Excerpts from Dissertation of John Fitzgerald: A Multilevel Analysis of Individual and Organizational Effects on Staff Attitudes Towards Use of Medication in Substance Abuse Treatment

Medications to Treat Substance Use Disorders

Significant advances in understanding the neurobiology of addictive disease have occurred during the past couple of decades, yet these discoveries have resulted in just a handful of medications that have successfully been brought to market (Institute of Medicine, 1998; Vocci, 2003a, 2003b). Currently, FDA approved drugs exist for the treatment of alcohol and opioid dependence, yet none have achieved widespread acceptance, a topic reviewed hereafter. Considering that 16 million Americans abuse alcohol and 19 million abuse illicit drugs (U.S. Department of Health and Human Services, 2005), the stakes remain high for increasing use of currently approved drugs and developing new medications for the treatment of addiction. This section reviews FDA approved medications specific to the treatment of substance abuse disorders, and provides a brief overview of what the future holds. Attention is focused on naltrexone, methadone, and buprenorphine, the three medications involved in the present study.

Studies conducted to test medication effects generally fall into two categories. *Efficacy* research refers to those studies that test the impact of a medication under controlled experimental conditions. The primary advantage of such studies is that they demonstrate the degree to which an outcome can be attributed to the effect of the medication (i.e., they maximize internal validity). This in part is accomplished by selecting study participants that meet specific criteria aimed at screening out extraneous factors that may confound the treatment effects. For example, participants in a study to test a medication for alcohol dependence might be required to have no other mental health diagnoses and no recent history of any other substance abuse. Such restrictions improve the internal validity of the study, but decrease the external validity of the results since study populations are often not representative of the populations of people who seek treatment.

Studies conducted under more realistic, real-world treatment conditions are often referred to as *effectiveness* studies. Medications are tested in various treatment settings (e.g., residential, outpatient), during particular times of treatment (e.g., beginning, middle, or end of treatment), and often with patients that have multiple co-occurring disorders. When treatment effects are found, such studies indicate the degree in which a medication can be generalized to other settings, times and conditions. The downside of such studies is that findings can often be hard to interpret when confounding variables are present. Where efficacy studies maximize internal validity at the expense of external validity, effectiveness studies have the opposite effect; they maximize external validity at the expense of internal validity. It is also worth noting that randomized controlled trials (RCTs) are often associated with efficacy research, but effectiveness studies can also be RCTs as well. Approved FDA medications to treat substance abuse disorders have all been subjected to both efficacy and effectiveness research to some degree, however efficacy studies are generally more common.

Medications to Treat Alcohol-Use Disorders

Currently, there exist three FDA approved medications to treat alcohol abuse disorders: disulfiram, naltrexone, and acamprostate. Disulfiram (Antabuse®) has been used for over 50 years and is available in both oral and implant forms. It impacts the metabolism of alcohol, resulting in unpleasant symptoms (e.g., nausea, vomiting, flushing) when even small amounts of alcohol are ingested. More than 135 studies have investigated its efficacy and effectiveness, yet only a handful of these have been RCTs (Garbutt, West, Carey, Lohr, & Crews, 1999). In spite of widely-held beliefs by counselors that disulfiram reduces drinking and deters relapse, the evidence suggests strongly that disulfiram has only moderate effects on alcohol consumption, and virtually no impact on abstinence rates (Garbutt et al., 1999).

Naltrexone (ReVia™), an opiate antagonist available since the 1980s to treat opioid dependence, was approved in 1994 as an adjunct to psychosocial treatments of alcoholism. Currently available in oral and injectable forms, naltrexone is believed to reduce drinking cravings by blocking the release of endogenous opioids associated with the rewarding effects of alcohol (Weinrieb & O'Brien, 1997). Initial RCTs showed naltrexone to be efficacious in reducing drinking frequency and the incidence of relapse (O'Malley et al., 1992; Volpicelli, Alterman, Hayashida, & O'Brien, 1992). Since that time, at least 20 published RCTs have provided additional support that naltrexone is an efficacious, safe, and useful adjunct to psychosocial interventions for reducing drinking behavior and the frequency of relapse (Carmen, Angeles, Munoz, & Jose Maria, 2004; Kranzler & Van Kirk, 2001). However, a few studies have challenged these finding by reporting that naltrexone was found to be no better than placebo (Chick et al., 2000; Krystal, Cramer, Krol, Kirk, & Rosenheck, 2001).

Although shown to be *efficacious* in well-controlled clinical trials, naltrexone's *effectiveness* in community-based treatment settings with heterogeneous populations has been mixed. In a recent study of alcohol dependent patients in a rural community treatment setting, Killeen et al. (2004) found support for use of naltrexone in patients continuing to drink in the early stages of treatment, but found no differences on drinking outcome measures at 12 week follow-up. This finding suggests that it may be more useful in the early stages of treatment to reduce drinking behavior or help patients gain initial abstinence, but not as useful in the long-term management of addiction. The authors suggest that marginal medication adherence, psychosocial instability, and polysubstance abuse all contributed to the poor outcomes in this study, and further effectiveness research in community-based settings is needed.

In July of 2004 the FDA approved acamprosate (Campral®) as a third alternative for the treatment of alcoholism. Also available in oral form, acamprosate is believed to exert its effect by restoring normal activity of glutamatergic neurotransmission adversely affected by chronic alcohol exposure, but the specific mechanism of action is still not well understood (Mason, 2005). It has been used extensively for the past 15 years, primarily in Europe, and been subject to many RCTs that have found it to be a safe, effective, and efficacious medication for reducing alcohol consumption (Carmen et al., 2004; Kranzler & Van Kirk, 2001; Mason, 2005). Some evidence suggests that acamprosate may be more useful for patients targeting long-term abstinence, whereas naltrexone may be more beneficial in programs focused on reduced or controlled consumption (Carmen et al., 2004).

There is recent evidence that combining acamprosate with naltrexone is more effective than either medication alone when used with cognitive behavioral therapy (Feeney, Connor, Young, Tucker, & McPherson, 2006). The study matched 236 patients across gender, age group, and alcohol dependence severity, and allowed patients to self-select one of three treatment options: (a) naltrexone with therapy, (b) acamprosate with therapy, or (c) naltrexone and acamprosate with therapy. Three groups of 59 patients were assessed over a 12-week period, in addition to a group of patients that chose therapy without any medication. On all outcome measures (e.g., attendance, abstinence rate, and relapse rate) a trend favored the combined medication and therapy approach, but the results never achieved statistical significance. As an effectiveness study, the authors point out the results are low on internal validity since patients were able to self-select their treatments. Further, issues related to medication compliance and differences between patients who take medications, and those who choose not to, need further investigation.

In summary, disulfiram, naltrexone and acamprosate provide three different pharmacological alternatives to the treatment of alcoholism. Efforts to increase support for use have primarily focused on naltrexone, but acamprosate will likely be a target of future efforts. Both have been subject to multiple RCTs and shown to be safe, efficacious, and beneficial when used concurrently with psychosocial interventions. Other medications have also been tested in the treatment of alcoholism (e.g., nalfemene, SSRIs, lithium, etc.), but results have yet to support their use (Garbutt et al., 1999). One recent innovation to enhance patient compliance is the development of a long-acting injectable naltrexone (Vivitrol™) that became available to patients in late 2006. A recent RCT found it to be well tolerated and effective at reducing drinking days, but its benefit over oral naltrexone has yet to be determined (Garbutt et al., 2005).

Medications to Treat Opioid Dependence

Currently, there are four FDA approved medications for the treatment of opioid dependence: methadone, buprenorphine, levo-alpha-acetymethadol (LAAM), and naltrexone. The most widely prescribed, methadone, was first introduced as a potential treatment against a backdrop of escalating heroin use in the 1960s. Dole and Nyswander (1965; 1967) are credited with first using methadone as a legal opioid substitution therapy. By acting on the same receptor sites as heroin, methadone satiates addictive cravings, while suppressing withdrawal symptoms for up to 24 hours (i.e., once daily dosing). At the same time, it does not produce sedation or a dulling of consciousness, and is thus unattractive as a drug of abuse (National Institute of Health, 1997). It currently is available in tablet, wafer, and liquid form, and used in 1,105 methadone clinics in 44 states nationwide (American Association for the Treatment of Opioid Dependence, 2004). It is estimated that of the approximate 810,000 heroin addicts in the U.S., about 20% receive treatment in methadone maintenance programs (American Methadone Treatment Association, 1998). Since its introduction as a therapeutic agent for opiate dependence, numerous RCTs have shown a consistent, statistically significant relationship between use of methadone and reductions in illicit opiate use, mortality, crime, and HIV risk behaviors, as well as improved rates of treatment retention and quality of life (Amato et al., 2005; Gossop, Marsden, Stewart, & Treacy, 2001; Marsch, 1998; National Institute of Health, 1997).

Despite being among the most effective evidence-based treatments available (National Consensus Development Panel on Effective Treatment of Opiate Addiction, 1998), its use has historically been plagued by numerous barriers. Many working in substance abuse treatment and the criminal justice system are philosophically opposed to nonabstinence-based interventions, and believe that ongoing use of a prescribed narcotic is immoral and fundamentally opposed to the goals of rehabilitation (U.S. Department of Health and Human Services, 1994). Methadone is also the most regulated pharmaceutical agent in the nation, requiring providers and patients to follow stringent guidelines that many consider aversive and unnecessary. The NIH consensus statement on methadone treatment went so far as to say "we know of no other area where the Federal government intrudes so deeply and coercively into the practice of medicine" (National Consensus Development Panel on Effective Treatment of Opiate Addiction, p 1940). Although diversion of methadone has been noted (e.g., street trade, theft, etc.), it frequently is the result of patients attempting to self-medicate outside of professional treatment (Cicero, Inciardi, & Munoz, 2005). Finally, lack of physicians trained in addiction interventions and limited funding have inhibited access to treatment (National Consensus Development Panel on Effective Treatment of Opiate Addiction, 1998).

Among the recommendations from the National Consensus Developmental Panel was the need for federal legislative change to improve substance abusing patients' access to opiate medications. Soon after, the *Drug Addiction Treatment Act of 2000* (DATA 2000) was passed, allowing qualified physicians to use Schedule III, IV, or V narcotics approved for treatment of opiate dependence. In 2002, buprenorphine became the first schedule III medication approved by the FDA to meet the criteria, heralding in a long awaited alternative to the often demeaning structure surrounding use of methadone. Patients could now receive treatment in a physician's office, although the Act limited physicians' prescribing to 30 patients at any given time. The limitation was enacted primarily to prevent physician practices from becoming too dependent on buprenorphine prescriptions, and did not apply to group medical practices or treatment programs. Buprenorphine is a partial agonist, exerting a *ceiling effect* at higher doses that makes it particularly safe in the treatment of opioid dependence, but that limits its usefulness in patients requiring higher levels of full agonist activity for treatment success (U.S. Department of Health and Human Services, 2004). Further, its long duration of action, minimal withdrawal symptoms upon cessation, and low level of physical dependence add to its favorable profile (Ling & Smith, 2002). Currently it is available in two sublingual tablet forms (Subutex® and Suboxone®), but Suboxone® has become the preferred medication because is contains naloxone, an opioid antagonist that helps deter diversion and misuse. Multiple RCTs have shown buprenorphine to be an efficacious treatment for opioid dependence (Amass et al., 2004; Johnson et al., 2000; Ling et al., 2005; Ling et al., 1998; Pani, Maremmani, Pirastu, Tagliamonte, & Gessa, 2000). Similar support is found for the buprenorphine-naloxone combination (Amass, Kamien, & Mikulich, 2000, 2001). Similar to methadone, there is evidence of improved outcomes in combination with psychosocial services (Law & Nutt, 2003).

Two other medications for opiate dependence treatment deserve mention. LAAM was approved by the FDA in 1993 after numerous RCTs showed it to be a safe and efficacious treatment (Fudala, Vocci, Montgomery, & Trachtenberg, 1997; Judson & Goldstein, 1983; Ling, Klett, & Gillis, 1978). It was hailed to quickly overtake

methadone as the treatment of choice for opiate dependence, but instead became a lesson in all that can go wrong when attempting to implement a new innovation into practice (Ling, Rawson, & Anglin, 2003). Almost eight years after its approval, fewer than 2% of opiate dependent patients in the U.S. were using LAAM (Rawson, Hasson, Huber, McCann, & Ling, 1998). A combination of limited marketing, state and federal regulatory hurdles, and the lack of a powerful advocate championing its use all contributed to its failure. Currently, it remains an approved medication by the FDA, but it is not being manufactured by any pharmaceutical company for patient use and is unavailable in pharmacies.

Finally, naltrexone gained FDA approval in 1985 for the treatment of opiate dependence. It is a complete antagonist, blocking the mu opioid receptors and taking away the effect of opiate drugs. It has been primarily used to maintain abstinence following detoxification, but a recent review of RCTs found insufficient evidence to justify its use in maintenance treatment (Kirchmayer et al., 2002). There is some evidence that when naltrexone is used in combination with benzodiazepines, it may improve a patient's ability to maintain abstinence from opiates (Stella et al., 2005).

In summary, methadone has been used successfully for over 35 years as an effective therapeutic agent for the treatment of opioid dependence, and is considered by many to be among the most effective of all addiction treatment interventions. But as successful as it may be, it remains a controversial agent that is used by only 20% of those in need, and has yet to garner consistent support from the treatment community. As an alternative, buprenorphine shows great promise in overcoming many of the methadone hurdles; but as the next section on medication barriers reveals, it remains largely unknown to many in the treatment industry two years after approval. Those pushing for its adoption need only look to the failure of LAAM to realize that bridging the gap between research and practice can be a daunting task.

Future Directions

The current arsenal of addiction medications may be limited, but significant effort is currently underway to discover new pharmacological agents. There are two primary approaches to the development of new medicines. The first, known as a *top-down* approach, occurs when researchers test whether a medication already on the market for a health issue other than addiction, may have some benefit for those struggling with addiction (Vocci, 2003a). One example is rimonabant, a drug that blocks cannabinoid-1 (CB1) receptors in the brain and used in the management of obesity. It is now being tested as a potential treatment for alcohol dependence since animals studies indicate that blocking CB1 receptors results in animals consuming less alcohol (National Institutes of Health Clinical Trials Center, 2006). Another example is baclofen, a decades-old medication approved for the treatment of muscle spasms and cramps in patients suffering from multiple sclerosis or spinal problems. A recent RCT demonstrated that baclofen may be effective in reducing cocaine use when used concurrently with psychosocial interventions (Shoptaw et al., 2003). At present, there is no approved medication for the treatment of cocaine dependence, but NIDA is currently using a top-down approach to test 21 medicines already on the market as possible options (Vocci, 2003b). Disulfiram (Antabuse) used for alcohol treatment was also recently shown to be an effective pharmacological agent for treating cocaine dependence when used with cognitive-

behavioral therapy (Carroll et al., 2004). A number of the SSRIs, including fluoxetine and venlafaxine, are also current candidates.

Development of new medications also occurs from what is known as a *bottom-up* approach, where new medicines result from scientific discoveries in the laboratory. Numerous drugs are now being assessed for possible treatments for cocaine (e.g., GBR 12909, NMDA modulators, CRF antagonists, etc.), and methamphetamine dependence (e.g. Loeline) (Vocci, 2003a). Taken together, significant resources are currently being devoted to pharmacological treatments for substance abuse disorders. Whether these investments will result in widespread benefit depends largely on their effectiveness, and on attitudes patients, providers, and the public have towards them.

The above review points to the important role medications can play in the treatment of substance abuse disorders. Naltrexone, buprenorphine, and methadone have all been used successfully to reduce addictive behavior and improve clinical outcomes, but none have become widely adopted in practice. Each medication has benefits and risks, and the best that can be said about their effectiveness is that they have all been shown to have moderate effect sizes in RCTs, a finding often used to justify their underuse. But as Orford (2001) points out, experts have searched long and hard for the best treatment for addiction, and in the process, have developed numerous psychosocial interventions that have all resulted in moderate effect sizes as well. In the absence of a gold standard, patients and providers benefit from a menu of options that include both psychosocial and pharmacological interventions, often used concurrently for the best outcomes.

Unintended Consequences

This study was motivated by a desire to improve treatment outcomes for patients with substance abuse disorders, particularly those who consistently relapse and have relied solely on psychosocial interventions. There is significant evidence that the majority of patients fall into this category (Hubbard, Flynn, Craddock, & Fletcher, 2001; Institute of Medicine, 1998; McLellan, Lewis, O'Brien, & Kleber, 2000), and that long-term outcomes may be improved in many of these patients by combining psychosocial treatment with addiction medications (Institute of Medicine, 1998, 2006; Volpicelli, Pettinati, McLellan, & O'Brien, 2001). But despite this evidence, few researchers have thought much about how increasing support for addiction medications might have unintended consequences.

Central to the systems approach is recognizing that any time a change is made to one part of a system, quite often there are unanticipated effects for the entire system. Chapter 2 introduced the idea of *dynamic complexity*, and discussed how the best intentions to improve a situation can often backfire as a result of not fully understanding the role of feedback in a system. When many variables are changing simultaneously, studies have shown that the ability of humans to make reasonable inferences about the behavior of a system over time are significantly limited, even when given complete and perfect knowledge of a system (Sterman, 2000). Given that most working in the substance abuse treatment field are stressed for time and operate with limited financial resources, it is not surprising that most change-related decisions are often based on incomplete information, habits, rote procedures, and simple mental models that quite often lead to outcomes that are less than desirable.

The previous section (and 3.1) highlighted the dire state of the current substance abuse treatment system, illustrating that the challenge is not to just increase support for addiction medications, but to enact entire systems changes that improve overall levels of addiction care on many fronts. As a result, there are inherent dangers in going about fixing the current system without significant thought as to how best to approach such a complex undertaking. The purpose of this section is not to discuss all the possible outcomes from such system-wide changes, but to highlight the most probable unintended effects of increasing use of addiction medications, and offer suggestions on how they may be appropriately addressed.

Over-reliance on use of addiction medications. A quick-fix mentality pervades society, fueled by advertising media suggesting that there are simple and fast solutions to losing weight, quitting smoking, and ending addictions. Even more, many of these solutions are based solely on the use of a medication. In the forward to the book *Combining Medication and Psychosocial Treatments for Addiction*, Distinguished Professor of Psychology and Psychiatry, William R. Miller states:

> I fear that the dispensing of medications for addictions could be thought of much as the prescription for antibiotics for infections. There are common features, of course, such as problems with medication adherence, but addictions center not on an invasive organism, but on a pervasive behavior. A busy schedule and a mind-set to treating acute illnesses can easily combine to produce a 'Just do it!' approach that frustrates both patient and practitioner, and becomes a self-perpetuating cycle (Volpicelli et al., 2001, p. xii).

It is not hard to see how counselors and prescribers, given time constraints and limited resources, might inadvertently scale back psychosocial interventions in lieu of medications appearing to have a positive effect. Patients may report significant behavioral change after beginning a medication, unaware they are overstating the pharmacological benefit and underestimating the need to maintain concurrent psychosocial recovery activities. Over time, both patient and clinician may fall into the trap described above, where relapse becomes inevitable.

For clinicians, the solution to a quick-fix mentality is maintaining awareness that addictive disorders are long-term, chronic medical conditions that require attention to multiple factors over long periods of time (McLellan et al., 2000; McLellan, McKay, Forman, Cacciola, & Kemp, 2005). Although addiction medications can be useful in preventing relapse, they are not panaceas for many of the problems that co-occur with substance abuse, such as developmental deficits and constrictions (e.g., self-regulation problems, inability identify and use emotions), relationship problems, legal issues, and mental health disorders (McLellan, Alterman, Metzger, Woody, & O'Brien, 1993). Thus formal academic education, continuing education trainings, and clinical supervision all provide valuable opportunities for educating counselors and prescribers about the nature of addiction, the appropriate use of medications, and the most effective methods for obtaining optimal outcomes.

Policy decisions that lead to adverse outcomes due to lack of buy-in from impacted stakeholders. At a time when there is a significant push to incorporate evidence-based practices into substance abuse treatment, there is also the risk that rash

efforts to do so may have unintended outcomes. An example of how this might happen was offered in Section 2.1, where a well-meaning program director quickly implements a policy to increase use of addiction medications, and then scratches his head months later when counselor turnover doubles and patient dropout rates increase. As discussed in the previous section of this chapter, there is significant evidence that implementing evidence-based practices, including appropriate use of addiction medications, is a complex undertaking that requires a significant amount of time and effort (Addiction Technology Transfer Centers, 2000; Fixen, Naoom, Blase, Friedman, & Wallace, 2005). Attempts by program administrators to short-change the implementation process will very likely lead to a host of unintended consequences that ultimately undermines the use of medications as an evidence-based treatment. Therefore, efforts to increase appropriate use of addiction medications in substance abuse treatment programs should include strong caveats to all counseling staff, administrators and prescribers, that findings from implementation research should guide programmatic changes.

Unbalanced consideration of the benefits, risks, and costs. Use of addiction medications is not without risks and costs. Although the benefits of these medications have been reviewed in Section 3.2, little has been said about the potential hazards they pose to patients and the economic impact of increasing their usage within the substance abuse treatment system. Although studies reviewed in section 3.2 provided evidence of the safety of FDA approved addiction medications, there are numerous examples of drugs that were long thought to be safe, but later confirmed to actually cause more harm than good (i.e., Prempro®, Vioxx®, Redux®) (Avorn, 2004). Although it is not likely that naltrexone, methadone, or buprenorphine will suffer the same fate, each of these medications can produce adverse side effects that vary between patients, and at times, necessitate that a patient stop taking a particular medication.

Prescribers and patients must always recognize that even mild side effects, including drowsiness, nausea, and headaches, can influence daily activities like driving and walking, resulting in consequences beyond the initial side effects of the drug (e.g., car accident, fall). Also, patients in treatment for substance abuse commonly have medical issues that require pharmacotherapy. Although patients, prescribers and pharmacists are jointly responsible for assessing risks associated with drug interactions, there is always a chance that such interactions get overlooked. There is also the issue about how to appropriately address medication risks clinically.

> The most commonly consulted source for risk information is the ponderous Physicians' Desk Reference, where its depiction may be both overwhelming and useless. The PDR uses an odd format for describing side effects. Its 3,500 pages of tightly packed small type comprise the FDA sanctioned listings that each manufacturer provides for its drugs; most descriptions are thousands of words long. Confusingly, risks can appear under one or more of several headings: Warnings, Contraindications, Precautions, and Adverse Reactions (Avorn, 2004, p. 163).

If addiction medications are to be used more frequently in substance abuse treatment, counselors and prescribers ideally need tools beyond the PDR that accurately and concisely characterize side effects as well as benefits, and help patients make informed

decisions about their care. Such tools may include web-based applications that review benefits and risks, brief publications that can be shared with patients, and in some cases, marketing materials from pharmaceutical manufacturers. In a recent edition of the *Addiction Professional* (2007), the official magazine of the National Association of Alcohol and Drug Abuse Counselors, an article titled *Pharmacotherapy: Integrating new tools into practice* provides an example of where counselors can gain knowledge of how best to utilize addiction medications in practice.

In addition to balancing benefits and risks, the equation must also include the economic impact of addiction medications for patients, as well as programs that offer medication services. Numerous studies have cited cost as a significant barrier to adoption (Mark, Kranzler, Poole et al., 2003; Mark, Kranzler, & Song, 2003; Thomas, Wallack, Lee, McCarty, & Swift, 2003), and for newer medications without generics (e.g., Subutex®, Suboxone®, Vivitrol®), this is legitimate issue with unintended consequences. One concern regarding the treatment of opiate addiction is that a two-tier system will develop, where patients with insurance will receive office-based treatment using buprenorphine, and those without insurance will have no alternative but to seek help from methadone maintenance clinics. In a similar manner, I recently had a conversation (2006) with a sales manager for the company marketing Vivitrol® - the newly FDA approved, extended-release, injectable naltrexone. Because the medication requires a monthly injection, he said patients ideally would have the cost covered by insurance not under their medication formularies, but as a surgery. Without insurance he estimated the cost around $600 per month. With a significant population of substance abusing patients having no insurance, or means for paying for addiction medications, the issue of cost has no simple solutions.

Another concern related to increasing use of addiction medications in substance abuse treatment programs is the ability of program administrators to effectively manage the costs associated with having prescribers on staff. As McLellan and Meyers (2004) have pointed out, most program administrators have minimal graduate business education, have commonly worked as counselors before taking on administrative roles, and often work second jobs as a way of improving their salaries. As a result, the development of an infrastructure to support medications services, given that many programs are already financially unstable, may present challenges beyond the capabilities of many administrators. For many programs, the best solution is to invest resources into a referral network of prescribers that are willing to work closely with counseling staff.

In summary, efforts to increase appropriate use of addiction medications should also include the development of a framework that patients, prescribers, and counseling staff can use to appropriately balance the benefits, risks and costs. Although there is no simple formula that can be followed in all cases, such a framework would optimally provide guidelines as to when addiction medications are a realistic treatment option for a particular patient. Such a framework would likely consider a patient's substance abuse history, treatment experiences, relapse rate, insurance coverage, motivation for pharmacotherapy, and any contraindications. Learning how to assess such factors and determine the best course of action in regards to medication, ideally should begin during graduate training, and then be reinforced in continuing education programs and clinical supervision. Substance abuse treatment programs should also provide information to

patients about the benefits, risks, and costs of medication in literature describing treatment services and options.

Abuse and diversion of opioid medications. An unintended consequence of efforts to increase the use of medications to treat opioid dependence is a likely increase in abuse and diversion of these medications. As reviewed in Section 3.2.2, when used appropriately, methadone and buprenorphine can be effective treatments for those struggling with addiction. But studies indicate that these medications are not immune to problems of abuse and diversion (Cicero & Inciardi, 2005a, 2005b; Cicero et al., 2005). Although much of this research has focused on the abuse and diversion liability of these medications in pain patients, there is evidence that some abuse and diversion may also occur among patients in substance abuse treatment. In one of the only reported studies on the abuse potential of buprenorphine in office-based treatment of opioid dependence, Cicero and Inciardi (2005) reported that a year after the launch of Subutex® and Suboxone®, very little abuse was found, and much less than that for methadone. Nevertheless, there is some indication that when methadone and buprenorphine are diverted or abused, such behaviors are related to patients attempting to self-treat addiction symptoms outside the scope of formal treatment, particularly in situations where there is limited treatment available.

With reports indicating a significant and growing problem with abuse of opioid analgesics in general (SAMHSA, 2004), mechanisms to better understand the prevalence, scope, and problem of abuse and diversion specifically in patients using methadone and buprenorphine for addiction treatment purposes is needed. Joranson and Gilson (2006) have argued that a public health approach provides the best mechanism to collect such information. There is a significant need for better data sources that investigate the motivations of abusers, the sources and ways in which diversion occurs and the ethnographic variability in abuse and diversion across different geographic locales.

Complex dosing may lead to non-adherence and increased likelihood of relapse. Although medications to treat substance abuse disorders can improve clinical outcomes, prescribers and counselors may take for granted that patients take the medications exactly as prescribed. Because addiction medications are commonly used for many months or years, and can involve multiple or complicated dosing schedules, patient adherence to treatment can suffer over time, particularly if the effects of the medication are not obvious. Thus far, no specific studies have examined addiction medication compliance, but there is evidence that for other chronic medical conditions, patients' ability to adhere to a specific pharmacotherapy regimen is limited.

> Hypertension, diabetes, and asthma are also chronic disorders, requiring continuing care throughout a patient's life. Treatments for these illnesses are effective but heavily dependent on adherence to the medical regimen for that effectiveness. Unfortunately, studies have shown that less than 60% of adult patients with type 1 diabetes mellitus fully adhere to their medication schedule, and less than 40% of patients with hypertension or asthma adhere fully to their medication regimens (McLellan et al., 2000, p. 1693).

The authors of the previous statement also make the point that low adherence to medication regimens is associated with low socioeconomic status, lack of social support,

and significant psychiatric comorbidity - the same issues that plague patients in substance abuse treatment. This suggests that when addiction medications are utilized in such patient populations, both prescribers and counselors should become acutely aware of adherence issues, and develop strategies to improve medication compliance.

In summary, addiction medications can play an important role in improving treatment outcomes for many patients, but also can be responsible for a number of unintended consequences. Hopefully by now, this dissertation has illustrated that the addiction treatment enterprise is dynamically complex, involving many different stakeholders, technologies, and treatments. Efforts to successfully incorporate appropriate use of addiction medications into such a complex system will likely fail if the above factors are not taken into consideration. Perhaps the best mechanism for addressing such issues is that outlined throughout this study: a systems approach.

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