Prescribing controlled substances during a prescription drug epidemic

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Summary

We are currently in the midst of an epidemic of deaths caused by the misuse of prescription medications. Opioids, benzodiazepines, and stimulants are among the most frequently misused controlled substances and are integral to the neurologist's armamentarium. Thus, the decision to prescribe a controlled substance and how to mitigate the associated risks of their misuse is often vexing to the clinician. This installment in the "Clinical Challenge" series provides a basic narrative overview of the epidemiology of prescription drug misuse, a summary of each of the major classes of misused drugs, and clinical recommendations regarding screening for misuse and reducing the risks associated with prescribing controlled substances.

We are currently in the midst of an epidemic of deaths caused by the misuse of prescription medications.¹ With over 22,000 deaths in 2010, drug overdose now surpasses motor vehicle accidents as the leading cause of accidental death in several states.¹ While opioid analgesics are implicated in 75% of these deaths, benzodiazepines, antidepressants, antiepileptics, and antiparkinson drugs round out the top 5 contributors to pharmaceutical overdose death.² These medications are standard to the neurologist's armamentarium; thus strategies to reduce the risks associated with their misuse are needed. We present a basic epidemiologic overview of prescription drug misuse, discuss each class of the commonly misused drugs, and provide some approaches to risk reduction and care

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Funding information and disclosures are provided at the end of the article. Full disclosure form information provided by the authors is available with the **full text of this article** at Neurology.org/cp.

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Table Characteristics that may help identify patients at risk for developing addiction to prescription drugs

Current or past substance use disorder, including current tobacco use
History of misusing prescription drugs
Mental health diagnosis
History of incarceration
Family history of a substance use disorder
Those receiving short-acting, immediate-release formulations

management. Only those medications with moderate to high abuse liability are discussed; therefore, we will not cover antiepileptic, antiparkinson, or antidepressant medications.

The majority of misused controlled substances come not from drug dealers but rather the single prescribing physician and friends/family members.³ Rogue Internet pharmacies account for fewer than 0.5% of misused controlled substances, and multiple prescribing physicians (i.e., doctor shopping), while of concern, may comprise only 30% of prescription opiate deaths.^{3,4}

There is no single definition of nonmedical use, or “misuse,” of prescription drugs. Large epidemiologic surveys define it as the use of these medications without a prescription or simply for the experience or feeling the drug causes.³ We also use it to mean use in a way that is not intended, such as via routes, frequencies, or dosages other than prescribed. More Americans misuse a prescription drug than those who have used cocaine, heroin, hallucinogens, and inhalants combined.³ There is no pathognomic sign that a patient is misusing prescription drugs. However, there are characteristics associated with the risk for developing addiction to prescription drugs. These include a personal or family history of a substance use disorder (including current tobacco use), previous incarceration, psychiatric comorbidity, and nonmedical use of the medication (table).⁵

Pharmacologic effects of frequently misused drugs include euphoria, sedation, and anxiolysis. Drugs with the highest risk for subsequent addiction rapidly elicit dopamine release in the striatum. Here both the magnitude and rapidity of dopamine release are of importance.⁶ Therefore, potent high-dose immediate-onset medications have greater abuse liability than do their less-potent lower-dose extended-release counterparts. A brief review of these medication classes is provided below.

Opioid analgesics

Opioid analgesics are used to treat moderate to severe pain. While their use in acute pain is generally accepted, their use in the management of chronic pain is controversial.⁷ Opioids are the most common pharmaceutical class that is misused, the most common class found in overdose deaths, and the most common class of prescription drug reported on admission to addiction treatment facilities.^{2,3} It is estimated that for every 825 people who misuse opioid analgesics, 130 meet diagnostic criteria for an opiate use disorder (a.k.a. addiction), 32 seek emergency care for an opioid analgesic-related problem, 10 seek treatment for an opiate use disorder, and 1 dies as a result of misuse.⁸ Of the overdose deaths related to prescription drugs in 2010, 75% involved opioid analgesics.²

From 1990 to 2008, overdose death rates, opioid analgesic sales, and addiction treatment admissions related to opioid analgesics increased in parallel.⁸ There is evidence that higher prescribed doses (>50 mg/day morphine equivalents), history of a substance use disorder, and diversion increase the risk of overdose death.^{4,8} While tolerance, or the loss of desired effect after repeated administration, to opioids does develop, it may not occur at the same rate for euphoria or analgesia as it does for respiratory suppression. Thus, a patient may escalate use prior to development of respiratory tolerance. This risk may be greater for long-acting

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opioids such as methadone. There is also variability in tolerance between opioids and patients switching from one opioid to another may unknowingly increase the risk for overdose. For prescribers, several guidelines recommend a reduction of 25%–50% in equianalgesic dose equivalency when switching from one opioid to another and a 75% reduction if the switch is to methadone.⁷ Physicians prescribing more than 100 mg of morphine equivalents per day to a patient may want to seek consultation from a pain specialist to explore opioid-sparing or nonopioid management strategies.

Because more than 30% of opioid analgesic deaths involve methadone, even though it comprises only 2% of opioid prescriptions, it warrants specific mention.⁹ Pharmacoepidemiologic studies indicate that the source of methadone in the majority of these cases is the pain prescriber and not the addiction treatment setting (i.e., methadone clinic).⁹ Education regarding methadone prescribing and dose escalation has reduced methadone-associated mortality in addiction settings and presumably could in pain settings.¹⁰ Free mentoring in methadone and other opioid prescribing is offered through the federally funded Prescribers' Clinical Support System for Opioid Therapies (<http://www.pcass-o.org/>).

Benzodiazepines

Benzodiazepines (BZDs) are used in the management of seizure disorders, spasticity, alcohol withdrawal, and anxiety disorders. In 2010, 2.2% of Americans misused tranquilizers, of which BZDs were the major constituent.³ Nearly 10% of these individuals met criteria for a BZD use disorder. Less information is available on the BZD-like “Z-drugs” such as zolpidem, zalcipon, zopiclone, and eszopiclone, but approximately 2.3% of Americans have a lifetime history of taking zolpidem without a prescription, and these medications are increasingly associated with emergency room visits.^{3,11}

Pharmacodynamically, both BZDs and the Z-drugs enhance the effect of gamma-aminobutyric acid (GABA), the major inhibitory neurotransmitter. Because they modulate a more specific GABA receptor subtype, the Z-drugs were thought to be less addictive and have less abuse potential than BZDs. They elicit a similar behavioral profile including reinforcing effects, abuse potential, tolerance, physical dependence, and subjective effects, however. While Z-drug addiction is uncommon, the risk increases at higher doses and in patients with a history of substance use disorders.¹²

In 2010, 29% of overdose deaths in the United States involved BZDs, and 77% of those deaths also involved opioid analgesics.² When not used in combination with other drugs, BZDs are implicated in only 3.7% of drug overdoses.² The danger with BZDs appears to be mostly in their synergism with other drugs, especially opioids and alcohol. BZDs produce behavioral disinhibition and amnesia and can enhance opioid-induced euphoria. Thus patients misusing both BZDs and opioids may lose track of how much they have taken and be inclined to take more. Prescribers, therefore, should take extra caution in using this class of medication in patients who use opioids or alcohol.

Stimulants

Stimulants are used in the management of attention-deficit/hyperactivity disorder (ADHD), narcolepsy, and obesity. The 2010 National Survey on Drug Use Health estimates that of

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the 7 million current nonmedical users of prescription medications, 1.1 million use stimulants.³ Though the percentage of past month users of prescription stimulants has remained stable, the Drug Abuse Warning Network data show that the number of emergency room visits related to nonmedical use of prescription stimulants has increased 189% since 2004.^{3,13}

The misuse of stimulants is most common in adolescents and is often associated with the desire for cognitive enhancement and euphoria.¹⁴ Use patterns tend to coincide with examination periods and as a means to counter the effects of binge drinking and marijuana use.¹⁴ As with opioids, immediate-release formulations have more abuse liability, and long-acting and tamper-resistant formulations have been developed to discourage misuse.

Although there is a higher risk of misuse and diversion of stimulants in those with a history of substance use disorders, it should be noted that a critical risk factor for having ongoing substance use disorders in adulthood is the persistence of ADHD symptoms and adequate treatment of ADHD in childhood is associated with a lower risk of subsequent drug and alcohol use disorders.¹⁵ When prescribing stimulants, we recommend establishing an accurate diagnosis of ADHD, refusal to provide first-time prescriptions during the weeks immediately preceding school examination periods, and evaluation for substance use disorders and binge drinking.

General risk management strategies

A Universal Precautions approach to prescribing opioids has been developed.¹⁶ Analogous to infection control precautions, this approach assumes that all patients and health care providers serve as vectors in transmitting prescription drug misuse and that procedures should be implemented to mitigate this risk. These procedures include making a clear diagnosis of the disorder being treated, assessing risk of drug misuse, obtaining informed consent regarding the abuse liability of controlled substances, and continually re-evaluating treatment effectiveness and patient adherence.¹⁶

Once a rigorous clinical assessment has established a clear indication for the prescription, the clinician and patient must balance the benefit of the medication in treating the diagnosis with the risks inherent to the medication. Risk in this instance includes the development of misuse and addiction. There are several tools to assess risk of misuse and diversion prior to starting opioid analgesics. The most common of these are the Opioid Risk Tool, the DIRE Score, and the Screener and Opioid Assessment for Patients with Pain.¹⁷ It should be noted that these tools assess risk and should not be used to determine whether or not opioids should be prescribed.

Assessment of risk should include a thorough history of drug use and substance use disorder diagnoses (revised diagnostic criteria were published in 2013), psychiatric diagnoses, and past treatment trials of similar medications. The National Institute on Drug Abuse has developed an easily administered online screening and decision support tool for substance use (<http://www.drugabuse.gov/nmassist/>). We also recommend discussing not sharing medications and keeping them in locked cabinets where they are safe from children and others who may wish to divert or misuse the medication.

While informed consent is generally associated with surgical procedures, it should be utilized whenever a medication with abuse liability is prescribed. Informed consent includes the nature

of the treatment, what to expect from treatment, responsibilities of both parties, reasonable alternatives, and benefits and risks/side effects. Generally a treatment agreement, signed by both parties, is acceptable as informed consent (for an example, see reference 7). While data supporting the effectiveness of treatment agreements are lacking, treatment agreements are considered a standard practice.¹⁸

The most important decision in risk management is whether to start the patient on a medication. Once that decision has been made, monitoring the effectiveness and adherence to treatment is critical. A functional assessment of changes in daily activities, quality of life, and medication side effects (such as oversedation) is helpful in weighing the effectiveness of the prescribed medication.¹⁶ Obtaining collateral information from a trusted source may also be helpful in confirming functional status. Medication adherence and other drug use can be assessed using regular drug screening, prescription monitoring programs (PMP) queries, and pill counts.

Urine drug screening is inexpensive, easily obtained, noninvasive, and widely available. Urine tests can be easily adulterated or falsified if not directly observed.¹⁹ Hair, blood, and saliva testing are alternatives. Urine drug testing should be used to screen for the presence of prescribed and nonprescribed medications and illicit drugs. Urine drug screening is generally a 2-step process. First, in an immunoassay (IA), a monoclonal antibody detects a specific class of drug. These are highly sensitive but not very specific and false-positives are common, especially for stimulants.¹⁹ Second, a confirmatory gas or liquid chromatography and mass spectroscopy can confirm IA results. Despite the marketing of urine drug tests that attempt to correlate patient anthropomorphic characteristics and medication dose to provide a “true” level that if exceeded indicates prescription misuse, there are no widely accepted peer-reviewed studies supporting this approach, and we recommend against the use of quantitative urine drug levels. Finally, drug testing does not definitively confirm whether prescription drug misuse has occurred and does not diagnose the presence of a substance use disorder.

Other strategies to monitor for medication adherence include PMP queries and pill counts. A PMP is a useful tool to detect prescribing by other providers, doctor shopping, and medications not disclosed during patient interview. While 49 states have an active or pending PMP, most are not in real-time and entail a lag of days to weeks, and results should be interpreted accordingly. Currently there is no nationwide PMP, so patients obtaining prescriptions across state lines can go undetected. We recommend querying the PMP prior to prescribing a controlled substance and intermittently thereafter based on patient risk and history.

Pill counts are useful to address whether the patient is using more medication than prescribed or diverting medication to other sources. When prescribing controlled substances, we inform patients that at any point prior to their next office visit they may be given 24-hour notice to return to clinic with their medications. Failure to bring the expected number of pills may be an indication of misuse and for closer patient assessment and monitoring.

The next step in risk management is the most difficult step; managing aberrant behaviors. Aberrant behaviors include misuse, addiction, diversion, prescription forgery, and recurrent prescription loss. In addition to signaling the presence of a substance use disorder, aberrant behaviors may indicate pathology progression, a new or worsened psychiatric diagnosis, cognitive dysfunction, or pseudoaddiction (addiction-like behaviors that result from inadequately treated pain). Regardless of cause, the presence of aberrant behavior will influence the plan and whether discontinuation of the medication is appropriate. A patient misusing medication to self-treat depressive symptoms may be handled differently than a patient selling medication or who is addicted to it.

At our urban safety net institution, a nurse- and pharmacist-led team monitors high-risk patients for adherence and provides decisional support to prescribers faced with aberrant behaviors. This team orders urine drug screens, manages callbacks for pill counts, and queries the PMP. A weekly interdisciplinary team composed of addiction medicine physicians, a pain physician, a pain psychologist, and general internists meets to discuss these patients. The

prescribing physician can ask the team for guidance on risk management. Often the team provides reminders for changing to long-acting or tamper-resistant formulations when appropriate and advises higher frequency monitoring, shorter time spans between prescriptions, a formal evaluation by an addiction medicine physician, or a psychological assessment prior to any decision to discontinue or escalate medications. These types of highly structured interventions can reduce aberrant behaviors and the risk of drug misuse.²⁰

When an opioid must be prescribed to a patient at high risk for misuse and, therefore, overdose, in addition to following the above recommendations, the clinician should consider prescribing the opioid overdose reversing medication naloxone (much in the same way glucagon is prescribed to diabetic patients at high risk for hypoglycemia). When friends and family members of these high-risk individuals are instructed in recognition of opioid overdose and the use of naloxone, overdose deaths may be reduced by as much as 50%.²¹ Information on training patients, friends, and family in overdose recognition and reversal with naloxone can be found at <http://prescribetoprevent.org>.

CONCLUSION

The basic approach to reducing prescription drug misuse we have described is not comprehensive but is a simplified list of easily implemented strategies that include assessing risk, monitoring adherence and function, and assessing aberrant behavior. Using this approach in a coordinated systematic fashion, within and between health care systems, can allow the clinician to focus on the underlying medical condition while reducing the burdens of a prescription drug epidemic.

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STUDY FUNDING

Supported by National Institute on Drug Abuse grant K23-DA024663 (G.B.).

DISCLOSURES

A. Pylkas reports no disclosures. G. Bart receives research support through a grant from the National Institute on Drug Abuse (K23-DA024663); serves on the board of the American Society of Addiction Medicine; and is an Associate Editor for *Addiction Science & Clinical Practice*. Full disclosure form information provided by the authors is available with the **full text of this article at Neurology.org/cp**.

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