreted cautiously.

Wang et al (2023) performed an SRMA of observational studies (cohort or case-control) that included patients with chronic cancer or noncancer pain, excluding studies of patients in palliative care or that only included patients who had a prior opioid OD. Eligible studies must have reported the outcome of fatal and/or non-fatal opioid OD.[7] Although the outcome from primary studies used by Wang et al appears to have been adjusted for concurrent SUD (eg, with multivariable models), included patients were a mix of patients with and without SUD[‡‡].

Compared to patients who were not co-prescribed an MR or SH with an opioid, filling prescriptions for MRs or SHs along with opioids was associated with a modestly increased odds of opioid OD based on high certainty evidence (adjusted odds ratio [aOR]; 95% CI: MRs, 1.28; 1.10 to 1.50; SHs 1.37; 1.20 to 1.56).[7] Except for one primary study included by Wang et al in their meta-analysis for MRs (Li et al), primary studies provided little explanation for which agents were included in the categories of MRs and SHs (refer to **Appendix B, Table B1** for details). Thus, we cannot be sure whether the pooled estimates calculated by Wang et al are representative of the MR and SH agents addressed by our report (eg, doxepin, ramelteon, etc.). Since Wang et al and the primary studies included by Wang et al reported separate categories for BZDs, we infer that this drug class was excluded from the pooled estimates for MRs and SHs. The MRs included by Li et al aligns with those included by our report except for dantrolene.[109] Among the 6 studies included in the meta-analysis for SHs, Turner et al included only zolpidem[104] and Salkar et al seemed to have only included NBRAs and MRAs.[110]

A few observational studies included by Wang et al reported the risk of opioid OD associated with specific MRs or SHs. Turner et al found a significant association between zolpidem use and opioid OD in adults with non-cancer pain, which was previously described above (see section 6.1).[104] In a retrospective cohort study of commercially insured US adults (18-64 years old) who were incident (ie, no opioid use in the prior 180 days) or prevalent opioid analgesic users without documented cancer or SUD, Li et al (2020) found that concomitant use of MRs as a class was associated with an increased hazard of OD (hazard ratio [HR]; 95% CI pooled from the incident and prevalent opioid use cohorts: 1.21; 1.00 to 1.48) after adjustment for potential confounders including prescribed use of other CNS depressants.[111]

[‡‡] 78% of all primary studies included by Wang et al (ie, not only those studies that address co-prescription of opioids with MRs or SHs) included patients with SUD (median of 9% of patients per study).

When examined by individual MR, co-use of an opioid with either baclofen (HR 1.83; 95%CI 1.11 to 3.04) or carisoprodol (HR 1.84; 95%CI 1.34 to 2.54), which along with cyclobenzaprine were the most commonly co-utilized MRs (observation period of 2005 to 2015), was significantly associated with opioid OD in the combined incident and prevalent user cohort. Neither use of cyclobenzaprine (HR 0.85; 95%CI 0.64 to 1.13) nor other specific MRs were significantly associated with opioid OD; however, the other MRs were used infrequently and had wide 95% confidence intervals, meaning uncertainty in the effect estimate. Evidence from Li et al also suggested that duration of MR use might impact the risk of opioid OD; co-use of a MR with an opioid for longer than 60 days was significantly associated with opioid OD, whereas duration <14 days was not (although an increased risk with the shorter duration cannot be ruled out based on confidence intervals). If combination use with an opioid is necessary, Li et al suggested that prescribers select MRs with a relatively lower risk in their study, like cyclobenzaprine or tizanidine. Moreover, given that most MRs are FDA-indicated for short-term use and the observation that longer use of MRs with opioids was associated with an increased risk of OD, Li et al advised undertaking long-term co-use of opioids and MRs cautiously.[111]

Table 6 below summarizes results from the SRMA by Wang et al for the risk of opioid OD associated with of MRs or SHs.

Table 6. Risk of Opioid Overdose Associated with Sedative-hypnotics or Muscle Relaxants, per the Systematic Review and Meta-analysis (SRMA) by Wang et al (2023)[7]

Co-prescribed drug class with an opioid	Number of included studies	Number of patients	Quality of evidence	Summary of results (95% CI)		
				Opioid OD (fatal or non-fatal) aOR[a,b]	Fatal OD absolute risk[c] per 1000	Non-fatal OD absolute risk[c] per 1000
Study description: *SRMA of 28 observational studies (21 cohort studies and 7 case-control studies) that evaluated predictors of fatal and non-fatal opioid OD after receiving an opioid prescription for chronic pain (noncancer- or cancer-related if pain persisted for at least 3 months) using administrative data.*						
Sedative-hypnotics (SHs)[d]	6	337,924	High	Opioid + SH vs no SH + opioid: 1.37 (1.2−1.6)	1.4 (1.2−1.6)	2.7 (2.4−3.1)
Muscle relaxants (MRs)[d]	5	19,776,855	High	Opioid + MR vs no MR + opioid: 1.28 (1.1−1.5)	1.3 (1.1−1.5)	2.6 (2.2−3.0)
Benzodiazepines	12	1,246,864	Moderate	Opioid + BZD vs no BZD + opioid: 1.79 (1.5−2.2)	1.8 (1.5−2.2)	3.6 (2.9−4.4)

[a] *Wang et al defined the magnitude of relative associations as large (pooled aOR ≥ 2.0 or ≤ 0.5) or small/trivial (pooled aOR <2.0 or >0.5).*

[b] *The pooled aOR was calculated by random-effects meta-analysis of the individual adjusted odds/risk ratios reported by primary studies; the factors adjusted for by each primary study was not reported.*

[c] *The absolute risk of fatal and nonfatal OD was calculated by using the adjusted odds ratio (aOR) and by employing a baseline risk, estimated from prior studies, of 1 per 1000 and 2 per 1000 for fatal and nonfatal OD, respectively.*

[d] *Other than 1 study reporting an association with MRs which included each MR included by this report other than dantrolene (Li et al 2020), individual primary studies contributing information did not describe which individual SHs and MRs contributed to the predictor category.*

Abbreviations: aOR; adjusted odds ratio; CI, confidence interval; MR, muscle relaxant; OD, overdose; SH, sedative-hypnotic; SRMA, systematic review and meta-analysis

6.2 Management of Risks from Concurrent Use of Opioids and Other Sedating Medications

Reviewed guidelines tend to recommend avoiding concurrent use of opioids and other sedating medications, if possible.[6,17,30] **Although reviewed guidelines provided few definitive recommendations about considerations for using sedating medications other than BZDs with opioids, they tended to acknowledge some clinical scenarios could necessitate combined use**. For example, even for BZDs, the CDC and ASIPP stated or implied scenarios where judicious co-use with opioids could be considered, particularly given the complex interplay between chronic pain and mental health conditions, and the possibility that stabilizing or improving mental health could lead to better pain management outcomes.[6,17] Regarding BZDs, CDC experts noted that "…rather than necessarily being a direct cause of overdose, benzodiazepines might serve as a marker of risk for overdose because of underlying conditions, in specific situations benzodiazepines can be beneficial, and that stopping benzodiazepines can be destabilizing" (page 53).[17] Regarding use of non-BZD SHs or MRs specifically, ASIPP pointed out that many patients in studies of long-term opioid therapy were also taking MRs, although no information was provided about outcomes of their use together.[6] **The VA/DoD guideline recommended (as an informal, non-graded statement) treatment and/or referral for treatment of insomnia or sleep disorders in patients with chronic pain, although use of pharmacologic agents for insomnia is not addressed specifically**.[30] When use of an opioid with a CNS depressant is indicated, providers should take steps to mitigate the risk of fatal OD/RD.

Table 7 summarizes strategies to minimize the risk of RD and/or OD that are mentioned by one or more reviewed general pain-focused guidelines. **Except for a few strategies specific to use of opioids with CNS depressants (eg, dose reductions and monitoring the patient more frequently), the information from guidelines that is summarized in Table 7 was provided as general guidance intended to be part of an overall approach to mitigating opioid-related harms.** Refer to **Appendix C, Table C1** for additional elaboration about the use of opioids with CNS depressants and strategies to mitigate opioid-related harms that is organized by guideline.

Regardless of use in combination with a CNS depressant, guidelines hinted that certain opioids may carry a comparatively higher risk of RD (eg, fentanyl, methadone).[6,17] To mitigate the risk of RD or OD and opioid misuse, the VA/DOD weakly prefers buprenorphine to full opioid agonists in the management of chronic pain among patients who require daily opioids.[30] Because buprenorphine is a partial MOR agonist, the positive linear relationship between opioid dose risk of RD plateaus,[17,30] and thus, it is considered by the VA/DoD to have a superior safety profile to full opioid agonists.[30] Nonetheless, the VA acknowledged that ODs from buprenorphine are possible when it is used in combination with CNS depressants in general (and when it is used by opioid-naïve patients).[30]

Guidelines tended to encourage offering (but not requiring) **naloxone** to patients receiving opioid therapy, particularly to patients with risk factors for RD/OD, but they provided little explicit criteria about who should receive naloxone.[6,17,30] ASIPP mentioned naloxone use may be particularly encouraged in patients who are taking higher opioid doses and have an OUD diagnosis.[6] The CDC especially recommends naloxone for high-risk patients with a history of SUD, who are taking BZDs, using higher daily opioid doses (≥ 50 MME), or who are returning to opioid use after loss of tolerance.[17]

Table 7. Summary of Pain Guideline-recommended CNS/Respiratory Depression Risk Mitigation Strategies from the ASIPP (2023),[6] CDC (2022),[17] and/or VA/DoD (2022)[30]

CNS-depressant related strategies
• **Guidelines tend to recommend avoiding use of sedating medications with opioids, when possible.** Such combinations should only be used if the potential benefits outweigh the risks.   ○ Guidelines emphasize avoiding co-use of BZDs in particular • If CNS depressants are used with opioids, increased caution is advised • **Consider dose-reductions of the CNS depressant and/or opioid (eg, when adding the other therapy type)**[112] (ASIPP) • Avoid unpredictable use – in some situations, stable use of the CNS depressant may be less risky[17] (CDC)
Opioid-related strategies

• Opioids should be used judiciously for situations that warrant their use. Follow general good opioid prescribing practices (eg, using the lowest effective dose; not initiating opioid therapy with long-acting opioids; avoid or use caution when prescribing IR and LA/ER opioids together (ASIPP, CDC)[6,17]
  ○ Risk of RD with most opioids increases as the dose increases (buprenorphine is an exception, and it is unknown if risks from tapentadol and tramadol are dose-dependent [CDC]). There is no "safe" dose threshold (CDC).[17]
  ○ The VA/DoD recommends against long-acting opioids for (1) acute pain, (2) as-needed use, and (3) at the start of long-term opioid therapy, due to the risk of OD and death (and development of OUD). Generally, though, there is a lack of comparative evidence between specific opioids and/or formulations.[30]
• Consider selecting a lower-risk opioid with respect to the active ingredient:
  ○ For chronic pain: ASIPP recommends tramadol, codeine, tapentadol or hydrocodone for mild to moderate pain; hydrocodone, oxycodone, hydromorphone, or morphine are first-line for severe pain – fentanyl is reserved for second line, and methadone for third line.[6]
  ○ For chronic pain in patients who require daily opioid use: buprenorphine is preferred to a full agonist opioid (VA) due to the theoretically lower risk of RD/overdose. Notably, co-use of CNS depressants also increases the risk of RD with buprenorphine.[30]
• Higher risk opioids
  ○ Methadone may carry a higher risk of RD/OD compared to other opioids (ASIPP, CDC).[6,17] Methadone should not be the first-line ER/LA (CDC).[17]
  ○ Fentanyl (transdermal) should be prescribed by prescribers familiar with its properties (CDC)[17]
  ○ Meperidine is not recommended to long-term use due to neurologic AEs (seizures); risks that are increased when used with BZDs (ASIPP)[6]

[a] *Strategies include formal (graded) or informal (non-graded) recommendations from guidelines to mitigate opioid-related harms, including those provided in the context of concomitant use of CNS depressants or in general. For specific guidance (not overarching summaries of all 3 guidelines), the guideline organization who made the recommendation is noted in parentheses following a summary of the statement.*

[b] *List may not be inclusive of all possible risk mitigation options.*

Abbreviations: ASIPP, American Society of Interventional Pain Physicians; BZDs, benzodiazepines; CDC, Centers for Disease Control and Prevention; CNS, central nervous system; DoD, Department of Defense; ER, extended release; IR, immediate release; LA, long-acting; PDMP, Prescription Drug Monitoring Program; VA, Veterans Affairs

Table 7. Summary of Pain Guideline-recommended CNS/Respiratory Depression Risk Mitigation Strategies from the ASIPP (2023),[6] CDC (2022),[17] and/or VA/DoD (2022)[30]

• For patients with compromised renal or hepatic function, select an appropriate opioid or dose-adjust the opioid to avoid accumulation of the opioid/metabolite (see opioid-specific guidance from the VA/DoD)[30] • Consider using abuse-deterrent opioid formulations (ASIPP),[6] although there is no or limited evidence for prevention of RD (CDC)[17]
Screen patients for overdose/RD risk factors, and consider Increasing the monitoring frequency

• When considering starting an opioid, as the patient for the risk of opioid-related harms including RD; this information should be used to help determine whether the potential benefits outweigh the risks (see Table 8 below about risk factors for RD/overdose)
• Ensure treatment of relevant behavioral health conditions is optimized before long-term opioid use (CDC)[17]
• Monitor for other substance(s) that could increase the risk of RD or other poor outcomes:
  ○ Monitor the PDMP before starting acute/chronic opioid therapy and periodically with long-term use (CDC)[17]
  ○ During longer-term opioid therapy, consider toxicology (CDC) or urine drug testing (VA)[30]
• **More frequent follow-up may be warranted in patients taking CNS depressants with opioids** (CDC, VA)[17,30]
• Consider interdisciplinary care for pain and behavioral health conditions for patients with chronic pain and high-risk behaviors (VA)[30]

Provide education and offer naloxone
• **Patients should be informed about the risks (sedation and RD) of taking opioids with CNS depressants** (ASIPP, CDC)[6,17] • Provide overdose prevention education to patients and offer education to caregivers (CDC)[17] • Guidelines suggest *offering* naloxone to patients (CDC),[17] especially to "high-risk" patients   ○ The CDC recommends https://prescribetoprevent.org for naloxone resources
Other
• The CDC advised including pharmacists in the patient's care if CNS depressants are used with opioids[17]

[a] *Strategies include formal (graded) or informal (non-graded) recommendations from guidelines to mitigate opioid-related harms, including those provided in the context of concomitant use of CNS depressants or in general. For specific guidance (not overarching summaries of all 3 guidelines), the guideline organization who made the recommendation is noted in parentheses following a summary of the statement.*

[b] *List may not be inclusive of all possible risk mitigation options.*

Abbreviations: ASIPP, American Society of Interventional Pain Physicians; BZDs, benzodiazepines; CDC, Centers for Disease Control and Prevention; CNS, central nervous system; DoD, Department of Defense; ER, extended release; IR, immediate release; LA, long-acting; PDMP, Prescription Drug Monitoring Program; VA, Veterans Affairs

6.3 Additional Risk Factors for Respiratory Depression and/or Opioid Overdose

Concomitant use of CNS depressants with opioids is one many risk factors for sedation, overdose, or RD that is mentioned by guidelines.

Table 8 summarizes risk factors that increase the risk of sedation, RD, and/or overdose during opioid therapy according to recent US pain management guidelines. Note that these risk factors were mentioned in any manner in the guidelines (ie, not necessarily as risk factors when using opioids with CNS depressants); however, it is generally understood that risk factors tend to compound with one another and patients with multiple risk factors are at a higher risk for opioid-related harm than most patients with a single risk factor.[108] Generally, the magnitude of risk for opioid-related harms associated with particular risk factor is not addressed by guidelines. The VA/DoD guideline considered active substance use disorder, elevated suicide risk, and concomitant use of BZDs to be relative contraindications to opioid therapy for chronic pain, implying that these characteristics carry a high risk for opioid-related harm.[30]

Overall, a recent robust SR and meta-analysis (SRMA) of observational studies by Wang et al (2023) reported similar risk factors for OD to those identified by 1 or more reviewed guideline. Wang et al considered some risk factors reported by guidelines to be modestly associated (ie, associated with a small significantly increased odds) with the risk of fatal or nonfatal opioid OD, such as heart failure, COPD, renal disease, and younger age. Moderate-to-high certainty observational evidence from cohort or case-control studies was found for a large association (ie, 2-fold or higher increase in adjusted odds) between fatal or non-fatal opioid OD and the following factors among patients with chronic, primarily non-cancer, pain[7]:

- Prior opioid OD
- Comorbidities: depression, bipolar disorder, mental health condition, pancreatitis, or current SUD
- Opioid prescriptions from ≥ 3 prescribers (versus <3)
- Filling opioid prescriptions at ≥ 4 pharmacies (versus <4)
- Total opioid dose ≥ 90 MMEs
- Use of fentanyl (versus other opioids)

Table 8. Guideline-recognized Risk Factors for Sedation, Overdose, or Respiratory Depression during Opioid Therapy, by Guideline and Risk Category

ASIPP (2023)[6]	CDC (2022)[17]	VA/DoD (2022)[30]
Opioid-related risk factors (ie, factors that might carry higher risks than other opioid therapy types)		
• Methadone • Long-acting/extended-release opioids • Total opioid dose – risk increases as dose increases, generally	• Methadone is associated with a disproportionate number of ODs • Long-acting/extended-release opioids; OD risk vs IR opioids was highest in the first 2 weeks of treatment, in 1 fair quality study • Higher opioid doses, especially ≥ 50 MME/day	• Long-acting schedule II opioids and short-acting schedule II opioids (versus use of non-schedule II opioids) showed a 2-4-fold increase in risk of opioid-related death in 1 study. Risk was highest with long-acting opioids. • Duration of treatment – risk of opioid-related death was 4-fold (after duration 31-89 days) and 20-fold (at >730 days) higher than with use <30 days in 1 study. • Higher opioid doses: generally, OD risk increases as dose increases
Comorbidity-related risk factors		
• Risk factors for sedation: CHF, sleep apnea, obesity • Diabetes, or pulmonary, renal or liver disease were associated with receipt of naloxone in patients prescribed opioids + gabapentinoids	• Substance use disorder • Sleep-disordered breathing (eg, sleep apnea) • Liver or renal disease • Mental health disorders	• Substance use disorder, especially untreated/not in remission • Poor cardiopulmonary, liver, or renal disease • Unstable mental health disorder, especially suicidality • History or TBI or a pain catastrophizing condition
Concomitant medications		
• CNS depressants	• CNS depressants, especially BZDs	• CNS depressants, especially BZDs (and alcohol)
Age		
• Older age is a risk factor for sedation, reduced liver or renal function, and overall risks from polypharmacy	• Older age (≥ 65 years)	• Younger age:"…age is inversely associated with the risk of opioid use disorder and overdose" (page 38)
Changes in opioid tolerance		
• Patients with OUD treated with naltrexone may have a higher risk of OD shortly after stopping treatment due to low opioid tolerance	• Patients who are at risk for exposure to a previously tolerated higher dose after loss of tolerance	
Other		
• History of opioid OD • Female sex and orthopedic surgery (along with other factors) were associated with requiring emergent naloxone in patients who received opioids + gabapentinoids in an observational study	• History of opioid OD	• Recent OD increases the acute OD risk

[a] *While we tried to capture all risk factors mentioned by guidelines, this should not be considered a comprehensive list*

Abbreviations: BZDs, benzodiazepines; CHF, congestive heart failure; CNS, central nervous system; MME, milligrams of morphine equivalents; OD, overdose; OUD, opioid use disorder; TBI, traumatic brain injury

6.4 Recommendations from Select Guidelines for Specific Pain Conditions

Since opioids can be used in the treatment of many conditions and the focus of this report is on the risk of RD when used with certain CNS depressants, for feasibility, we did not systematically search for all recent US guidelines that might address opioid use. We are aware of recent guidelines from the American Society of Clinical Oncology (ASCO; 2022) and National Comprehensive Cancer Network (NCCN; 2024), which addressed management of cancer-related pain in adults, and a guideline from the American Society of Hematology (ASH; 2020) that addressed management of acute and chronic pain associated with sickle cell disease (SCD).

Generally, guidelines for use of opioids to treat cancer-related pain in adults from the NCCN and ASCO provided similar guidance for mitigating the risk of RD or OD to those for treatment of non-cancer pain. Both guidelines acknowledged CNS depressants as a risk factor for opioid-induced CNS depression and/or RD, but other than for benzodiazepines, risks of using specific classes of CNS depressants was not provided.[113,114] ASCO (2022) provided guidance on the management of opioid-related AEs and described that "Respiratory depression is typically preceded by sedation and is uncommon during chronic opioid administration" (page 922).[113] The NCCN also advised that sedation usually precedes RD, and that progressive sedation should prompt evaluation of the cause, including consideration to modifications to sedating medications.[114] Poor cardiopulmonary reserve is a risk factor for opioid-induced sedation or respiratory dysfunction per the NCCN; extra caution is advised when titrating opioid doses in patients with chronic lung disease, a compromised upper airway, sleep apnea, decreased performance status, and/or poor renal or hepatic function.[114] When RD is a concern, the NCCN advised (1) considering opioid dose reductions or administering opioids less frequently (ie, increased time between doses); (2) ensuring patients did not accidentally administer an opioid patch; and (3) monitoring the patient's status closely.[114] To mitigate the risk of sedation and RD, ASCO advised limiting polypharmacy, and offering naloxone to patients at higher risk whose care goals align with using naloxone. Risk factors that might warrant naloxone according to ASCO included using ≥ 50 MMEs daily, and concurrent use of BZDs, gabapentinoids, or other CNS depressants.[113] The NCCN also stated that naloxone can be made available to caregivers of patients with cancer-related pain; the NCCN encouraged its use for patients with medically unstable RD (patients with "stable" RD might alternatively be carefully observed, although the treatment setting is not specified) whose care goals align with naloxone use.[114]

Overall, principles for the safe and appropriate use of opioids for patients with SCD are like those for pain from other causes. Opioids are a mainstay of treatment for acute SCD-related pain in children and adults. There is a paucity of data to guide treatment of SCD-related chronic pain, thus the ASH encouraged delivering patient-centered care that incorporates shared decision-making. Generally, the ASH recommended reserving opioids for patients refractory to other treatment options who continue to benefit from the therapy. Limited information was provided by ASH about risk factors for RD or OD, other than the risk increases as opioid dose increases. ASH encouraged avoiding use of sedating medications and alcohol in combination with chronic opioid therapy but provided no information specific to use of MRs or SHs with opioids. Prescribing naloxone to patients with SCD receiving chronic opioid therapy was encouraged by the ASH.[112]

7.0 UTILIZATION DATA FOR CONCURRENT USE OF AN OPIOID WITH A MUSCLE RELAXANT AND/OR A SEDATIVE-HYPNOTIC

During the study period (April 1, 2023 to March 31, 2024), 15,888 Utah FFS patients filled at least 1 outpatient pharmacy prescription for a reviewed agent: 10,406 filled an opioid, 6,357 filled an MR, and 2,389 filled an SH. Some patients are represented in more than one category, as they filled more than one type of prescription during the study period.

Among the overall cohort of patients who filled an opioid, MR, or SH (n=15,888), the median age was 40 years (25th – 75th percentile being 30 – 51), and most patients (n=14,599; 91.9%) were 18 years old or older.

Subgroups of patients with at least 1 day of overlapping days' supply (as calculated per Section 2.1) include those filling: an opioid + MR, an opioid + SH, or an opioid + MR + SH.

The median age of patients with *any* overlap (of any duration) of an opioid + MR and/or + SH tended to be higher (median of 46 years old) than the overall cohort, and nearly all patients (≥ 99%) with overlapping prescriptions were ≥ 18 years old. Most patients in the overall cohort who filled any opioid, MR, or SH, and the subgroups with an overlapping supply of an opioid + MR and/or SH were female (≥ 59%). The median duration of Medicaid eligibility during the study period in the overall cohort and subgroups was 366 days (25th – 75th percentile being 284 – 366 days in the overall cohort).

Refer to **Appendix D, Figure D1** for a flow diagram showing the disposition of patients who filled a prescription for an opioid, MR, and/or SH, and **Appendix E, Table E1** for additional descriptive statistics about age, sex, and duration of Utah Medicaid eligibility during the study period in the overall cohort and subgroups.

7.1 Patients with Concurrent Use Based on Prescription Days' Supply

Of the 10,406 patients who filled an opioid prescription during the study period, 1,835 (17.6%) had an overlapping days' supply (of at least 1 day) with a MR prescription, and 461 (4.4%) had an overlapping days' supply with an SH prescription. One hundred and forty-four patients (1.4% of those who filled an opioid) had an overlapping supply of an opioid, MR, and SH. Patients with an overlapping opioid and MR prescription encompassed 29% of all patients who filled a MR (n=6,357) and overlapping opioid and SH prescriptions occurred for 19% of patients who filled an SH (n=2,389).

The days' supply for most patient's opioid prescriptions did not have overlap with a MR and/or SH. **Of the 10,406 patients who filled an opioid, 7,591 (72.9%) did not fill any prescription for an MR or SH during the study period.** Patients who filled an MR or SH *without* overlapping prescriptions with an opioid encompassed 590 (5.7%) and 155 (1.5%) of opioid recipients.

As is common for analyses relying on days' supply, our descriptive analysis is subject to limitations that could result in an overestimation of the number of patients with overlapping use of an opioid with MR and/or SH. We used pharmacy prescription data as an approximation of patient's actual medication use, which may not accurately reflect patient usage. Additionally, we had to make assumptions in our calculation of days' supply of opioids, MRs, and SHs that could have overestimated the number of days'

supply (eg, among patients who filled overlapping prescriptions for IR and ER prescriptions of the same active ingredient). Thirdly, patients were counted as having overlapping supply if the overlap was for as little as 1 day.

7.1.1 Percentage of overlapping days (POD) out of all opioid days or days of Medicaid eligibility

To reflect the duration of overlapping days' supply for opioids with an MR and/or SH, we calculated the overlapping days with an opioid and MR and/or SH as a percentage of the total days with (1) opioid supply and (2) Utah Medicaid coverage. Overall, the mean/median POD with an opioid + MR and/or + SH was numerically higher when calculated as a percentage of total days with an opioid supply versus when calculated as a percentage of total days Medicaid coverage; this is to be expected, as says with an opioid are only a subset of all coverage days, resulting in a smaller denominator. This may also suggest that patients tended to be prescribed these medications together for shorter durations relative to the length of Medicaid coverage, on average. The median (25th – 75th percentile) total number of overlapping days of medication supplied for opioid + MR, opioid + SH, and opioid + MR + SH subgroups was 13 (5 – 47), 17 (6 – 56), and 24 (7 – 78.5), respectively. Refer to **Appendix E, Table E2** for additional descriptive statistics about the number of overlapping days by overlap subgroup.

Of the 1,835 patients with an overlapping opioid and MR prescription, the mean (standard deviation [SD]) POD with opioid + MR out of total days with an opioid supply was 67.4% (34%). The median POD with opioid + MR out of total days with an opioid supply was 76.9% (25th – 75th percentile being 38.7% – 100%). Additionally, the mean (SD) and median (25th – 75th percentile) POD with opioid + MR out of total days with Medicaid coverage were 15.9% (25%) and 4.4% (1.6% – 15.6%), respectively.

Of the 461 patients with an overlapping opioid and SH prescription, the mean (SD) and median (25th – 75th percentile) POD with opioid + SH out of total days with an opioid supply were 74.9% (31.6%) and 95.8% (50% – 100%), respectively. With respect to the POD with opioid + SH out of all Medicaid-covered days, the mean (SD) was 17.9% (27.4%) and the median (25th – 75th percentile) was 5.3% (1.9% – 16.7%).

Of the 144 patients with an overlapping opioid + MR + SH prescription, the mean (SD) POD with all 3 prescription types out of total days with an opioid supply was 54.7% (35.5%), and the median (25th – 75th percentile) was 52.1% (16.9% – 96.2%). Out of total Medicaid-covered days during the study period, the mean (SD) and median (25th – 75th percentile) POD with opioid + MR + SH were 19.5% (26.6%) and 7.3% (1.9% – 24.6%), respectively.

Table 9 provides descriptive statistics for the individual POD with the overlapping medication classes among patients who had at least 1 overlapping prescription.

We also calculated descriptive statistics for the POD among all 10,406 patients who filled an opioid, which includes patients with or without overlap (see **Appendix F, Table F1**). As expected, the mean PODs out of days with an opioid supply and out of days with Medicaid coverage were lower than when calculated only among patients who had an overlapping prescription (as described above).

Table 9. Descriptive Statistics for the Individual Percentages of Overlapping Days' Supply with an Opioid + Muscle Relaxant and/or + Sedative-hypnotic in Relation to Total Days of Opioid Supply or with Medicaid Coverage, among Patients with an Overlap[a,b]

Overlapping medication class(es)[c]	N with overlap	Descriptive statistics for % of days with overlap	
		Mean (SD)	Median (25th – 75th percentile)
Overlapping days as a percentage of the total days with an opioid supply			
Opioid + MR	1,835	67.4 (33.6)	76.9 (38.7 to 100)
Opioid + SH	461	74.9 (31.6)	95.8 (50 to 100)
Opioid + MR + SH	144	54.7 (35.5)	52.1 (16.9 to 96.2)
Overlapping days as a percentage of the total days with Utah Medicaid coverage			
Opioid + MR	1,835	15.9 (24.9)	4.4 (1.6 to 15.6)
Opioid + SH	461	17.9 (27.4)	5.3 (1.9 to 16.7)
Opioid + MR + SH	144	19.5 (26.6)	7.3 (1.9 to 24.6)

Abbreviations: %, percentage; MR, muscle relaxant; SD, standard deviation; SH, sedative-hypnotic

[a] The percentage of overlapping therapy days was calculated for each patient as the total number of days of overlapping days' supply (for opioid + MR, opioid + SH, or opioid + MR + SH) divided by either (1) the total number of days' supply of opioids or (2) the total number of days of Utah Medicaid eligibility, during the study period (April 1, 2023 to March 31, 2024).

*[b] Descriptive statistics were calculated among the Utah Medicaid Fee-for-Service patients who had at least 1 day of overlap among filled outpatient pharmacy prescription for the respective medication classes (ie, the total N with overlap). Refer to **Appendix F, Table F1** for the percentage of overlapping days among all patients who filled an opioid prescription (with or without overlap).*

*[c] Refer to **Appendix A** for a list of medications that were included in each drug class of interest.*

7.1.2 Combinations filled

Among patients who had an overlapping days' supply of an opioid prescription with an MR and/or SH, we examined the combinations filled by active ingredient (**Table 10**). Only combinations filled by at least 11 patients are reported. Each combination row reflects the number of unique patients with that overlapping combination; patients could be represented in more than more group if they filled more than one combination during the study period.

Of the 1,835 patients with overlapping days' supply of opioids and MRs, 60 different opioid + MR combinations (by active ingredient) were identified during the 12-month study period. Twelve opioids and all 9 MRs were included in at least 1 overlap occurrence. The combination filled by the most unique patients was oxycodone + cyclobenzaprine (filled by 24.4% of patients with an opioid + MR overlap). The top 5 combinations of opioids + MRs, by patient frequency, involved some pairing of the opioids oxycodone, hydrocodone, or tramadol with the MRs cyclobenzaprine, methocarbamol, or tizanidine. Overall, including combinations not shown in Table 10, few patients filled combinations involving

fentanyl (included among 4 combinations with a total patient frequency of up to 21[§§]), methadone (included among 5 combinations with a total patient frequency of up to 11[§]), or buprenorphine (included among 5 combinations with a total patient frequency of up to 21).

Table 10. Distribution of Patients by Opioid + Muscle Relaxant and/or + Sedative-hypnotic Combinations[a]

Combination by active ingredients[b]	FFS patients with combination,[c,d] N (% of unique patients with overlap)
Opioid and muscle relaxant combinations (total N with overlap = 1,835)	
Oxycodone + cyclobenzaprine	447 (24.4)
Hydrocodone + cyclobenzaprine	257 (14.0)
Oxycodone + methocarbamol	255 (13.9)
Oxycodone + tizanidine	242 (13.2)
Tramadol + cyclobenzaprine	187 (10.2)
Oxycodone + baclofen	186 (10.1)
Hydrocodone + methocarbamol	144 (7.8)
Hydrocodone + tizanidine	139 (7.6)
Tramadol + tizanidine	107 (5.8)
Hydrocodone + baclofen	87 (4.7)
Tramadol + methocarbamol	80 (4.3)
Tramadol + baclofen	78 (4.3)
Morphine + cyclobenzaprine	32 (1.7)
Codeine + cyclobenzaprine	22 (1.2)
Morphine + baclofen	21 (1.1)
Hydromorphone + cyclobenzaprine	16 (0.9)
Codeine + methocarbamol	16 (0.9)
Codeine + tizanidine	15 (0.8)
Morphine + methocarbamol	14 (0.8)
Opioid and sedative-hypnotic (total N with overlap = 461)	
Oxycodone + zolpidem	161 (34.9)
Hydrocodone + zolpidem	123 (26.7)
Tramadol + zolpidem	62 (13.4)
Oxycodone + eszopiclone	32 (6.9)
Oxycodone + doxepin	30 (6.5)
Tramadol + eszopiclone	24 (5.2)
Hydrocodone + eszopiclone	22 (4.8)
Codeine + zolpidem	18 (3.9)

[§§] Total frequency may include the same patient more than once.

Table 10. Distribution of Patients by Opioid + Muscle Relaxant and/or + Sedative-hypnotic Combinations[a]

Combination by active ingredients[b]	FFS patients with combination,[c,d] N (% of unique patients with overlap)
Hydrocodone + doxepin	15 (3.3)
Morphine + zolpidem	14 (3.0)
Opioid, muscle relaxant, and sedative-hypnotic (total N with overlap = 144)	
Oxycodone + cyclobenzaprine + zolpidem	22 (15.3)
Oxycodone + tizanidine + zolpidem	14 (9.7)
Hydrocodone + cyclobenzaprine + zolpidem	13 (9.0)
Hydrocodone + tizanidine + zolpidem	13 (9.0)
Tramadol + cyclobenzaprine + zolpidem	12 (8.3)

Abbreviations: FFS, Fee-for-service; N, number of patients

[a] Based on outpatient pharmacy prescription claims filled by Utah Medicaid FFS patients between 4/1/2023 and 3/31/2024

[b] Prescriptions with the same active ingredient were grouped together regardless of the formulation or strength

[c] Each patient was counted only once per row, regardless of how many times they filled the same prescription combination. Unique patients could be counted more than once per category if they filled more than one unique prescription combination.

[d] Only combinations that occurred among at least 11 unique patients are reported.

Of the 461 patients with overlapping days' supply of an opioid and SH, 50 unique combinations were identified. Eleven opioids and 8 of 9 SHs (no fills were for tasimelteon) were involved in at least 1 overlap. The combination filled by the most unique patients was oxycodone + zolpidem (filled by 34.9% of patients with an opioid + SH overlap). The top 5 combinations of opioids + SHs, by patient counts, involved some pairing of the opioids oxycodone, hydrocodone, or tramadol with the SHs zolpidem, eszopiclone, or doxepin. Similar to combinations of opioids and MRs, opioids fentanyl, methadone, and buprenorphine are minimally represented in overlaps; each unique combination involving these agents was filled by fewer than 11 patients.

Of the 144 patients with overlapping days' supply of an opioid + MR + SH (by active ingredient), 83 different combinations were identified during the study period. These combinations included 11 unique opioids, 6 unique MRs (no overlaps with dantrolene, chlorzoxazone, or metaxalone), and 8 SHs (no overlaps with tasimelteon). The most frequent combination, by patient count (filled by 15.3% of patients with an opioid + MR + SH overlap), was oxycodone + cyclobenzaprine + zolpidem. Zolpidem was the SH in each of the top 5 most frequent combinations; while oxycodone, hydrocodone, or tramadol was the opioid, and cyclobenzaprine or tizanidine was the MR. Combinations with fentanyl, methadone, and buprenorphine were filled by few patients.

8.0 SUMMARY AND RECOMMENDATIONS

Opioids are a heterogeneous class of compounds used primarily for the management of moderate-to-severe, acute or chronic pain;[1,2] some are also indicated to treat cough (eg, codeine- or hydrocodone-containing products), diarrhea (ie, opium tincture), or opioid use disorder.[18,27,87,90,97] Opioids can contribute to respiratory depression (RD) through various mechanisms, for example by acting in the central respiratory control center and/or inducing dose-dependent central sleep apnea (CSA).[3-5,92] Opioid-related mortality is predominantly attributed to overdoses (ODs) resulting from RD.[6] In recent years, opioid-related mortality cases often involved misuse of illicit opioids (eg, fentanyl), and much less often, prescription opioid use.[9] Thus, the 2023 American Society of Interventional Pain Physicians (ASIPP) chronic pain guideline emphasized that "….the illicit opioid epidemic is not a prescription drug epidemic" (page S35).[6]

Owing to the risk of misuse and death from opioids in general (including illicit/diverted use), many policies have been implemented over the past 10-15 years to promote their judicious and safe use. In 2016, the US Food and Drug Administration (FDA) required opioid analgesics and cough products to carry a black box warning (BBW) highlighting the risk of RD and death when opioids are taken in combination with benzodiazepines (BZDs) or other central nervous system (CNS) depressants, such as (skeletal) muscle relaxants (MRs) or sedative-hypnotics (SHs). Despite nearly all evidence reviewed by the FDA about the risks of concurrent opioid use with CNS depressants being limited to opioid *analgesics* with BZDs, the FDA extended the BBW to include opioid *cough* products and any CNS depressant due to their similar pharmacologic characteristics.[11]

Non-opioid CNS depressants may cause or contribute to RD by directly depressing the central respiratory drive and/or affecting other aspects of respiration, such as the respiratory muscles.[3] Due to differences in respiration during sleep versus wakefulness, hypnotics may also indirectly impair respiration by inducing changes in sleep architecture.[66] In addition to warning of the increased risk of RD and death when used concomitantly with a CNS depressant in general (the BBW), opioid prescribing information declares that opioids can potentially compound the neuromuscular effects of MRs, possibly increasing the magnitude of RD.[92,94] While respiratory changes induced by a non-opioid CNS depressant might not lead to clinically significant impairment in a healthy individual, the changes could become significant in a patient who is taking another CNS depressant such as an opioid and/or in patients with a predisposing comorbidity (eg, obstructive sleep apnea [OSA]).[67] While the increased risk of RD associated with concurrent use of opioids and BZDs is often emphasized, less attention has been given to the concurrent use of opioids with other CNS depressants.

To support the safe use of prescription opioids in the Utah Medicaid Fee-for-Service (FFS) population, this report aimed to review evidence about the risks of RD from the concomitant use of opioids with non-BZD and non-barbiturate MRs and/or SHs, as well as to examine the most recent 12 months of data on the combined use of these agents among the Utah Medicaid FFS population. The reviewed MRs encompass 9 unique active ingredients with heterogeneous pharmacological profiles, most of which are FDA-approved for acute (eg, 2-3 week) treatment of musculoskeletal-associated spasms/pain.[35-38,41] Exceptions that are approved for treatment of spasticity rather than spasms include baclofen,

dantrolene, and tizanidine.[14,39,40] Reviewed SHs comprise 9 unique active ingredients, classified into 4 drug sub-classes:

1. non-BZD benzodiazepine receptor agonists (NBRAs/Z-drugs; eszopiclone, zaleplon, zolpidem);
2. melatonin receptor agonists (MRAs; ramelteon, tasimelteon);
3. orexin receptor antagonists (ORAs; daridorexant, lemborexant, suvorexant); and
4. histamine receptor antagonist and tricyclic antidepressant (TCA), doxepin.

Except for tasimelteon, all reviewed SHs are FDA-indicated for treating sleep onset and/or sleep maintenance insomnia.[52-60] Based on FDA safety communications, prescribing information for individual MRs and class-representative SHs, and drug interaction results from Lexidrug, **all MRs and SHs can be considered CNS depressants with the potential to increase opioid-related safety risks**.[11,14,15,35-41,68-71]

While FDA safety guidance and reviewed pain-focused guidelines tend to treat non-BZD MR and SH agents uniformly regarding the risks associated with concurrent opioid use,[6,11,17,30,112,114] these agents have heterogeneous properties; therefore, we infer that the magnitude of interaction with opioids could vary by drug class or even by agent. On a class level, observational studies including a mixed population with and without diagnosed substance use disorder (SUD) support an association between opioid OD and concurrent use of an opioid with a non-BZD MR or SH.[7] However, comparative empirical evidence of individual agents or sub-classes of SHs being associated with OD and/or RD when used with an opioid seems limited, precluding firm conclusions about differences in the relative magnitude of risks. At least one observational study is available that assessed active ingredient-specific risks rather than grouping all agents together indiscriminately. This study found some combinations of MRs with opioids were associated with increased risk (ie, carisoprodol or baclofen) and some combinations associated with neutral risk (eg, cyclobenzaprine or tizanidine).[111] The study authors suggested that the comparatively less risky MRs agents could be preferable if concurrent use of an MR and opioid is necessary.[111]

Based on a non-systematic search for expert opinion reviews, observational evidence, and prescribing information, the following MRs or SHs *might* carry a comparatively increased risk of RD when used with an opioid relative to other options:

- *NBRAs, especially zolpidem*: All NBRAs modulate $GABA_A$ receptors, which could theoretically impair respiratory drive.[3] After adjustment for other risk factors, an observational study showed an increased risk of OD among patients who used zolpidem with an opioid.[70] Unlike other reviewed MRs and SHs, including the other NBRAs eszopiclone and zaleplon,[72,73] zolpidem carries a specific warning for RD, advising that RD has been observed in patients who used zolpidem, especially among people with pre-existing respiratory impairment.[70] Additionally, zolpidem prescribing information indicates concurrent use with opioids may increase the risk of RD.[70]
- *MRs carisoprodol and baclofen*: Carisoprodol and its metabolite (meprobamate) bind to $GABA_A$ receptors, which could theoretically impair respiratory drive.[5,48] Baclofen, a GABA analog, potentially acts on $GABA_B$ receptors.[49] An observational study demonstrated a significant association between opioid OD and concurrent use of an opioid with carisoprodol or baclofen.[111]

Prescribing information for opioid analgesics and recent pain-focused guidelines generally offer similar guidance about the concurrent use of an opioid and CNS depressant; neither source provided specific guidance on the concurrent use of an opioid with non-BZD MRs or SHs.[6,17,30,94,96,112,114] Guidelines and prescribing information discourage the simultaneous use of opioids and CNS depressants,

recommending it only when the potential benefits outweigh the risks (guidelines)[6,17,30] or "…for use in a patient for whom alternative options are inadequate" (opioid analgesic prescribing information).[94,96] Opioid analgesics and opioid cough products carry similar warnings about concurrent use with CNS depressants, though cough product prescribing information specifically recommends avoiding such combinations.[27,90] To mitigate risks associated with the concurrent use of CNS depressants and opioid analgesics, opioid prescribing information advises: (1) using the lowest effective dose for the shortest duration necessary, (2) educating patients about the risk of and monitoring for RD/sedation, and (3) considering naloxone.[87-89,91-96] Pain-focused guidelines also advise considering dose reductions when adding the second agent,[6] considering more frequent follow-up,[17,30] offering naloxone,[17] and involving pharmacists in patient care.[17] Notably, while naloxone can reverse opioid-induced RD, it does not reverse RD caused by non-opioid agents. [4]

Reviewed general pain-focused guidelines recognize concurrent use of opioids with CNS depressants as one of many risk factors for opioid-related RD or OD.[6,17,30] Additional opioid-related factors associated with a potentially higher risk of RD or OD include the use of methadone or long-acting (LA) opioids and higher opioid doses.[6,17,30] The 2022 Department of Veteran's Affairs/Department of Defense (VA/DoD) guideline weakly prefers buprenorphine (a partial opioid agonist) over full opioid agonists for patients with chronic pain requiring a daily opioid because it is considered to carry a lower risk of RD, although RD may still occur when used in combination with a CNS depressant.[30]

A 2023 systematic review and meta-analysis (SRMA) of observational studies by Wang et al among patients with chronic pain identified the following characteristics as having a large association with opioid OD, based on moderate-to-high-certainty evidence: (1) prior opioid OD, (2) having ≥3 opioid prescribers or ≥4 pharmacies, (3) having a fentanyl prescription, (4) using higher opioid doses, or (5) having a comorbidity of active SUD, any mental health condition, depression, bipolar disorder, or pancreatitis.[7] Concurrent use of an SH or MR with an opioid was also associated with an increased risk of opioid OD, but the magnitude of this association was smaller than for the aforementioned factors. The estimated absolute risk per 1,000 people for the factors with a large association ranged from 4 to 12 for non-fatal OD and 2 to 6 for fatal OD in a mix of patients with and without SUD. However, the absolute risk of OD per 1,000 people associated with SH or MR overlapping use was lower, ranging between 2.6 and 2.7 per 1,000 (non-fatal OD) and between 1.3 and 1.4 per 1,000 (fatal OD). The reference background absolute risk in the general population was estimated as 2 per 1,000 for non-fatal OD and 1 per 1,000 for fatal OD.[7]

We performed a cross-sectional descriptive analysis to identify the number of Utah Medicaid FFS patients who filled outpatient prescriptions with at least 1 overlapping days' supply of an opioid (except for buprenorphine formulations for opioid use disorder [OUD]) with a non-BZD/non-barbiturate MR and/or SH within the past-year (April 1, 2023 to March 31, 2024; the study period). Additionally, we calculated the percentage of overlapping days (POD) of (1) opioid + MR, (2) opioid + SH, and (3) opioid + MR + SH, out of (a) the total number of days' supply of an opioid, as well as (b) the total number of days with Utah Medicaid coverage. The following summarizes findings from our descriptive analysis:

- Among the overall cohort of patients who filled an opioid, MR or SH (n=15,888; with or without overlap), the median age was 40 years old (25th – 75th percentile, 30 – 51 years). Nearly all patients (≥99%) with overlapping prescriptions of opioid + MR and/or + SH were aged 18 or older. The

median duration of Medicaid eligibility in the overall cohort was 366 days (25th – 75th percentile, 284 – 366 days).

- The number of patients with an overlapping days' supply of an opioid + MR and/or + SH during the study period was as follows:
  - **Opioid + MR (n=1,835),** representing 17.6% of unique patients who filled an opioid during the study period (overlapping and non-overlapping; the opioid cohort), and 29% of unique patients who filled an MR during the study period (overlapping and non-overlapping; the MR cohort).
  - **Opioid + SH (n=461),** representing 4.4% of the opioid cohort and 19.3% of all patients who filled an SH during the study period (overlapping and non-overlapping; the SH cohort).
  - **Opioid + MR + SH (n=144)**, representing 1.4% of the opioid cohort, 2.3% of the MR cohort, and 6.0% of the SH cohort.
- The median POD out of total days with an opioid among each subgroup of patients with overlapping prescriptions, ranging between 52.1% (for opioid + MR + SH) and 95.8% (for opioid + SH), was higher than the median POD out of total days with Utah Medicaid coverage (ranging 4.4% to 7.3% across overlap subgroups). While this suggests that the durations of opioid therapy and MR/SH therapy were often of similar length (ie, pain and insomnia co-morbidities occurring at the same time), it may also suggest that on average, patients tended to fill these medications concurrently for shorter durations than the length of Medicaid eligibility. The median (25th – 75th percentile) total number of overlapping days of medication supplied for the opioid + MR, opioid + SH, and opioid + MR + SH subgroups was 13 (5 – 47), 17 (6 – 56), and 24 (7 – 78.5), respectively.
- We also assessed the active ingredients of overlapping combinations with the highest patient frequency. The most frequent opioid + MR combination, by patient count, was oxycodone + cyclobenzaprine, filled by 24.4% of patients in the opioid + MR subgroup. Among patients in the opioid + SH subgroup and opioid + MR + SH subgroup, the most frequent combinations, by patient count, were oxycodone + zolpidem (filled by 34.9% of patients with overlap) and oxycodone + cyclobenzaprine + zolpidem (filled by 15.3% of patients with overlap), respectively.

Limitations of our descriptive analysis should be considered when interpreting the results. Concurrent use of opioids with MRs and/or SHs was inferred based on prescriptions filled, the days' supply of those prescriptions, and the prescription fill dates, which may not accurately reflect actual patient usage. Additionally, we did not consider details about the formulations of opioids, SHs and MRs (eg, use of LA products), which might confer greater risks when used in combination. Moreover, overestimation of days' supply can occur for patients who are on a chronic pain regimen involving an ER and IR medication of the same molecule. While we excluded buprenorphine products FDA-indicated for OUD, we did not consider the indications for use of any of the included products (eg, administrative diagnosis codes such as for cancer or hospice care, etc.).

8.1 Considerations for Policies and/or Other Programs

Currently, Utah Medicaid policy for pharmacy-dispensed prescriptions specific to concurrent use of opioids with a CNS depressant is that use of a benzodiazepine with a long-acting (LA) opioid within 45 days of each other requires prior authorization (PA). To receive this combination, providers must provide a clinical rationale and supportive diagnoses for use of the opioid + BZD, or otherwise describe that one or the other will not be continued, as the dispensing point-of-service edit may be unable to discriminate switches/substitutions of therapy. The PA form for the use of the opioid + BZD combination also addresses other aspects of opioid therapy, requiring providers to attest to various practices, such as discussion with the patient of potential harms of combining an opioid with a CNS depressant, or giving the patient education on and a prescription for naloxone, if appropriate.[115]

If it is desired to query concomitant use of opioids with non-benzodiazepine and non-barbiturate MRs and SHs[***] in the Utah Medicaid population, implementing one or more of the options below can be considered. Considering the heterogeneity of the overall risk profile of patients who receive these combinations, we suggest prioritizing retrospective drug utilization review (retroDUR) or educational interventions rather than stricter and more unilateral approaches/restrictions. For any policy or interventions, implementation feasibility should be considered, given the frequency of use of these medications along with the potential high frequency of legitimate co-morbidities. RetroDUR (and PA) criteria could be reserved for patients not in hospice or palliative care.

May consider performing educational outreach and/or retroDUR to providers of patients with ongoing fills of concurrent prescriptions for an opioid with an MR and/or SH, particularly for subgroups of patients that *may* be at greater risk. The intention of the outreach is not to deny access to necessary medications for legitimate comorbidities, but rather to bring attention to certain aspects in case the provider is unaware or if the patient is in a position to modify therapy.

Outreach (eg, by phone or fax) could discuss the risks from concurrent use and encourage use of alternative medications or non-pharmacologic treatments, as appropriate/feasible. If concurrent use is necessary, using the lowest effective dose for the shortest duration possible, monitoring at an increased frequency, and/or prescribing naloxone could be encouraged.

1. Interventions may consider targeting prescribers to patients in one or more of the following subpopulations that are likely at higher risk for opioid-induced RD:
    a. May consider initially targeting prescribers to patients filling an opioid, MR, and SH concurrently (ie, patients taking multiple [3+] different CNS depressants).
        i. Evidence suggests that opioid-related risks increase as the number of risk factors for RD increases.[105,107,108] A retrospective cohort study among Washington Medicaid patients found

[***] MRs addressed by this report included baclofen, carisoprodol, chlorzoxazone, cyclobenzaprine, dantrolene, metaxalone, methocarbamol, orphenadrine, and tizanidine. As of May 2024, cyclobenzaprine, methocarbamol, orphenadrine, baclofen, and tizanidine are preferred options on the Utah Medicaid Preferred Drug List (PDL). SHs addressed by this report included the non-BZD benzodiazepine receptor agonists (eszopiclone, zaleplon, zolpidem); melatonin receptor agonists (ramelteon, tasimelteon); orexin receptor antagonists (daridorexant, lemborexant, suvorexant); and doxepin 3 mg or 6 mg tablets (Silenor). Of these agents, PDL-preferred options as of May 2024 include eszopiclone, zaleplon, zolpidem, and ramelteon.

the point estimate for opioid-related death with concurrent use of opioids with MRs + SHs (including barbiturate and non-barbiturate hypnotics) with opioids (adjusted HR [aHR] 3.9, 95%CI 1.4 to 10.7) was higher than from concurrent use of opioids with SRs alone (aHR 2.8, 95%CI 1.8 to 4.2).[116]

b. Prescribers with patients filling prescriptions for an opioid + MR and/or + SH from ≥ 3 different prescribers or ≥ 4 different pharmacies.
   i. Evidence of moderate certainty suggests use of multiple pharmacies or multiple opioid prescribers are risk factors with a large association with opioid OD (adjusted OR > 4).[7]

c. Prescribers with patients with a history of opioid OD who continue to fill an opioid with MR, SH, and/or benzodiazepine.
   i. History of opioid OD is one of the largest individual risk factors for opioid OD (adjusted OR 5.85, 95%CI 3.78-9.04; high-certainty evidence).[7] Patients with a possible OD could be identified by submitted ICD-10 diagnosis codes for opioid poisoning (eg, T40.0X, T40.1X, T40.2X, T40.3X, T40.4X, T40.601-T40.604, T40.691-T40.694[†††]).[117,118]

d. Prescribers with patients filling ≥ 90 MME of opioid with higher dosages of zolpidem (eg, zolpidem ER 12.5 mg, or zolpidem IR 7.5 mg or 10 mg[58]).
   i. Higher opioid doses, especially those exceeding 90 MME, increase the risk of opioid OD.[7]

e. Prescribers with patients filling an opioid + MR and/or + SH prescription who have a diagnosis for sleep apnea, COPD, or other respiratory compromising diagnoses.
   i. While there are many comorbidities that increase the risk of opioid-induced RD and/or OD,[7] opioid prescribing information emphasizes patients with compromised respiratory function as being at higher risk for life-threatening RD.[27,89-91,94,96]

f. Prescribers with patients filling the higher doses of zolpidem (eg, zolpidem ER 12.5 mg or zolpidem IR 7.5 mg or 10 mg[58]) with an opioid, since patients may not have tried the lower dose or an alternative SH.
   i. Since some evidence suggests that LA opioids carry a higher risk of OD than short-acting opioids,[7] may consider targeting the combination of a LA opioid plus high-dose zolpidem to consider changes to the SH therapy.

If additional PA is desired, may consider one or more of the additions below to the opioid PA. However, caveats to the PA should be considered. For example, consider that if a broad PA is implemented (ie, for all patients with any concomitant use of opioid + MR and/or SH), this might create a barrier to care if the administrative burden becomes unfeasible for provider offices. PA criteria should also be implemented cautiously to ensure patients are not denied necessary treatment when the benefits are considered to outweigh the risks. Accommodations should be made for patients who need continued access to co-prescribed medications during tapered discontinuations of long-term therapy.

[†††] Includes opioid poisoning diagnosis codes for any opioid, including heroin (T40.1X), and all attributable causes (eg accidental, intentional, etc.). Refer to cited sources or other sources for details.

1. In addition to benzodiazepines, request that providers provide a clinical rationale for concurrent use of an opioid with MR or SH.
    a. Like BZDs, concurrent use of a non-BZD MR or SH with an opioid has been shown to increase the risk of opioid OD[7]; however, the evidence has often grouped all non-BZD MRs or SHs together, even though the risk may vary among agents within the class. While opioid prescribing information and pain-focused guidelines advise avoiding this combination, **if possible**, among patients with pain, they also acknowledge that co-morbidities such as insomnia should be treated if the benefits outweigh the risks.[6,17,30,94,96]
    b. Given that there may be situations where the potential benefits outweigh the risks from co-treatment, a PA form could have prescribers attest that the patient has tried and failed or is not a candidate for/does not have access to non-pharmacologic treatments for comorbid insomnia (eg, cognitive behavioral therapy), or that the patient has active muscle spasms or spasticity for the use of co-prescribed MRs. Using the lowest effective doses for the shortest duration necessary and increased patient monitoring frequency should be encouraged.
    c. PA criteria could also be tailored to target a particular type of opioid, MR and/or SH combination. For example, criteria could discourage initiating LA opioids when an MR or SH is necessary, or criteria could discourage combining an opioid with potentially/theoretically higher risk agents (baclofen, carisoprodol, or zolpidem). Some evidence suggests that LA/ER opioids carry a higher risk of RD or OD than SA opioids, or that certain MRs or SHs may be more problematic in combination with opioids than others.[7,17,30,104,111]
        i. Alternatively, retroDUR interventions could be designed to target/alert prescribers of combinations that potentially may be more risky (see example suggestions above).

May consider performing additional data analyses regarding the Utah Medicaid population of interest or gathering more medical literature information (ie, observational studies) about the risks of concurrent opioid use with CNS depressants.

1. For feasibility, this report did not systematically search for all empirical evidence (eg, observational studies) regarding the risks of using opioids with MRs and/or SHs; though, a recent systematic review was included. Nor did this report address other considerations for use of these agents together. The queried subgroups of Medicaid patients with opioid + MR and/or SH overlap could yield additional descriptive data. For instance, the diagnoses of patients with overlap could be explored/described, or more detail could be gleaned about the medications within combinations used (eg, LA or SA formulations, MME of opioids used, strength, etc.) or outcomes (eg, overdose). While such information may not be required to make policy changes, future reviews could address these concerns if additional detail is desired.

2. Risks from concurrent opioid use with gabapentinoids (ie, gabapentin or pregabalin) was not addressed by this report. Yet, in 2019 the FDA required labeling changes to gabapentinoids to reflect the possible risk of RD when used with opioids.[86] Along with BZDs, some pain guidelines also mentioned gabapentinoids as agents that increase the risk of RD when used with opioids.[6,17] While it may not be advisable to add a restriction to these agents, future educational interventions could address this risk.

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APPENDIX A – INCLUDED OPIOIDS AND CNS DEPRESSANTS

Table A1. Active Ingredients of Included Prescription Opioid, Muscle Relaxant, and Sedative-hypnotic Products

Medication Class	Active Ingredient(s)[a]
Opioids	*Mono-ingredient or combination products including one or more of the following agents:* Codeine, dihydrocodeine, alfentanil, benzhydrocodone, buprenorphine (all products except those for OUD – see below), butorphanol, fentanyl, hydrocodone, hydromorphone, levorphanol, meperidine, methadone, morphine, nalbuphine, oliceridine, opium, oxycodone, oxymorphone, pentazocine, remifentanil, sufentanil, tapentadol, tramadol The following buprenorphine products indicated for OUD were excluded[b]: • All buprenorphine-naloxone combination products • Buprenorphine products with one of the following GPI-14 codes: ○ 65200010100760, 65200010100780, 65200010102320, 6520001000E515, 6520001000E518, 6520001000E520, 6520001000E523, 6520001000E530, 6520001000E560, 6520001000E565, 6520001000E570, 6520001000E575
Non-benzodiazepine muscle relaxants	*Mono-ingredient or combination products including one or more of the following agents:* Baclofen, carisoprodol, chlorzoxazone, cyclobenzaprine, dantrolene, metaxalone, methocarbamol, orphenadrine, tizanidine
Non-benzodiazepine and non-barbiturate sedative-hypnotics	Eszopiclone, zaleplon, zolpidem, ramelteon, doxepin (3 mg or 6 mg tablet only), daridorexant, lemborexant, suvorexant, tasimelteon[c]

Abbreviations: FDA, United States Food and Drug Administration; GPI-14, 14-digit Generic Product Identifier; MR, muscle relaxant; OUD, opioid use disorder; SH, sedative-hypnotic

[a] For our cross-sectional descriptive analysis and review of guidelines and prescribing information, we considered any products that contained one of these active ingredients, including mono-ingredient or combination products.

[b] Buprenorphine products that are FDA-indicated for pain were included, which are the buprenorphine buccal film (Belbuca), buprenorphine transdermal patch (Butrans, generic), and buprenorphine immediate-release injection (Buprenex, generic).[22]

[c] Tasimelteon is in the hypnotics class, although unlike other sedative-hypnotics, it is FDA-indicated for non-insomnia sleep disorders including Smith-Magenis syndrome and non-24-hour sleep-wake disorder.[56]

APPENDIX B – SPECIFIC MUSCLE RELAXANTS OR SEDATIVE-HYPNOTICS INCLUDED IN OBSERVATIONAL STUDIES USED BY WANG ET AL (2023)

Table B1. Medications Included in the Muscle Relaxant and Sedative-hypnotic Categories, by Cohort or Case-control Study Included in Pooled Estimates for Opioid Overdose by Wang et al (2023)

Primary study	Adjusted OR (95% CI) of opioid overdose by medication type[7]		Included MR/SH agents, per the primary study
	MRs	SHs	
Salkar 2021[110]	4.02 (1.35 to 11.99)	4.32 (1.24 to 15.04)	Included "…sedative-hypnotics (non-benzodiazepine receptor agonists, short-acting benzodiazepine receptor agonists, intermediate-acting benzodiazepine receptor agonists, intermediate-acting benzodiazepine receptor agonists, and selective melatonin agonists), benzodiazepine, muscle relaxants…" (page 369)
Li 2020[111]	1.21 (0.99 to 1.47)	NA	MRs included: baclofen, carisoprodol, chlorzoxazone, cyclobenzaprine, metaxalone, methocarbamol, orphenadrine, tizanidine[109]
Hayes 2020[119]	1.25 (0.90 to 1.73)	1.33 (0.91 to 1.95)	Included "…benzodiazepines, skeletal muscle relaxants…hypnotics/other non-benzodiazepine sedatives" (page 5)
Nadpara 2018[120]	1.40 (1.28 to 1.53)	1.34 (1.22 to 1.48)	Authors did not report which medications were included in each category. Categories of non-opioid drugs of interest included benzodiazepines, muscle relaxants, and other sedatives (which was separate from categories antidepressants, and antipsychotics)
Kaplovitch 2015[121]	NA	1.01 (0.31 to 3.30)	Authors did not report which medications were included in each category. Benzodiazepine usage and "other psychotropic drugs and CNS depressants" were separate from past medication use categories, which were separate from categories for SSRIs/SNRIs, other antidepressants, and antipsychotics.
Turner 2015[104]	NA	1.54 (1.29 to 1.85)	"…we summed days' supply for antidepressants (i.e., SSRIs, SNRIs and tricyclics), benzodiazepines, and zolpidem" (page 1082); because Wang et al included a separate category for benzodiazepines,[7] the SH category here is likely for zolpidem only.
Zedler 2014[122]	1.10 (0.88 to 1.37)	1.10 (0.80 to 1.51)	Authors did not report which medications were included in each category. Categories of non-opioid drugs of interest included benzodiazepines, muscle relaxants, and other sedatives (which was separate from categories from antidepressants and antipsychotics)

Abbreviations: CI, confidence interval; CNS, central nervous system; MR, muscle relaxant; NA, not applicable (data was not included in the pooled estimate by Wang et al); OR, odds ratio; SH, sedative-hypnotic; SNRI, selective norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor

APPENDIX C – INFORMATION ABOUT CONCOMITTANT USE OF OPIOIDS AND CNS DEPRESSANTS AND RESPIRATORY DEPRESSION FROM RECENT PAIN GUIDELINES

Table C1. Select Recent Pain or Opioid-prescribing Guideline Recommendations on the Risks of Concomitant Use of Opioids and CNS Depressants, and Risk Factors and Risk Mitigation Strategies for Respiratory Depression

Information/Guidance on concomitant use of opioids and CNS depressants (Strength/LOE, if applicable)	**Opioid prescribing and/or safety guidance, with a focus on managing the risk of sedation and/or respiratory depression (Strength/LOE, if applicable)**
American Society of Interventional Pain Physicians (ASIPP), 2023 *Focus: Prescribing opioids for chronic non-cancer pain*	
• **Other than BZDs and gabapentinoids, the guideline is not specific as to which CNS depressants have demonstrated an increased risk of RD when used with opioids** • Studies of long-term opioid therapy have included patients also taking muscle relaxants • CNS depressants, including BZDs, **hypnotics, or sedatives,** may exacerbate opioid-related sleep problems, including CSA or OSA • Serious risks of long-term opioid use increase with higher doses, and "…the combination of opioids with benzodiazepines and other drugs" (page S80) • Inhibition of opioid metabolism by another medication increases the risk for OD	• RD is one of several risks of long-term opioid use • No tools for assessing RD risk specifically were directly provided (only tools for identifying people at risk for OUD) • Little guidance on use of naloxone; "All prescribers of opioids for pain management should expand the use of naloxone to prevent overdoses" (page S65) • Patients should be informed about the risks (eg, sedation, RD) of taking opioids with sedating drugs • General guidance on good practices for safe and appropriate use of opioids (not comprehensive): ○ Initiate opioids at a low dose, preferably with a short-acting opioid (moderate LOE; moderate to strong) ○ Reserve methadone for pain resistant to other opioids (strong LOE; strong) ○ Long-acting opioids are associated with more adverse effects compared to short-acting opioids (moderate LOE; moderate) with similar effectiveness; use high doses of long-acting opioids only when necessary (moderate LOE; moderate), and combinations of short- and long-acting opioids should be used cautiously ○ **At opioid initiation, adjust the dose of other CNS depressants, if possible** ○ OD deaths may be reduced by using abuse-deterrent opioid formulations • Safety considerations for certain populations/at-risk groups: ○ Patient characteristics associated with requiring naloxone when receiving opioids and gabapentinoids: older age (≥ 65 years), female sex, receipt of patient-controlled analgesia, receipt of orthopedic surgery, and presence of a predisposing? comorbidity (diabetes; pulmonary, kidney, or liver disease). ○ People with CHF, OSA, CSA, older age, and/or obesity are at increased risk for opioid-associated sedation ○ If possible, avoid chronic opioids in patients with severe OSA or people at high risk for sedation ○ Extra caution should be used in older adults due to poor organ function and risks from polypharmacy. ○ People with a history of nonfatal opioid OD: consider discontinuing opioids, or reducing the total dose ○ Patients who recently stopped naltrexone have reduced opioid tolerance and are at increased risk of an OD
Centers for Disease Control and Prevention (CDC), 2022 *Focus: Prescribing opioids to adults (≥ 18 years) for acute, subacute, or chronic pain (except pain due to SCD or cancer, for palliative/hospice care, or for OUD)*	
• **Exercise caution when using opioids with BZDs and consider the risks versus benefits of using opioids with CNS depressants** (3B) due to the risk of potentiating RD (although other than for gabapentinoids and BZDs, empirical evidence demonstrating an increased risk of OD/RD is not cited).	• Clinicians should follow general good prescribing practices for opioids, *such as* maximizing use of non-opioid medications for acute (3B) and chronic pain (2A) and limiting use of opioids to situations where the anticipated benefits likely outweighs the risks; initiate opioid therapy with IR not ER/LA opioids (4A); and use the lowest effective opioid dosage (3A) ○ Before starting and periodically during opioid therapy, providers should check the PDMP to identify whether the patient is receiving additional opioids or other medications that increase the risk of an OD (4B) ○ Providers may consider toxicology testing to monitor for use of medications/non-prescription products that may increase risks from opioids (4B); results can be used to weigh the risks versus benefits of the opioid therapy at the current dose, to provide education and/or naloxone, and to inform the reevaluation frequency.

Abbreviations: ASIPP, American Society of Interventional Pain Physicians; BZD, benzodiazepine; CDC, Centers for Disease Control and Prevention; CHF, congestive heart failure; CNS, central nervous system; CSA, central sleep apnea; DoD, Department of Defense; ER, extended release; LOE, level of evidence; MME, milligrams of morphine equivalents; OD, overdose; OSA, obstructive sleep apnea; OUD, opioid use disorder; PDMP, Prescription Drug Monitoring Program; RD, respiratory depression; SCD, sickle cell disease; SUD, substance use disorder; TBI, X; VA, Veterans Affairs

*ASIPP LOE for formal recommendations: **Evidence type,** moderate=there are minor and/or limited study quality concerns; strong=there are minor or no study quality concerns; **Recommendation strength,** weak to moderate=use shared decision making, there is a consensus that certain patients could benefit; moderate to strong=moderate certainty of a moderate to large patient benefit; strong=high certainty of a large patient benefit.*

*CDC LOE for formal recommendations: **Evidence type,** 2= RCTs with limitations or very strong observational evidence; 3=observational evidence or RCT evidence with large limitations; 4=clinical experience, or other evidence (observational or RCT) with significant limitations; **Evidence category**, A=most patients should receive the recommendation; B= individualized decision-making for each patient's scenario and preferences (ie, some, but not all patients should receive the recommendation).*

VA/DoD LOE for formal recommendations: Strong vs weak recommendations indicates the overall level of confidence that the benefits outweigh the risks, which was informed by the quality of the evidence and the magnitude of differences between the possible harms vs benefits, patient preferences, or other considerations.

Table C1. Select Recent Pain or Opioid-prescribing Guideline Recommendations on the Risks of Concomitant Use of Opioids and CNS Depressants, and Risk Factors and Risk Mitigation Strategies for Respiratory Depression

Information/Guidance on <u>concomitant use</u> of opioids and CNS depressants (Strength/LOE, if applicable)	**Opioid prescribing and/or safety guidance, with a focus on <u>managing the risk of sedation and/or respiratory depression</u> (Strength/LOE, if applicable)**
○ **Examples of CNS depressants include muscle relaxants, non-BZD sedative-hypnotics, and sedating anticonvulsants (eg, gabapentinoids).** ○ Observational evidence is cited that demonstrated increased risk of OD when using opioids + BZDs, and opioids + gabapentinoids (especially at higher doses) ○ Do not withhold opioids for OUD (ie, methadone, buprenorphine) for concurrent use with CNS depressants ○ Some clinical scenarios may require prescribing opioids with BZDs. Scenarios of greater risk from use of BZDs + opioids include "…unpredictable use of either medication, with use of higher-dosage opioids and higher-dosage benzodiazepines in combination, or with use of other substances including alcohol…" (page 53) • It may be necessary to taper the opioid or other sedating medication to reduce the risk of RD (the specific example given is for use of BZDs) • Involvement of pharmacists may be helpful when managing patients receiving opioids + CNS depressants	○ Before starting opioid therapy, provide education to patients on opioid-related risks, including the risk of mortality from RD and increased risk of RD when opioids are used with BZDs, sedatives, alcohol, illicit drugs, and other opioids. • Before and during opioid use, clinicians should assess each patient's risk for harms and develop plans to mitigate risks, including offering naloxone to patients at increased risk of an overdose (4A). It is emphasized that the recommendation is to *offer naloxone, not to require it.* More frequent evaluation of the risks versus benefits is advised in patients with a risk factor. ○ *Overdose risk factors include:* prior overdose, patients with a history of SUD or sleep-disordered breathing, use of BZDs, patients using higher opioid doses (≥ 50 MME/day), or patients at risk for exposure to a previously higher tolerated opioid dose after loss of tolerance ○ Listed factors that increase the risk for harms and may be considered as factor for tapering to a reduced opioid dosage or discontinuation of opioid therapy (if benefits do not outweigh the risks) include concomitant use with benzodiazepines, risk for falls, certain comorbidities (eg, sleep apnea, liver or kidney disease). ○ Provide education about the OD risks to patients with SUD and patients with a prior non-fatal opioid OD, and take steps to mitigate risks, including offering naloxone. ○ To mitigate the risk of RD, avoid prescribing opioids to patients with moderate-severe sleep-disordered breathing (eg, sleep apnea) ○ Risk of an opioid OD tends to increase as the total opioid dose increases; there is not an established dose threshold below which there is no OD risk. It is advised to initiate or increase the dose of opioids using the lowest effective dose, and to continuously evaluate the risks versus benefits to avoid increases in the dose without a corresponding increase in benefit (3A). ○ When reducing the dose after long-term opioid therapy, providers should educate patients about diminished tolerance and the increased risk of OD with higher opioid doses, and offer naloxone. ○ Patients with mental health disorders may have an increased risk of an opioid OD • "Unless there are indications of a life-threatening issues such as warning signs of impeding overdose (e.g., confusion, sedation, slurred speech), opioid therapy should not be discontinued abruptly, and clinicians should not rapidly reduce opioid dosages from higher dosages" (4B) • "Methadone has been associated with disproportionate numbers of overdose deaths relative to the frequency with which it is prescribed for pain" (page 29). For methadone, the "…peak respiratory depressant effect occurs later and last longer than peak analgesic effect" • Enhanced vigilance and monitoring are advised when prescribing opioids to older adults (≥ 65 years) and patients with liver or renal impairment.
Department of Veterans Affairs (VA)/Department of Defense (DoD), 2022 *Focus: Primarily, prescribing opioids to adults with chronic pain (acute pain is briefly addressed)*	
• Advises treating/referring patients with chronic pain and insomnia or sleep disorders as needed, although use of medications to treat insomnia is not specifically addressed • **Use of opioids and BZDs is not recommended (strong); no formal recommendations were provided about use of opioids with other medications** • Guideline was informed by a literature search that included searching for "Prescribed opioids plus mediations with CNS effects (prescribed and over the counter)" (page 73), which included muscle relaxants,	• Provided guidance on safer opioid prescribing in general, *such as (not comprehensive)*: optimizing non-opioid pain treatments; initiating opioids only if the potential benefits outweigh the risk (risk assessment includes checking for contraindications, evidence of OUD, using a risk screening tool) – recommended against opioids for chronic non-cancer pain in general (strong); educating the patient about risks and naloxone rescue; using the lowest effective dose; and continuing opioid agonist therapy if the patient does not have evidence of harms (eg, OUD, self-injurious behaviors, opioid diversion) or risk factors for harm and the patient is benefiting from treatment (eg, evidence of improved pain and/or function). The VA/DoD recommends against (strong) long-acting opioids for (1) acute pain, (2) as-needed use, and (3) at the start of long-term opioid therapy, due to the risk of OD and death. ○ Listed two screening tools: RIOSORD (Risk Index for Overdose or Serious Opioid-Induced Respiratory Depression), and STORM (Stratification Tool for Opioid Risk Mitigation) (see **Section X** for additional details). Factors which can increase harms from opioids include age, gender, socioeconomic status, opioid? dose, opioid formulation, and combination use with other medications. "We recommend against long-term opioid therapy, particularly for younger age groups, as age is inversely associated with the risk of opioid use disorder and overdose" (strong). ○ Suggested screening for behavioral health conditions and pain catastrophizing for patients with <u>acute pain</u> considering opioid therapy (weak); these patients are at increased risk for OD and other poor outcomes. For patients with chronic pain, screening for behavioral health conditions, history of TBI, pain catastrophizing is recommended (strong), as many of these conditions are associated with an increased risk of OD or other harms.

Abbreviations: ASIPP, American Society of Interventional Pain Physicians; BZD, benzodiazepine; CDC, Centers for Disease Control and Prevention; CHF, congestive heart failure; CNS, central nervous system; CSA, central sleep apnea; DoD, Department of Defense; ER, extended release; LOE, level of evidence; MME, milligrams of morphine equivalents; OD, overdose; OSA, obstructive sleep apnea; OUD, opioid use disorder; PDMP, Prescription Drug Monitoring Program; RD, respiratory depression; SCD, sickle cell disease; SUD, substance use disorder; TBI, X; VA, Veterans Affairs

*<u>ASIPP LOE for formal recommendations:</u> **Evidence type,** moderate=there are minor and/or limited study quality concerns; strong=there are minor or no study quality concerns; **Recommendation strength,** weak to moderate=use shared decision making, there is a consensus that certain patients could benefit; moderate to strong=moderate certainty of a moderate to large patient benefit; strong=high certainty of a large patient benefit.*

*<u>CDC LOE for formal recommendations</u>: **Evidence type,** 2= RCTs with limitations or very strong observational evidence; 3=observational evidence or RCT evidence with large limitations; 4=clinical experience, or other evidence (observational or RCT) with significant limitations; **Evidence category**, A=most patients should receive the recommendation; B= individualized decision-making for each patient's scenario and preferences (ie, some, but not all patients should receive the recommendation).*

<u>VA/DoD LOE for formal recommendations</u>: Strong vs weak recommendations indicates the overall level of confidence that the benefits outweigh the risks, which was informed by the quality of the evidence and the magnitude of differences between the possible harms vs benefits, patient preferences, or other considerations.

Table C1. Select Recent Pain or Opioid-prescribing Guideline Recommendations on the Risks of Concomitant Use of Opioids and CNS Depressants, and Risk Factors and Risk Mitigation Strategies for Respiratory Depression

Information/Guidance on <u>concomitant use</u> of opioids and CNS depressants (Strength/LOE, if applicable)	**Opioid prescribing and/or safety guidance, with a focus on <u>managing the risk of sedation and/or respiratory depression</u> (Strength/LOE, if applicable)**
tricyclic antidepressants like doxepin, and z-drugs for sleep, among other classes/agents	○ Suggested using buprenorphine in place of full opioid agonists among patients requiring daily opioid treatment to reduce the risk of opioid OD (weak) ○ Hydromorphone ER is not indicated for patients who are opioid-naïve due to the risk of RD ○ Prescribing naloxone and education about its use is one of several suggested risk mitigation strategies for patients with increased opioid-related risks (ie, due to non-adherence, comorbidities, OUD) ○ Factors that should be promptly addressed/require change in opioid therapy (eg, switching from full opioid agonist to partial opioid agonist): SUD without treatment, unstable behavioral health condition including suicidal ideation, medical comorbidity affecting opioid safety profile (ie, poor cognitive, cardiopulmonary, renal, or liver disease), acute risk factors for OD (recent OD, sedation, medications like benzodiazepines or alcohol), drug diversion ○ More frequent follow-up is recommended for use of opioids with benzodiazepines or use of higher-dose opioids (absolute cut-off not specified; possibly ≥50 MME; risk of OD is dose-dependent, with increased risk observed with MME totals of 20-<50, 50-<100, and >100 versus 1-19 MME), and patients with SUD or other behavioral health condition, among other factors. Using the lowest effective opioid dose (strong) and for the shortest duration (strong) is advised.

Abbreviations: ASIPP, American Society of Interventional Pain Physicians; BZD, benzodiazepine; CDC, Centers for Disease Control and Prevention; CHF, congestive heart failure; CNS, central nervous system; CSA, central sleep apnea; DoD, Department of Defense; ER, extended release; LOE, level of evidence; MME, milligrams of morphine equivalents; OD, overdose; OSA, obstructive sleep apnea; OUD, opioid use disorder; PDMP, Prescription Drug Monitoring Program; RD, respiratory depression; SCD, sickle cell disease; SUD, substance use disorder; TBI, X; VA, Veterans Affairs

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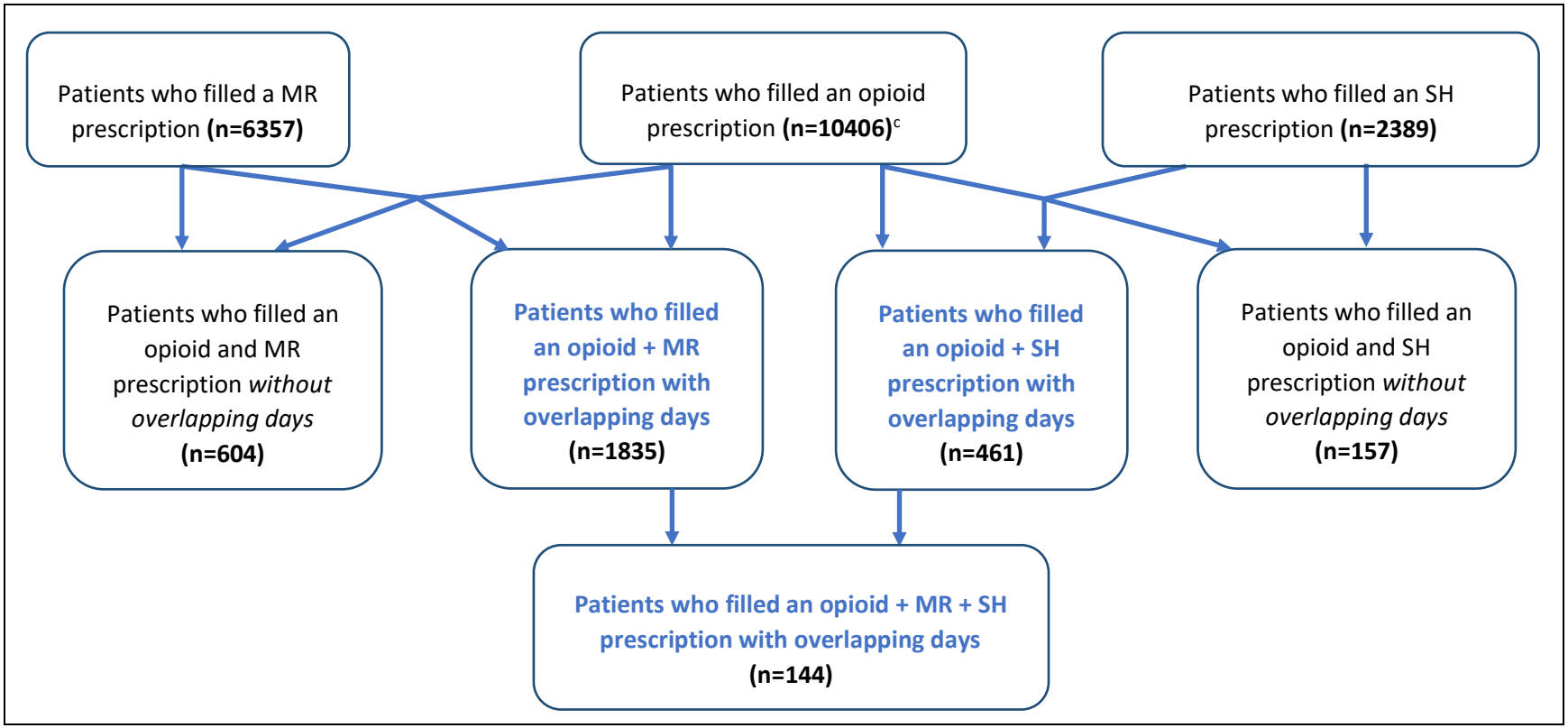
*<u>CDC LOE for formal recommendations</u>: **Evidence type,** 2= RCTs with limitations or very strong observational evidence; 3=observational evidence or RCT evidence with large limitations; 4=clinical experience, or other evidence (observational or RCT) with significant limitations; **Evidence category**, A=most patients should receive the recommendation; B= individualized decision-making for each patient's scenario and preferences (ie, some, but not all patients should receive the recommendation).*

<u>VA/DoD LOE for formal recommendations</u>: Strong vs weak recommendations indicates the overall level of confidence that the benefits outweigh the risks, which was informed by the quality of the evidence and the magnitude of differences between the possible harms vs benefits, patient preferences, or other considerations.

APPENDIX D – UTAH MEDICAID PATIENT COHORT DISPOSITION

Figure D1. Utah Medicaid Patient Cohort Disposition for April 1, 2023 to March 31, 2024[a,b]



Abbreviations: MR, (skeletal) muscle relaxant; SH, sedative-hypnotic

*[a] Based upon outpatient pharmacy prescription claims for an opioid, non-benzodiazepine MR, and non-nonbenzodiazepine and non-barbiturate sedative-hypnotic (see list of included active ingredients in **Appendix A**). Overlapping days was determined from each prescription's days' supply.*

[b] Patients can be included in more than one medication class category.

[c] Of the 10,406 patients who filled an opioid, 7,591 (72.9%) did not fill a prescription for any reviewed MR or SH during the study period.

APPENDIX E – DESCRIPTIVE CHARACTERISTICS OF THE OVERALL COHORT AND BY OVERLAPPING SUBGROUP

Table E1. Age, Sex, and Duration of Medicaid Eligibility in the Overall Utah Medicaid FFS Cohort and by Co-prescription Subgroup

Characteristic	Overall cohort with any opioid, MR, or SH prescription (n=15,888)	Subgroups with overlapping days' supply of prescriptions		
		Opioid + MR (n=1,835)	Opioid + SH (n=461)	Opioid + MR + SH (n=144)
Age in years				
Mean (SD)	39.6 (14.6)	45.6 (11.8)	45.5 (11.2)	46.7 (10.1)
Median (range[a])	40 (30 to 51)	46 (38 to 55)	46 (37 to 55)	46 (39 to 54)
n ≥ 18 years (%)	14,599 (91.9)	1,818 (99.1)	460 (99.8)	144 (100)
Female sex				
n (%)	9,403 (59.2)	1,105 (60.2)	314 (68.1)	93 (64.6)
Days of Medicaid eligibility				
Mean (SD)	315.1 (83.9)	324.9 (78.4)	330.0 (70.3)	339.0 (59.2)
Median (range[a])	366 (284 to 366)	366 (306 to 366)	366 (306 to 366)	366 (366 to 366)

[a] *Range is the 25th to the 75th percentiles.*

Abbreviations: FFS, Fee-for-Service; MR, muscle relaxant; SD, standard deviation; SH, sedative-hypnotic

Table E2. Summary Statistics for the Total Number of Overlapping Days' Supply During the Study Period[a] by Co-prescription Subgroup

Summary Statistic	Total number of overlapping days of medication supplied		
	Opioid + MR (n=1,835)	Opioid + SH (n=461)	Opioid + MR + SH (n=144)
Mean (SD)	51.1 (85.1)	58.8 (92.9)	63.5 (88.1)
Median (range[b])	13 (5 to 47)	17 (6 to 56)	24 (7 to 78.5)

[a] *Calculated from outpatient medication fills among Utah Medicaid FFS patients during the study Period of April 1, 2023 to March 31, 2024.*

[b] *Range is the 25th to the 75th percentiles.*

Abbreviations: FFS, Fee-for-Service; MR, muscle relaxant; SD, standard deviation; SH, sedative-hypnotic

APPENDIX F – PERCENTAGE OF OVERLAPPING PRESCRIPTION DAYS AMONG ALL PATIENTS WHO FILLED AN OPIOID PRESCRIPTION

Table F1. Descriptive Statistics for the Individual Percentages of Overlapping Days' Supply with an Opioid + Muscle Relaxant and/or + Sedative-hypnotic in Relation to Total Days of Opioid Supply or Medicaid Coverage among Patients Who Filled an Opioid (with or without Overlap)[a,b]

Overlapping medication class(es)[c]	N who filled an opioid	Descriptive statistics for % of days with overlap	
		Mean (SD)	Median (25th – 75th percentile)
Overlapping days as a percentage of the total days with an opioid supply			
Opioid + MR	10,406	11.9 (29.3)	0 (0 to 0)
Opioid + SH	10,406	3.3 (16.8)	0 (0 to 0)
Opioid + MR + SH	10,406	0.8 (7.6)	0 (0 to 0))
Overlapping days as a percentage of total days of Utah Medicaid coverage			
Opioid + MR	10,406	2.8 (12.1)	0 (0 to 0)
Opioid + SH	10,406	0.8 (6.8)	0 (0 to 0)
Opioid + MR + SH	10,406	0.3 (3.9)	0 (0 to 0)

Abbreviations: %, percentage; MR, muscle relaxant; SD, standard deviation; SH, sedative-hypnotic

[a] The percentage of overlapping therapy days was calculated for each patient as the total number of overlapping days' supply (for opioid + MR, opioid + SH, or opioid + MR + SH) divided by either (1) the total number of days' supply of opioids from patients with or without overlap, or (2) the total number of days of Utah Medicaid eligibility in patients filling opioids during the study period (April 1, 2023 to March 31, 2024).

[b] Descriptive statistics were calculated among the Utah Medicaid Fee-for-Service patients who filled at least 1 opioid prescription (n=10.406), including patients with or without overlapping days' supply of an opioid with an MR and/or SH.

*[c] Refer to **Appendix A** for a list of medications included in each drug class of interest.*