precision diagnostics

# Precision DDI™ & Drug Testing

## A Clinical Decision Support System

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A Clinical Decision Support System

**Managing Editors**

**Jack Kain, PharmD**

Clinical Toxicologist

Precision Diagnostics

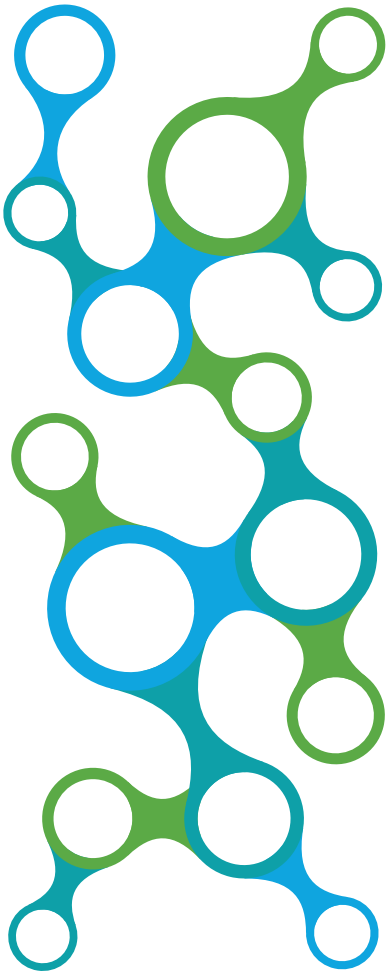
San Diego, California

**Kevin Krock, PhD**

Director of Research & Development

Precision Diagnostics

San Diego, California



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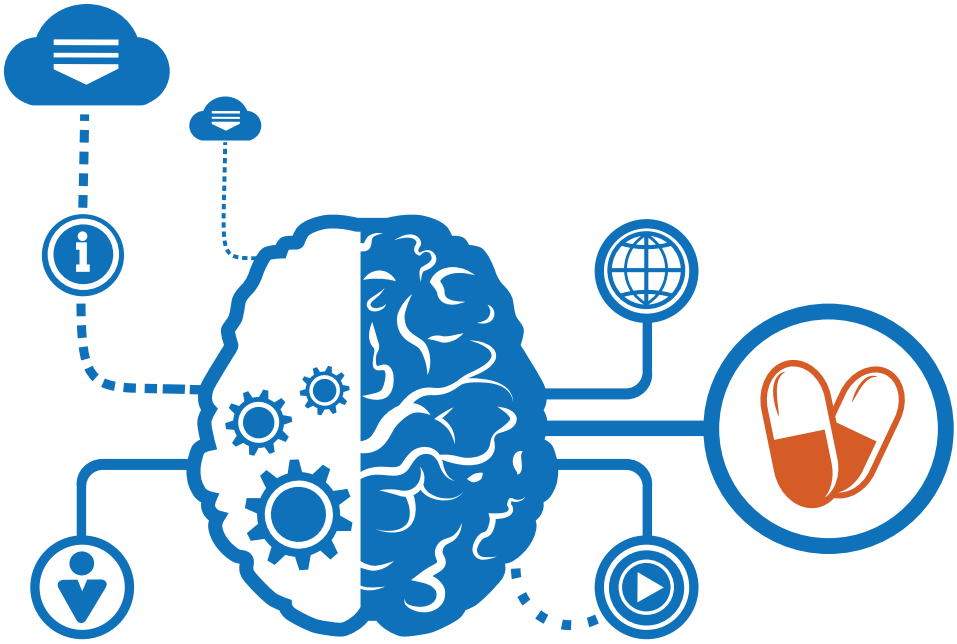
# Introduction

Precision DDI™ is an integrated clinical decision support tool that provides clinicians with additional insights into risky drug combinations which are detected in patient urine and oral fluid specimens. Precision DDI™ provides referenced drug information which describes administration, adverse reactions, contraindications, dosing, mechanism of action and the pharmacokinetics of a particular medication. Precision DDI™ promotes better patient outcomes by opening up a new level of dialogue between clinicians and their patients in order to decrease the illicit utilization of life threatening drug combinations. This module focuses on the pharmacology of DDIs, the incidences of potential DDIs which can occur in pain management, family medicine, addiction and behavioral health specialties. It also captures the costs incurred on the health system as DDIs or dangerous drug combinations are manifested into overdose syndromes.



Drug-drug interactions (DDIs) are a notable type of adverse drug event that affect millions of patients each year and are estimated to cause up to 5% of hospital admissions.[1] A DDI has the ability to modify the action or effect of another drug administered successively or simultaneously.[2] Effective clinical practices, particularly addiction treatment and pain management, should include the knowledge of potential DDIs and methods to lessen or mitigate their occurrences. Chronic co-prescribing of multiple drugs, or polypharmacy, often happens when a patient has several conditions and/or chronic disease states. A very common consequence of polypharmacy is the increased propensity for DDIs.[2]

In a study of chronic low back pain, patients on long-term opioid analgesics, an overall reported prevalence of DDIs was 27%.

In a study of chronic low back pain, patients on long-term opioid analgesics, an overall reported prevalence of DDIs was 27 %.[1] In relation to patients who are being treated for addiction or substance use disorder, these patients are more likely to be polydrug users which increases the potential for DDIs by adding three potential groups of drugs into the mix: 1) illicit drugs, 2) misused prescription drugs and 3) emerging psychoactive substances. Many patients with substance use disorders also manifest one or more co-occurring psychiatric disorders, making them more likely to be prescribed psychiatric medications. This increases the risk of DDIs between the substances of abuse and prescribed psychiatric medications.

In pain management, review of clinical evidence noted by the Centers for Disease Control (CDC) found that currently available risk stratification tools (Opioid Risk Tool, Screener and Opioid Assessment for Patients with Pain Version, SOAPP-R and Brief Risk Interview) show insufficient accuracy for the classification of patients as being at low or high risk for abuse or misuse.[3] Insufficient accuracy in risk stratification has led to a failure in identify underlying substance use disorders that predispose patients to adverse drug reactions such as DDIs. The CDC recently noted clinicians should utilize prescription drug monitoring program (PDMP) data and drug testing as appropriate to assess for concurrent substance use which might place pain patients at higher risk for opioid use disorder and overdose. Clinicians should provide counseling on increased risks for overdose and opioid use disorder when opioids are combined with alcohol or other drugs (benzodiazepines), thereby increasing the risk for DDIs.[3]

CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION

| Table 1: 2016 CDC Guideline for Prescribing Opioids for Chronic Pain: Recommendations 9-11 [3] |
|---|
| **Recommendation 9:**<br>Clinicians should review the patient's history of controlled substance prescriptions using state prescription drug monitoring program (PDMP) data to determine whether the patient is receiving opioid dosages or **dangerous drug combinations** that put him or her at high risk. |
| **Recommendation 10:**<br>When prescribing opioids for chronic pain, clinicians should use **urine drug testing before starting opioid therapy and consider** at least annually to **assess for prescribed medication** as well as **other controlled prescription drug and illicit drugs.** |
| **Recommendation 11:**<br>Clinicians should avoid prescribing opioid pain medication and benzodiazepines **concurrently** whenever possible. |

Urine drug testing can provide information about drug use not reported by the patient. This can allow for the identification of deleterious drug combinations which are largely correlated with causing overdose syndromes. The CDC recommends clinicians use unexpected results to take steps to improve patient safety (change in pain management strategy, tapering or discontinuation of opioids, more frequent re-evaluation, offering naloxone or referral for treatment of substance use disorder.[3] The CDC has articulated that clinicians should communicate to their patients that urine

The CDC has articulated that clinicians should communicate to their patients that urine drug testing is intended to improve their safety.

drug testing is intended to improve their safety.[3] It is recommended that clinicians who consider opioid therapy for chronic pain in patients with drug or alcohol disorders should incorporate strategies which mitigate risk, such as offering naloxone and increasing monitoring. As long as those patients are not diagnosed with active cancer and are not receiving palliative or end-of-life care.[3]

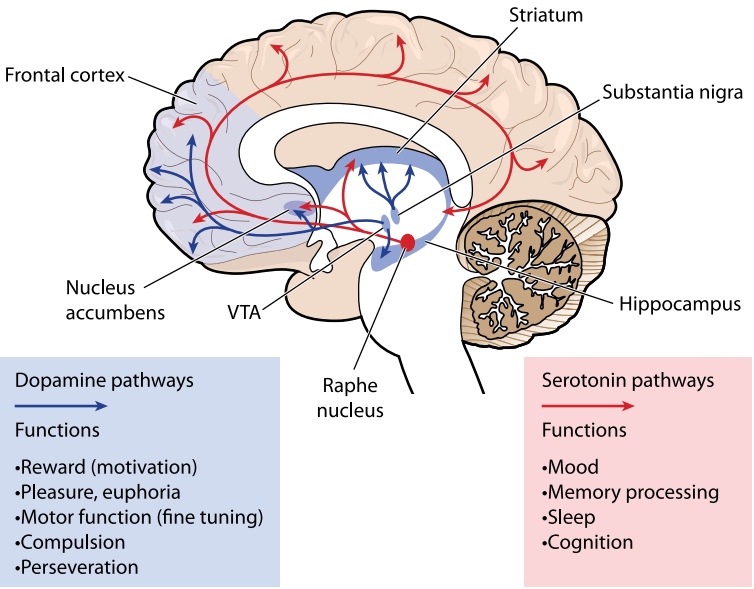
# Chapter 2: Understanding the Mechanisms Underlying Addiction


Substance use disorders are "a cluster of cognitive, behavioral and physiological symptoms indicating an individual continues using the substance despite significant substance related problems."[4] A substance use disorder is further defined by compulsive patterns of behavior, impairment in social & occupational settings & functions and recurrent use despite exacerbation of physical and psychiatric issues. Treatment plans should include a multifaceted approach which incorporate counseling, educational programs & software and medication assisted treatment. According to the DSM-5 criteria, substance use disorders can be stratified into different levels of severity (mild, moderate and severe). A patient must manifest a minimum of 2 criteria to be diagnosed with a clinically meaningful substance use disorder as displayed in Table 2.[4]

| Table 2: DSM-5 Diagnostic Criteria for Substance Use Disorders[4] |
|---|
| 1. Substance is taken in larger amounts or over a longer period than was intended. |
| 2. Unsuccessful efforts to cut down or control substance use. |
| 3. A great deal of time spent in activities necessary to obtain the substance, use it or recover from the substance's effects. |
| 4. Craving, or a strong desire or urge, to use the substance. |
| 5. Recurrent substance use resulting in a failure to fulfill major role obligations at work, school or home. |
| 6. Continued substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance. |

| |
|---|
| 7. Important social, occupational or recreational activities are given up or reduced because of substance use. |
| 8. Recurrent substance use in situations in which it is physically hazardous. |
| 9. Substance use is continued despite knowledge of having persistent or recurrent physical or psychological problems that are likely to have been caused or exacerbated by the substance. |
| 10. Tolerance. |
| 11. Withdrawal. |
| **Severity: Mild** (2-3 symptoms); **Moderate** (4-5 symptoms); **Severe** (6 or more symptoms)<br>Pattern of substance use leading to clinically significant impairment or distress, as manifested by **at least 2 of the following** within a 12-month period. |

**Figure 1:** The Reward System




Advances in neuroimaging have enabled clinicians to observe changes within the brain which occur as a result of the repeated use of substances. Just as diabetes affects the pancreas, addiction affects the brain's structure and function, causing it to associate compulsive behaviors with pleasure. Addictive substances cause a surge of dopamine in the brain's reward system (nucleus accumbens), leading to a feeling of euphoria which encourages the brain to seek out the drug again.[5,6] See Figure 1. Ordinarily, we must put in time and effort to achieve joy or ecstasy, psychoactive substances provide a potent shortcut to generate these feelings. To put it into perspective, addictive substances provide 2 – 10 times the amount of dopamine that natural rewards are known to provide.[6] In time, a person's addicted and overwhelmed brain produces less and even eliminates dopamine receptors which ultimately lead to tolerance. Higher doses are then needed to achieve euphoria. Memories of euphoria lead to "cravings" which contribute to relapse when surrounded by environmental cues or stimuli (seeing a beer bottle).

# Chapter 3: The Clinical Pharmacology of DDIs

DDIs may occur at all levels of drug passage throughout the body. A drug's reaction in the body is determined by pharmacokinetic (what the body does to the drug) and pharmacodynamic (what the drug does to the body) principles. Pharmacokinetic drug interactions may have pharmacodynamic consequences associated with them. However, pharmacodynamic drug interactions can arise in the absence of pharmacokinetic interactions. These same principles explain the mechanisms that underlie DDIs.[7] A large amount of DDIs are the result of alterations in drug metabolism caused by other drugs which share similar biochemical and metabolic pathways. The drug affected by the interaction is called the "**object drug**." The drug which causes the interaction is referred to as the "**precipitant drug**." DDIs generally occur in the GI tract, blood stream, transport proteins and liver.

## Pharmacokinetic Drug Interactions

In a pharmacokinetic drug interaction, a precipitant drug may affect the absorption, distribution, metabolism and/or excretion of an object drug.[7,8] See Figure 2.

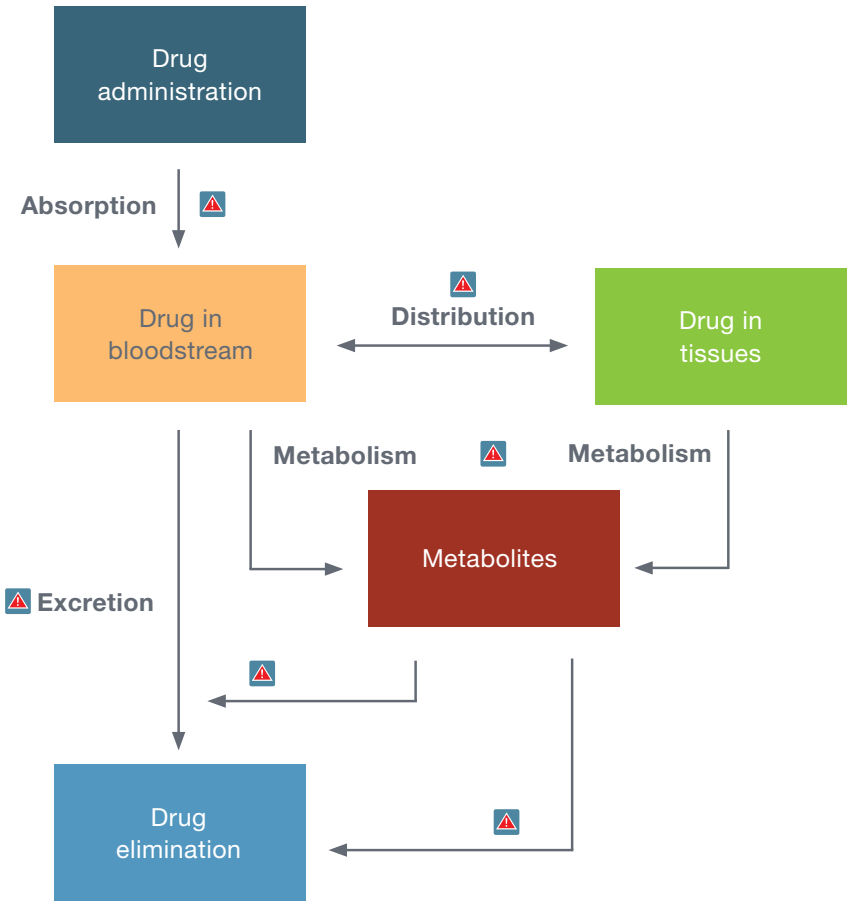



**Figure 2:** Absorption, Distribution, Metabolism and Excretion may be affected by a precipitant drug and lead to a DDI

## CYP450

The liver is the most prominent site of drug metabolism in humans and contains an abundance of drug metabolizing enzymes including the cytochrome P450 (CYP450) enzyme system and alcohol dehydrogenase. The CYP450 enzyme system contains over 50 different enzymes.[9] Six enzymes in particular (CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4 and CYP3A5) are responsible for the metabolism of 90% of all medications as seen in Table 3.[9]

**Table 3:** CYP450 Enzymes

| CYP450 Enzymes | Percentage of Drugs Metabolized |
|---|---|
| 2B6 | Metabolizes 2-8% of medications.[10,11] |
| 2C9 | Metabolizes 10-20% of medications.[10,11,12] |
| 2C19 | Metabolizes 2-5% of medications.[9,10,11] |
| 2D6 | Metabolizes 20-30% of medications.[10,11,13] |
| 3A4 | Metabolizes 40-50% of medications.[10,11] |

Drug metabolism mediated through the CYP450 enzyme system is responsible for a substantial amount of DDIs. Drugs that are metabolized by the CYP450 enzyme system can be divided into three categories that characterize their level of influence with a particular CYP450 enzyme (e.g., CYP2D6). The three categories of influence include: 1) substrate, 2) inducer and/or 3) inhibitor. In clinical pharmacology, a substrate is a substance that is acted upon by an enzyme. Drugs that are substrates for a particular CYP450 enzyme bind to it and then undergo biotransformation by the enzyme to form a different byproduct. Hydrocodone binds to CYP2D6 and metabolizes into hydromorphone as shown in Figure 3. If two drugs are substrates of the same CYP450 enzyme, competitive inhibition between the two drugs can lead to higher than intended levels of one of the drugs.[1] It should be noted it is possible for a drug to be a substrate of multiple CYP450 enzymes. For example, methadone (Dolophine®) is metabolized into 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP) primarily by CYP3A4, CYP2B6, CYP2C19 and to a lesser quantity CYP2C9 and CYP2D6.[14]


**Figure 3:** Hydrocodone metabolizes into hydromorphone via cytochrome 2D6 liver enzyme

## Enzyme Inhibitors

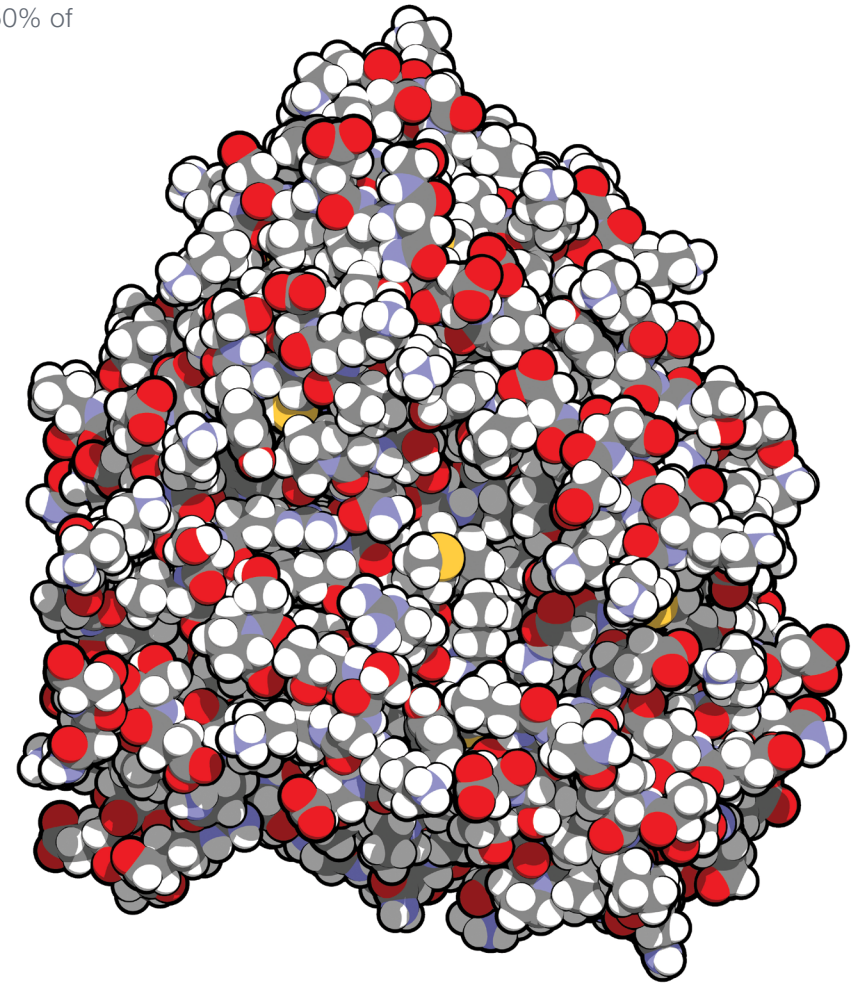
Inhibitors are drugs that bind to a particular CYP450 enzyme and block the enzyme's metabolic capacity. The inhibitor paroxetine (Paxil®) binds to CYP2D6 and blocks its capacity to metabolize other drugs. It is possible for a drug to be a substrate of a CYP450 enzyme and simultaneously inhibit its own metabolism also known as auto-inhibition. Fluoxetine (Prozac®) is metabolized by CYP2D6 but it is also an inhibitor of CYP2D6, thereby, inhibiting its own metabolism into norfluoxetine.[9,15,16]


Drugs which can inhibit CYP450 enzyme activity generally lead to increases in plasma concentrations of target medications or illicit substances and ultimately cause an adverse event. In vitro studies have demonstrated agents such as fluoxetine (Prozac®) and paroxetine (Paxil®) inhibits the metabolism of stimulants such as methamphetamine (crystal meth) through inhibition of CYP2D6.[17] This results in higher than anticipated plasma concentrations of methamphetamine and the potential to develop serotonin syndrome. In contrast, fluoxetine (Prozac®) inhibits CYP2D6 and may prevent a patient who is also taking hydrocodone (Vicodin®) from experiencing a sufficient level of pain relief that is to be expected from the more potent metabolic byproduct known as hydromorphone.

## Enzyme Inducers

Inducers (phenobarbital) are drugs that bind to a particular CYP450 enzyme (CYP2C9) and increase or catalyze its metabolic activity. It is possible for a drug to be a substrate of a CYP450 enzyme and simultaneously induce its own metabolism also known as auto-induction. Carbamazepine (Tegretol®) is primarily metabolized by CYP3A4 and CYP2C8 but is also an inducer of both of these enzymes, thereby, catalyzing its own metabolism.[18,19]

**Figure 4:** Human CYP3A4 biochemical structure responsible for the metabolism of 40-50% of medications



Drugs which can induce CYP450 enzyme activity generally lead to decreases in plasma concentrations of certain medications or illicit substances and ultimately sub-therapeutic plasma concentrations of a drug. In the patient with substance use disorder this could lead to symptoms of withdrawal and drug seeking behaviors to fulfill a craving. For example, buprenorphine (Suboxone®) is metabolized by CYP3A4. Inducers of CYP3A4 such as phenobarbital may catalyze the metabolism of buprenorphine and lead to symptoms of opioid withdrawal or inadequate analgesia.[20,21]

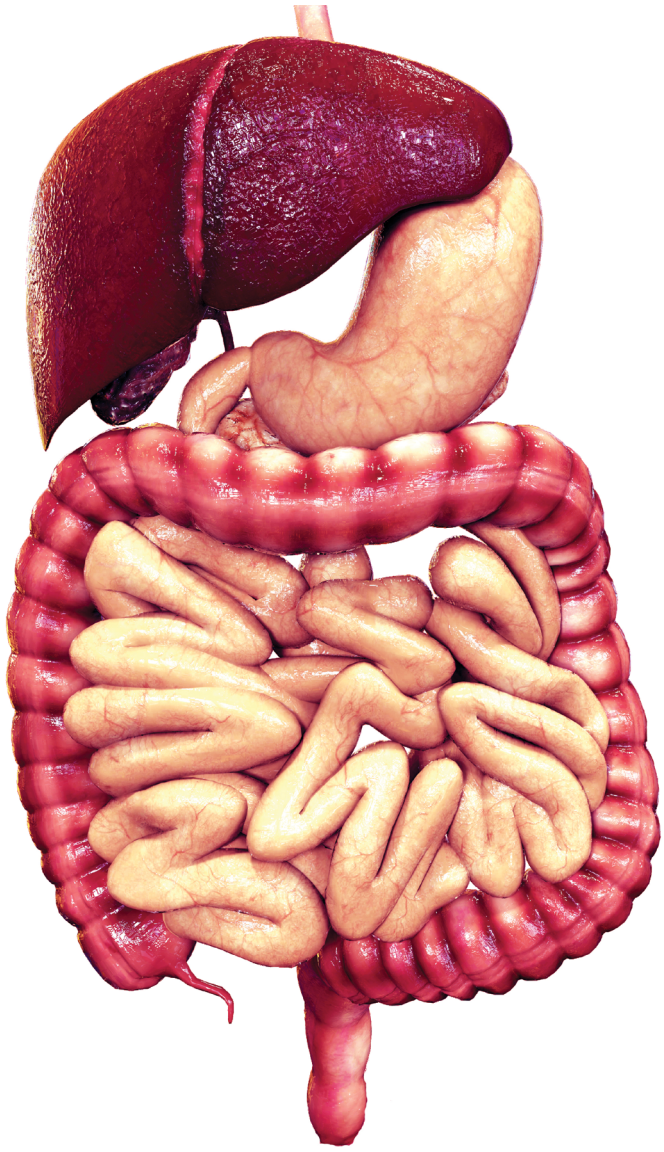
## Drug-Protein Displacement

The binding of drugs to plasma proteins found in the plasma and various tissues in the human body is an additional pharmacokinetic parameter to understand. By binding to transport proteins, drugs can be transported to their particular sites of metabolism. When one drug displaces another drug from its normal plasma protein binding site, the variable or free blood concentration of the displaced drug increases and its pharmacologic effect tends to increase.[7] An increase in pharmacologic effect may result in a DDI. Common plasma proteins which drugs bind to include human serum albumin, lipoproteins and alpha-1-acid glycoprotein.[22] Due to its high protein binding affinity, it has been opined that marijuana may lead to DDIs by displacing other highly protein bound drugs (warfarin) from their binding sites.[23] An additional drug known to be highly protein bound is diazepam (Valium®) and as a result may be displaced by other highly protein bound drugs. A double-blind randomized placebo controlled study evaluated the effects of sertraline (Zoloft®) on the protein binding

pharmacokinetics of diazepam (Valium®). This study did find a decrease in the systemic clearance of diazepam (Valium®) when compared to the placebo group. However, the differences in the magnitude of systemic clearance of diazepam between the sertraline group and placebo group were not considered meaningful.[24]

## Gastrointestinal (GI) Absorption DDIs

When provided through the oral route, solid dosage forms (tablets, capsules) of drugs are disintegrated into small particles within the GI tract. Disintegration of a drug allows for more rapid absorption as it becomes dissolved into a solution within the GI tract. Drugs must be in solution form in order to pass from the GI tract into the blood stream. The small intestine is the primary site of absorption for orally administered drugs. Very few drugs are absorbed to a significant extent from the stomach.



DDIs can occur within the GI tract which may lead to altered drug absorption. There are several mechanisms through which a single drug may affect the GI absorption of another drug: 1) drug binding in the GI tract, 2) alterations in GI motility, 3) alterations in GI pH, 4) alterations in intestinal flora and 5) alterations in drug metabolism within the wall of the intestine. On many occasions that exact mechanism of GI absorption DDIs is not established.[7] One example of a GI absorption DDI, opioids are known to slow down GI motility and on many occasions lead to opioid induced constipation. A decrease in GI motility caused by the oral consumption of an opioid can expose another drug to the acidic environment of the stomach leading to increased degradation of a drug and ultimately sub-therapeutic concentrations of the object drug. This type of DDI has been documented when oral methadone (Dolophine®) is administered with stavudine (Zerit®) and may result in sub-therapeutic concentrations of stavudine, an antiretroviral therapy for HIV.[25]

## Pharmacodynamic Drug Interactions

In a pharmacodynamic drug interaction, two drugs used in conjunction, may have additive or antagonistic pharmacologic effects.[7,8] These types of interactions can be correlated to the additive or antagonistic effects of opioids, sedative hypnotics (benzodiazepines), muscle relaxants (carisoprodol), alcohol and more. A substantial amount of pharmacodynamic drug interactions usually occur in rapid onset and lead to overdose and death

in pain management and/or populations with substance use disorders. This section outlines the most notable types of pharmacodynamic DDIs in pain management and substance use disorders.

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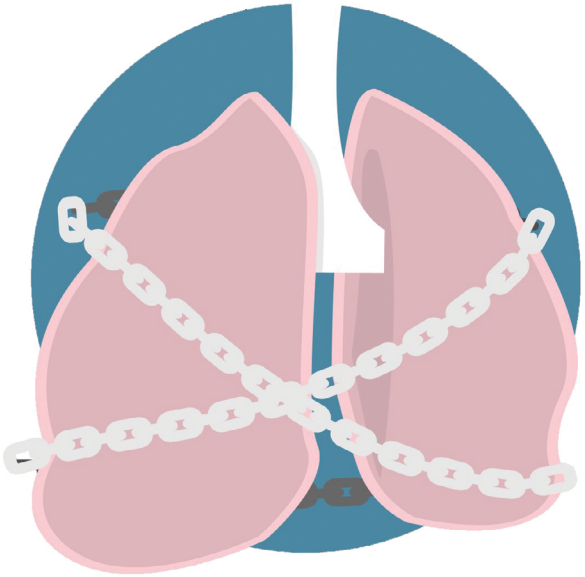
## CNS Depression

Arguably the most notable type of pharmacodynamic drug interaction in pain management and substance use disorder is the increased propensity for central nervous system (CNS) depression. This depression can occur with the use of a single drug which has CNS depressant activity. CNS depressants typically include analgesics, anesthetics, sedatives, hypnotics and some muscle relaxants. As the name implies, these drugs suppress the activity of the central nervous system, slow brain activity and lead to symptoms such as blurred vision, sleepiness, impaired motor control, impaired cognition, slowed reflexes and breathing and reduced sensitivity to pain. Benzodiazepines (Xanax®) can cause a dose-related CNS depressant activity that may fluctuate from mild impairment of task performance to hypnosis.

Most CNS depressants perform on the brain by affecting the neurotransmitter known as gammaaminobutyric acid (GABA). Generally, CNS depressants work to increase GABA levels, thereby inhibiting brain activity. This leads to a drowsy or calming state of mind which facilitates the treatment of pain, anxiety and sleep disorders. When CNS depressants are combined with other depressants either through prescription or substance abuse there is an increased susceptibility to additive or synergistic CNS depressant effects which may be unanticipated to clinicians and/or patients. This may result in overdose syndromes (sedation, coma and respiratory depression) which can result in hospitalizations and fatalities.



Opioids (oxycodone, hydrocodone, fentanyl, methadone, heroin) when combined with other CNS depressants (alcohol, benzodiazepines, muscle relaxants, hypnotics) are notorious for causing severe respiratory depression. Opioid induced respiratory depression occurs by activating Mu-opioid receptors throughout the central nervous system including the pre-Botzinger complex in the mammalian brain, a complex that is vital for generating respiratory rhythm.[26] In severe respiratory depression, an individual's oxygen and carbon dioxide levels become substantially impaired. When this occurs a patient may go into a semi-conscious state or become unconscious entirely and ultimately experience respiratory arrest. This particular manifestation of a DDI can prove to be fatal in the absence of immediate medical attention and/or the failure to administer naloxone (i.e, Narcan®).

## Serotonin Syndrome

Serotonin syndrome is a potentially life-threatening adverse drug reaction that may occur as a result of using serotonergic drugs in combination or in high dose monotherapy. Serotonin syndrome is precipitated through the over-activation of both peripheral and central postsynaptic 5HT-1A and most notably, 5HT-2A receptors.[27,28] Clinical signs and symptoms of excess serotonin levels in the body include tremors, diarrhea in mild cases and/or severe life-threatening cases can include delirium, neuromuscular rigidity and hyperthermia. The incidence of serotonin syndrome has increased over the past 20 years as a result of better diagnostic criteria, increased prescribing of older and newer SSRIs and polypharmacy.[28,29] Serotonin syndrome has an incidence rate of approximately 14-16 percent of persons who overdose on SSRIs (e.g., Prozac®).[28–30] There are several drug classes implicated in causing serotonin syndrome. Included are the antibiotic linezolid,


The incidence of serotonin syndrome has increased over the past 20 years as a result of better diagnostic criteria, increased prescribing of older and newer SSRIs and polypharmacy.

triptans (sumatriptan), antidepressants [SRIs, SNRIs, buspirone (BuSpar®), tricyclic antidepressants, monoamine oxidase inhibitors (MAOIs)], antipsychotics, anticonvulsants, antiparkinsonian agents, analgesics (meperidine, tramadol), cough and cold preparations containing dextromethorphan and herbal products (St. John's wort).[30]

Serotonin syndrome is a potential pharmacodynamic DDI which has strong implications in pain management, behavioral health and patients with substance use disorders. Substances with known abuse potential pose a risk to cause serotonin syndrome in patients who are co-prescribed or co-abuse certain medications for pain (fentanyl), opioid addiction (methadone), illicit use of non-prescribed medications (Adderall®) and more. Substances implicated in causing this type of DDI, prescribed and/or abused, in these patient populations include dextromethorphan (Delsym®), cyclobenzaprine (Flexeril®), tramadol (Ultram®), meperidine (Demerol®), fentanyl (Duragesic®), buprenorphine (Suboxone®), methadone (Dolophine®), oxycodone (OxyContin®), amphetamines (Adderall®), methylenedioxymethamphetamine (MDMA or Ecstasy), and synthetic cathinones (bath salts). Due to the nature of substance use disorder and the prevalence of co-occurring psychiatric disorders in pain management, many patients take prescribed antidepressants such as the SSRIs [sertraline (Zoloft®), fluoxetine (Prozac®)], SNRIs [venlafaxine (Effexor®), duloxetine (Cymbalta®)] and TCAs [amitriptyline (Elavil®), imipramine (Tofranil®), nortriptyline (Pamelor®)] in conjunction with prescribed therapeutic pain regimens, opioid addiction treatments and/or illicit substances of abuse.[27–31] The concurrent use of these medications commonly found in pain management, addiction treatment and behavioral health predispose a patient to serotonin syndrome, a potentially life-threatening DDI.

## QT Interval Prolongation & Torsades de Pointes (TdP)

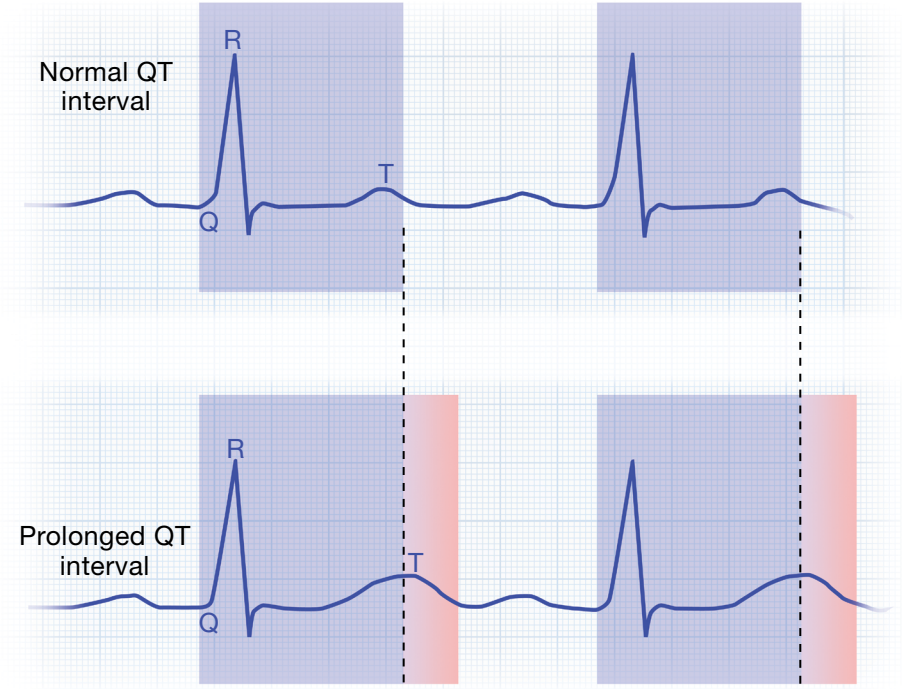



**Figure 5:** Many drugs have been required by the FDA to carry additional labeling on the potential risk of causing QT interval prolongation and TdP

Drug-induced QT interval prolongation can lead to a life threatening ventricular arrhythmia known as torsades de pointes (TdP). TdP can cause sudden cardiac death. QT prolongation is the most frequent and arguably the most feared type of drug-induced pro-arrhythmia.[32] In fact, identification of QT prolongation and TdP has prompted the removal of several drugs from the U.S. market such as terfenadine, astemizole, grepafloxacin and thioridazine.[33] Many other drugs have been required by the Food and Drug Administration (FDA) to carry additional labeling characterizing the potential risk of QT prolongation and TdP.

Drugs that are known to individually induce QT prolongation and TdP can further potentiate the risks of developing QT prolongation and TdP when used concurrently with other drugs that also cause QT prolongation and TdP. For example, quetiapine (Seroquel®), an atypical antipsychotic, when administered with methadone (Dolophine®), an opioid analgesic, can lead to an increased risk of developing QT prolongation and TdP, a DDI.[34] In another example, amitriptyline (Elavil®) when administered with methadone (Dolophine®) and/or quetiapine (Seroquel®) due to polypharmacy and/or substance abuse can also lead to QT interval prolongation and TdP.[35,36] In addition, SSRIs such fluoxetine (Prozac®) when administered with methadone (Dolophine®) can result in QT prolongation and TdP.[37] Co-administration of drugs that are known to individually induce QT prolongation and TdP should be done with extreme caution and an assessment of the treatment risks versus benefits.[34–37] See Figure 6.

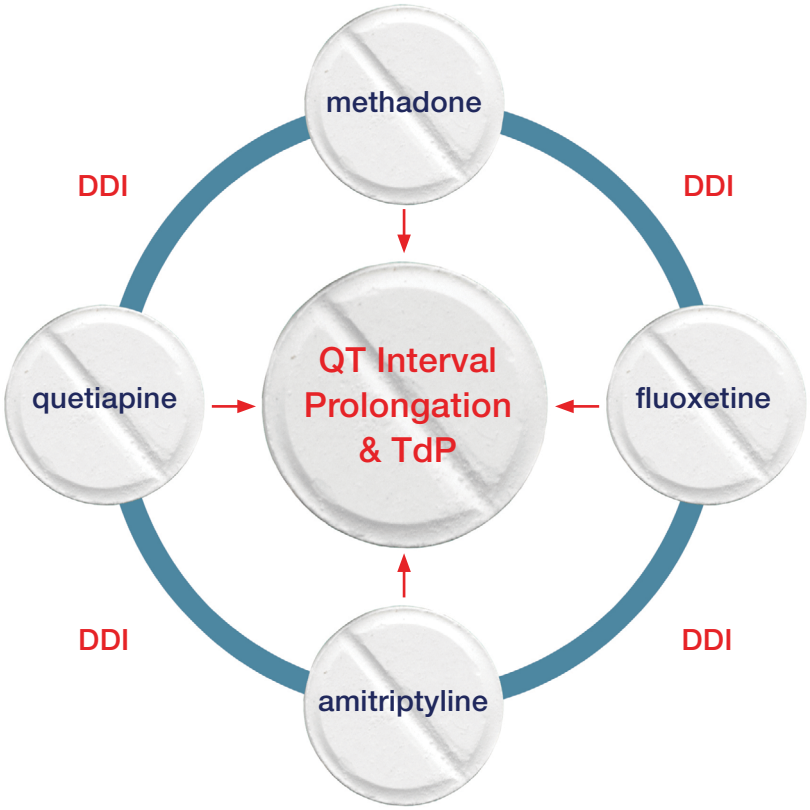



**Figure 6:** Drugs known to individually induce QT interval prolongation should be done with extreme caution.

# Chapter 4: Epidemiology & The Economic Burden of Overdose Syndromes

### Prescription Opioid Abuse, Dependence and Misuse - A Substantial Economic Burden

A component of identifying and developing prevention strategies that are cost-effective depends upon the understanding of the economic burden imposed by adverse health outcomes (overdose syndromes). In 2007, the overall societal impact of opioid misuse, dependence and abuse was estimated to be $55.7 billion.[38] Since 2007, opioid abuse, misuse and dependence has continued to rise. The yearly number of prescription opioid overdose deaths, between 2007 to 2013, increased by over 1,800 cases[39] and the annual number of persons who abuse or are dependent on prescription opioids has increased by over 200,000 people.[40] Furthermore, it is estimated that prescription opioid abuse, dependence and overdose in the U.S. has added up to an aggregate economic burden of $78.5 billion.[41] Approximately two-thirds of the costs were associated to health care, substance abuse treatment and lost productivity.[41]

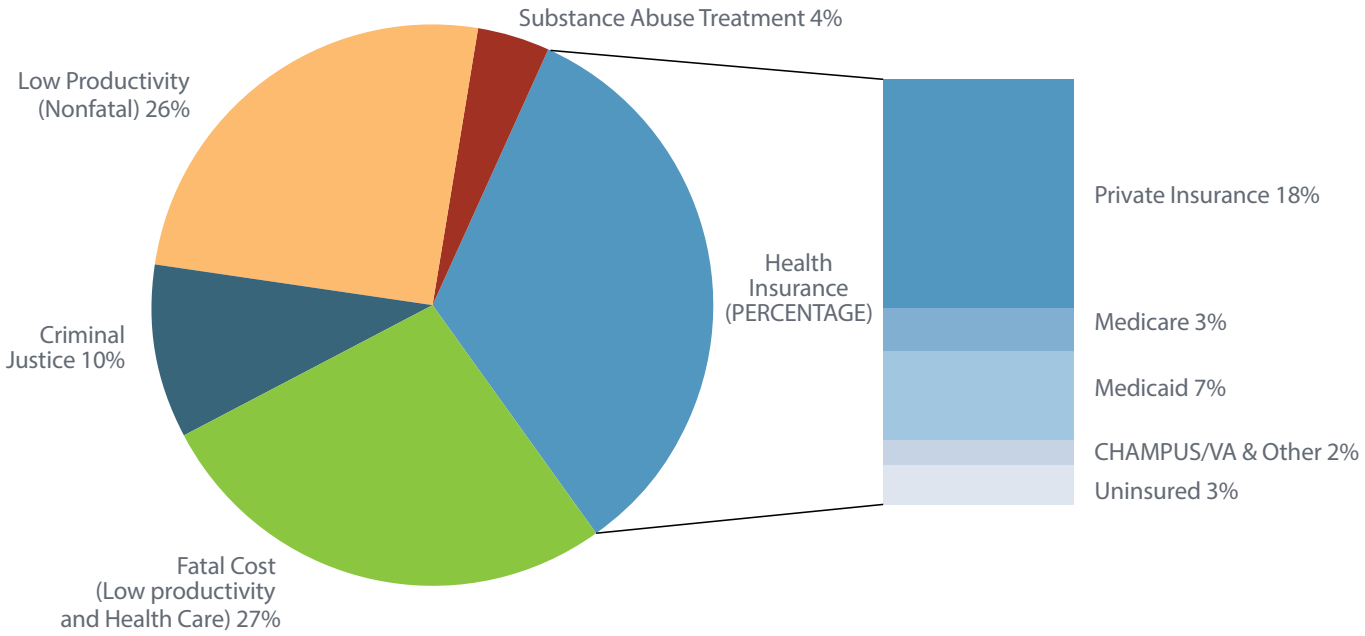
Furthermore, it is estimated that prescription opioid abuse, dependence and overdose in the U.S. has added up to an aggregate economic burden of $78.5 billion.

Total spending for healthcare and substance abuse treatment in 2013 accounted for $26.1 billion from insurance and $2.8 billion from other sources.[41] Fatal cases accounted for an estimated $21.5 billion in costs.[41] Annual health insurance costs in 2013 increased after diagnosis with a prescription opioid misuse disorder. The cost differential between all three types of insurances (Private Insurance, Medicare and Medicaid) were found to be large and statistically significant. The

largest cost difference was found to be in the Medicare population at over $17,000. Private insurance has a cost increase of $15,500 and Medicaid reported over $13,700.[41]

The costs of lost productivity in 2013 as a result of 1) premature death from prescription opioid abuse or dependence, 2) reduced productive hours for abuse/dependence and 3) incarceration contributed substantially to the total economic burden. More specifically, lost productivity in non-fatal cases of opioid abuse, dependence and overdose attributed to an estimated $20.4 billion in costs or 26% of the total economic burden. Lost productivity in fatal cases totaled an estimated $21.4 billion or 27.3% of the total economic burden.[41] See Table 4.

**Table 4:** Distribution of the Economic Burden of Prescription Opioid Overdose, Abuse and Dependence




## Substance Use Disorder & Emergency Department (ED) Visits

The number of deaths from prescription drugs, between 2001 to 2014, increased 2.8 fold. There was a 3.4-fold increase in the total number of overdose deaths involving opioid pain relievers and a 5-fold increase in the total number of benzodiazepine related deaths. There was a 42% increase in the total number of deaths involving cocaine and a 6-fold increase in the total number of deaths involving heroin.[42] See Tables 5 – 9. The CDC has estimated that 91 Americans die every day from opioid overdose.[43] Individuals who are found to be addicted to opioids are forty times more likely to develop an addiction to heroin.[44]

Table 5

## National Overdose Deaths

### Number of Deaths from Prescription Drugs

Total Female Male

Source: National Center for Health Statistics, CDC Wonder

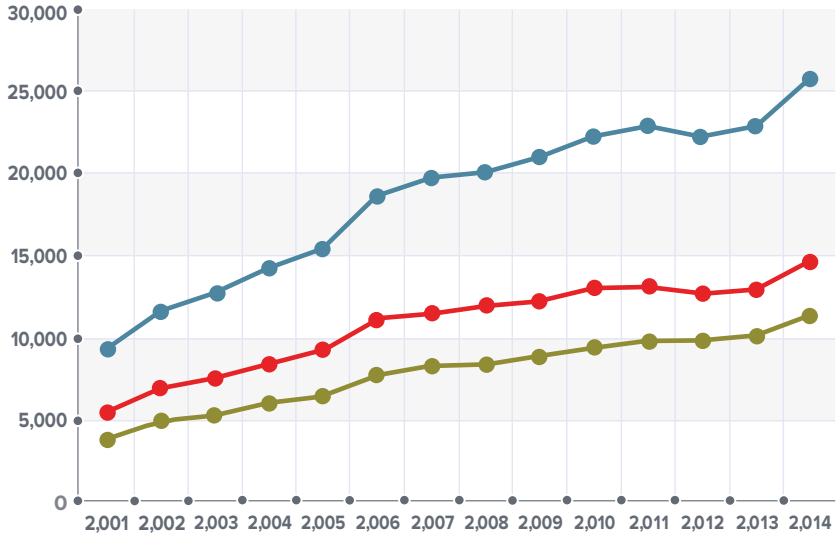



Table 6

## National Overdose Deaths

### Number of Deaths from Opioid Pain Relievers

Total Female Male

Source: National Center for Health Statistics, CDC Wonder

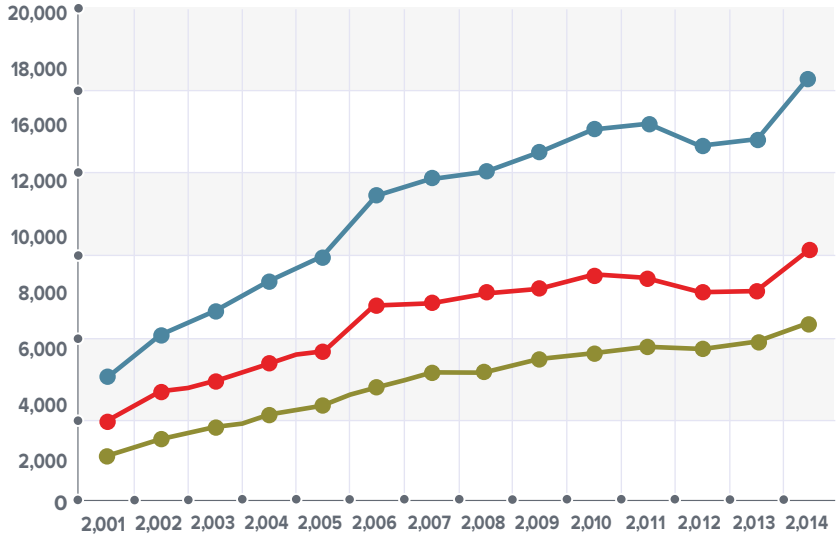


Table 7

## National Overdose Deaths

### Number of Deaths from Benzodiazepines


Source: National Center for Health Statistics, CDC Wonder

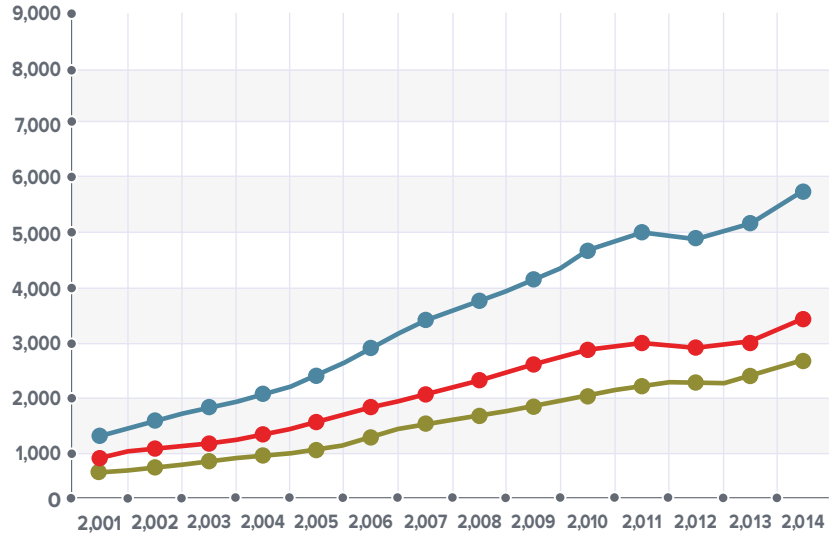



Table 8

## National Overdose Deaths

### Number of Deaths from Cocaine


Source: National Center for Health Statistics, CDC Wonder

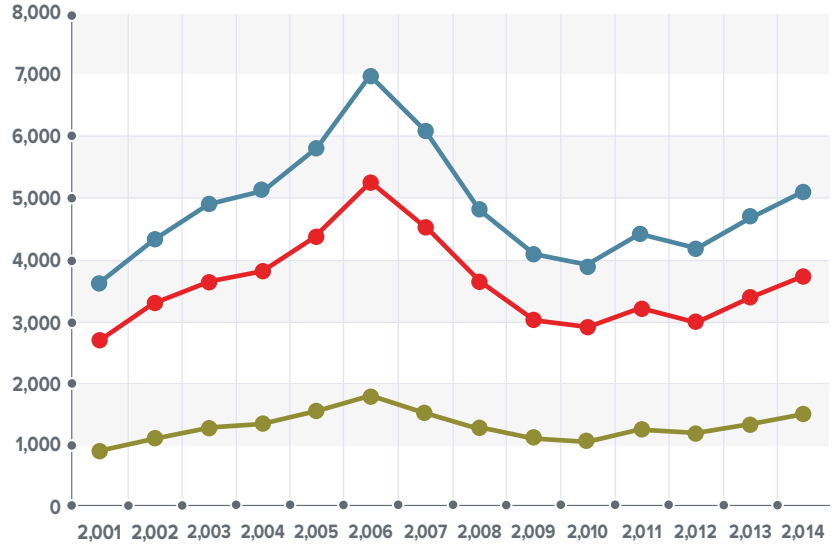
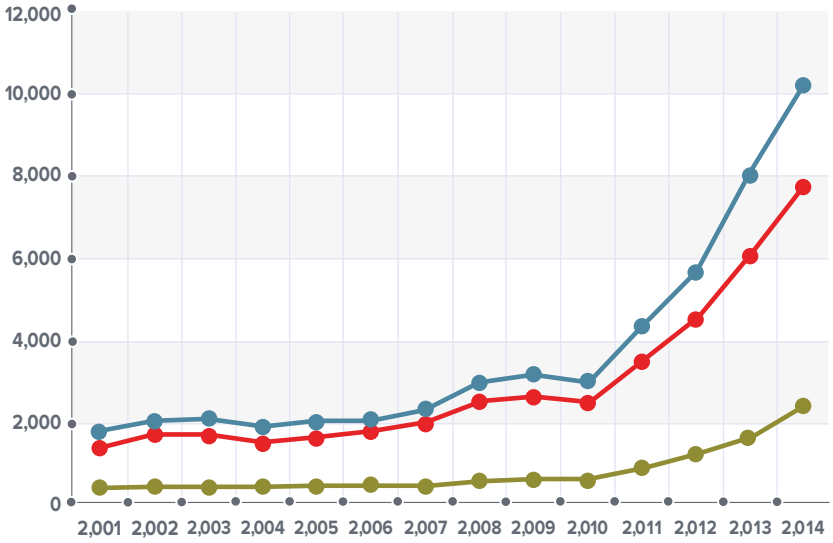



Table 9

## National Overdose Deaths

### Number of Deaths from Heroin


Source: National Center for Health Statistics, CDC Wonder



According to data collected by the Drug Abuse and Warning Network (DAWN), a public health surveillance system managed by the Substance Abuse and Mental Health Services Administration (SAMHSA), there were nearly 4.6 million drug-related emergency department visits nationwide in 2009. 45% involved drug abuse, 21.2% involved illicit drugs and 14.3% involved alcohol used in combination with other drugs. In 2009, nearly one million ED visits involved an illicit drug, either alone or in combination with other drugs.[45]

**Table 10: 2009 DAWN Estimates on Emergency Department Visits from Illicit Drug Use, Alone or in Combination[44]**

| Drug | Number of ED Visits |
|---|---|
| Cocaine | 422,896 |
| Marijuana | 376,467 |
| Heroin | 213,118 |
| Stimulants, including amphetamines and methamphetamine | 93,562 |
| Others (PCP, ecstasy and GHB) | Much less frequent |

It was estimated by DAWN, in 2009, that 519,650 ED visits were related to the use of alcohol in combination with other drugs. Alcohol was most frequently combined with analgesics, stimulants, sedatives, cocaine, marijuana, psychotherapeutic agents (anti-depressants and antipsychotics) and heroin.[45]

**Table 11: 2009 DAWN Estimates on Emergency Department Visits from Alcohol Used in Combination with Other Drugs[44]**

| Drug | Number of ED Visits |
|---|---|
| Central nervous System Agents (analgesics, stimulants, sedatives) | 229,230 |
| Cocaine | 152,631 |
| Marijuana | 125,438 |
| Psychotherapeutic agents | 44,217 |
| Heroin | 43,110 |

In 2009, the most frequently reported drugs for non-medical use resulting in ED visits were opiate/opioid analgesics. Opioid analgesics were present in 50 percent of 1.2 million non-medical use ED visits. Psychotherapeutic agents commonly used to treat sleep disorders and anxiety were present in more than one-third of non-medical ED visits. The high reported incidence included single ingredient opioid formulations (oxycodone) and combination formulations (hydrocodone with acetaminophen). Another alarming find was the co-administration of methadone with oxycodone and hydrocodone formulations. These combinations accounted for one of the most frequently reported occurrences that led to ED visits.[45] See Tables 10 – 12.

**Table 12: 2009 DAWN Estimates on Emergency Department Visits from Non-medical Use of Pharmaceuticals or Dietary Supplements[45]**

| Drug | Number of ED Visits |
|---|---|
| Hydrocodone (alone or in combination) | 104,490 |
| Oxycodone (alone or in combination) | 175,949 |
| Methadone | 70,637 |

## Chronic Pain

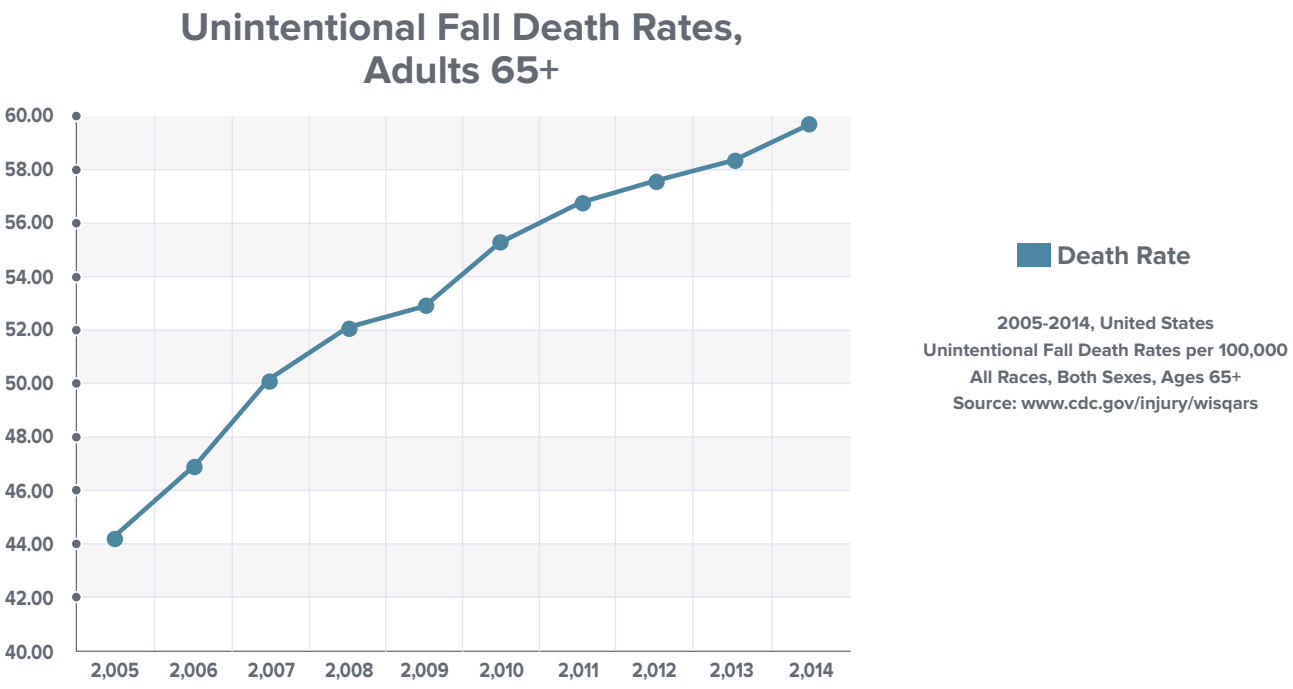
Chronic opioid users being treated for chronic, non-cancer pain, especially patients with osteoarthritis and/or chronic low back pain, are also at an increased risk of experiencing a DDI due to polypharmacy.[46] The economic burden associated with DDIs in patients with chronic pain is significant. For example, one study found a large percentage of patients who were treated with at least one prescription long acting opioid for ≥ 30 days, between 2008 and 2010, experienced a DDI. More specifically, among 57,752 chronic, non-cancer pain patients, 5.7% or 3,302 were exposed to a potential DDI. In addition, the healthcare costs associated with a potential DDI versus no potential DDI were significantly higher. The monthly costs were estimated to be $3,366 versus $2,757 in patients exposed to a potential DDI of major clinical significance versus patients who were not exposed to a potential DDI. The higher health care costs, an estimated $609 difference, were the result of outpatient and inpatient medical costs.[47]

## Geriatrics

Falls and fractures are a known leading cause of morbidity and mortality in elderly populations. 2.8 million elderly patients a year are treated in emergency departments for fall injuries. 800,000 patients a year are hospitalized because of an injury caused by a fall which typically involves trauma to the hip or head.[48] The incidence of falls in the elderly population has been estimated to occur at least once a year in 30% of people age 65 and older and in 50% of those age 80 and older.[49] Fall injuries are considered among the top 20 most expensive medical conditions.[50] In 2015, Medicare costs for falls totaled over $31 billion. The average hospital cost for a fall injury is estimated to be over $30,000 and the costs of treating fall injuries only rise with age.[51]

Fall injuries are considered among the top 20 most expensive medical conditions.

**Table 13:** Unintentional Fall Death Rates, Adults 65+




Source: www.cdc.gov/injury/wisqars

Falls within an elderly population can be devastating and result in severe injuries, loss of function, loss of independence and/or death. Increased risk of falls and fractures from the utilization of narcotic analgesics in the elderly population can be attributed to the central nervous system (CNS) effects of these medications. In patients older than 65 years with an injury related to a fall, 32% of these patients experienced a severe injury. Furthermore, death was seven times more likely than for patients younger than 65 years of age. Even after accounting for age and comorbidities, the prescribing of narcotic analgesics in elderly patients with chronic pain has been shown to increase the risk of falls and fractures.[52–54] The continued prescribing of medications with CNS effects will continue to predispose elderly patients (65 or older) to fall-related injuries. Nearly half of older adults still fill a potentially inappropriate medication. Despite the potential for benzodiazepines (Xanax®, Valium®) to increase the risk of falls, fractures and cognitive impairment, use of benzodiazepines in elderly patients remain at an estimated 9%.[55,56]

## Workers' Compensation

Substance use disorder among American employees negatively impact U.S. industries through lost productivity, workplace injuries and accidents, employee absenteeism, increased illness/comorbidities and low employee

morale. This results in substantial costs for U.S. companies. U.S. companies lose billions of dollars each year due to alcohol and drug related problems. In 2007 alone, the economic cost of drug abuse resulted in an estimated $120 billion in lost productivity mainly attributed to labor participation costs, participation in drug abuse treatment, incarceration and premature death.[57] In 2009, nearly one in twelve full-time workers age 18 or older reported past-month use of an illicit drug. Unemployed workers were twice as likely to report drug use.[58] The prevalence of substance use disorders differed across U.S. industries. The lowest rates of heavy alcohol use, illicit drug use and substance use disorder from 2003 to 2012 were in education, healthcare and social assistance and public administration. Alternatively, higher rates were seen in mining, construction and the accommodations and food service industries.[59]

Clinicians and/or case managers can have a substantial impact on worker's compensation claims through a comprehensive examination of a claimant's entire clinical and social history or situation. Medication reviews can identify a problem and utilize evidence-based recommendations to promote safe and effective outcomes.[60,61] Utilization of drug testing can identify potential drug-related problems that include therapeutic duplication, drug-age interactions (AGS Beers Criteria), DDIs and issues in medication adherence. This provides clinicians and/or case managers with opportunities to improve treatment outcomes. Identification of drug interactions can explain aberrant or non-adherent claimant behaviors. Clinicians can use laboratory test results to make clinical recommendations on behalf of the claimant and improve his or her ability to return to work full-time or part-time.

# Chapter 5: Drug Testing & Clinical Decision Support Tools: A Clinical Decision Support System

**Clinical Decision Support System**

Adherence to treatment recommendations is the strongest predictor of treatment effectiveness in chronic disease states.

Precision Diagnostics provides laboratory testing and dynamic reporting to aid in clinical decision making. Our state-of-the-art laboratory test results are considered clinical decision support tools which are meant to 1) identify underlying addiction & substance abuse, 2) identify relapse in close proximity to when it occurs, 3) assess medication adherence and 4) assess drug safety through Precision DDI™. Adherence to treatment recommendations is the strongest predictor of treatment effectiveness in chronic disease states.62,63 The relapse rates for hypertension (50% - 70%), type 1 diabetes (30% -50%) and asthma (50% - 70%) are similar to the relapse rates for substance use disorder (40 - 60%)

in patients who are non-adherent to their treatment recommendations.[64] Urine and/or oral fluid drug testing provide an objective methodology for identifying compliance or adherence to a medication regimen prescribed by physicians and/or mid-level practitioners. Compliance can ensure lower relapse rates and promote better treatment outcomes. Drug testing can also identify the presence of non-prescribed medications that would imply a relapse in substance use disorder.

Precision Diagnostics NextGenTM testing platform provides an unparalleled level of granularity. We can identify underlying addiction by using statistically derived cutoffs – made possible by using the most state-of-the-art LC/MS/MS technology on the market – which decreases the propensity for false negative results. A false negative result occurs when the concentration of the analyte (drug) being tested is lower than the laboratory's ability to detect it. In other words, saying a drug is not present in a patient's system when it is actually present is a false negative result.

Clinically speaking, a false negative result is the failure to identify underlying addiction and/or relapse due to outdated or inherent weaknesses in laboratory methodologies. Failing to identify addiction and/or relapse when it occurs can have drastic impacts on the health of a patient such as increased risk of fatal overdose, drug-drug interactions, increased risk of emergency department visits and increased risk of developing co-morbid disease states. Identifying heroin use by detecting 6-MAM allows a clinician to understand that his or her patient is at an increased risk of acquiring HIV and Hepatitis B/C viruses through IV drug use which is characteristic of heroin abuse. False negative results can prevent practitioners from providing interventions necessary to appropriately treat addiction and/or chronic pain. This results in more costs incurred on the patient, community and health system in its entirety.

A substantial amount of data on drug interactions between opioids, benzodiazepines, selective serotonin reuptake inhibitors, serotonin norepinephrine reuptake inhibitors, amphetamines and muscle relaxants has accumulated. Precision DDI™ is a clinical decision support tool that is integrated with drug testing in order to promote drug safety and identify potential harms. It reports on dangerous drug combinations detected within human matrices of patients being treated for a substance use disorder, mental health disorders and chronic pain. Precision DDI™ also integrates evidence-based American Geriatric Society (AGS) Beers Criteria with drug testing to detect drugs and drug combinations that are potentially inappropriate for use in elderly populations. The AGS Beers Criteria was first published in 1991, making it have the longest tenure for criteria of potentially inappropriate medications (PIMs) that are utilized by older adults (65 and older). The AGS Beers Criteria is a component to Precision DDI™ and a comprehensive approach for safe medication use in elderly patients.[65] The importance of this evidence based criteria is demonstrated in many publications regarding the prevalence of PIMs) that can predispose elderly patients to an increased risk of falls, fractures, cognitive impairment and other harms.

# Chapter 6: Transition of Care & Actionable Interventions

## Primary Care Transitions

Primary care physicians can also play an important role in transitions of care by utilizing drug testing to identify patients with substance use disorder and by providing medication assisted treatment (Suboxone®) for patients who are awaiting transition into specialized treatment facilities for addiction. An estimated 1 in 4 patients in the primary care setting struggle with an opioid use disorder.[3] Through the utilization of drug testing, primary care physicians can also identify dangerous drug combinations as a result of polypharmacy and/or polydrug abuse.

Primary care physicians and/or clinicians on staff can then communicate potential DDIs to specialized treatment facilities during the "hand-off" to the appropriate level of care.

An estimated 1 in 4 patients in the primary care setting struggle with an opioid use disorder.

Patient outcomes and treatment should focus on the patient's values and quality of life (employment, relationships, physical and mental health).[66–68] In the primary care setting, it is not uncommon to have patients or treatment plans which focus more on harm reduction rather than abstinence in the early phases of recovery. Frequent follow-up should be recommended for patients who are not ready for the next level of specialized care (addiction treatment) in order to monitor for patterns of drug use (through drug testing), set treatment goals, assess progress and to ensure continued motivation.[68]

## Actionable Clinical Interventions from Precision DDI™

Clinical decision support tools are effective if integrated within the workflow of a clinical practice. Many clinicians want the tools to be available and alert them during or before an anticipated patient encounter in order for alerts/reports to be actionable. In addition, having alerts customized to a particular health condition can make clinical decision support tools more effective. Reliability and correctness of the information is very much valued by clinicians.[69] While clinical decisions are not always clear-cut and clinicians are always encouraged to use their own best judgement when considering the entire picture of the patient, the following are actionable suggestions for how to respond to a DDI result that is integrated with drug tests.

- Clinicians communicate the life-threatening risks of of DDIs to patients with **substance use disorders (SUDs)** in order to reduce the incidence of relapse and discourage substance abuse.
- Clinicians communicate the life-threatening risks of DDIs to patients in **pain management** in order to reduce the potential for new manifestations of addiction and/or discourage co-abuse of drugs like the benzodiazepines.
- Clinicians identify a case of **polypharmacy** through PrecisionDDI™ and communicate the DDI report to other prescribers (primary care physicians, OBGYNs, psychiatrists and addiction specialists) treating the patient.
- Clinicians in a **primary care** setting identify a case of polydrug abuse and begin **transition of care** to specialized treatment facilities. Clinicians communicate DDI results and DDI history upon the "hand-off" to specialized treatment facility.
- Clinicians appropriately assess the risks vs benefits of continuing to co-prescribe certain drug combinations and appropriately **reduce or discontinue drug therapy** to decrease the potential for overdose.

- Clinicians are alerted to previously unknown DDIs and consider **increased monitoring** if the patient is at risk for overdose.
- Clinicians are alerted to DDIs that may affect drug levels in urine, oral fluid and blood thereby **influencing the interpretation** of laboratory test results.
- Clinicians are alerted to **(PIMs)** in **elderly patients** and measure the risks versus the benefits of continuing therapy with the offending medications.

# Conclusion

## Polypharmacy and Polydrug Abuse

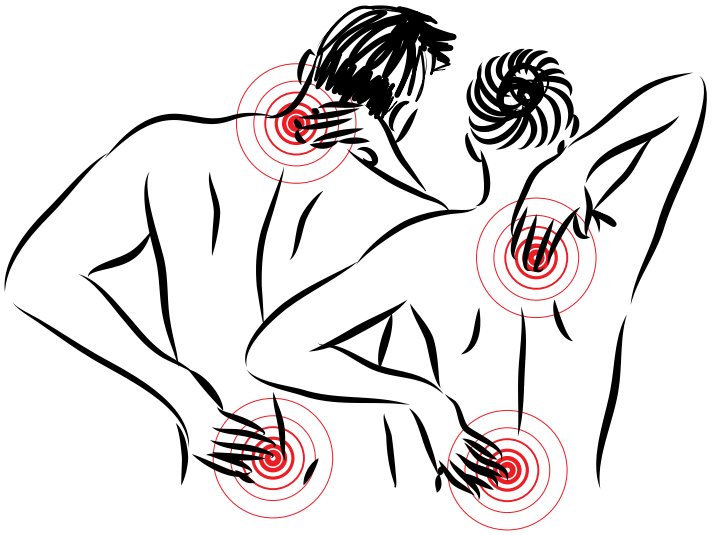
In 2014, approximately 22.5 million individuals age 12 and older needed treatment for substance use disorder. However, only 2.6 million people (11.6%) with a substance use disorder received specialty treatment. It has been reported that most adults in need of treatment for a substance use disorder did not receive it due to a lack of access, insufficient financial resources, stigma, inadequate insurance coverage or low motivation.[70] Much like diabetes, hypertension and asthma, a substance use disorder is a chronic disease state in which relapse is to be expected. Treatment of a substance use disorder is a lifelong process which necessitates frequent monitoring (urine drug testing) and multiple social and clinical interventions to address the biopsychosocial needs of the patient.

Patients with substance use disorders are more likely to have chronic medical comorbidities which include pain-related disorders (arthritis, headaches, lower back pain) and psychiatric conditions (anxiety, depression) which result in increased healthcare utilization and cost.[71] It was found about 2 in 5 adults who met the criteria for a substance use disorder also met the criteria for a mental illness.[72] It is the presence of psychiatric comorbidities that generate the potential for polypharmacy and polydrug abuse. Anti-relapse medications and

medication assisted treatment (MAT) are known to improve treatment outcomes. It is when these psychoactive medications are co-prescribed to treat comorbid psychiatric conditions or co-abused to feed a craving which exposed patients to drug combinations that can cause overdose syndromes, emergency department visits and fatalities. These risks may be unbeknownst to the clinician and the patient.

It was found about 2 in 5 adults who met the criteria for a substance use disorder also met the criteria for a mental illness.

In pain management, patients with chronic pain can benefit from psychology and/or psychiatric evaluation and treatment. Pain and depression are often comorbid disease states in the chronic pain patient. Depression is a common complaint of patients with mood disorders and anxiety.[73–76] It is also common for the chronic pain patient to experience a deterioration of social, marital and financial relationships which correlate to emotional trauma and hopelessness. In these patients we can expect cognitive behavioral therapy and support to be provided by psychologists or psychiatrists. Polypharmacy is also common place in patients being treated for chronic pain. Particularly, the co-prescribing of opioids (Vicodin®) with antidepressants (SSRIs, TCAs), muscle relaxants (Soma®) and/or anxiolytics (Xanax®) can be anticipated and ultimately lead to overdose syndromes characterized by drug-drug interactions. It has been found that about 67% of patients with chronic non-cancer pain receiving opioids were taking additional prescription drug.[47]



Finally, older adults frequently have multiple chronic health conditions which subject them to polypharmacy. Prescription medications among elderly patients in the Unites States has increased substantially from 1988 to 2010, with the use of 5 more medications tripling to about 40%. The amount of antidepressant medication use during this time period was among the most substantial increase. While the use of (PIMs) has decreased since the dissemination of the 2003 AGS Beers Criteria, over 15% of non-institutionalized older adults were still using a PIM in 2009-2010.[77] The 2015 update to the AGS Beers Criteria recommends that if opioids must be used in elderly patients then other central nervous system (CNS) active medications should be reduced or discontinued. Further identifying the need for adequate pain control while balancing the potential harms of using opioids or leaving pain untreated in the elderly.[65]

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