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OPIOIDS, SUBSTANCE ABUSE & ADDICTIONS SECTION

Review Article

Crossroads of Pain and Addiction

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Abstract

Background. Despite the fact that chronic pain and addiction often coexist, few pain training programs offer significant experiential and didactic training in drug abuse and addiction. Similarly, addiction medicine programs often offer little training in pain management. What follows is a review of the intersection between these two specialties from the perspective of clinicians that practice both.

Objective. The objective of this study was to review the historical backdrop, terminology, vulnerability, and neurobiology of addiction; explore the effects of drug, delivery system, timing, and environment on drug self-administration; and review strategies used in managing patients with coexisting addiction and chronic pain.

Setting. The University of Florida has training programs in both pain management and addiction medicine. The collaboration of these two subspecialties has led to the development of a successful pain management clinic that manages difficult patients based on the strategies that are discussed.

Conclusions. It is possible to successfully manage patients with coexisting chronic pain and addictive disorders. Addiction medicine and pain management training programs should offer didactic and experiential training in both subspecialties.

Key Words. Pain Training Programs, Drug Abuse, Addiction, Chronic Pain

Sentence Summary

Patients with coexisting addictive disorders and chronic pain are common and represent some of the most difficult patients in the field of medicine. With proper training and help from addiction specialists, these patients can be successfully managed.

Introduction

Though chemical dependence affects an estimated 15% of our population, physicians receive remarkably little training in addiction medicine [1]. A study in 2001 showed that on the average, out of the thousands of hours of didactic and clinical medical education physicians receive, less than 12 hours are devoted to addiction [2]. In the field of pain management, this is especially disappointing given the fact that we prescribe many medications that are linked with drug abuse, addiction, and diversion [3]. Yet most pain management fellowship programs do not include experiential addiction medicine rotations. It is very difficult to appreciate the power of the drive to self-administer drugs, withdrawal anhedonia, as well as the altered thinking and denial that occurs with addiction. Likewise, without this exposure, it is difficult to appreciate the efficacy of drug treatment and the power of a recovery program to normalize behavior [4].

Uncontrolled chronic pain is so common among patients being treated for addiction that it has been recommended that treatment facilities develop comprehensive and structured pain programs [5]. Jamison et al. showed that 37% of patients in methadone maintenance and 24% of inpatients in drug treatment facilities reported severe chronic pain [5]. However, the prevalence of addiction in those being treated for chronic pain is less clear with wide ranging estimates varying from 2.8% to 50% depending on the study as well as the definition of addiction used [6]. Furthermore, there is evidence that patients with coexisting pain and addiction have a

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"syndrome of pain facilitation" with decreased pain tolerance, increased anxiety, depression, and sleep disturbances [7–9].

Pain patients with a coexisting substance disorder are among the most challenging patients in medicine. As pain is subjective and can exist without physical findings, our assessment and plan depends on what our patients tell us. The philosophy widely endorsed by pain management providers is *"pain exists whenever the patient says it does"* [10,11]. In contrast, deception (both of self and others) accompanies addiction as evidenced by the witticism often heard in the rooms of Alcoholics and Anonymous (AA) *"How do you tell an addict is lying . . . his lips are moving"* [12]. Thus, addiction compromises the most useful tool we have in pain management, the patient's account of their pain history and the efficacy of our treatment plan.

Licensing boards and regulatory authorities expect us to spot deception. However, a recent study showed that most physicians are unable to do so and though physicians in all specialties are deceived by factitious disorders such as malingering or Munchhausen's syndrome, only in pain management, where controlled substances are prescribed, can missing deception lead to loss of licensure and criminal penalties [13]. Arguments over drug type and quantity driven by intense addiction-driven motivation can occur and there is a high incidence of psychiatric comorbidity [14–16]. Finally, frustration can result when despite our best efforts, patients with untreated addiction fail to improve or even worse, potentially disastrous complications such as drug overdose occur [17].

Iatrogenic Addiction

Though it is clear that opioids can cause physical dependence and trigger relapse in those recovering from addiction, it is still being debated whether or not they can actually cause addiction. At the turn of the century, it was generally believed that anyone who used opioids long term became addicted and the cure for addiction was simply to muster up the will power necessary to deny oneself opioid-induced euphoria and endure the discomfort of physical withdrawal [18]. The inability or unwillingness to do so was believed to be secondary to a weak will or moral corruption. Without an understanding of addiction vulnerability, for much of the 20th century, the prevailing view was simply that chronic use of opioids created addiction and those who were supplying opioids were causing addiction. According to the October 17, 1903 issue of JAMA, "*Unfortunately, a large number of cases (of addiction) are reported as directly due to careless prescribing by physicians. Physicians must be guarded and careful in the use of such remedies and must discourage in every possible way the use of proprietary remedies containing them*." [19] In fact, as late as the 1970s, physicians were advised against prescribing opioids for chronic pain . . . even cancer pain [20].

The belief that chronic use of opioids resulted in iatrogenic addiction came under scrutiny in the 1980s when several studies suggested the actual risk was miniscule [21,22]. Though these early studies were flawed by such factors as small sample size, or use of acute rather than chronic pain patients, they were influential in changing pain practice to a "give them as much as they need" philosophy [22]. However, optimism dampened in the face of perceived increases in abuse and addiction, known increases in prescription abuse, endocrinopathy and opioid induced hyperalgesia [23–25]. Today, our increased understanding of opioid induced neuroplasticity and addiction vulnerability suggests a more balanced approach that acknowledges both the risks of chronic opioid therapy (COT) as well as the benefits. It seems likely that though opioid pain medications can produce changes in the brain that can potentially result in the disease of addiction, the relative ease with which this occurs depends on such factors as genetics, history of traumatic stress, and psychiatric illness [26]. Other drugs such as crack cocaine seem to overwhelm the midbrain with dopamine and induce the neuroplastic "rewiring" to such an extent that even those who are not genetically preloaded more easily succumb to addiction [27].

In the past, physical dependence (as manifested by a withdrawal syndrome) was synonymous with addiction. Today, we understand that that even though the two often occur together, they are not the same thing. In fact, they do not have to occur together [28]. For example, the abrupt discontinuation of "non-addictive" substances such as *paroxetine*, *venlafaxine*, and *baclofen* often produce physical withdrawal symptoms whereas the "addictive" drugs, *crack cocaine* and *amphetamine* produce few classic physical withdrawal symptoms [29–32]. Though somewhat oversimplified the difference between the two can be summed up by the observation. "*A non-addict will go through physical withdrawal and say that he will never take the drug again, and won't, whereas a patient with the disease of addiction will go through physical withdrawal and say he is never going to take the drug again, and will*." [33] Addiction implies using despite consequences, preoccupation with obtaining the drug, loss of control when using the drug, and thinking changes that often involve denial and rationalizations that justify continued use despite sometimes catastrophic consequences [34].

Vulnerability

Numerous animal, genetic, and epidemiological studies have shown that vulnerability to addiction is profoundly influenced by heredity and life events. Animals can be bred to be susceptible or resistant to drug-seeking behavior. This also appears to be true with humans as evidenced by family tree, twin studies, and more recently, genetic markers. Furthermore, a history of abuse, and physical or emotional trauma markedly increases the risk for drug abuse and addiction [35–38]. Patients who suffer from posttraumatic stress disorder (PTSD) experience increased baseline sympathetic

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nervous system overactivation, and exaggerated withdrawal symptoms [39,40]. Uncomfortable emotional memories are often triggered by reminders of the trauma and coexisting axis 1 and 2 pathology, and emotional dysregulation are common [41–44]. Opioids and other potentially addictive drugs may be used to self-medicate these uncomfortable sensations. Patients with a history of traumatic stress may have difficulty correctly interpreting physical sensations, and pain is often magnified out of proportion to the organic pathology [45]. These patients often suffer from fibromyalgia, chronic headaches, temporomandibular joint (TMJ) syndrome, back, neck, abdominal, and pelvic pain. Coping mechanisms are often poor, and trust issues may complicate care and reduce compliance.

It is not surprising that a history of traumatic stress represents a risk factor for addiction as addiction and PTSD share a common neurobiology characterized by prefrontal cortical dysfunction, and depressed midbrain dopamine [46–49]. Furthermore, there is evidence that the combination of PTSD-related emotional triggers, drug triggers (people places and things), and stresses (pain) have a synergistic effect on drug cravings [40].

Addiction is associated with axis 1 (depression and anxiety), axis 2 (borderline, antisocial) disorders, impulsivity, and a "thrill-seeking" personality [15,50]. Whether these traits or disorders constitute predisposing factors that lead to addiction are associated factors that co-occur with addiction (possibly by sharing a common neurobiology), or are in some cases the result of addiction is not clear as correlation does not necessarily imply causation. There is a common misperception that addictive behavior is secondary to psychiatric comorbidity and if the underlying disorder is treated, the addiction will go away. However, addiction is a primary neurobiological disease rather than a secondary disorder. According to psychiatrist and former head of the National Institute on Drug Abuse (NIDA), Robert DuPont, MD:

> When an individual uses an abused drug nonmedically, he or she is seeking brain reward, not treatment. To confuse this drug-using behavior with treatment is to misunderstand addictive behavior and to encourage a false sense that the primary clinical task is to lower the dysphoria associated with the comorbid condition in order to stop the nonmedical drug use. Even the most effective treatment of comorbid disorders is unlikely to halt the addictive drug use [51].

A history of prior or current drug use increases the risk for future drug use and addiction. Recent evidence suggests that those who currently smoke or have smoked tobacco or marijuana may have increased vulnerability [52]. This is supported by animal studies showing that exposing rats to delta-9-tetrahydrocannabinol (THC) during the 2 weeks post-birth increased the likelihood of conditioned place preference conditioning to heroin at 8 weeks, and THC-treated "adolescent" rats not only used 25% more heroin when later tested, but also possessed more opioid receptors [53,54].

Finally, the under-medication of chronic pain enhances the risk of addiction [55]. The stress from pain augments dopamine overflow in the VTA-MFB-Acb reward axis, drug-seeking and drug taking behavior, the rewarding effects of addictive drugs, and augments drug—induced incentive motivation. As Eliot Gardner, chief of the neuropsychopharmacology section of NIDA states:

> For all these reasons, elimination of the stress produced by the undertreatment of pain is a medical imperative; failure to do so invites rather than prevents addiction [55].

Drug Control Measures and Opiophobia

From a historical perspective, the fear many physicians have of treating chronic pain with opioids (opiophobia) is understandable [56]. In 1914, the *Harrison Narcotics Act* was introduced as a piece of legislation that focused on taxation. However, this act morphed into a drug enforcement instrument in 1919, when it was reinterpreted as having "*the moral purpose of discouraging the use of drugs except as a medicine*." Though seemingly reasonable, this wording opened the door to the prosecution of doctors because those suffering from addiction were not considered patients, and thus prescribing opioids could not be considered medical care. Over the next 14 years, more than 77,000 violations, mostly by physicians, were prosecuted [57,58]. The Harrison Act was finally repealed in 1970 when the Controlled Substances Act was introduced, giving rise to the United States Drug Enforcement Administration (DEA) 3 years later. In the late 1990s, stories of OxyContin addiction and the well-publicized arrest of overprescribing doctors continued to perpetuate unease over prescribing opioids for the management of chronic pain.

According to the *National Prescription Drug Threat Assessment* prepared by the National Drug Intelligence Center in conjunction with the DEA, it is clear that prescription drug abuse is an enormous public policy issue. According to the Office of National Drug Control Policy (ONDCP) data, in 2005, there were over 8,500 deaths involving prescription pain relievers, an increase of 114% since 2001 [59]. Furthermore, between 2004 and 2006, emergency room visits increased 39%, drug treatment admissions increased 74%, and 1 in 5 new drug abusers are initiating use with potent opioids such as *oxycodone* and *hydrocodone* [59]. Indeed, while most illicit drugs have shown considerable declines in use over the past decade, most prescription drugs have not. In fact, many have shown steady increases [59].

Most studies show that the risk of licensure or legal issues is extremely low with only a very small percentage of all physicians getting onto trouble. However, when the denominator is changed to self-designated pain physicians and the numerator is changed to DEA investigations, the number calculated is a less reassuring 15% [60]. Factors that are correlated with increased risks are poor documentation [61], failure to address addiction issues, lack of Board Certification, and advanced prac-

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titioner age. However, with proper screening, appropriate evidence-based prescribing practices, and use of an opioid agreement, the likelihood of licensure or legal issues is low [62]. There appears to be momentum building to increase the regulatory oversight of pain management clinics. For example, in Florida legislation has been passed that calls for the implementation of an inspection process of pain clinics, their prescribing practices, and possibly physician training. Also being developed is a statewide database that will allow pharmacists and prescribing physicians to know all of the scheduled medications their patients are receiving [63]. Hopefully, the adoption of such measures will help eliminate so called "pill mills," legitimize good clinics, improve patient care, and help pain management physicians make more informed clinical decisions.

Though there is evidence to support the efficacy and safety of opioid analgesics for nonmalignant pain, perceptions and attitudes have been slow to change [64]. Many still view the practice of prescribing opioids for chronic pain as bad medicine [65]. For example, a study revealed that over 50% of pharmacists feel that patients should not be given pain medications for longer than a month, and in another survey, prosecutors when presented with scenarios describing acceptable opioid regimens felt the physicians should be investigated [65].

Terminology

A lack of consensus on terminology has plagued the specialties of both pain management and addiction medicine. Currently, there is no agreement on the definition of pain, or even the duration of symptoms before it is considered chronic pain. In an effort to help promote uniformity when discussing addiction, experts from the American Society of Addiction Medicine, the American Pain Society, and the American Academy of Pain Medicine formed a consensus panel in 2001 to define tolerance, physical dependence, and addiction [31]. According to this panel, *tolerance* can be defined as 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. *Physical dependence* is characterized by a drug class-specific withdrawal syndrome resulting from abrupt cessation, dose reduction, decreasing blood levels of the drug, or administration of an antagonist. This is a secondary manifestation and is not the same as addiction. *Addiction* is a primary neurobiological disorder, or brain disease with genetic, psychosocial, and environmental underpinnings. Much like obsessive–compulsive disorder, addiction has behavioral manifestations [31]. These include impaired control over drug use, compulsive use, continued use despite harm, and craving. Addiction is also characterized by denial prompting the phrase often heard in addiction treatment settings: "*addiction is the only disease that tells you that you don't have it*." Possibly, in an effort to avoid the stigma attached to the word "addiction," the *Diagnostic and Statistical Manual of Mental Diseases and Disorders, Fourth Edition* uses the term *chemical dependence* which should not be confused with *physical dependence.*

However, what appears to be addiction is not always addiction. The term *pseudoaddiction* is used to describe behavior that can occur when pain is inadequately controlled. Problematic behaviors such as doctor shopping, illicit opioid use, and running out of medications early are considered characteristic of addictive behavior. However, in pseudoaddiction, these behaviors are actually an attempt to obtain additional pain relief due to inadequate dosing or increasing symptoms. Though function and mood deteriorate when additional opioids are given to patients suffering from addiction, function and mood improve in pseudoaddiction. Patients may also use opioids in an effort to self-treat psychiatric disorders. For example, opioids may temporarily decrease depression, anxiety, and ameliorate uncomfortable PTSD symptoms [66]. Furthermore, people use drugs and alcohol recreationally to get "high," experience euphoria or pleasure, "chill out," escape, relieve boredom, increase energy, or to just feel altered or different. Unlike patients who suffer from addiction, recreational users generally have normal neural reward pathways. Therefore, these patients can choose to quit in the face of consequences, increased maturity, or as a condition of receiving care in a pain management clinic. Chemical coping refers to the inappropriate use of medications, such as opioids, to temporarily elevate mood, to be calm, or, in some cases, increase energy in an effort to help one cope with life's stresses or challenges. Finally, patients can obtain drugs to sell or use for other secondary gain.

Neurobiology

To understand addictive behavior, it is helpful to have a basic understanding of the underlying neurobiology. The drive to "feed an addiction" can be incomprehensibly powerful, and the inability of those with addiction to control this drive, or even recognize that they have a problem and accept help is mystifying to those who do not understand the disease. Research suggest that we evolved such that substances and activities like food, sex, and nurturing that perpetuate us as a species trigger the activation of dopaminergic circuits in the midbrain [67]. Not only is this activation linked with pleasure, but also salience. Projections to limbic and precortical areas trigger desire, expectation, and planning [68]. Addictive drugs such as opioids, alcohol, and stimulants activate these circuits more than natural reinforcers [69,70]. Moreover, the ongoing dopamine release embeds emotional memories, and primes the brain to react emotionally and motivationally in response to triggers (people, places, and things), future drug exposure, and the expectation of drug exposure. This is accompanied by deactivation of areas that are involved in rational thinking and impulse control. These changes manifest as cravings, rationalizations, and denial, or what AA calls "*stinking thinking*." Animal and human studies suggest that vulnerability to addiction is largely the result of low baseline midbrain dopamine activity (reward deficiency syndrome) resulting in exaggerated salience being attributed to drugs, as well as decreased

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baseline inhibitory control [71–72]. Recently, it has become clear that addictive behaviors have other diving forces. For example, negative reinforcement results from both withdrawal anhedonia and the anxiety driven by sympathetic rebound. There may also be a down regulation of endogenous dopamine production in response to natural rewards as well as reorganization of brain circuits, moving the focus away from circuits associated with "reward" to those related to "habit" in the more dorsal parts of the striatum [73]. This may explain why people with the disease of addiction keep using drugs, despite the loss of the ability to experience pleasure from drugs [74,75].

Recent neuroimaging studies suggest that drug exposure, memory triggers, and stress can trigger a hijacking phenomenon whereby the patient is suddenly overwhelmed by desire for the drug, rationalizations, and loss of the resolve not to use [76]. The neurobiological changes associated with addiction are long lasting and possibly permanent, though partial normalization can be expected with time [77]. Addiction treatment and recovery programs such as AA and Narcotics Anonymous (NA) can markedly diminish the likelihood of a return to addictive behavior [78]. Indeed, patients in recovery often achieve a high level of integrity and self-honesty, becoming model citizens and highly compliant pain patients [79,80].

Patient Care—General Considerations

Gourlay and Heit have developed useful guidelines that borrow from the universal precautions model found in infection control. They provide a framework for care that should be universally applied to all patients that minimizes risks to both patient and provider and include establishing a diagnosis, pretreatment psychiatric and addiction assessment, obtaining informed consent, utilization of an opioid agreement, obtaining a baseline assessment of pain relief and function, reassessment of the five As, analgesia, aberrancy, affect, adverse side effects, and activities of daily living at every clinic visit that justify ongoing COT and other pertinent documentation. If during the opioid trial pain and function are not improving, opioids should be weaned and discontinued.

Effect of Drug, Delivery System, Timing and Environment

Drug reinforcement is influenced by drug pharmacodynamics, pharmacokinetics, as well as the circumstances that surround obtaining the drug. In general, opioids that are full mu agonists are more reinforcing than partial or mixed agonists, and drugs that are absorbed rapidly are more reinforcing than gradual release formulations [81,82]. As previously discussed, the pattern of drug taking also seems to play a role with PRN administration being more reinforcing than scheduled administration. Furthermore, the same drug if taken recreationally tends to be more reinforcing than if taken in a clinical setting for pain. In fact, there are animal and human studies that suggest that the existence of pain itself may counteract the euphorigenic properties of opioid analgesics, and help protect "real" pain patients from developing iatrogenic addiction [83,84].

Initial Encounter

The initial patient encounter presents an opportunity to screen for chemical dependence, vulnerability, psychiatric pathology, discuss treatment philosophy, and assess compatibility. Standardized screening tests such as the Screener and Opioid Assessment Tool for Patients with Pain (SOAPP), and the Opioid Risk Tool (ORT) are helpful and can be included in a packet that is mailed to the patient prior to the first appointment, filled out in the waiting room or administered during the interview. The SOAPP is a questionnaire that assesses the risk of opioid abuse. The test lists 14 items and assesses the frequency of their occurrence. The 0–5 sub-scores are then added together producing a total score. A score of 8 or higher suggests increased risk. Patients may be informed of this as a part of the consent for opioid treatment. Higher scores should help with the risk/benefit assessment for the suitability of opioid therapy, opioid choices, and the need for more frequent and intensive monitoring [85].The ORT is another questionnaire that asks yes or no questions about known specific risk factors such as family and personal substance abuse history, age, preadolescent sexual abuse, and psychological disease [86]. The ORT is very brief and correlates well with risks. However, as the yes/no questions stand out as obvious face value screening questions, they may invite dishonesty if the patient senses that their honest answers might exclude them from opioid therapy [85–87].

There are many red flags that suggest addiction, abuse, misuse or diversion that can come out in the initial history and exam: [88–95]

Aberrent Red Flags When Prescribing COT

1. Personal history of drug treatment, drug-related arrests, or driving under the influence (DUI) or drugs or alcohol [86].
2. Family history of addiction, especially first degree relatives [86].
3. Tobacco use [96].
4. Young age [86].
5. History of physical, emotional, or sexual abuse [86].
6. Novelty-seeking/thrill-seeking personality [97].
7. Process addictions: sex, gambling, food, etc.
8. History of emergency room (ER) visits for opioids [98].
9. No medication bottles brought or amounts/dates do not "add up."
10. Statements such as "I have a high tolerance."
11. Preference for more reinforcing rapid onset opioids.
12. Knowing "too much" about different opioids benzodiazipines, etc.
13. History of teenage tobacco, alcohol, marijuana, or substance abuse.
14. History of discharge or noncompliance with other pain clinics.

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15. Traveling long distances to the pain clinic [99].
16. Inability or unwillingness to obtain records.
17. Requesting medications that are highly abused such as Soma, barbiturates, stimulants [100].
18. Use of street drug vernacular such as "Oxy's," "Roxy's," "bars," "xanny bars," "Dance" [101].
19. Focus on opioids [102].
20. Buying medications on the street or obtaining them from friends or relatives.
21. Doctor shopping [103].
22. Unwillingness to consider nonopioid adjuncts, interventional treatment modalities, or physical therapy [98].
23. Numerous "allergies" to less reinforcing medications . . . "narrowing the options" [98].
24. Inability or unwillingness to produce urine for drug testing [98].
25. Physical findings: drug-related tattoos, track marks, needle bruising, "seed burns", pupil dilation or constriction, tachycardia, tachypnea, or hypertension suggestive of withdrawal anxiety, lethargy, altered mental status, slurred speech, and unsteadiness of gate.
26. Appearance does not correlate with professed physical dysfunction . . . "tanned and toned."
27. Liver dysfunction, hepatitis B or C.

Caring for the Patient with Pain and Addiction

According to the book of AA, also called the "Big Book," "*once a pickle, never a cucumber again."* [104] This statement, based on the empirical observations of a recovering alcoholic stockbroker over 70 years ago still reflects the 21st century consensus that addiction is a chronic disease that can be controlled and not cured [104,105]. Though the "hijacking" phenomenon that results in relapse and the return to drug use is less likely to occur with increasing recovery time, we know that relapse can still be triggered by the reinstitution of drugs, drug reminders ("people, places, and things), and stress. Furthermore, animal studies and human observation suggests that any reinforcing drug, even those from an entirely different class can trigger cravings and relapse [90]. Thus, by giving a recovering pain patient a benzodiazepine for sleep, Soma for muscle relaxation, or allowing the use of alcohol or cannabis, cravings can be triggered that can result in the reinstatement of drug use. Furthermore, as already discussed, uncontrolled pain is a potent trigger for relapse. As both drug therapy for pain and pain itself can trigger relapse, caring for patients with coexisting pain and addiction can be extremely challenging.

Several important tenants apply to managing coexisting pain and addiction. First, addiction must be recognized and controlled prior to the initiation of COT, and second, neither pain nor addiction will improve unless both problems are addressed. It is thus necessary for pain management specialists to have a basic understanding of addiction medicine and access to an addictionologist. There is a need for specialists who are experts in both pain management and addiction, and innovative fellowship programs such as the American Society of Addiction Medicine (ASAM) addiction/pain medicine fellowship at the University of Florida, that are currently addressing this need. Furthermore, it is important to understand that detoxification is not treatment and alone does little to decrease the likelihood of future relapses. Therefore, patients need expert addiction treatment that provides education, personal and family therapy, tools to deal with relapse triggers, initiation into a recovery support program such as AA or NA, medical and psychiatric care, continued posttreatment care, and accountability. During detoxification, inappropriate medicine regimens can be safely changed over to an appropriate regimen.

The appropriate medication management of a pain patient in recovery for coexisting chemical dependency requires that strict protocols be in place and should involve an addiction medicine specialist. In general, treatment decisions should not be made by the patient. Thus, opioid medications, if needed, should be administered on a scheduled basis and PRN breakthrough medications should be avoided. In early recovery, it is helpful to have these medications administered to the patient by a caring third party, usually a non-enabling family member.

Patients with coexisting addiction and pain should be monitored very closely and their treatment structured. They should have frequent random drug testing and pill counts, avoid all mind altering drugs, never self-adjust doses, and should avoid all over-the-counter drugs unless permission is given [106]. They have a responsibility to get approval from their addictionologist/pain specialist prior to filling any prescriptions for controlled substances obtained from other physicians. Furthermore, they should maintain an active recovery program, and adding this as a requirement to their treatment agreement should be considered. Family members may benefit from attending Al-Anon or Ala-teen meetings.

It is helpful for pain specialists to be knowledgeable of recovery programs such as AA and NA. It is suggested that patients attend daily AA or NA meetings for the first 90 days of their sobriety ("*90 in 90*"), and on a regular basis afterwards. They should have a sponsor who can help them reality test, work the steps, and provide support and guidance. By attending open AA and NA meetings pain specialists can acquire a feeling for what these organizations are all about as well as knowledge that can be used in recovery monitoring [107]. As those in recovery should attend frequent 12-step meetings, they should be able to recite many, if not all, of the 12 steps from memory. It is useful to ask the patient to recite one of the steps from time to time, as a rough way to verify meeting attendance. If they cannot, they probably have not been going to meetings as the 12 steps, 12 traditions, and the promises are recited at the beginning of most meetings. AA and NA have daily meetings throughout the United States, in most foreign countries, on the Internet, and even on cruise ships. There are also many other 12-step support groups such as cocaine anonymous and emotions anonymous.

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Recovering patients should also understand that taking prescribed medications for pain or psychiatric conditions do not preclude 12-step meeting attendance and do not violate the "traditions" that guide these organizations [108]. Finally, treatment should be tailored to individual needs as no single treatment is appropriate for all individuals. There are alternatives such as Celebrate Recovery, cognitive behavioral therapy, motivational enhancement therapy, rational recovery, and outpatient rehab programs that may be more appropriate for some patients [109].

Early recovery is an especially dangerous time for patients. Their neurochemistry is still normalizing, they may lack a firmly established recovery program, and their pain control may not yet be optimized. Patients who have recently been through "detox" may continue to experience uncomfortable post-acute withdrawal (PAW) symptoms for many more months. These symptoms include insomnia, anhedonia, fatigue, depression, anxiety, pain amplification, emotional lability, difficulty concentrating, and disturbing dreams that often involve drug use. PAW symptoms slowly improve over time [110–112]. Though the discomfort produced by these symptoms can be a strong relapse trigger, many of the medications that ameliorate these symptoms are powerful relapse triggers. Thus, pharmacologic sleep aids, stimulants, and anxiolytics should be avoided in most cases. However, if after careful consideration of risks and benefits they are felt to be needed, they should be carefully chosen to minimize relapse risks. Nonpharmacologic strategies such as relaxation, good nutrition, sleep hygiene, yoga, exercise, and cognitive–behavioral and family therapy are preferred. Patients should be encouraged to develop interests and passions, and pain management should facilitate their efforts. Recovering patients may need to be continuously reminded that the answer to discomfort or life's problems generally does not come in a pill and that, as addiction is a serious life threatening disease, recovery takes precedence over everything else. After all, by neglecting a recovery program and relapsing, everything else will eventually be lost anyway. Therefore, excuses such as lack of time, energy or transportation should not be accepted.

Pain management physicians who are caring for pain patients with coexisting addiction should have an understanding of drug properties that influence relapse potential. Non-narcotic medications such as nonsteroidal anti-inflammatory drugs (NSAIDS), serotonin-norepinephrine reuptake inhibitors (SNRIs), *gabapentin*, *tizanidine*, and *pregabalin* are reasonable choices, though pregabalin is a schedule 5 medication and may have some abuse potential. Benzodiazepines, especially those that are rapid onset and short-acting such as *alprazolam* should be avoided. If after much consideration a benzodiazepine is needed, a long-acting variety such as *clonazepam* is preferred and should be given only QHS if possible. For sleep, non-triggering medications such as *trazodone*, *mirtazapine* and *ramelteon* are preferred over the "benzodiazepine like" medications, *zolpidem*, *eszopiclone*, and *zaleplon*. *Quetiapine* may also be effective though accounts of quetiapine abuse are increasing [113]. The muscle relaxant carisoprodol is reinforcing, has significant abuse potential and should be avoided. Though *carisoprodol* is not controlled on a federal level, it is a schedule 4 drug in many states, and has "street value" [114]. *Tramadol* is another nonscheduled drug that can trigger addiction and relapse [103]. In general, stimulants should be avoided. However, if after carefully weighing the risks and benefits it is felt that they are needed to counteract sedation or as an antidepressant adjunct, slow-release long-acting *methylphenidate* or the "stimulant-like" medication *modafinil* may be less reinforcing [115–117].

If opioids are required to manage pain, long-acting slow-release forms are preferred [118]. PRN breakthrough opioid analgesics should be avoided for several reasons. First, they are more reinforcing. Second, it is important to exclude recovering patients from treatment decisions and third, rapid release medications trigger a rapid rate of dopamine rise and establish a strong chronological link between pill ingestion and mood changes [82]. Reasonable opioid choices include methadone and slow-release forms of morphine and oxymorphone. As previously mentioned, the relative ease of defeating the drug delivery system should be taken into consideration. For example, the opioid can be removed from the time release matrices of *extended release oxycodone* and *fentanyl patches* [119–121].

Sublingual *buprenorphine* is a schedule 3 opioid available in 2- and 8-mg tablets and may be an excellent choice for patients with coexisting chronic pain and addiction [122]. As buprenorphine is often used by treatment centers to "detox" off of other opioids, it can often be continued both as a craving ameliorating opioid substitute and as an analgesic. Positive effects of buprenorphine include decreased cravings, receptor blockade from other opioids, and analgesia. As is the case with *methadone*, buprenorphine has a shorter duration of analgesia than are its effect on craving and withdrawal, and therefore should be dosed TID or QID. Buprenorphine is a partial agonist, with a ceiling effect on receptor activation. Therefore, when switching a patient from another opioid to buprenorphine, care must be taken as withdrawal can be precipitated. Typically, buprenorphine is not given until the patient is experiencing withdrawal symptoms from the discontinuation of the previous opioid [123].

There are two sublingual buprenorphine preparations: *Suboxone* and *Subutex*. Unlike Subutex, Suboxone contains a small quantity of naloxone. When used sublingually, the added naloxone has no clinical effect and is added only to decrease street value by making it undesirable for intravenous use. In addition to a disolvable sublingual tablet Suboxone is now also available in a sublingual film. In general Suboxone is preferred for most patients. However, generic Subutex (buprenorphine) is now available in a generic formulation, and therefore may be a more feasable choice for some patients with financial limitations. Both Suboxone and Subutex are pregnancy category C, and pass into breast milk [124]. Using Suboxone or Subutex as an opioid replacement in patients suffering from addiction requires a special certification DEA number,

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and there is a patient limit of 30 in the first year, and 100 thereafter. However, as with methadone, Suboxone and Subutex can be used for pain management without the need for a special DEA identification number, nor are there any limits on the number of patients that one can be treating with this novel opioid [125].

Drug Testing

In clinical practice, urine drug tests are the mainstay as they are relatively inexpensive, noninvasive, and provide a fairly wide time window of detection. The motivation behind testing should be directed toward helping the patient maintain compliance, recognizing addiction to facilitate treatment, and identifying diversion [126]. In the clinical setting, physicians are expected to interpret drug-testing results. Unfortunately, recent studies suggest most physicians are poorly prepared to do so [127]. The proper response to an unexpected result should be individualized though diversion for the purpose of selling or trading typically mandates discontinuation of all opioids and consideration of clinic dismissal.

Standard tests, such as the Substance Abuse and Mental Health Services Administration's standard workplace drug panel (SAMHSA 5) are not adequate in the pain clinic setting [128]. This test will only be positive for opiates if morphine or codeine is present [129]. Therefore, many of the most commonly used opioids in pain management such as hydrocodone, oxycodone, hydromorphone, methadone, buprenorphine, and fentanyl could be missed and patients have been inappropriately discharged from pain practices and accused of diversion by doctors who are unaware of the testing limitations [130]. With methadone and buprenorphine, urine drug testing for both the parent molecule as well as metabolites are available as an added safeguard against adulteration [131,132]. In the office, the initial screening test is usually an immunoassay test. These are economical and often involve polyclonal or monoclonal antibodies that react with the drug and/or metabolite. A positive test can be followed up with confirmatory gas chromatography-mass spectrometry (GC-MS) or equivalent testing [129]. Although accurate, urine drug tests are not 100% accurate, and false negatives, false positives, and misinterpretation of true negatives and positives can occur. Causes of potentially inappropriate urine drug screen (UDS) results include metabolic conversions of a prescribed substance to another (nonprescribed) substance, consumption of other legal sources of drug (i.e., poppy seeds), limited assay specificity, presence of drug in the urine that is below the cut off, and human error (i.e., mislabeling) [133]. It is extremely important to understand the limitations of your own tests. Most drug testing companies have experts and medical review officers (MROs) available to explain the nuances of their company's-tests and to help with interpretation.

An example of an *in vivo* conversion that can lead to an inappropriate interpretation is the *conversion of morphine to hydromorphone*. There exists a small subgroup of individuals that possess a metabolic pathway that can metabolize high doses of morphine into detectable levels of hydromorphone [133]. There have been reports of patients being accused of inappropriate hydromorphone ingestion who have later been shown to have this variant [133].

Even if accurate, UDS testing can result in erroneous conclusions. For example, poppy seeds actually do contain small amounts of morphine. A positive opioid screen can thus occur from the ingestion of poppy seed containing foods. This follows from the low threshold of 300 mcg/L found in most commercial UDS tests. [134]. Though this level will show a positive result on UDS tests, follow up testing that quantifies the actual morphine level can distinguish poppy seed morphine levels from medicinal morphine levels as the former rarely exceeds 15,000 mcg/L [135]. Poppy seeds can also be differentiated using hair testing as discussed below. Heroin is rapidly converted into 6-MAM and then to morphine. Therefore, it is difficult to detect heroin using urine drug screening specifically or heroin or its metabolite, 6-MAM unless heroin was used very recently (hours). Codeine is metabolized to morphine by the cytochrome P450 2D6 enzyme which may largely account for its analgesic properties. Therefore, codeine use may give a true positive result for morphine [136]. Perhaps, the most unreliable drug screens are those for amphetamine/methamphetamine. Some over-the-counter cold medications contain chemicals that can produce positive screening test results such as *phenylethylamine*, *ephedrine*, *pseudoephedrine*, or *phenylpropanolamine*. Furthermore, depending on the type of test and company, a positive can also result from the ingestion of the antidepressant, *bupropion*, the MAO inhibitor, *selegiline*, and *Vicks VapoRub* [133]. Many screening tests will not pick up the non-amphetamine stimulant *methylphenidate*, as well as the benzodiazepine, *clonazepam* [133]. Finally, it is important to remember that *alcohol* is not detected by standard urine drug testing. Therefore, it is helpful to have a breathalyzer readily available. To screen for alcohol ingestion, *ethylglucuronide* (*EtG*) testing is widely available and can detect recent (up to 80 hours) ethanol ingestion [126,137].The EtG test is so sensitive that trace exposure from mouthwash or hand cleaner use has been purported to produce a positive result, though a level exceeding 500 ng/mL is strongly correlated with deliberate alcohol ingestion [138].

Unfortunately, urine drug screens can be defeated. "Clean" urine may be obtained via the Internet as are devices that are difficult to visually detect unless and can maintain the urine at an appropriate temperature. Therefore, urine drug screens should be witnessed if there is suspicion of urine substitution. Manipulation of a urine specimen can be detected by several methods of specimen validity testing. Typically, urine maintains a temperature of 90–100°F within 4 minutes of voiding. Urine pH may fluctuate throughout the day but typically ranges between 4 and 9. Values outside of this range suggest contamination or adulteration. Urine creatinine concentration typically ranges between 20–250 mg/d and specific gravity between 1.003 to 1.020. The most common way to avoid detection is to

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dilute the urine through aggressive fluid ingestion or by adding tap water. This may reduce the amount in the urine to levels below the lab cut off. In general, a creatinine concentration that is less than 20 mg/dL, or specific gravity of less than 1.003 suggests dilution [126,133].

Other matrices that can be tested for drugs include hair, oral fluid, and sweat. Hair testing has grown in sophistication and is virtually impossible to defeat. This test is extremely sensitive and specific and can pick up use in the past three or more months (hair grows about half an inch per month) as well as estimate the duration and continuity of use. However, recent use will be missed by hair testing as it takes approximately 1 week for hair to grow from the follicle to a length where it can be collected. Hair testing is not impeded by coloring or bleaching. Pubic, axillary, or other hair may be used if scalp hair is absent [126,139]. Poppy seed consumption will not yield a positive hair test so this is a good method to differentiate between the two. Furthermore, the metabolite of heroin, 6-MAM can be picked up by hair testing, thus this matrix provides can be used to differentiate heroin from prescription morphine [136,140]. Other useful hair test includes EtG, and fentanyl. Hair testing may miss cannabis use as concentration levels of THC are relatively low in the body and hair compared with most other drugs. In fact, marijuana must be used approximately twice per week for the entire 90 days to yield a positive result [141]. Oral fluid testing is also available and offers an alternative for patients who cannot produce urine. However, most on-site kits only test for the inadequate SAMSA 5 and as is true of hair testing, oral fluid testing is relatively insensitive to marijuana [126].

Opioid Agreement and Aberrancy

Aberrancy includes a wide spectrum of behaviors that violate the clinic rules or the opioid agreement. Though concerning, they do not necessarily imply addiction [66]. Examples include:

1. Buying, selling, stealing, borrowing, or trading prescription drugs.
2. Forging or altering prescriptions.
3. Injecting or snorting oral formulations.
4. Ingesting, injecting, or snorting fentanyl removed from patches.
5. Current abuse of alcohol or illicit drugs.
6. Multiple dose escalations.
7. Falls, accidents, sedation.
8. Stolen of lost prescriptions.
9. Multiple prescribers or ER visits to obtain analgesics
10. Deterioration of relationships, work, mood, or appearance.
11. Arrests, legal problems.
12. Missing appointments, showing up unannounced.
13. Frequent phone calls.
14. “Medications aren’t working”
15. “Only oxycodone or OxyContin works for me.”
16. Requesting Soma and Xanax.
17. Isolation from friends and family.
18. Resisting drug changes despite adverse physical or psychological effects.
19. Requests for short acting opioids (i.e., “Roxies”), or more highly abused medications and formulations such as OxyContin, Xanax, etc.
20. Aggressive complaining about the need for more drugs.
21. Requesting specific drugs.
22. Drug hoarding during periods of reduced symptoms.
23. Using drug to treat other symptoms, elevate mood, or relax.
24. Anxiety or sedation.
25. Suggestive behavior, statements, or clothing.
26. Physical signs such as unkept appearance, tachycardia, bradycardia, altered mentation, needle marks, bruises, nose bleeds, weight loss, slurred or rapid speech, dilated or constricted pupils, impaired cognition.
27. Concerned family and friends.
28. Calls from pharmacies.
29. UDS with nonprescribed drugs, lacking prescribed drugs, dilute or adulterated.
30. Inability to produce urine.

Opioid therapy is a privilege based on strict adherence to the terms of the opioid agreement. Typically, this agreement spells out the risks and benefits of COT, clinic expectations, and rules. These rules often include the expectation to show up for appointments, to obtain controlled medications only from their pain specialist and to take them exactly as prescribed, avoid all illicit drugs, and licit drugs like alcohol, the need to use one pharmacy, to bring pill bottles for pill counts, be able to provide urine or other medium for testing if asked. These agreements often state that patients are solely responsible for the safekeeping of their medications and that if these medications are lost or stolen, they may not be replaced. Furthermore, they may spell out the expectation that patients have a primary care provider and agree to see specialists such as psychiatrists, psychologists, or addiction medicine specialists if recommended. Selling, trading, or giving away medications are obviously proscribed. Aberrancy occurs when these rules are violated, and can be grounds for the discontinuation of all controlled prescription medications [103,142–144].

Management of aberrant behavior is individualized and depends on the reason. Often, this simply requires education to remind the patient not to self-adjust medications or to take more or less than prescribed. Usually, minor aberrancies occur early in the clinic relationship and can be corrected by reviewing the clinic rules, their agreement to follow these rules, and the reasons for the rules. Patients are humans, and sometimes we overestimate their ability to comprehend what we say as well as our ability to communicate what we want them to know.

Other times, aberrancy requires action. For example, if it is felt that overuse of medications is secondary to abuse, correction is needed or opioid therapy is not an appropriate therapeutic modality and should be discontinued. If

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overuse is secondary to addiction, treatment or an evaluation should be mandated. If the patient is unwilling to go, controlled medications should not be refilled. This may provide the motivation for the patient to get into treatment [145]. A judgment should also be made as to whether or not the patient is in immediate danger to himself or others. If this is thought to be the case, many states have a mechanism such the Florida *Marchman Act* whereby a patient can be mandated to undergo an immediate evaluation [146]. Other scenarios that may account for aberrancy include pseudoaddiction (opioid tolerance, the development of hyperalgesia, new, or worsening pain generator), self-treatment of psychiatric disorders, or cognitive dysfunction, each of which requires judgment, knowledge, and often a willingness to aid the patient in finding help. Lost or stolen medications typically mandate a police report. If the story is believable, and this is the first time, replacing the medication may be considered. If medications have been lost or stolen in the past or other aberrant behaviors have occurred, discontinuation of opioid therapy is likely indicated.

When aberrancy is suspected, monitoring should be intensified by increasing testing frequency, and broadened to include additional drugs if indicated. Other testing media such as hair and fingernails may be helpful. Finally, it may be reasonable to prescribe only several days worth of controlled medications at a time [145]. Collateral information from other physicians, relatives, and acquaintances may be helpful, though the Health Insurance Portability and Accountability Act (HIPPA) privacy rules should be respected. However, if a patient is uncooperative, and refuses to sign reasonable releases to obtain information, it may be appropriate to consider discontinuing controlled medications or clinic discharge [147].

Summary and Conclusions

In summary, those suffering from addiction have a life-threatening disease, as opposed to a moral shortcoming. Though they may occur together, addiction is not the same as physical dependence as manifested by physical withdrawal. Physical withdrawal is temporary and the disease of addiction is permanent. Addiction, like other chronic disease such as diabetes, bipolar disorder, and hypertension can be controlled but not cured. Iatrogenic addiction occurs as a result of the complex interplay of COT and vulnerability. Though there is ample evidence to suggest that the behavioral changes associated with addiction are secondary to neurobiological changes, normalization of addictive behavior can occur with treatment and maintained by a good recovery program [148].

Patients with the disease of addiction often suffer from coexisting chronic pain. Indeed, the prevalence is so high that it has been recommended that drug treatment centers develop their own structured and comprehensive pain management programs. Currently many physicians screen for a history of addiction with the goal of denying patients the opportunity of becoming clinic patients. However, adequate pain control is a medical imperative as failure to do so both invite addiction and is a powerful trigger for relapse. The fact that opioid analgesics also invite addiction and trigger relapse creates a "catch 22." Fortunately, with adequate screening of prospective patients, vigilant monitoring, appropriate therapeutic and medication choices, contingency management, and addiction medicine specialty input, risks can be minimized and those with coexisting pain and addiction can be successfully managed. New medications such as buprenorphine offer an attractive and possibly safer alternative to conventional opioid therapy.

It is important to understand that addiction is a primary disorder and the evaluation and ongoing care of patients with coexisting chronic pain and addiction should be approached from a framework of compassion rather than judgment. Though psychiatric comorbidity is common in both chronic pain and addiction patients, treating the psychiatric disorder will not cure addiction. Primary treatment for addiction is necessary, as is an ongoing recovery program as addiction is a chronic disease. Though addiction is common, costly to society and life-threatening, physicians receive little training in the recognition and treatment of this potentially devastating disorder. As pain management operates in the crossroads of symptom relief and addictive disorders, practitioners should receive didactic and experiential training in the basics of addiction medicine, chemical dependency treatment, and recovery programs. Furthermore, they should not hesitate to involve addiction medicine specialists in the care of questionable or difficult patients.

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