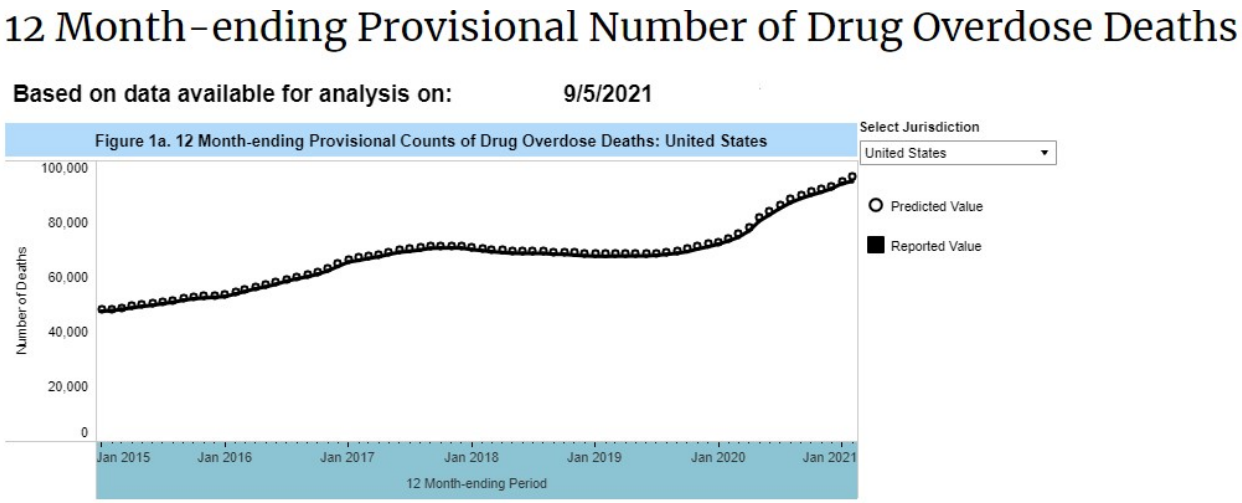
Opioid Drug Interactions: Ongoing Awareness Amidst the COVID-19 Pandemic and Opioid Epidemic

In recent years, there has been a significant growth in the understanding of prescription opioid use and misuse, addiction, and overdose. This has led to an increase in published warnings and evidence-based practices from government agencies such as the CDC to assist with curbing the opioid epidemic. Despite a slight downward trend in opioid overdose deaths from 2018-2020, potentially indicative of progress in battling the opioid epidemic, there has been a significant increase in overdose deaths correlating with the onset of the COVID-19 Pandemic (Figure 1).

Figure 1:



Source: https://www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm

Although the driving factor in many recent opioid overdose deaths has been synthetic opioids other than methadone, partially due to an increase in circulation of illicitly manufactured fentanyl and other designer opioids, providers prescribing opioids for acute and chronic management of pain must remain keenly aware of other risk factors capable of contributing to adverse drug events involving opioids. [1,2] The safety of concurrent use of opioids and benzodiazepines in relation to additive central nervous system (CNS) depression and overdose has been well characterized, but DDIs involving other substances must also be considered. Due to the manner in which many opioids are metabolized, there is significant opportunity for both toxicity and reduced efficacy in patients with complex comorbidities receiving treatment with multiple medications. Recent publications on this topic have characterized the following outcomes related to opioids, drug interactions (DDI), and patient impact:

- Clinically significant interactions involving opioids in individual with chronic pain are frequently identified (~30% of patients) and occur more often in polypharmacy patients.[3,4]
    - Interactions involving opioid metabolism can contribute to reduced analgesic effectiveness or increased opioid-related adverse effects.[3]
- Adverse events associated with opioid use and concomitantly prescribed medications contributing to opioid-related DDIs are extremely diverse, which can create difficulty in identification of the root cause of a patient's problem.[5]

To further describe commonly encountered DDIs involving prescription opioids as well as the potential outcomes, a database of Aegis' InterACT Rx test results, which identifies concurrently ingested

compounds in urine and oral fluid specimens capable of contributing to drug interactions, was analyzed. An analysis of 23,080 test results from individuals prescribed opioids (i.e, codeine, fentanyl, hydrocodone, hydromorphone, oxymorphone, oxycodone) demonstrated three frequently identified types of interactions and other prescription or non-prescription substances. Within this population, at least one interaction was identified in 71% of samples, and 62% of samples had at least one interaction identified involving an opioid. Additional information about the primary types of interactions identified is described below.

Interactions Potentiating Central Nervous System Depression

The contribution of drug interactions to an increased risk for adverse drug events, including overdose, in patients on opioid therapy has been well characterized in literature.[6-8] A recent publication assessing rates of nonopioid medications prescribed to individuals prescribed opioids with an identified overdose demonstrated that amongst other classes of drugs, benzodiazepines, skeletal muscle relaxants (i.e., baclofen), and gabapentin were significantly associated with the event.[9] Though the opportunity for adverse events is well understood by providers, and actions are often taken to minimize (e.g. minimizing total daily dose, utilization of PRN prescribing), it is still of great importance to have heightened awareness within this patient population, especially as it relates to ingestion of compounds that are unbeknownst to the prescriber. Benefit of the concurrent use of interacting compounds may at times outweigh the possibility of an adverse drug event, but the risk for an event can significantly compound in situations where there are multiple, additive interactions present. Of the more than 30,000 DDIs involving opioids identified in our analysis:

- Nearly 60% of samples (N: 13,261) had a DDI with the potential to cause additive central nervous system depression; these interactions accounted for 82% (N: 25,059) of all DDIs identified.
- Though the reported severity of these interactions varied, nearly 20% of samples (N: 2,474) included identification of multiple substances resulting in three or more unique interacting combinations and DDIs (Mean: 1.8, Range: 1-15).
- The frequency at which prescription and non-prescription substances were found in combination with a prescription opioid resulting in a DDI capable of contributing to central nervous system depression is characterized in Table 1.

Table 1: Concomitantly Ingested Prescription, Non-Prescription Substances Resulting in CNS Depression Related DDI

Interacting Co-ingested substances	Number identified (N: 25,059 total interactions)	Frequency
Gabapentin or Pregabalin	8,308	33%
Skeletal Muscle Relaxants	6,983	28%
Benzodiazepines	4,240	17%
Antipsychotics	1,854	7%
Alcohol or Alcohol Metabolites	1,544	6%
Promethazine	1,276	6%
Sedative Hypnotics	854	3%

Prevalence of Drug Combinations Impacting Opioid Metabolism

Commonly prescribed opioids, including those that were part of this analysis, are prone to pharmacokinetic drug-drug interactions due to the fact that many are both CYP3A4 and CYP2D6 substrates. For this reason, the metabolism, and effects, of these medications can be altered by DDIs capable of inhibiting or inducing metabolism, potentially contributing to toxicity or reduced therapeutic efficacy.[10] Although mitigating toxicity and adverse effects involving opioids is often top of mind, interactions capable of contributing to reduced efficacy of opioids in pain management must be considered due to the potential for precipitation of withdrawal, risk for overuse, and impact on overall healthcare utilization.[6]

- Within our analysis, 3,625 interactions involving common metabolic inhibitors or inducers were identified, and these were found in 14% (N: 3,173) of samples included.
- Of those samples with a pharmacokinetic DDI identified, 13% (N: 397) included multiple drug combinations contributing to interactions impacting opioid metabolism.
- Commonly identified classes of prescription and non-prescription substances contributing to pharmacokinetic interactions with opioids are summarized in Table 2.

Table 2: Concomitantly Ingested Prescription, Non-Prescription Substances Resulting in Pharmacokinetic DDIs

Interacting Co-ingested substances	Number of times identified (N: 3,625 total interactions)	Frequency	Metabolic Pathway Impacted
Antidepressants	2274	63%	CYP2D6 Inhibition (Reduced Efficacy)
Antimicrobials/ Antivirals	479	13%	CYP3A4 Inhibition (Increased Toxicity)
Antiepileptics/ Anticonvulstants	273	8%	CYP3A4 Induction (Reduced Efficacy
Antihypertensives	260	7%	CYP3A4 Inhibition (Increased Toxicity)
Grapefruit	247	7%	CYP3A4 Inhibition (Increased Toxicity)
Cimetidine	92	3%	CYP3A4 Inhibition (Increased Toxicity)

Interactions between Stimulants and Prescription Opioids

According to a recent data brief published by the National Center for Health Statistics, overdose deaths involving opioids and psychostimulants (e.g., methamphetamine, amphetamine, and methylphenidate) has been on the rise since 2017. Though this trend is likely secondary to illicit drug use, the risk for an interaction with a similar adverse effect profile is worth considering in patients receiving treatment with both prescription stimulants and opioids. Concurrent use of a prescription stimulant, even in individuals that are taking medications appropriately, has the potential to mask early warning signs of adverse drug events in individuals prescribed opioids for chronic pain, such as drowsiness or inability to focus.

- Our data showed that 3% (N: 686) of samples had an interaction identified involving a stimulant (i.e. amphetamine, methylphenidate, methamphetamine) and a prescription opioid.

- Of those samples a stimulant-opioid interaction identified, 72% (N: 497) also had an additional DDI that could potentially contribute to central nervous system depression, and on average, had at least 2 of these types of DDIs reported (Range: 1-12). Concurrent use of stimulants and central nervous system depressants should be closely monitored.

Pharmacokinetic and pharmacodynamic drug interactions can create significant risk for adverse drug events in individual requiring opioid therapy for management of chronic pain. Although electronic medical record systems equipped with automated clinical decision support assist in identifying DDIs, it is important to be keenly aware of DDIs in this patient population, and to utilize all methods available to mitigate the occurrence of adverse events. Although continuity of care has begun to normalize as we've become more well-equipped in managing the impact of the COVID-19 pandemic on patient care, we must remain vigilant in assessing for and reducing the opportunity for patients to be negatively impacted by drug interactions.

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