Opioid Addiction: Review of Current Legislation and Treatment Options

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Goal:

To review legislation targeted at decreasing opioid pain reliever availability for illicit use and current treatment options for the detoxification and maintenance treatment for opioid addiction.

Objectives

- Describe recent legislative and regulatory actions taken in attempt to decrease substance abuse
- Explain the neurobiological mechanisms involved in the formation of addiction
- Detail available pharmacological treatment options for opioid dependence

Introduction

According to the DSM-5, substance use disorders are characterized by impairment of functioning in occupational and social roles, increased or larger than intended use

of a substance, and continued use despite known physical or psychological problems related to the substance.[1] Not only has the rate of substance use increased among Americans aged 12 years and older since 2002, but an increasing number of these individuals are also seeking treatment for their addiction, especially when the substance used is a controlled substance pain reliever.[2] Steps are currently being taken by both federal and state governments to decrease the diversion of opioid pain medications to lessen the potential for nonmedical use, as well as increasing the flexibility of access to opioid treatment programs and funding for addiction treatment for criminal offenders. In recent years, new pharmacological treatment options have been approved for maintenance treatment of opioid addiction.

Statistics

According to the 2013 National Survey on Drug Use and Health, it has been estimated that 24.6 million Americans aged 12 years or older used at least one illicit substance in the study timeframe.[2] The rate of use among those aged 12 years or older in 2013 has increased compared to that in 2002, 8.7 percent versus 9.4 percent, respectively. Of the 4.1 million people who sought treatment for a problem related to the use of an illicit substance, 746,000 described the problem as related to pain reliever use.

Approximately two million people were first time users of nonmedical psychoactives in 2013.[2] Of those, 1.5 million people were new nonmedical users of pain relievers. When asked how these pain relievers were obtained, 53 percent of nonmedical users reported "from a friend or relative for free," 21.2 percent were prescribed the medication, 10.6 percent bought them from a friend or relative, and 4.3 percent obtained pain relievers from a drug dealer or stranger.

Of the 2.3 million incarcerated American adults, 1.5 million, or 65 percent, meet DSM-IV-TR criteria for substance abuse.[3] Another 458,000, or 20 percent, are considered to be substance-involved, where they were under the influence of a substance at the time of their arrest or committed a crime to obtain a substance.

Healthcare and overall (including lost work productivity and crime) costs associated with illicit substance use totaled approximately $11 billion and $193 billion, respectively, in 2010.[4] In 2005, $74 billion was spent by federal, state, and local governments to convict, incarcerate, and parole adult and juvenile offenders that were substance-involved.[3] In the same year, $632 million was directed to the prevention and treatment of substance-involved offenders by federal and state governments. This means that for every dollar spent on substance use, $0.96 goes toward legal consequences and $0.02 goes toward prevention and treatment.

Legislative/Regulatory

Medications containing hydrocodone have been increasingly recognized as some of the most widely abused prescription drugs in the United States.[2] One proposed

mechanism for decreasing the abuse of hydrocodone-containing drugs was to tighten regulatory restrictions on these products. On March 20, 2013, the Safe Prescribing Act of 2013 (S. 621) was introduced to Congress.[5] This Act promoted the reclassification of hydrocodone combination products from Schedule III controlled substances to Schedule II controlled substances.[6] Proponents of this reclassification stated that it reflected hydrocodone-containing products' high potential for misuse and addictions, as well as granted law enforcement the ability to more closely monitor product distribution.[7] Arguments against the Act cited the ability to call in these products over the phone and provide refills on Schedule III controlled substance prescriptions, easing distribution for those in an emergency and for patients who chronically take these medications.[8] The bill was assigned to the Senate Judiciary Committee the same day it was introduced[5]; however, regulatory authorities became involved in the reclassification decision prior to full legislative action on the matter.

On January 25, 2013, the Federal Drug Administration's (FDA) Drug Safety and Risk Management Advisory Committee voted 19-10 on the recommendation to reclassify hydrocodone-containing combination products as Schedule II controlled substances.[6] Subsequently, the Drug Enforcement Administration (DEA) published a final rule on August 22, 2014, reflecting the recommendation of the advisory committee and rescheduling hydrocodone combination products from Schedule III to Schedule II. This reclassification rule became effective on October 6, 2014.[9]

Another mechanism at the federal level to decrease abuse is aimed at the treatment of opioid addiction. The Drug Addiction Treatment Act of 2000 (DATA 2000) expanded the Narcotic Addict Treatment Act of 1974 by allowing physicians to prescribe Schedule III, IV, and V substances specifically approved by the FDA (as opposed to solely Schedule II substances) in a treatment setting other than an Opioid Treatment Center (i.e., methadone clinic).[10] Physicians apply for a waiver under DATA 2000 that relieves much of the regulatory burden associated with prescribing opioids for addiction treatment.[11] In order to obtain the waiver, a physician must hold a valid state license and DEA registration number and also have a specialty certification in addiction medicine or other training in the treatment of opioid-addicted patients. Additionally, physicians must also have the ability to refer a patient to non-pharmacological addiction treatment. For those granted the waiver, a physician cannot have more than 30 patients on addiction treatment for the first year of the waiver. The physician can submit a second notification after the first year delineating the intent to treat up to 100 patients for addiction at a time.

A recent change was made in January 2013 to the federal law concerning the amount of buprenorphine products a patient can be dispensed while participating in an Opioid Treatment Center.[8] Previously, treatment programs were only able to dispense a one

week supply of buprenorphine product to a participant in their program. A patient would have to wait for one year before the program would be able to dispense a two week supply. With this rule change, the time limit restriction has been removed for buprenorphine products only, while being kept in place for methadone. This change will allow treatment programs to be more flexible with the amount of buprenorphine product dispensed, hopefully encouraging more participation because of decreased burden on the patient. The opioid treatment program must still evaluate and determine that the patient is capable of responsibly handling opioid drugs for the duration of the dispensed day supply.

Changes at the state level are also being made to decrease substance abuse. Indiana House Bill (HB) 1006 makes the most significant changes to the criminal code since the last revision in 1977.[12] The focus of the revision is to make the criminal code more effective with a focus on public safety.[13] The current four felony classes will be divided into six levels, with a level one felony being the most severe.[12] Credit for good behavior has also been changed. Currently, offenders serve at least 50% of their sentence. With HB 1006, offenders will serve at least 75% of their sentence, and the worst offenders will serve at least 85%. Non-violent low level offenders, including those that committed some substance-related crimes, would be placed in intense probation programs, that have shown to help the offender identify the root cause of the reason for crime and therefore reduce recidivism.

Major additions to the law surrounding alcohol and drug programs funding have also been included in this revision.[12] The Indiana Judicial Center (IJC) is now able to award grants that will allow probation departments and community corrections programs to increase substance abuse treatment. The IJC will be working with the Division of Mental Health and Addiction as well as the local probation department of the community corrections program to determine the amount of the grant. Additionally, the mental health and substance abuse counseling that is administered under the grant must be provided by a certified mental health or addiction provider. HB 1006 was signed into law on May 6, 2013, and took effect July 1, 2014.

One tool that is available for pharmacists and other providers to decrease substance abuse and diversion is Indiana Scheduled Prescription Electronic Collection and Tracking Program (INSPECT). Created in 2004, when grant funding and legislative action allowed for the creation of INSPECT as we know it today, the prescription drug monitoring program (PDMP) is a database of information for healthcare professionals to assist in the decision making process, as well as a tool law enforcement can use for investigation.[14] Pharmacies are required to submit data on all controlled substances within seven days of the dispensing date. Those allowed to view the data include licensing boards, the Attorney General's Office, and law enforcement in an active investigation and healthcare practitioners involved in making treatment decisions.

INSPECT has lead the way in data exchange. INSPECT was the first PDMP to participate in interstate data sharing with Ohio in 2011 and Indiana was the first state to share data with all neighboring states.[14] It was also the first PDMP to integrate its data into its state's health information exchange in 2012. This has allowed providers to see INSPECT data within a patient's internal electronic medical record, eliminating the need to access two different systems. Lastly, INSPECT was the first PDMP to provide and allow for unsolicited reporting to providers. Still in pilot stages, the program will send a secure email to a prescriber when it detects a dispensing pattern of multiple prescribers used in a short time period. Also, prescribers are allowed to send notices to another prescriber alerting him or her of the potential over-dispensing of scheduled substances. Continued improvements in the ability to data share with and between practitioners will hopefully decrease over-prescribing of controlled substances.

The Neurobiology of Addiction

A common question remains for many health care professionals regarding addiction, that being "why do people continue to use substances often to the detriment of their physical and mental health, relationships, and financial and legal security, and why can they not stop?" There is a common lack of understanding, both by health care professionals and the general public, that there is a neurobiological basis for addiction that has a growing body of documentation in the clinical literature and in research.

It is useful to understand that addiction is best considered to be drug craving with drug-seeking behavior in spite of negative consequences. This is different from "tolerance", which is the need for increasing amounts of a substance to achieve a specific pharmacologic effect; or "dependence", defined as a physical need for the substance by the body, for which lack of use can cause withdrawal effects.[15]

While several neurotransmitter systems and brain circuits have been implicated in the process of addiction, it has been established that all drugs that lead to addiction increase dopamine in the mesolimbic dopamine pathway and the nucleus accumbens.[16] Initial use of a substance of abuse will lead to an increase in dopamine and a pleasurable feeling of reward. This initial use is considered to be the "acute drug reward". Over subsequent doses, the user will attempt to reach a similar feeling of reward, but is often unable to do so, due to a decrease in the activity or volume of dopamine released for each dose. The reward threshold increases, requiring the user to ingest higher doses in an attempt to gain a "high". A decrease in the reward system function can persist and lead to long-term biochemical changes that fuel a cycle of substance use, abstinence, a conditioned response to the thought of substance use, motivation to procure the substance (craving), and vulnerability to relapse.[15] Over time, the individual develops a hypo-functioning dopamine reward system leading to anhedonia (loss of

capacity to experience pleasure), lack of motivation for everyday activities, and an increase in drug-seeking behaviors. It is postulated that continued substance use is an attempt by the individual not to seek a "high", but rather, to restore a functional dopamine reward system and allow normal feelings of pleasure.[17] For opioids, while dopamine does play a crucial role in addiction, other neurotransmitters (opioid peptides, endocannabinoids) and brain structures (central nucleus of the amygdala) are also involved.[15] Due to physical changes to neurochemistry and biological systems in addiction, it may take several years of abstinence for these changes to revert to "normal", and the person with addiction remains vulnerable to relapse. For this reason, persons with addiction in remission will likely always consider themselves "recovering", requiring continued treatment and supportive psychotherapy for indefinite periods of time.

Opioid Addiction Treatment

There are currently four pharmacological treatment options being utilized for opioid detoxification and maintenance. While not curative, these medications are beneficial for significantly decreasing withdrawal symptoms and cravings and for blocking the opioid effects as a result of relapses. Furthermore, maintenance therapy has also proven to significantly decrease morbidity and mortality, the possibility of new human immunodeficiency virus infection, illegal activity, and illicit opioid usage.[18] Optimal functioning is the ultimate goal of treating opioid dependence. Abstinence alone does not assure optimal functioning, and detoxification does not in itself address the chronic dysfunctions of addiction. Ongoing engagement in addiction treatment and counseling is an important variable in how effective treatment will be. [19]

The treatment courses are opioid detoxification and maintenance. The majority of opioid dependent individuals participate in both courses, typically numerous times throughout the progression of their drug-using careers.[20] Detoxification involves the use of medications to bring a patient from an opioid-dependent to an opioid-free state. Medications, like methadone, buprenorphine/naloxone, and naltrexone, are designed to decrease withdrawal-related discomfort and complications. Maintenance therapy includes the replacement of an abused opioid with a medically prescribed opioid that can be given either daily or monthly with counseling.[21] Detoxification by itself is not a long-term treatment for opioid addiction while maintenance therapy yields the best outcomes.[19]

The most effective medication options for detoxification and maintenance include methadone, buprenorphine/naloxone, intramuscular (IM) naltrexone, and oral (PO) naltrexone.

Pharmacological Treatments for Opioid Dependence

Methadone

Methadone, a full mu-opioid receptor agonist and N-methyl-D-aspartate (NMDA) antagonist, acts as replacement therapy for opioid dependence.[22] Available as a racemic mixture, the R-isomer provides potent analgesic effects. The S-isomer contributes to the potential side effects including a prolonged QT interval. The long half-life of the medication, 24-36 hours, allows for once daily dosing for easier administration. The typical starting dose is 20-30 mg once daily with typical maintenance doses of 80-120 mg once daily.[23] Treatment duration depends on the individual but usually lasts at least one year and can continue for two or more years. Methadone is primarily metabolized by cytochrome P450 3A4; however, it is also metabolized to a lesser extent by cytochrome P450 2D6 2B6, 2C19, and 2C9, leading to significant drug interactions.[22] Medications like carbamazepine, nevirapine, phenobarbital, rifampin, saquinavir, and St. John's wort may induce methadone metabolism leading to withdrawal symptoms while macrolide antibiotics, ketoconazole, fluvoxamine, clopidogrel, itraconazole, raloxifene, sertraline, and ticlopidine may delay methadone metabolism leading to increased methadone concentrations and a higher risk of side effects and toxicity. Similar to opioids, the most common side effects of methadone include constipation, dizziness, sedation, lightheadedness, nausea, and vomiting. Less common side effects include itching, dry mouth, headache, weakness, and hypotension. Contraindications for methadone include respiratory depression, acute or severe bronchial asthma, hypercarbia (high blood levels of carbon dioxide), known or suspected paralytic ileus (decreased motor activity of the gastrointestinal tract), and concurrent use of selegiline. A significant concern regarding the use of methadone is the potential for prolongation of the QT interval; therefore, other medications that could prolong the QT (e.g., antiarrhythmics, antipsychotics, tricyclic antidepressants, fluoroquinolone antibiotics) should be used with caution. Methadone therapy should not be abruptly discontinued since tolerance and physical dependence may occur with long-term therapy. Methadone withdrawal symptoms include restlessness, yawning, perspiration, myalgia, chills, lacrimation, anxiety, irritability, joint pain, weakness, abdominal cramps, nausea, vomiting, diarrhea, hypertension, and increased respiratory or heart rate. Methadone is an inexpensive and convenient option for many patients.

Buprenorphine/Naloxone (Suboxon®,Zubsolv®, Bunavail™)

Buprenorphine is a partial mu-receptor agonist and kappa-receptor antagonist.[22] Due to poor bioavailability, buprenorphine is administered sublingually, thereby eliminating the extensive hepatic first pass metabolism. With a quick onset of action of 30-60 minutes and peak effect in approximately 90-100 minutes, the half-life of buprenorphine ranges from 20 to 73 hours.[24] The usual dose range is 4-32 mg given once daily based on the half-life. Buprenorphine's partial agonist effects lessen the possibility of an accidental

overdose but also limits buprenorphine's maximum efficacy compared to full agonist therapies. For example, the maximum dose of sublingual buprenorphine is 24-32 mg which is approximately 60-70 mg of methadone.[20]

While buprenorphine is available in a sublingual film tablet form, it is more commonly combined with naloxone, a competitive mu-receptor antagonist.[24] Since naloxone has minimal oral absorption but is highly bioavailable parenterally, it causes rapid reversal of opioid effects. Therefore, the combination product limits the potential for abuse. Presently, several formulations of buprenorphine/naloxone are available: sublingual film (Suboxone®), sublingual tablet (Zubsolv®, generic), and buccal film (Bunavail™).[25-29]

Several key considerations must be discussed when assessing the differences amongst buprenorphine/naloxone formulations and products. According to manufacturers, Suboxone® sublingual film strengths correspond to generic sublingual tablet strengths; however, the manufacturers further state that not all strengths and combinations of the two product formulations may have the same bioavailability.[25,27] Particularly at higher doses (8mg buprenorphine/2mg naloxone and higher), Suboxone® sublingual film may have a higher bioavailability when compared to sublingual tablets of the same strength.[29] This possible difference in exposure between the two product formulations necessitates patient monitoring and possible dosage adjustments if a switch between product formulations occurs.[25,27] Although similarly available as a sublingual product, Zubsolv® tablets utilize an alternative sublingual formulation from other buprenorphine/naloxone products, which provides for a comparable blood concentration of medication at lower doses.[30] According to the manufacturer, the 5.7 mg/1.4 mg Zubsolv® product is equivalent to the 8 mg/2 mg generic sublingual tablet product and Suboxone® sublingual film product.[26,30] In contrast to the various sublingual products available on the market, Bunavail™ is the buccal film formulation of buprenorphine/naloxone approved by the FDA in June 2014. Per manufacturer data, Bunavail's™ bioavailability is two times the bioavailability of Suboxone®, allowing for approximately half the dose of medication to be utilized for effective treatment. The manufacturer of Bunavail™ considers that the ability to use lower doses of active medication may decrease misuse potential and side effects.[31] The 4.2 mg/0.7 mg Bunavail™ product is considered to be equivalent to the 8 mg/2 mg buprenorphine/naloxone sublingual tablet.[28]

Similar to methadone, buprenorphine is metabolized by cytochrome P450 3A4. Potential drug interactions include protease inhibitors, azole antifungals, macrolide antibiotics, phenobarbital, carbamazepine, phenytoin, and rifampin.[2,18] Side effects include sedation, nausea/vomiting, dizziness, headache, and respiratory depression with the most common being constipation and nonspecific headache.[2]

Methadone or buprenorphine maintenance?

The decision to use either methadone or buprenorphine for maintenance therapy is patient-specific. Methadone may be a better option if the patient has an unstable lifestyle (e.g., homeless, needs structured follow-up, or needs more comprehensive services) and/or has financial issues or lacks insurance.[23] Since a patient may have a higher daily dose of methadone, it may be a better option for individuals that are more dependent.

Naltrexone (ReVia® and Vivitrol®)

Oral naltrexone, a competitive mu-receptor antagonist, was originally approved by the FDA for the treatment of alcohol dependence.[22] However, it has been studied for the treatment of addiction to heroin and other opioids. Naltrexone is unique in that it does not lead to tolerance or dependence. Since naltrexone is an opioid antagonist, compared to methadone and buprenorphine which are opioid agonists, it inhibits the reinforcing effects of opioid use.[20] The individual does not experience the euphoria associated with opioid use, so, theoretically, he or she will either stop taking opioids or stop taking the naltrexone.[18] The dose of naltrexone is directly correlated to the medication's duration of action. For example, 50 mg of naltrexone will inhibit the effects of 25 mg of intravenous heroin for up to 24 hours, 100 mg will increase the duration of action to 48 hours, and 150 mg will confer effects for 72 hours.[20] The typical dose range for the oral formulation varies from 25-150 mg per day. It can be given as little as two or three times per week due to its long duration of action. However, daily administration is preferred by some clinicians in an effort to encourage habitual use and generate higher mu-receptor blockade. Initiation of naltrexone is an important clinical consideration since it will displace the opioid from the receptor eliciting withdrawal quickly. Naltrexone should not be initiated until the patient has been opioid-free for at least five to seven days with short-acting opioids and at least 7-10 days with methadone.[18] Additionally, compliance is essential since the opioid blocking effects diminish approximately 24-48 hours after the last dose. Naltrexone undergoes first-pass hepatic metabolism to 6β-naltrexol.[32] There are no significant drug interactions. Potential side effects of naltrexone include headache, nausea, abdominal pain, dysphoria, and depression.[20] These are most likely to occur in the first four weeks of treatment but generally subside over time or can be treated with clonidine. An important monitoring parameter for naltrexone is liver function since it can cause elevated liver transaminases especially with high doses. Consequently, if a patient's liver enzymes are greater than three to five times the upper limit of normal, naltrexone should not be initiated.

In an effort to improve compliance, a sustained-release delivery system was developed as an intramuscular formulation. Pharmacokinetic studies have shown that plasma levels of naltrexone are maintained for at least 28 days leading to the administration schedule of every four weeks.[18] Vivitrol®, the month-long depot formulation of naltrexone, was FDA-

approved for the treatment of opioid dependence in 2010.[32] Side effects specifically attributable to the intramuscular formulation include injection site reaction (including cellulitis, induration, hematoma, abscess, and necrosis), nausea, headache, and fatigue.

Table 1. Summary of Medications (Adapted from [22-28,33])

Medication	Mechanism of Action	Dosage and Frequency	Adverse Effects	Additional Clinical Points
Methadone	Opioid agonist at the mu-receptor and antagonist at NMDA receptor	20-120 mg orally daily	Constipation, sweating, urinary retention, dose-related sexual dysfunction in men, cardiac conduction defects, respiratory depression, sedation	Metabolized by cytochrome P450 3A4, QTc prolongation, must be slowly tapered before discontinuing, risk of overdose
Buprenorphine/ naloxone	Partial mu-receptor agonist and antagonist at the kappa-receptor (buprenorphine) with competitive antagonist at the mu- and kappa-receptors (naloxone)	Suboxone® film and generic buprenorpine/naloxone tablet: 4 mg/1 mg – 24 mg/6 mg sublingually daily Zubsolv® tablet: 2.8 mg/0.72 mg – 17.1 mg/4.2 mg sublingually daily Bunavail™ film: 2.1 mg/0.3 mg – 12.6 mg/2.1 mg buccally daily	Sedation, nausea, vomiting, dizziness, headache, respiratory depression, constipation	Metabolized by cytochrome P450 3A4, easier to detoxify *with* but harder to detoxify *from*
Naltrexone	Competitive antagonist at the mu-receptor	380 mg IM every four weeks 25-150 mg PO daily	Anxiety, nausea, myalgia, headache, abdominal pain, dysphoria, depression	Monitor liver function tests, available in oral and intramuscular formulations

Other Treatments

These four medications are by no means the only treatment modalities utilized in opioid detoxification.[18] Clonidine and other supportive measures are important aspects in treatment. Clonidine is an alpha-2 adrenergic agonist typically used for hypertension. Due to the hyperactivity associated with opioid withdrawal, clonidine 0.4 to 1.2 mg per day may be useful. On the other hand, it is not effective for other symptoms of withdrawal like insomnia, fatigue, muscle aches, nausea/vomiting, and restlessness. Due to its potent antihypertensive effects, clonidine should be tapered slowly upon discontinuation due to the potential for rebound hypertension when abruptly stopped. For the treatment of withdrawal-related insomnia, clonazepam, trazodone, and zolpidem have been utilized. However, benzodiazepines used be used with extreme caution due to the potential for abuse. For muscle aches, pain medications without the risk of abuse or dependence are recommended, such as nonsteroidal anti-inflammatory drugs. For nausea/vomiting, prochlorperazine or ondansetron are recommended. The goal is to alleviate the symptoms of opioid-withdrawal using medications without the potential for abuse.

Conclusion

Substance abuse and dependence is a significant problem in the United States. It is the single largest contributor of crime in the country.[34] Illicit substance abuse considerably affects the healthcare system and community as a whole. The government has recognized its damaging effects which has led to tighter restrictions in legislation and improved access to opioid treatment. While not curative, treatment options like methadone, buprenorphine/naloxone, and naltrexone, significantly aid in opioid detoxification and maintenance.

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Questions

The majority of pain relievers used for nonmedical reasons are obtained from:

A. A friend or relative
B. Drug dealer
C. Co-worker
D. Physician

Mechanisms that have been proposed or enacted to decrease substance abuse include:

A. Change hydrocodone-containing products to a Schedule I controlled substance
B. Increase the restrictions on the availability of buprenorphine products
C. Decrease grant funding for substance abuse treatment for probation departments and community corrections programs
D. Expand INSPECT services to include prescriber-to-prescriber communication

Pharmacies are required to submit data on all controlled substances to INSPECT within how many days of the dispensing date of the medication?

A. 1 day
B. 30 days
C. 7 days
D. 15 days

An increase in which neurotransmitter is thought to be responsible for the feeling of reward that is experienced by substances users?

A. Acetylcholine
B. Dopamine
C. Norepinephrine
D. Serotonin

Which statement best describes the definition of addiction?

A. The need to use increasing amounts of a substance to achieve a specific pharmacologic effect.
B. A physiological need for a substance, for which lack of use can cause withdrawal symptoms.
C. Occasional use of and desire for a substance, from which the user can abstain for long periods of time.
D. Physical and psychological drug craving with drug-seeking behavior despite negative consequences.

Naloxone is used in combination with buprenorphine to:

A. To increase absorption
B. To make buprenorphine stable at room temperature
C. To act as an abuse deterrent if injected
D. To decrease the dosing frequency from daily to monthly

Which of the following is a significant drug interaction with methadone?

A. Atorvastatin
B. Clopidogrel
C. Aspirin
D. Lisinopril

Which lab values should be monitored closely during naltrexone therapy?

A. Liver function
B. Platelet count
C. Renal function
D. Lipid panel

Which opioid treatment option can be dosed once monthly as an intramuscular injection?

A. Methadone
B. Buprenorphine
C. Buprenorphine/naloxone
D. Naltrexone

Which of the following clinical concerns is significant with methadone treatment?

A. Prolongation of the QT interval
B. Pruritus
C. Skin necrosis
D. Elevated liver enzymes