

Chapter 2

Scope of the Problem: Intersection of Chronic Pain and Addiction

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Introduction

The prevailing medical and societal view of opioids is a pendulum, swinging between opiophobia and opiophilia. Like this image, the intersection between pain and addiction is a moving target. Various stakeholders have attempted to find a balance between addressing the crisis of chronic pain in society, while not exacerbating the problem of substance abuse. We need to balance the benefits and harms of opioids and other controlled substances with the risks of addiction.

Over the past 15–20 years, there has been a call to re-evaluate the role of opioids in the management of chronic, non-cancer pain. This has led to a dramatic expansion in legitimate prescribing of opiates. The rhetoric that accompanied this expansion tended to overstate the benefits and trivialize the risks of improving access to prescription opioids. As a result of improved availability, prescription drug abuse has been amplified. This appropriate concern makes physicians and caregivers much more cautious about opioid prescribing. The pendulum thus appears to be swinging from opiophilia back to opiophobia.

Physicians are concerned that opioids have long-term limited efficacy, that hyperalgesia may occur for those taking long-term opioids, and that addiction and abuse are real concerns that physicians need to be concerned with. On the other

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hand, some practitioners believe that these drugs, like many other classes of drugs, have benefits as well as risks. To derive the benefits and contain the risks takes time, expertise, assessment and reassessment, along with open, honest and detailed doctor–patient communication. Opioids cannot be used in a one-size-fits-all fashion. Patients who are treated with opioids need to be adequately assessed and triaged to the appropriate level of care. Significant time and decision making are required to safely prescribe opiates.

There is a general agreement that opioids are only first-line in certain situations (postoperative; severe acute; end-of-life care). However, the risk–benefit ratio is relatively low for an older person with arthritis or other medical comorbidities that contraindicate the use of nonsteroidal anti-inflammatory drugs. It is reasonable to prescribe opioids in some settings, as long as coordinated and monitored care is provided.

While opioid medications do have potential abuse, the risk of addiction shows significant patient variability. This depends upon the patient's history of addiction, psychiatric comorbidities, environmental stressors, and the way in which opioid therapy is delivered (with or without the appropriate level of safeguards for their level of risk). The epidemic of prescription drug abuse is not simply the result of the drugs being “powerful and highly addictive” but is also related to a failure to assess risk, match the use of appropriate safeguards, and then employ the safeguards and monitor the patients in a manner necessary to ensure safety. When a high-risk patient is treated as if they have a low risk, this can lead to abuse diversion or addiction.

There are several risk factors for addiction delineated below:

The agent must be

- Readily available;
- Relatively low cost;
- Rapidly enter the CNS;
- Demonstrate efficacy as a rewarding agent.

Environment must be

- Occupation;
- Peer group;
- Culture;
- Social instability.

Host must be

- Genetic predisposition;
- Familial problems;
- Coexisting psychiatric disorder.

Opioid pain therapy means there will be such an exposure. Identifying the latter two issues requires time and assessment.

People with pain are almost inevitably evaluated at a vulnerable time. Frequently a person with chronic pain begins medical treatment after a prolonged period of

time, and the pain may be considered chronic in nature (6–12 months). During this time, they start to relinquish pleasurable activities, restorative sleep is disrupted, libido is reduced, depression develops, they cannot work, and there may be financial stressors.

If there is an exposure at a vulnerable time and the person has any of the known vulnerabilities—younger age (85 % of the addictions in the world are manifested by the age of 35, so an exposure in a young person results in greater risk than in an older person), male gender, personal or family history of addiction, current psychiatric problems such as major depression, post-traumatic stress disorder (PTSD), panic disorder etc., history of sexual trauma, and a history of smoking. When these vulnerabilities are unassessed or unaccounted for in the context of an opioid exposure, this may lead to problematic behavior. However, when appropriate safeguards are instituted, these treatments can be successful. There are settings in which monitoring can be less frequent or intense. For example, the older person with arthritis, no personal or family history of addiction, and no current psychological problems (and not surrounded by friends, family members, or others who might “borrow” some of their medicines) can probably be seen monthly and manage a 30-day supply of opioids without problem. On the other hand, a traumatized, 27-year-old coal miner in southeastern Kentucky with a history of PTSD, depression, marijuana use, and cigarette smoking will be more complicated. He may need treatment for his psychological problems, an alteration in the medical regimen (our team might well have used a long-acting opioid such as a 24-h, once-per-day morphine preparation doled out in small supplies, such as 7 tablets, and see the person weekly), and the provision of tools to help in coping. He will need tools to safeguard his medication supply, and we may also choose to employ certain longer-acting medications, perhaps even one that has an abuse deterrent formulation to deter crushing or altering the formulation so as to help deter misuse. A 30-day supply of short-acting opioids (possibly 120–240 tablets) prescribed to this man without safeguards and monitoring is likely to be problematic.

Key Definitions

Unfortunately, the intersection of pain and addiction is clouded by several overlapping, poorly defined terms and phenomenologically difficult to separate concepts. Thus, we start with a definition of terms.

Addiction

Addiction is a relapsing brain disease characterized by compulsive and overwhelming involvement with the use of a drug, despite harmful consequences [1]. It begins with a voluntary decision to use a drug; however, control over usage

decreases radically over time due to recurrent drug use. The behavioral pattern of substance abuse is generally thought to be chronic, and recovery is possible but is a lifelong process. The transition from voluntary user to addict happens through changes to the structure or wiring of the brain from repeated drug exposure. An individual who continues to use the drug despite physical, psychological, and social harm is considered to have an addiction problem. Addiction implies loss of control and is often confused with physical dependence, which is actually a different phenomenon [2].

If a physician believes that their patient is suffering from addiction, they should evaluate the 4 Cs—compulsive use, continued use despite harm, loss of control, and cravings. These must be assessed as part of an evaluation of addiction.

Physical Dependence

Physical dependence is characterized by the manifestation of physical withdrawal symptoms when a drug is discontinued or the dose is reduced. It can also lead to pseudo-addictive behaviors when a patient requires a drug in order to function normally [3]. Behaviors such as aggressively complaining about the need for higher doses or occasional unilateral drug escalations, which appear to be addicted on the surface, may be indications that the patient's pain is not well managed [4].

Tolerance and physical dependence on a drug can develop for both pain relief and the euphoric effects of a drug and can be produced by psychological and pharmacological factors. Withdrawal symptoms, such as sweating, anxiety, and insomnia, can occur when a patient has developed dependence on an opioid, and the drug is discontinued. It is thought to be caused by rebound at the central adrenergic nuclei [5]. Withdrawal symptoms can lead patients to seek opioids from both legitimate and illegitimate sources. While the current DSM-5 excludes tolerance and withdrawal from the diagnostic criteria for substance-use disorder during medical drug treatment, it should be noted that pain patients who are treated continuously with opioids may not manifest any aberrant behaviors.

A law in the state of Washington came into effect in 2012 that attempts to limit the amount of opioids that can be prescribed for those with chronic pain without consultation from an expert. This law was passed in response to high death rates from prescription opioid overdoses in the state. In some cases, some physicians began to taper patients who were using high-dose opioids who had for years. Several patients experienced reemergence of anhedonia and severe pain, both of which were likely to be effects of withdrawal. In this setting, tapering patients' high opioid doses may have destabilized them, leaving them with constant cravings and aberrant behavior [5].

Many clinicians confuse physical dependence with addiction. Physical dependence has been suggested to be a component of addiction, and it has been proposed that patients who seek to avoid withdrawal symptoms construct behaviors that reinforce drug-seeking behavior. However, these assumptions are not supported by

experience acquired during opioid therapy for chronic pain. Animal models have provided indirect evidence for a fundamental distinction between physical dependence and addiction through opioid self-administration. This demonstrates that in the absence of physical dependence, drug-taking behavior is allowed to persist. However, clinical observation also fails to support the conclusions that analgesic tolerance plays a significant part in the development of addiction [2].

Tolerance

Tolerance occurs when an individual becomes habituated to a drug and needs the dose increased to maintain the same effect as an earlier dose. There has been a long-standing basic definition of tolerance as a pharmacologic property highlighted by the need for increasing doses to maintain effects. Tolerance and physical dependence are both common occurrences among patients taking opioids for chronic pain and are unrelated to true addiction [1].

The widely accepted 2001 definition by the American Academy of Pain Medicine, the American Pain Society, and the American Society of Addiction Medicine makes it clear that such a definition is too narrow. Their consensus document states that tolerance “is a state of adaptation in which exposure to a drug induces changes that result in a diminution of one or more of the drug’s effects over time” [6]. Opioids are usually begun at a low dose in order to minimize side effects, and are increased as tolerance develops to the side effects. Early upward dosing is therefore expected. In addition, pain relief is often accompanied by an increase in physical activity, and the increased activity in itself often requires additional medication to provide adequate pain relief. This in itself can explain why early dose escalation is so frequently found. Delayed dose escalation may also herald the appearance of a progressive painful lesion or the development of new pains. In the absence of tolerance, the greatest need for opioid titration occurs during the first 3 months for most patients, and thereafter, further dose escalation may be gradual and minimal unless a mitigating event like disease progression or new injury occurs [2].

Withdrawal

Withdrawal symptoms occur due to the cessation or decrease in the amount of drug that an individual has been taking. The individual must first have developed a physical dependence to the drug in order to experience withdrawal symptoms. Withdrawal symptoms such as nausea, muscle aches, diarrhea, and insomnia can develop within minutes to several days after the reduction in opioid use that had previously been heavy or prolonged [7].

Opioid-Induced Hyperalgesia

Opioid-induced hyperalgesia (OIH) has been suggested as an explanation for the decreased analgesic efficacy of opioids in some patients requiring high doses. Chronic opioid use may increase sensitivity to specific pain stimuli but not others and does not produce allodynia [2]. It has been shown that opioids can cause nociceptive sensitization, can aggravate existing pain, or potentially cause new pains [8, 9]. The mechanisms and signal transduction pathways that mediate OIH are very similar to those of neuropathic pain and opioid tolerance. Hyperalgesia should be considered when patients have unexplained pain that is unassociated with the original pain or increasing levels of pain when their dosage of opioids has also increased. Treatment of hyperalgesia generally includes reducing the opioid dosage or utilizing NMDA receptor antagonists [9, 10].

While hyperalgesia clearly exists in animal models, there is inconsistent evidence to support or refute the existence of opioid-induced hyperalgesia in humans in clinical settings. However, animal models have limitations for accurately predicting human opioid pharmacology [11]. There is significant evidence in the animal literature to suggest that rodents exposed to very low doses of opioids showed signs of hyperalgesia, whereas those exposed to larger doses resulted in a reduction in sensitivity to painful stimuli. There are no animal studies, however, that examine hyperalgesia in chronic pain, so one should be careful in attributing increased sensitivity to pain to hyperalgesia since the evidence supporting it is somewhat thin [12].

Hyperalgesia, or at least decreased opioid effectiveness, also might be explained by low testosterone (hypogonadism) caused by long-term opioid use. Passik and colleagues [13] have recently shown that low testosterone lowers the pain threshold and triggers decreased pain tolerance in men undergoing androgen ablation. Perhaps treating these patients with hormone replacement therapy could help treat their pain sensitivity and restore efficacy of their regimen in the absence of opioid dose escalation or taper. Certain types of people also could be predisposed to this problem as well, such as those with a personal or family history of addiction [14].

Chemical Coping

Chemical copers occasionally use their medications in non-prescribed ways to cope with stress. A major hallmark of chemical coping is the fixation on the procurement of drugs for pain and the inflexibility about non-drug components of care. Medication use becomes central to life, while other interests become less important, and as a result, chemical copers in treatment often fail to move forward toward stated psychosocial goals. They are typically uninterested in treating pain or coping with pain non-pharmacologically. It should be noted, however, that while all addicts are chemical copers, not all chemical copers have addiction disorders.

Chemical copers also occasionally self-escalate their medication dosage in times of stress and sometimes need to have prescriptions refilled early [15]. The treatment approach for these types of patients might rely mainly on the use of long-acting opioids with a de-emphasis on drug-taking as a way of managing pain throughout the day. Psychotherapy and rehabilitative approaches are particularly important for this group of patients. Motivation for multiple lifestyle changes should be introduced so that the patients can regain the desire to live full lives despite having the disease of chronic pain [16].

Risks of Death and Other Comorbidities

Opioid prescribing has increased dramatically in North America from the time when opioids were mainly being prescribed to cancer patients. The population of non-cancer opioid users is much more diverse in terms of age, psychiatric and addiction histories and comorbidities, and duration of exposure [17]. The results of this change, however, have been mixed. Rather than the self-titration model based on the assumption that risk of misuse and addiction was uniformly minimal across patients (generally a cancer pain model), a specific type of risk stratification model was created for these types of patients. Some of the risk factors include younger age, personal or family history of addiction, a history of sexual trauma, and active mental health comorbidity. These types of risks were seen as indicators in a poor outcome in opioid therapy, unless the delivery of this therapy was tailored to the needs of the individual with the implementation of safeguards such as urine drug testing and prescription monitoring programs [3]. In 2013, for example, an estimated 7.7 million adults aged 18 or older (3.2 % of adults) had co-occurring mental illness and substance-use disorders in the previous year. The percentage of adults who had co-occurring mental illness and substance-use disorders in the past year was highest among adults aged 18–25 (6.0 %), followed by those aged 26–49 (4.5 %) and then by those aged 50 or older (1.1 %). Co-occurring mental illness and substance-use disorders were higher among males than females (3.6 % vs. 2.8 %) [18].

A co-occurring mental illness is one of the stronger risk factors for abuse for patients on opioid therapy. An estimated 2.3 million adults aged 18 or older (1.0 % of adults) had co-occurring serious mental illnesses (SMI) and substance-use disorders in the past year in 2013. Percentages were similar for adults aged 18–25 (1.7 %) and those aged 26–49 (1.4 %), both of which were higher than among adults aged 50 or older (0.4 %). Adults with major depressive disorders also had a high use of substance abuse disorder in the past year at an estimated 3.3 million adults in the USA [19]. About half of adults with those comorbidities received either mental health care or substance-use treatment (47.8 %), including 7.7 % who received both types of care.

Another example of the risks patients involved who use opioids was documented in a survey in Denmark that revealed that 22.5 % of men and 27.8 % of women aged 65 and older reported chronic pain [20]. Out of these men and women, 35 %

of them were not satisfied with the type of pain treatment that was offered. Patients who are dissatisfied with their care could possibly seek out other types of pain relievers, such as non-prescribed medication. In one study of 100 patients with chronic pain (average age near 50), 23 tested positive for illegal drugs and 12 tested positive for opioids even though they had no prescription and denied taking opioids [21]. In another study of primary care patients in a Veterans Affairs facility who were receiving opioids for the treatment of chronic pain (average age 59), 78 % reported at least one indicator of medication misuse during the prior year, with significantly more of those who misused pain medications reporting comorbid substance-use disorder [22]. This is consistent with a more recent examination of a subset of data from the Researched Abuse, Diversion and Addiction-Related Surveillance system (RADARS) that found that though severe chronic pain is common in adults entering treatment for prescription opioid abuse, it is exponentially more prevalent in adults older than 45 years (70 %) relative to adults aged 18–24 (45 %) [23]. Older adults represent a particularly vulnerable population based on the fact that chronic pain and severe mental illness are comorbid problems [3].

Pill Mills

In the past ten years, prescription drug abuse has exploded around the country. There have been stories of pain clinics being opened up in Florida and Georgia by former auto-traders and twenty somethings, none of whom had medical degrees. In other states, only individuals with medical licenses may own and operate pain clinics. The pill mill epidemic became a national problem in 2010, and lax laws in Florida allowed it to become the nation's hot spot to easily buy prescription drugs. Many individuals came from out of state to buy prescription drugs from Florida, and the state became colloquially known as the "OxyContin Express." However, in the last several years, many "pill mills" have been shuttered and their owners and doctors arrested due, in part, to new prescription drug monitoring programs (PDMPs) that have been put into place. Missouri is currently the only state without a PDMP as of 2015. This increase in states with PDMPs is not surprising after states with the largest problems, such as Florida, enacted laws to curb the tide of overdose deaths and misuse of painkillers. After Florida enacted laws requiring legitimate pain clinics to register with the state and dispensers to report state's PDMP, they were able to shut down 250 rogue pain clinics and the number of high-volume oxycodone prescribers dropped from 98 in 2010 to 13 in 2012. The policy changes in Florida were followed by a decline in the prescribing of drugs but an increase in deaths associated with heroin, hydromorphone, and morphine after 2010, which might be a sign of a switch to the use of street drugs and alternative opioids [24].

Organized crime also has ties to the pill mill industry and helped to fuel the growing problem of prescription pill abuse. In 2013, the New Jersey State Commission of Investigation found that corrupt doctors had been charging Medicare for prescriptions and were funneling the reimbursements into bank

accounts linked to the Russian mafia. New Jersey is working on a series of reforms that would help combat this type of drug problem and prevent future pill mills from being able to set up shop so easily. The plan involves imposing prescription standards for physicians, establishing harsher penalties for prescription drug diversion and oversight of medical practice and ownership, and enhancing New Jersey's prescription monitoring program [25].

Problems with Diversion

Diversion is one of the many problems that can occur with opioid prescription use. In 2013, there were 6.5 million current (past month usage) non-medical users of prescription-type drugs, including 4.5 million non-medical users of prescription pain relievers aged 12 and older. In 2013 as well, 2.2 % of adolescents aged 12–17 were current non-medical users of prescription-type drugs, including 1.7 % who used pain relievers. Of the 22.4 million adults aged 18 or older who used illicit drugs in 2013, 2.5 % of those used non-medical prescription-type drugs including 1.7 % who used pain relievers [18].

Signs to watch for that could indicate that patients are diverting their opioid medications include: [26]

1. Strange stories—Be wary of new patients with stories that do not seem right or make sense. Some may deliberately request appointments at the end of office hours or ask to be seen right away because they have to “catch a plane” or “need to get to an important appointment.”
2. Reluctance to cooperate—Diverters will often refuse a physical examination or deny you permission to access previous medical records. These patients might leave the office suddenly if things are not going their way.
3. Unusual high or low understanding of medications—many diverters may request specific medication brands and may resist any attempts to prescribe them generic forms or substitutes.
4. Strange symptoms—Diverters might fake or exaggerate symptoms.

Problems with Opioids with Muscle Relaxants and Anxiolytics

Prescribing both benzodiazepines and opioids for a patient can potentiate respiratory depression, leading to serious consequences if they are not monitored correctly. Of the 22,767 deaths relating to pharmaceutical overdose in 2013, 16,235 (71.3 %) involved opioid analgesics, and 6973 (30.6 %) involved benzodiazepines [27]. Patients with chronic pain who use opioids alongside benzodiazepines (BZD) are at a higher risk for overdosing and demonstrate more aberrant behaviors.

Combining BZD and opioids increases the euphoric effects of the opioids. For example, it appears as though the addition of a BZD drug to methadone or buprenorphine may allow one to achieve a more powerful opioid effect often described as “heroin-like” [28]. To improve patient outcomes, clinicians should monitor for treatment compliance, screen for aberrant behavior, document medical necessity, and adjust treatment to clinical changes when necessary. Regardless of the risk that patients might possess for aberrant behaviors, patients on chronic opioid therapy should periodically undergo urine drug testing to confirm that the patients remain adherent to their prescribed treatment [29].

Opioid Risk Stratification

It is essential that proper assessments be completed to take reasonable steps to guard against abuse and diversion and to ensure that patients will be treated safely and effectively. A chronic pain assessment should include a detailed assessment of the pain itself, including intensity, quality, location, and radiation of pain. It also should ask about the identification of factors that increase and decrease the pain as well as a review of the effectiveness of various interventions that have been tried to relieve the pain. Clinicians should also assess the impact of pain on sleep, mood, level of stress, and function in work, relationships, and recreational activities since improvement in these areas may be a goal of pain treatment and a measure of the efficacy of interventions. If an individual has a predilection toward recreational drug use, prescription of opioids could lead to the abuse and/or diversion of the drugs and at worst, addiction. Several patient factors have been found to be predictive of a patient’s risk for opioid misuse or abuse. A mental health disorder is a moderately strong predictor of opioid abuse, while a history of illicit drug and alcohol abuse or legal problems is also predictive of future aberrant drug behaviors. Tobacco use is highly prevalent among substance misusers, and the Screening Instrument for Substance Abuse Potential (SISAP) and the Screener and Opioid Assessment for Patients with Pain (SOAPP) include tobacco use as a factor in determining risk [3, 30, 31].

Assessment

There are several methods of assessment that the clinician can use to obtain details about the type of pain that a patient has and also as a tool to evaluate the best pain management strategy to employ.

Pain Assessment and Documentation Tool (PADT)—This type of assessment is a two-sided chart note that assesses pain relief, side effects, and aspects of functioning as well as potential aberrant drug behavior. It consists of 41 items and takes about 10 min to administer and score. It helps to assess the long-term patient

progress on opioid therapy for chronic pain. PADT is a chart note intended to help clinicians to assess and document their observations when treating chronic pain patients on opioid therapy. The tool is based on the assumption that systematic pain assessment and documentation can assist in improving patient care [32].

Numerical Opioid Side Effect (NOSE) assessment tool—One available tool for the quantification of adverse effects is the NOSE assessment tool. The NOSE instrument is a simple, rapid, self-administered tool which has the potential to be utilized in a busy clinical setting to document and longitudinally follow trends of opioid adverse effects. The NOSE assessment tool is easy to administer as well as easy to interpret and may provide clinicians with important clinical information which could potentially impact various therapeutic decisions [33].

Opioid Risk Tool—This tool has 5 items that cover questions about family history of drug abuse, personal history of drug abuse, age, history of sexual abuse, and psychological disease. It takes less than a minute to administer and score, and it assesses the risk of aberrant behaviors when patients are prescribed opioids for chronic pain. One of its features is that it provides excellent discrimination between high- and low-risk patients. It also has the advantage of having brief and simple scoring [34].

Screening Tools

Screener and Opioid Assessment for Patients with Pain—Revised (SOAPP-R)—SOAPP-R is a 24-item self-administered screening tool developed and validated for those persons with chronic pain who are being considered for long-term opioid therapy. It takes less than 10 min to complete it, a quick and easy way to predict aberrant drug-related behaviors. This questionnaire includes subtle items that encourage the patient to admit to certain factors that are positively correlated with opioid misuse yet outwardly are not perceived to lead to reprisals. Any individual who scores more than 18 on the SOAPP-R is rated as being at risk for opioid misuse [31].

Urine drug test (UDT)—UDT is one of the most widely available methods for monitoring opioid use in pain and addiction patients. It is a valuable tool that can help physicians in the clinical setting. Most evidence suggests that UDT is best used in concert with other clinical monitoring tools, such as continuous assessments of a patient's pain levels, quality of life, risk stratification for possible misuse, checks of the state prescription database, and psychosocial indicators [35]. The value of urine drug testing to pain clinicians has grown considerably as laboratories offering more accurate, sensitive, and specific forms of testing are now capable of providing these results in clinically actionable time frames.

There are two different testing methodologies that can be used in UDT, immunoassay and chromatographic; the latter category can be further subdivided into gas chromatography mass spectrometry (GC-MS) and liquid chromatography tandem mass spectrometry (LC-MS/MS). Immunoassay tests, also called point-of-care testing (POCT), are primarily used for on-site testing as the method is inexpensive, convenient, and less accurate and is the preferred initial test for

screening. The immunoassay test (IA) uses antibodies to detect the presence of numerous drugs or drug classes and can determine whether a class of a substrate is present or absent [36]. It uses antibodies that are designed to bind to a specific type of drug without binding to the other substrates in the sample. This type of test exhibits adequate sensitivity for many purposes such as the forensic or vocational or screening in pain management. However, it typically does not identify specific metabolites and often does not distinguish between different drugs of the same class (e.g., opioids) and thus not able to function as the definitive testing method for pain management clinicians. Cross-reactivities with other substances also are very common with this type of test, and this can produce many false positives, such as quinolone antibiotics and opiates or poppy seeds and opiates. The observed interference from cross-reactivity with substances other than the drug of interest may vary from assay to assay [37]. POCT also has higher cutoff levels than laboratory testing which can produce a high rate of false negatives (i.e., missed opportunities for clinicians to be informed about and intervene in cases of illicit drug use or the use of non-prescribed legal drugs).

Urine drug testing also is performed in laboratories that use GS-MS or LC-MS/MS technology which is a more highly sensitive and definitive method of testing than immunoassay tests. In many instances, this type of technology is used in confirmation testing as a second test positively identify a drug or metabolite from a positive specimen but this also approach it has been shown should not be limited to confirmation of positives alone given the high rate of false negatives in the pain management setting. This type of testing is often used as the sole testing method since it provides more accurate information as it typically measures the concentrations of all drugs, metabolites, and illicit substances ordered. One of the key clinical differences between LC-MS/MS and GC-MS is that LC-MS/MS can function more independently from IA; LC-MS/MS does not depend on and thus is not subject to the inaccuracies of the IA method, as it can test for many drugs at the same time. This is unlike GC-MS which depends on the IA result to guide the preparation for subsequent testing as the specimen must be volatilized individually for all individual drugs; thus, it is less versatile functioning outside of the confirmation of positive mode.

Pharmacogenetic testing—Numerous genes are involved in the pharmacokinetics and pharmacodynamics of opioid analgesia, the discussion of which is beyond the scope of this chapter. Here, we will discuss the ways in which genotyping can be used, in part, to predict pain responses for patients and to help avoid adverse drug reactions and thus are related to improving adherence to prescribed medication. The two genetic profiles that can greatly affect drug metabolism are ultrarapid metabolizers (Have 1 or more alleles which result in increased enzyme activity) or poor metabolizers (Have 2 non-functional alleles with little to no enzyme activity). The impact on each genetic profile on the opioid depends on the role of the enzyme in the metabolism of the drug.

Successful implementation of pharmacogenetic testing in a clinical practice can assist patients and clinicians with therapeutic decisions, risk communication, and reduce healthcare costs [38]. Choosing medications to which a given patient is more

likely to respond might very well be a way in which clinicians can avoid poorly treated pain that might lead to overuse of medication or pseudo-addiction like behaviors on the part of the patient.

Another example of how genetics can affect the drug metabolism of chronic pain patients is the occurrence of withdrawal symptoms between scheduled doses of a drug in users with a specific genotype that could lead to overuse of opioids. In our clinical experience, we saw this not infrequently; patients on short-acting medications would begin to feel unwell at the end of a dosing interval, and this in turn was often a cue for taking the next dose (and not necessarily increasing pain). Perhaps particular genetic phenotypes might be even more vulnerable to withdrawal symptoms between opioid doses, such as a CYP2D6 ultrarapid metabolizer. A number of opioids are metabolized by the CYP450 system, which includes the CYP2D6-specific enzyme. Some of the opioids that are metabolized by this enzyme are broken down into metabolites for analgesic effectiveness and for elimination from the body. CYP enzyme expression and function can vary greatly between patients and they can be categorized as a poor metabolizer (inactive or minimally active enzyme), as an intermediate metabolizer (underactive enzyme), as an extensive metabolizer (normal enzymatic function), or as a rapid or ultrarapid metabolizer (overactive enzyme). The ultrarapid metabolizers will metabolize the opioids much more quickly than the extensive and intermediate metabolizers, while the poor metabolizers have little or no enzymatic functionality. If a CYP2D6 ultrarapid metabolizer takes short-acting hydrocodone, they might go into withdrawal between doses, prompting them to take the medication more frequently, which could lead to loss of control. Switching to a long-acting medication or one targeting an alternate metabolic pathway would potentially avoid this issue and could lead to a resolution of this problem [39].

Conclusion

Opioid prescribing has increased dramatically in the last several years. Some have benefited, but others have been harmed. With nearly 70 million people in the USA reporting chronic pain, any argument that one particular therapy is right or wrong for all or nearly all of them is not worth pursuing. It is clear that there are risks and benefits that can be balanced with time, expertise, and the use of the tools and strategies that have emerged over the past few turbulent years. What people suffering with pain need is neither a blank check for opioids nor a complete avoidance of them on the part of their providers. Pain physicians need to balance the treatment of pain with concerns of addiction. Healthcare providers need to be careful and open-minded so that they can artfully derive a treatment program—with or without opioids—that can help them live a full and meaningful life. Our humanity is not manifest in our willingness to provide opioids or protect people from them; our humanity is manifest in maximizing what we can do to help and minimizing harming those who trust in us.

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