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Medications for Substance Use Disorders

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Abstract

In this article, the authors briefly review the pharmacotherapeutic agents that are currently available for the treatment of substance use disorders. Nicotine replacement therapies are most effective for tobacco cessation. Naltrexone, acamprosate, and disulfiram are effective for reducing alcohol use. The most effective pharmacotherapies for opiate use disorders are agonist therapies, including methadone and buprenorphine. The authors also examine recent advances in medication development for other substance use disorders such as stimulant addiction. The role of medication adherence and behavioral treatments and the integration of behavioral and pharmacotherapeutic interventions are also discussed.

Keywords

Substance use disorders; detoxification; relapse prevention; nicotine; alcohol; opioids; social workers

INTRODUCTION

Substance use disorder (SUD) has been conceptualized as a chronic relapsing medical illness with relapses and remissions and a strong genetic component similar to diabetes type II and hypertension (McLellan, Lewis, O'Brien, & Kieber, 2000). Risk for relapse is heightened because the neurobiological changes in brain pathways created by many years of alcohol and/or drug use do not completely revert to normal after the detoxification process. The intensity and nature of the behavioral intervention can influence the outcome of treatment for patients with SUDs. The use of medications in the treatment of SUD can also play a major role in preventing relapse and facilitating longer periods of abstinence. More effective medications have been developed over the past 30 years, and subsequently, pharmacotherapy has progressively played a more important role in the treatment of addictions. Medications are mostly used as adjuncts to psychosocial treatments and the role of pharmacotherapy in treatment depends on the specific type of SUD (Barber & O'Brien, 1999).

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Pharmacological agents have three broad objectives: management of acute withdrawal syndromes through detoxification, attenuation of cravings and urges to use illicit drugs (initial recovery), and prevention of relapse to compulsive drug use (O'Brien, 2005). Treatment retention and harm reduction can also be enhanced by the use of agonist therapies such as methadone and buprenorphine.

In this article, we review the current state of pharmacological agents for some SUDs and examine the recent advances and challenges in medication development for other addictions. We discuss how medications can be combined with psychosocial and behavioral treatments as a component of a multimodal treatment plan and examine the challenges of integrating medications with behavioral therapies.

Medications for Withdrawal Syndromes, Initial Recovery, and Relapse Prevention

Medications can help alleviate the withdrawal manifestations among patients with severe physical dependence to help patients feel more comfortable during the early stages of treatment after stopping alcohol or drug use. Reducing withdrawal symptoms can, in turn, help the patient to stay abstinent and remain in treatment rather than being caught into a vicious cycle of using drugs to relieve withdrawal symptoms, thereby, continuing drug dependence.

Most pharmacotherapies target the brain receptors of neurotransmitters/neuromodulators that are dysregulated as a result of the specific addiction. Most medications for SUD fit into three general classes including: (a) full agonist medications, (b) partial agonists, and (c) antagonist medications. Full agonists directly stimulate receptor sites in the brain—for example, methadone binds to the opiate receptor similar to the action of heroin. Full agonist medications are used as replacements for the abused drug, and the patient continues to take the medication as a long-term therapy to maintain his or her recovery. Partial agonists act like agonists but do not stimulate the receptor to the same degree. Partial agonists are sometimes used for detoxification, following which the client remains drug free. Buprenorphine is a partial agonist that was recently developed for detoxification and for use as a maintenance medication for patients who are at risk for relapse into physical dependence on opioids. Agonist medications are taken daily to avoid withdrawal and cravings that can lead to relapse. Antagonist medications bind to the receptor but do not stimulate it and prevent agonists from binding. Naltrexone, discussed further below, is an example of an antagonist medication that was developed for the treatment of opioid dependence. The actions of these medications are discussed more fully later in this article.

Medications could potentially be more effective in the context of psychosocial treatment. None of any of the psychotherapeutic approaches interfere with the use and impact of medications; in fact they work synergistically to attenuate substance use and reduce the probability of relapse (McCaul & Petry, 2003).

NICOTINE

Tobacco use is highly comorbid among patients with SUDs and is the most common cause of premature death and disability among patients who are in recovery from other SUDs (Le Strat, Ramoz, & Gorwood, 2010; van Meijgaard & Fielding, 2012). Research suggests that smoking cessation may facilitate abstinence from alcohol and other drugs, and clients using tobacco should be educated about these findings as a potential motivator for reducing tobacco use (Bobo, McIlvain, Lando, Walker, & Leed-Kelly, 1998; Carmody et al., 2012; Holt, Litt, & Cooney, 2012). Pharmacotherapy is considered a mainstay of treatment for smoking cessation (Tonnesen, 2009), and recommended therapies, including combinations of counseling and medication, produce abstinence rates of about 40% after 1 year (Batra,

2011; George & O'Malley, 2004). First-line therapies (treatments that are recommended by the Food and Drug Administration [FDA] as having the most evidence of effectiveness) include nicotine replacement therapies (NRT), bupropion SR (Zyban), and varenicline (Chantix) (Henningfield, Fant, Buchhalter, & Stitzer, 2005; Nides, 2008).

NRTs replace the nicotine obtained from smoking to prevent withdrawal symptoms and improve smoking cessation outcomes. Replacement medications are used because of the low success rate of total "cold turkey" withdrawal from nicotine. Approved formulations include the transdermal nicotine patch, nicotine gum, nicotine lozenge, nicotine vapor inhaler, and nicotine nasal spray. Behavioral therapies used in conjunction with an NRT increase quit rates. Behavioral interventions typically include establishing a quit date, counseling about quitting, and receiving brief advice on strategies to support stopping (Lancaster, Stead, Silagy, & Swoden, 2000; Nides, 2008). NRT is started on the quit date, and success in quitting on the quit date is highly predictive of end-of-treatment success (George & O'Malley, 2004; Wu, Wilson, Dimoulas, & Mills, 2006). NRT is usually a short-term therapy, but longer term treatment can have additional benefits in smokers who are severely addicted. NRTs have been demonstrated to be efficacious compared to placebo on measures of abstinence (not even a puff) at the end of clinical trials and at later time points (6 and 12 months) (Nides, 2008; West et al., 2000). A strategy for further improving the efficacy of NRT is to combine one medication that allows for passive nicotine delivery (e.g., transdermal patch) with another medication that permits ad libitum nicotine delivery (e.g., gum, nasal spray, inhaler). The rationale for combining NRT medications is that smokers may need a slow delivery system to achieve a constant concentration of nicotine to relieve cravings and withdrawal symptoms, as well as a faster acting preparation that can be administered as needed for immediate relief of breakthrough cravings and withdrawal symptoms (Sweeney, Fant, Fagerstrom, McGovern, & Henningfield, 2001). Although research studies show that combination NRT is more effective than single NRT, the labeling on all of these NRT products continues to warn patients not to combine them (Ebbert, Hayes, & Hurt, 2010).

Bupropion SR, an atypical antidepressant, has been demonstrated to be efficacious in improving quit rates compared to placebo in short-term and long-term follow-up (George & O'Malley, 2004; Hurt et al., 1997). In some studies, bupropion has demonstrated very similar outcomes to NRT, but unlike NRT, bupropion is taken for 1 to 2 weeks prior to the quit date and then continued postquit date (Hughes, Stead, & Lancaster, 2004; Jorenby, 2002).

The partial nicotine agonist varenicline is used for a 1- to 2-week period while continuing smoking prior to the actual smoking cessation. Varenicline stimulates $\alpha 4\beta 2$ nicotinic receptors in the brain but not fully, as nicotine does. However, unlike nicotine that has a short duration of action requiring the user to have multiple daily doses, varenicline has a relatively long period of action in the body that requires only twice daily use. This partial stimulation decreases cravings and has been shown to increase the chances of a successful quit attempt, compared to unassisted smoking cessation attempts (Coe et al., 2005; Gonzalez et al., 2006; Hays, 2011).

Although patients are provided with recommendations to not use tobacco products while using NRT, NRT, bupropion, and varenicline are safe even when used by individuals who may use tobacco (Hays & Ebbert, 2010).

There are a number of unapproved clinically available treatments for tobacco dependence that are recommended as second-line therapies, such as clonidine and nortriptyline. Clonidine is a medication that decreases blood pressure and also eases withdrawal

symptoms from opioid dependence such as muscle aches, sweating, and anxiety. Its action has been shown to be effective against nicotine withdrawal, including cravings for nicotine. Nortriptyline is an antidepressant medication that is superior to placebo for increasing tobacco quit rates. The neurochemical changes induced by nortriptyline that reduce depressive symptoms are likely to be the same that are responsible for helping people reduce tobacco use (Gourlay, Stead, & Benowitz, 2004; Hughes, Stead, & Lancaster, 2005). Side effects caused by nortriptyline limits its usefulness as an aide for stopping tobacco use.

An intriguing novel therapeutic approach is vaccination against nicotine. The basic principle of this approach is that, after entering the systemic circulation, a substantial proportion of nicotine can be bound by antibodies, thereby reducing its distribution into the brain. As a consequence, the rewarding effects of nicotine are diminished, and relapse to smoking is less likely to occur (Kosten & Owens, 2005). However, results of clinical trials have been disappointing in that an increase in quit rates was only observed in small groups of smokers who displayed particularly high antibody levels (Hatsukami et al., 2005). Ideally, vaccines could potentially become part of a multifaceted approach to treating tobacco addiction that includes counseling and pharmacotherapy.

ALCOHOL

Medications for Detoxification and Medical Stabilization

Chronic dependence on alcohol can result in periods of severe withdrawal syndromes marked by increased heart rate and blood pressure, anxiety, and withdrawal seizures and in severe cases delirium tremens and even death (Kosten & O'Conner, 2003). Medications for alcohol withdrawal syndromes include benzodiazepines that act on gamma-aminobutyric acid (GABA) at the GABA (A) receptors in the brain to stimulate release of GABA. GABA is a neurotransmitter that is responsible for decreasing activity throughout the nervous system and acts to gradually detoxify the patient from alcohol by reducing heart rate, blood pressure, sweating, and anxiety associated with alcohol withdrawal. During detoxification benzodiazepines are systematically decreased to address the most important need, which is to prevent the occurrence of seizures and delirium. Alcohol-related seizures and or delirium tremens can result in death. Benzodiazepines can also improve treatment outcome but should only be used on a short-term basis. They should be avoided as a long-term strategy for controlling alcohol dependence because physical tolerance of these medications can occur rapidly and can result in dangerous interactions if patients using the medication relapse into alcohol use (Anton et al., 2006).

It is important to emphasize that the detoxification process serves as only a first step to stabilize patients medically and support the transition from alcohol dependence to recovery. Patients must be engaged in active psychotherapy and behavioral treatment following detoxification to remain abstinent from alcohol.

Medications to Attenuate Substance Use and Reduce Relapse

Disulfiram (Antabuse) is the first FDA-approved medication for alcohol dependence and has been available for over 50 years. It works by inhibiting aldehyde dehydrogenase, the enzyme that converts acetaldehyde to acetate in the breakdown of alcohol. As acetaldehyde builds up the disulfiram-ethanol reaction (DER) occurs. The DER includes unpleasant and potentially dangerous symptoms such as sweating, nausea, vomiting, facial flushing, tachycardia, hyperventilation, shortness of breath, and hypotension. In severe reactions, arrhythmias and myocardial infarction, seizure, and death can occur. The DER is an aversive state that serves to extinguish an addictive behavior through negative reinforcement and behavioral counterconditioning. By taking the medication daily, the patient knows that he or she will have such a reaction if he or she drinks alcohol. This knowledge, in turn, leads to refraining

from drinking. The intended use of disulfiram is to help the patient achieve an initial period of abstinence that facilitates the involvement in psychosocial treatment (Banys, 1988; Fuller & Gordis, 2004).

At the recommended average maintenance dose of 250 mg daily, disulfiram is considered a safe and well-tolerated medication used as an adjunctive pharmacotherapy in an abstinence-oriented treatment setting to prevent alcohol use and relapse.

Almost 40 years elapsed from the time disulfiram became available before a multisite randomized clinical trial of 605 participants meeting modern standards of clinical trial design was published (Fuller et al., 1986). This and other efficacy trials have shown mixed results. Primarily, it was determined that compliance with the medication was a significant barrier to its effectiveness. Only 19% of the patients taking disulfiram did so consistently (Buonopane & Petrakis, 2005; Fuller et al., 1986). Recent reviews of disulfiram treatment have endorsed supervised disulfiram (Anton, 2001; Buonopane & Petrakis, 2005; Hughes & Cook, 1997) while concluding that unsupervised disulfiram administration is of limited utility. This addresses the major problem that is medication adherence as patients can avoid the DER reaction by stopping the medication. High levels of motivation for abstinence are required for disulfiram to be effective. Additional research indicates that, in general, older men with more severe drinking histories who are more socially stable and are attending Alcoholics Anonymous (AA) are more likely to adhere to medication regimens and to achieve improved outcomes (Swift, 2003).

Naltrexone (Revia) is a good example of an anticraving medication for the long-term treatment of alcohol dependence. Naltrexone is a competitive opioid antagonist that presumably blocks the rewarding aspects of drinking by occupying opioid receptors. When naltrexone is present in the brain, alcohol cannot stimulate the release of dopamine, thereby, reducing the intoxicating effect of alcohol. One hypothesis for the ability of naltrexone to reduce drinking following a lapse in abstinence is that it precipitates sedation and causes patients to avoid alcohol to attenuate additional sedation.

Naltrexone has been shown to reduce the frequency and intensity of drinking, to reduce the risk of relapse to heavy drinking, and to increase the percentage of days abstinent (Garbutt, 2009). The effect size, or the degree to which naltrexone is effective, is similar to that with NRT for smoking cessation. The majority of published controlled studies of naltrexone show improved efficacy compared to placebo. However, one Veterans Administration study of naltrexone among patients with more severe alcohol dependence showed no benefits from it (Krystal et al., 2001). A major issue with naltrexone in outpatient long-term treatment settings is the variability of adherence to it. Several studies have shown efficacy in preventing relapse only if patients not taking naltrexone regularly are excluded from the sample. Lack of compliance with the medication is strongly correlated with higher relapse rates (Gonzalez & Brogden, 1988; Minozzi et al., 2006; Roth, Hogan, & Farren, 1997). Another important limitation is that opioid-based analgesics will not be effective for patients taking naltrexone. For example, patients who may rely on opiate medications like hydrocodone (Vicodin) for relief following dental procedures must be informed of the need to stop the medication or ask for a non-opiate-based analgesic.

The average dose is 50 mg daily. Naltrexone is usually well tolerated, and the most frequent side effects are mild nausea and headache. A depot injection formulation of naltrexone (Vivitrol) has been developed that is administered once monthly with a slow release into the body. It has shown efficacy in reducing heavy drinking outcomes because it offers the advantage of increased medication adherence (Garbutt et al., 2005; Lobmaier, Kornor, Kunoe, & Bjorndal, 2008). The depot form of naltrexone has the potential to be very

effective for reducing rates of alcohol dependence in the general population as a recent study showed that prescribing and monitoring it is feasible in primary care settings (Lee et al., 2010).

Acamprosate (Campral) was approved in 2004 by the FDA as a relapse-prevention medication for alcohol dependence. It affects various neurotransmitters and structurally resembles GABA and glutamate. Glutamate is the primary neurotransmitter for increasing neurologic activity. Acamprosate acts on gabaergic receptors but primarily it modulates glutamate receptors. It can be thought of as either a glutamate modulator or a weakly potent and partial N-methyl-D-aspartate (NMDA) antagonist. This results in its primary effect of decreasing withdrawal. It is more effective when given in the period initially after the cessation of acute withdrawal, possibly related to its effects on the NMDA receptors, and ability to diminish protracted hyperglutamatergic states that drive relapse by negative reinforcement (i.e., “relief” craving versus “reward” craving as seen with naltrexone) (Hopkins, Garbutt, Poole, West, & Carey, 2002; Tambour & Quertermont, 2007). Specifically, acamprosate acts to decrease cravings to drink brought on by the desire to feel relief from withdrawal symptoms.

The efficacy data on acamprosate has been mixed. Acamprosate has shown no greater benefit than placebo for alcohol dependent patients in the COMBINE Trial (Anton et al., 2006), the largest multisite study of treatment for alcohol dependence to date in the United States. However, acamprosate has been extensively studied in Europe, and those studies showed that acamprosate versus placebo significantly increased the proportion of patients who were already abstinent who remained continuously abstinent. The U.S. trials included a limited number of patients who required detoxification before treatment, in contrast with the European studies where most patients were detoxified prior to treatment (Mason, 2003; Mason, Goodman, Chabac, & Lehert, 2006).

Considering the difference between European and U.S. studies, it has been argued that patients with more severe dependence and higher baseline levels of motivation would benefit more from acamprosate. Furthermore, consistent with its primary action, patients who receive the medication over the protracted withdrawal period are more likely to benefit from acamprosate compared to patients requiring detoxification or who start the medication late in the withdrawal period (Littleton, 2007). The recommended dose of acamprosate of 666 mg 3 times daily is well tolerated. Diarrhea is the most common adverse effect.

Topiramate (Topamax) is a medication already approved for the treatment of epilepsy. It has been studied because of its ability to augment GABA function and inhibit glutamatergic pathways. These combined neurologic activities can decrease dopaminergic activity and, possibly, alcohol reward. Patients taking topiramate will, therefore, find it easier to drink less or become abstinent. Topiramate is started without an initial period of abstinence. In two major controlled trials, topiramate was found to be more effective than placebo for reducing heavy drinking, drinks per drinking day, and increasing percent of abstinent days (Johnson et al., 2003; Johnson et al., 2007). Topiramate is not FDA approved (also called “off label”) prescribing to treat alcohol dependence. Further research is needed to determine which subpopulations of alcoholics would benefit most from topiramate. Topiramate has a number of side effects including mild cognitive impairment and requires a low titration (the medication must be started at a low dosage and gradually increased) over a few weeks before a fully effective dose is reached.

Research has been conducted using the newer antidepressants serotonin specific reuptake inhibitors (SSRI), for example, fluoxetine and citalopram, as adjuncts in the treatment of alcoholism. However, these medications have been found to be of limited utility. The overall

findings suggest that SSRIs may be of some use in reducing alcohol use in subpopulations such as those with depression and alcohol dependence (for reviews, see Buonopane & Petrakis, 2005; Kelly, Daley, & Douaihy, 2012).

OPIOIDS

The most effective pharmacotherapies for opioid use disorders are the agonist therapies. As mentioned above, by occupying the sites stimulated by opioids, agonist medications essentially “turn on” the receptors. The therapeutic approach involves using medications that have similar actions to those of the abused drug but that have different pharmacokinetic profiles. Medications like methadone are longer acting and have fewer drug-like effects, and are, thereby, less reinforcing. In the case of opioids, methadone and buprenorphine are the most commonly used medications.

Methadone

Once stabilized on methadone individuals who are addicted to opiates who use short-acting opioids such as heroin will no longer experience peaks of euphoria or the aversive effects of withdrawal such as anxiety, agitation, diarrhea, and insomnia. As a result, the patient is no longer preoccupied with drug-seeking behaviors. Maintaining the patient on methadone reduces criminal activity substantially and transferring the patient from intravenous heroin use to an oral medication (e.g., methadone) dramatically reduces HIV and hepatitis C (HCV) risk exposure from injection drug use (Farre, Mas, Torrens, Moreno, & Cami, 2002; McLellan, Arndt, Metzger, Woody, & O’Brien, 1993). When adequate doses are used, methadone maintenance also diminishes the intensity of shorter acting opioids through cross-tolerance. This means that drug responses to a particular drug (e.g., methadone) transfers to other drugs from the same class (e.g., heroin) and reduces their reinforcing effects, which, in turn, decreases the intensity of cravings for the drug. The combination of control of aversive effects and prevention of reinforcement makes methadone maintenance an extremely effective treatment as objectively measured with opiate-free urine drug testing (Mattick, Breen, Kimber, & Davoli, 2003).

Methadone maintenance is considered a long-term treatment for opioid dependence even though it has been used on a short-term basis to detoxify patients from opioids. The optimal maintenance dose of methadone is between 80 mg and 120 mg (Donny, Walsh, Bigelow, Eissenberg, & Stitzer, 2002). Counseling is a mandated and an essential component of methadone maintenance. Because methadone promotes good treatment retention, it allows counselors to work with patients on improving many aspects of their life that have been affected by drug use and criminal activity. Several studies have shown that patients treated with methadone maintenance showed improved psychosocial function in areas of employment, and family and social relations (G. Gonzalez, Oliveto, & Kosten, 2004).

Methadone can be fatal in overdose and can increase risk of severe liver disease with the concomitant use of other substances such as alcohol or sedative-hypnotics such as benzodiazepines and barbiturates (Kreek, Oratz, & Rothschild, 1978). There is also a potential for diversion to illegal trafficking that has resulted in a very strict federal and state regulatory requirements for programs and patients. For example, patients must attend the clinic daily for observed daily dosing at the beginning of treatment and be monitored closely with the use of urine drug testing. As patients become free from other drugs, more stabilized, and show consistent attendance to counseling, they may be offered take-home methadone privileges, provided they continue in treatment and engage in recovery activities.

Buprenorphine

In accordance to the Drug Abuse Treatment Act of 2000, in October 2002, the FDA approved the use of buprenorphine/naloxone (Subutex), opioid partial agonist, as a schedule II agent to treat opiate dependence in outpatient office-based practices. Physicians who receive 8 hours of training and a waiver from the Department of Health and Human Services are qualified to prescribe buprenorphine.

The availability of buprenorphine has added another treatment option for opioid dependence with significantly less regulatory requirements compared to methadone. To mitigate the potential for abuse of the substance and diversion, buprenorphine has been developed in a sublingual (pills or film sheets that dissolve under the tongue) with naloxone (Suboxone). Naloxone is an opioid antagonist that actually nullifies the effect of buprenorphine when it is taken by injection or intranasally. Patients with addictions who may want to use the medication to become intoxicated often want to use drugs in these ways because of the increased intensity of the high, compared to taking drugs through the gut. The combination of buprenorphine with naloxone thereby reduces the risk of it being abused.

Buprenorphine is a long-acting (up to 48 hours) high-affinity partial μ opioid agonist, which causes it to act as a functional antagonist blocking the effects of pure μ agonists. Because it is a partial agonist unlike methadone, a pure agonist, it is safer in overdose because it has a ceiling effect on respiratory depression. Buprenorphine is considered to cause a reduced euphoric effect compared to methadone and therefore is less likely to be diverted (Anton et al., 2006; Fischer et al., 2006). Suboxone has become the treatment of choice for detoxification from opioids. The typical maintenance dose of Suboxone is 12 mg to 16 mg. Rarely doses higher than 16 mg might be useful but would necessitate a thorough reevaluation of the patients treatment needs.

Maintenance treatment is administered in three phases: induction, stabilization, and maintenance (Batki, Kauffman, Marion, Parrino, & Woody, 2005). Drug counseling should be considered an intimate requirement in all phases of buprenorphine treatment. The induction phase focuses on reducing the aversive effects of opiate withdrawal, and it starts only when the patient is in the beginning of opiate withdrawal. The goal of the stabilization phase is to eliminate withdrawal symptoms and manage side effects and gradually titrate or adjust up to an adequate dose of the medication. The maintenance phase requires close monitoring and also addresses relapse prevention. Patients should be seen at frequent intervals (e.g., at least weekly during the first month of treatment) based upon the individual circumstances of the patient. Periodic assessment is necessary to determine adherence with the dosing regimen, effectiveness of the treatment plan, and overall patient progress.

Once a stable dosage has been achieved and patient assessment (e.g., urine drug testing) does not indicate illicit drug use, less frequent follow-up visits may be appropriate. A once-monthly visit schedule may be reasonable for patients on a stable dosage of Suboxone who are making progress toward their treatment objectives. Continuation or modification of maintenance on the medication should be based on the physician’s evaluation of treatment outcomes and objectives such as: tolerance of medication and lack of toxicity, absence of medical or behavioral adverse effects, abstinence from illicit substance use including alcohol and benzodiazepine use, and the patient’s adherence to treatment, including counseling and involvement in recovery-oriented activities.

Suboxone dosages can either be maintained or tapered down. A significant number of studies showed that buprenorphine at medium and high doses was superior to placebo in terms of diminished illicit drug use and treatment retention. However, buprenorphine given in flexible doses was less effective than methadone for retaining patients in treatment and

for reducing opiate use (Mattick, Kimber, Breen, & Davoli, 2008). These results indicate that the full μ agonist, methadone, may be more suited for those patients with very severe addiction.

Naltrexone

The action of naltrexone to block dopamine makes it a potential alternative to opiate replacement treatment for opioid dependence. Unlike agonist therapies, naltrexone has been used as a relapse prevention strategy in an abstinence-oriented setting that builds on the long-acting affinity μ opioid receptor antagonist effects. Patients addicted to opioids cannot get high from opioids while on naltrexone, and it has been hypothesized that they will not want to use opioids, thus improving the likelihood that they will remain abstinent (Minozzi et al., 2006). Furthermore, naltrexone has some benefits over replacement therapies, including no risk of overdose, no addictive potential, and diminished stigma effect that is often associated with opiate replacement therapy.

However, naltrexone has been in limited use as a medication for opiate addiction due to significant problems with treatment retention. In addition, several trials of naltrexone failed to support the efficacy of naltrexone compared to placebo in the treatment of opioid addiction. As discussed above in relation to alcohol dependence, a depot preparation of naltrexone (Vivitrol) is available and has been FDA approved for the treatment of opioid dependence, which addresses the adherence (Lobmaier et al., 2008). Studies of naltrexone injection have only recently been conducted but have shown the superiority of naltrexone over placebo for treatment retention and increasing days abstinent from opioids (Gastfriend, 2011). The need to detoxify (7 to 10 days opioid free) before starting treatment with naltrexone injection is a barrier to treatment for some patients. Because of its antagonist effects naltrexone cannot be given to patients who have been using opioids without this 7- to 10-day opioid free period as taking it would precipitate an acute withdrawal syndrome. A major limitation of injectable naltrexone is its high costs and poor penetration of insurance coverage.

NEW MEDICATIONS AND FUTURE OPTIONS

At the present time there are no FDA-approved medications to treat cocaine, methamphetamine, and cannabis dependence, although the antianxiety medication buspirone has been found to be helpful for reducing cannabis dependence in one clinical trial (Weinstein & Gorelick, 2011). A dopamine agonist medication modafinil that is a weak stimulant has been found to be effective against cocaine cravings and has little potential for abuse (Dackis, Kampman, Lynch, Pettinati, & O'Brien, 2005; Shorter & Kosten, 2011). The development and testing of new medications that target specific drug addictions has been actively pursued. For example, dronabinol has shown some effectiveness for reducing cravings for cannabis and, therefore, may be of benefit against cannabis dependence.

The most innovative strategy is for immunizing against cocaine dependence. The medication, TA-CD, stimulates an antibody response that binds to cocaine molecules, causing them to be too large to cross the blood–brain barrier, thereby, nullifying the effect of the drug (Shorter & Kosten, 2011). In addition, some available medications have been studied in particular SUD, for example, disulfiram for cocaine. One randomized study showed greater reductions in cocaine use among patients receiving behavioral therapy or interpersonal therapy when they received disulfiram instead of placebo (Carroll et al., 2004). The impact of disulfiram on cocaine use was not related to changes in alcohol use. Another example, dopamine agonists have been studied in patients who are dependent on cocaine and methamphetamine. It is important to report that, despite these promising treatments, many medication trials have been done with little success.

COMBINATION THERAPY

Given the nonspecific pharmacodynamics properties of alcohol and other drugs, and their effects involving multiple neurotransmitters, it would make sense that a combination of medications might be necessary and helpful to optimize treatment outcomes. Moreover, within a particular setting, medications could theoretically be combined to target multiple processes that drive the addiction cycle. For example, relapse prevention medications that reduce cravings for alcohol (i.e., naltrexone) could be combined with those that reduce withdrawal symptoms (i.e., acamprosate). Another combination is disulfiram and naltrexone that might be used during the stabilization phase of recovery, after detoxification. For tobacco addiction, nicotine withdrawal could be addressed using a nicotine patch and acute exacerbations of cravings and urges by nicotine gums or lozenges. Some of these strategies could be sequenced depending on the drug's mechanisms of action, patient preference, insurance coverage issues, and costs. Most important is to discuss treatment options with the patients and tailor them to the patients' needs.

COMBINATION OF MEDICATION AND PSYCHOSOCIAL TREATMENT

All studies of pharmacological treatments have incorporated some form of counseling such as brief intervention, psychoeducation, or even a comprehensive behavioral treatment. Behavioral interventions such as contingency management and medication compliance therapy have the potential to influence adherence to medication and retention in treatment that is a major limitation of using pharmacotherapy alone (Miller, Yahne, Moyers, Martinez, & Pirritano, 2004; Pettinati, 2004). Similarly, early treatment with medication could help the patient achieve abstinence, which in turn increases the patient's ability to learn new coping skills and benefit more from behavioral therapy. Clearly medication and behavioral therapies work synergistically to improve outcomes (Carroll & Shottenfeld, 1997; Volpicelli, 2001). In addition, some behavioral therapies could be specifically focused on taking advantage of the pharmacological effects of the medications, for example, drinking-reduction strategies in the context of naltrexone treatment.

There is mounting evidence pointing to the efficacy of combination treatments of medications and behavioral therapies (Kelly et al., 2012; Pettinati, Volpicelli, Pierce, & O'Brien, 2000; Zweben & Zuckoff, 2002). The most common behavioral therapies that have been combined with pharmacological interventions include contingency management, community reinforcement approach, motivational interviewing and medication compliance therapy, and behavioral family therapy (Anton et al., 2006; Datillio, 2009; Heffner et al., 2010; Meyers, Smith, & Lash, 2003).

A potential problem when using behavioral therapy and medication could be related to patient's poor participation in the behavioral intervention due to excessive reliance on the medication and/or a low commitment to recovery. These clinical situations should be monitored, and treatment plans adjusted as indicated. Although, in general, behavioral treatments enhance the effectiveness of NRT, in some clinical situations, NRT appears to be effective regardless of the additional supportive intervention (Lancaster et al., 2000). In fact, NRTs have been available without a prescription since shortly after their release and can be used without any direct practitioner's intervention. Conversely, for some situations, combinations of treatments are no more effective than an evidence-based pharmacotherapy or behavioral therapy alone. Finally, due to the severity of the condition, combinations of psychotherapeutic approaches, behavioral and pharmacological interventions are usually needed to influence the outcomes of treatment for patients with co-occurring SUDs and psychiatric disorders. For some particularly severe comorbidities such as the schizophrenia/

cannabis dependence comorbidity, the intensity of treatment must be increased markedly because pharmacological treatments alone have significant limitations (Kelly et al., 2012).

INTEGRATION OF PHARMACOTHERAPY AND BEHAVIORAL INTERVENTIONS IN TREATMENT SETTINGS

Adherence to the medication regimen is multifactorial. The characteristics of the medications include its effectiveness, side effects, dosing regimens, cost, and insurance coverage. Patient factors include motivation for change, motivation to adhere to the medication schedule, cognitive functioning, social support network and environmental supports for adherence, and attitudes, beliefs, and knowledge about the medications, the illness, and recovery process. Behavioral interventions should be targeted toward enhancing adherence and addressing any potential psychological issues interfering with medication adherence. Supervised administration of medication by either a family member or a concerned significant other or the treatment program is the most easily and commonly implemented behavioral approach to improve adherence to medication. Contingency management (Petry, 2011) in which medication adherence is rewarded can also significantly improve medication compliance and treatment outcome.

As discussed earlier, behavioral therapies and pharmacotherapy are mostly integrated together in the individualized treatment plan. Pharmacotherapy can play a major role at different stages of the recovery including initial abstinence and relapse prevention. Pharmacological treatment requires establishing a working alliance with the patient and conducting a comprehensive medical assessment to determine the most appropriate options and to evaluate their safety profile. Assessing the patient's motivation for change and willingness to take medication and stay adherent to them are also very important aspects of the medical evaluation. Close collaboration with other nonmedical members of the treatment team helps facilitate the role of the medication in the overall treatment plan. Family and concerned significant others involvement in treatment is a crucial aspect of the integrated treatment plan because of their influence on patient compliance. Individual and group therapists, as well as case managers, must understand what symptoms or syndromes medications target and be able to reinforce the value of the medication as an important method for improving treatment outcomes.

PHARMACOTHERAPY AND THE ROLE OF SOCIAL WORKERS

Social workers who have knowledge of the benefits of pharmacotherapy for SUD can be of significant help to their clients with substance use problems. Social workers are often on the "front line" of health care. For example, social workers often see clients in their home and are the health care workers who most often work directly with family members. In this capacity social workers observe events and obtain information regarding substance abuse unavailable to other clinicians. Social workers can literally save lives by educating clients about the importance of receiving medication for withdrawal from alcohol and benzodiazepine dependence. Similarly social workers are in a critical position to inform clients who need treatment for alcohol and opioid dependence about the potential benefits of naltrexone and acamprosate for alcohol dependence and naltrexone, buprenorphine, and methadone for opioid dependence.

Another challenge that social workers face is addressing client's attitudes about Alcoholics Anonymous/Narcotics Anonymous participation and the use of medications for drinking or using and co-occurring psychiatric disorders. It is important to be aware of the myth that circulates around that people involved in 12-Step programs are pressured and even forced to stop taking their medications if they want to benefit from the 12-Step programs. Although

some individuals and sponsors involved in 12-Step programs express negative opinions about psychotropic medications (Rychtarik, Connors, Dermen, & Stasiewicz, 2000), this is not supported by the core 12-Step literature. A study showed that 12-Step attendees as a whole were less likely to endorse abstinence from medications for psychiatric problems then were clients in other forms of treatment (Tonigan, 2003). So clearly attending 12-Step meetings is compatible with taking psychotropic medications. In fact secondary analyses from Project MATCH suggested that current AA members may be modestly more favorable about the use of such medications, but this finding requires replication (Tonigan & Kelly, 2004).

We provide two illustrations below of specific examples where social workers can help their clients by using their knowledge of how medications are therapeutic in the treatment of substance use disorders.

1. A child welfare or mental health worker social worker visiting the home of a male adult client with depression notices evidence of alcohol abuse and engages him in a conversation about his use of alcohol. The client admits to drinking daily. The social worker emphasizes the importance of getting professional help for detoxification and strongly recommends he accept a referral to a local detoxification center. The client notes that he has been through the process before but cannot seem to stay in recovery due to his depression and severe cravings for alcohol. The social worker is able to educate the client about the medications now available to help with alcohol cravings and how antidepressants that improve depression at the same time may provide relief from the circular pattern of detoxification-depression-craving and continued use of alcohol. The social worker also assesses the client's and his wife's willingness to attend mutual self-help groups and recommends that they consider participation. The social worker responds appropriately with regard to making the referrals or not (as indicated by their response) and emphasizes that he or she will be following up with the client the next day to determine the status of the referrals.

2. A hospital social worker frequently comes into contact with patients who use tobacco. Her contacts occur following medical events that indicate the significant risk tobacco use represents to the health of her patients. The social worker has many unique opportunities during these "teachable moments" to provide education about the value of nicotine agonist therapies, including varencline. She knows that her patients have a significant addiction that causes significant cravings. However, she also know that their ambivalence is at a low ebb at this particular time and can result in their responding to intervention now, even though they may not have done so in the past. She also notes that they will likely respond best to a combined approach of medication, behavioral interventions, and emotional support. Her hospital conducts a continuously scheduled stop smoking group for their patients, and she knows the therapist who conducts the therapy. Following a brief session where she explains the value of combined medication and behavioral therapy for smoking cessation, she asks each of her patients if he or she would like to find out more about the program. For those who do she introduces her patients to the stop smoking therapist before they leave the hospital. For those who do not she invites them to call her at any time if they change their mind. She also gives each patient a brochure about the stop smoking program that includes information about how to contact the stop smoking specialist.

CONCLUSION

Addiction is a chronic disorder that requires a long-term approach. In recent years, pharmacotherapies have been developed and now play an important role in the treatment of SUDs at the levels of detoxification, initial recovery, and relapse prevention. Medications add to the benefits of psychosocial interventions and work synergistically in combination with behavioral therapies. Despite the significant advances in the development of effective medications for SUDs, medications are underused by physicians, and pharmacotherapy should be a larger part of practice. Notwithstanding this recommendation questions remain that should be the target of research. For example, future research might investigate the following: Which combination of medications are the most effective for treating particular SUDs? How are combination therapies and patient-matching treatment issues addressed so that treatment is most effective? Recent developments in pharmacogenetics might inform medication treatment decisions in the near future. Advances in vaccine technology are the most exciting approaches on the horizon as potential treatment for some SUDs such as nicotine and cocaine dependence.

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