Düşünen Adam The Journal of Psychiatry and Neurological Sciences 2012;25:1-7
DOI: 10.5350/DAJPN20122501001

Guest Editorial

Pharmacopsychosocial Treatment of Opioid Dependence: Harm Reduction, Palliation, or Simply Good Medical Practice?

Peter R. Martin[1], A.J. Reid Finlayson[2]

[1]Prof. Dr., [2]Assoc. Prof. Dr., The Addiction Center (PRM and AJRF) and Department of Psychiatry (PRM and AJRF) and Pharmacology (PRM), Vanderbilt University School of Medicine

Address reprint requests to: Prof. Dr. Peter R. Martin, The Addiction Center (PRM and AJRF) and Department of Psychiatry (PRM and AJRF) and Pharmacology (PRM), Vanderbilt University School of Medicine, Nashville Tennessee 37212, USA

E-mail address: peter.martin@Vanderbilt.Edu

Opioid alkaloids have been used medicinally for centuries as analgesics, for their antidiarrheal and antitussive properties, and as hypnotics. Opioids were initially derived from the poppy plant (Papaver somniferum) by the ancients of the Mediterranean Basin. Written records of the medicinal uses of opioids date to before the time of Hippocrates (460–377 BC). Paracelsus prescribed opium in a medicinal drink of wine and spices in the 16th century. Sir William Osler, the renowned Canadian physician of the late 1800's remarked that opium was "God's own Medicine". Opioids are considered superb medications by modern physicians, who widely prescribed them still and for the most part without significant adverse consequences.

Yet there is a "dark side" to opioids for those who develop dependence on these drugs (1). Opioids have significant dependence liability because of compelling biphasic central effects, behavioral activation at low doses and sedation at higher doses, accompanied by allostatic neuroadaptation of the CNS, leading to use of rapidly escalating doses. These dynamics may be amplified in persons having altered dopamine receptors in the limbic system, suggesting a possible genetic association (2). Dependent individuals may be unable to stop compulsive self-administration of opioids, in part because of these plastic changes in the brain akin to learning and memory that are highly resistant to modification. Synaptic alterations in neurons of the reward and limbic circuits may irreversibly modify emotions and responses to the environment, thereby permeating the behavioral repertoire of the addict. Accordingly, it may be impossible for most actively dependent individuals to live a fulfilling life simply because so much of their effort becomes devoted to activities necessary to obtain illicit opioids, use them, and recover from their use. Indeed, some individuals who have been dependent on opioids may never be able to return to a normal emotional life without intensive ongoing therapeutic support that allows the acquisition of new learning and more effective coping. The goal of the psychiatrist is to assist the opioid dependent patient to achieve recovery from an opioid-focused life, to help the individual to live a full and balanced life that is no longer fixated on drugs.

Those who addictively use opioids often develop complications, less from opioid use per se than from a life outside the law, a direct consequence of their involvement with illicit drugs. The life and exceptional achievements of Dr. William Halsted, first chief of Surgery at Johns Hopkins Hospital, suggests that

chronic opioid use may not necessarily be incompatible with a productive life. (Halsted turned to daily morphine use in a futile attempt to "cure" his cocaine dependence, contracted via self-administration of cocaine during research studies to develop a surgical anesthetic. Halstead had ready, unrestricted access to inexpensive, high-grade morphine, so he encountered few of the problems common to users of street narcotics.) However, as opioids are obtained from "the street" (via illegal means), as is the case for the majority of addicted individuals, drugs are often injected without using safe sterile techniques, in uncertain quantities, or with potentially toxic impurities present. Also, individuals frequently must engage in criminality or risky sexual practices to obtain access to drugs. Accordingly, the economic burden of opioid dependence is profound for society in terms of HIV and hepatitis C virus transmission, direct healthcare costs, and indirectly through criminal activity, absenteeism, and lost productivity.

Opioids can be administered intravenously, subcutaneously, transdermally, orally, or by inhalation. Heretofore, it was believed that injection opioid use was most addictive and hazardous to users due to accidental overdose and infectious complications because it was associated with irresistible and compulsive drug use, with intense euphoric effects, and with a particularly severe withdrawal syndrome if the drug is discontinued. However, it is now recognized that discontinuing orally administered high potency prescription opioids (e.g. oxycodone) is equally challenging for a dependent individual (3). Through widespread availability, misinformation, and the surreptitious ("Trojan Horse-like") nature of effects on behavior, oral opioid use may actually represent a greater public health concern than previously appreciated. Opioid dependence, due predominantly to oral not intravenous use, currently represents the fastest growing addiction problem in the United States (4), and internationally, there are an estimated 15.6 million illicit opioid users (5). Deaths from overdose of prescription analgesics have more than tripled in the past decade in the U. S. according to an analysis by the Center for Disease Control and Prevention, now rivaling those due to other illicit drugs and even motor vehicle accidents (4). These deaths can occur as individuals seek a greater degree of intoxication or attempt suicide because of hopelessness associated with co-occurring psychiatric disorders. In fact, the presence of psychiatric co-morbidities, either predisposing to, or as a consequence of out-of-control opioid use, is the rule rather than the exception in opioid dependent individuals. For this reason, many believe that prescription opioids have a particular affinity for the mentally ill who tend to selectively become dependent when prescribed these medications for pain (6).

We now face the imperative of both preventing opioid dependence as well as effectively managing the disorder and its complications. Opioid dependence cannot be attributed to physician misprescribing alone, as access to these drugs through illicit means has become quite easy and prevalent. Therefore, an increasing emphasis on teaching physicians how to prescribe these medications safely must be combined in equal measure with strategies to identify and manage the clinical consequences of the widespread abuse of opioids. The focus in this editorial is helping those who are opioid dependent return to a productive and fulfilling life and reducing their very high risk of infectious and other complications as well as deaths due to overdose.

Historically, treatment of opioid dependence consisted of assisting the individual to achieve total abstinence from drugs using religious, social and psychotherapeutic means of support. Of course, the implicit expectation was that motivational underpinnings of the addict's life could be sufficiently restructured during treatment (often lasting one year or more if delivered in a therapeutic community) to allow other more adaptive ways of coping with the vicissitudes of life than by using opioids. It was hoped that relapse could subsequently be avoided by a voluntary "choice" to not use drugs, undergirded by mutual social support from peers also on the road to recovery. What has become evident is that opioid dependence is a chronic, relapsing, potentially fatal illness—of the same genre as diabetes or hypertension—and that continuous treatment and lifelong support

may be necessary to prevent complicating morbidity and premature mortality (7).

Physician Health Programs in the United States achieved a model of sustained recovery from opioid dependence, which may be replicable, but currently is not available to those without the considerable support from their profession as well as significant disciplinary consequences of failure (loss of one's license to practice medicine). The model is complex, and utilizes motivational enhancement, comprehensive assessment and intensive treatment, oversight of care, complete abstinence from all substances of abuse, assertive linkage to recovery support groups, and sustained monitoring with higher level of intervention if necessitated by relapse (8). Some short-term success has also been reported by drug courts, which apply similar treatment principles to addicts facing incarceration (9). However, only a minority of opioid addicts successfully achieved extended abstinence over the long term using a psychosocial model of treatment alone (10). For most, opioid dependence was characterized by a deteriorating clinical course associated with significant morbidity and mortality during repeated relapses. A competing perspective held by some psychiatrists was opioid dependence as simply a manifestation of other underlying psychiatric issues rather than a disorder in its own right (the "self-medication" hypothesis) (11). As a corollary of this viewpoint the primary psychiatric disorder should be the focus of treatment, with the hope that if the "underlying disorder" were treated, the opioid dependence would spontaneously resolve. Finally, some societies have chosen to view opioid dependence in criminal, rather than medical terms—incarceration may stop opioid self-administration, but it is questionable whether such individuals often return to a healthful and balanced life (12).

In the last half of the 20th century, a significant paradigm shift has occurred in conceptualizing opioid dependence as a bone fide medical disorder in its own right (7), not simply a bad habit or the voluntary choice to use the drug to relieve emotional or physical pain (13). An important focus of clinical investigation became elucidation of pathophysiologic brain changes that can contribute to development of opioid dependence (14) and prescribing the appropriate medication to help treat opioid dependence became feasible (15). The recognition that addiction is caused by fundamental changes in brain limbic and reward pathways has suggested to clinical scientists the potential to modify some of these neuroadaptations using the tools of molecular neuroscience and pharmacology (16).

The major role for pharmacologic treatment of opioid dependence has traditionally been acute detoxification to relieve the withdrawal symptoms that accompany cessation of drug use. Withdrawal from chronic opioid self-administration consists of: 1) specific signs and symptoms which mirror the pharmacological actions of opioids (e.g., intoxication with opioids causes severe constipation, while withdrawal causes the opposite, diarrhea); and 2) generalized autonomic hyperactivity due to a "stress response" to overcome the homeostatic disequilibrium that emerges as chronic opioid use is discontinued. This withdrawal syndrome is very uncomfortable (like a bad case of the flu with sweating, muscle aches, cramps, nausea, diarrhea, vomiting, lachrymation, rhinorrhea), and can be associated with extreme feelings of anxiousness. However, opioid withdrawal is not life threatening unless the patient has medical problems that are adversely affected by the autonomic instability (e.g., coronary artery disease or pregnancy).

A commonly employed strategy for alleviating opioid withdrawal has been administration or tapering of the long-acting opioid, methadone. Recently, the partial mu-opioid agonist buprenorphine has become the preferred medication for opioid withdrawal treatment; however, care must be taken to ensure that the patient is actually in withdrawal prior to starting buprenorphine, because administration of this partial agonist can precipitate or worsen withdrawal if mu-opioid receptors are still occupied by the opioid of abuse. Detoxification can also be accomplished by using an alpha2-noradrenergic agonist (e.g., clonidine and lofexidine) which partially blocks autonomic opioid withdrawal symptoms by inhibiting noradrenergic outflow from neurons in the brain to the periphery and modulates the activity of cells in the gut responsible for

fluid absorption and intestinal motility.

Although detoxification may be achieved technically within a few days, it is increasingly recognized that detoxification alone does not affect the long-term course of opioid dependence. Protracted (post-acute) withdrawal symptoms such as anxiety, depression, and insomnia as well as cravings for opioids may persist beyond detoxification and require prolonged attention. In fact, some of these post-withdrawal symptoms may be sufficiently problematic that they are considered as representing, and may be treated as an independent other psychiatric disorder (e.g., depression, post-traumatic stress disorder, etc.). Hence psychosocial supports should begin early in detoxification and proceed indefinitely throughout recovery.

Pharmacologic agents specifically treat the chronic condition of opioid dependence by diminishing craving, preventing relapse when the patient has attained abstinence, and reducing harmful consequences of opioid use. These medications can be highly complementary to psychosocial approaches. An intuitive strategy to treat opioid dependence, initially implemented in the 1970s, is the pharmacological blockade of opioid effects in the event the recovering individual attempts to use again. Naltrexone is an opioid antagonist that competitively blocks the binding of opioids to their receptors. Thus, an individual who injects an opioid, such as heroin, while taking naltrexone will not experience the "high" that normally accompanies use of the drug. As a result, abstinence is facilitated as stimulus-response circuits associated with relapse to opioid use may be extinguished over time. Although naltrexone can effectively prevent the "high" associated with opioid abuse, it does not directly alleviate cravings or withdrawal effects, and there is a significant likelihood of non-adherence and relapse. Accordingly, naltrexone has been effective only in opioid addicts with strong motivation to remain drug-free or those who have supervised administration of the medication (This approach may be helpful for some patients, such as professionals in safety sensitive occupations, who are prohibited from participating in maintenance treatment with opioid agonists and have much to lose should relapse occur).

An injectable, long-acting naltrexone preparation has recently been approved by the U.S. Food and Drug Administration (FDA) for the treatment of opioid dependence. Sustained-release naltrexone is injected intramuscularly once a month and has been demonstrated to reduce opioid use and increase retention in treatment for opioid dependence. It may be useful especially for those with low adherence to treatment (17). Naltrexone should only be administered when there are no traces of exogenous opioids in the system, because antagonism of any remaining mu agonist by naltrexone can lead to the development or exacerbation of opioid withdrawal symptoms.

Another pharmacologic approach is the use of methadone, a long acting agonist for maintenance treatment of opioid dependence. Because methadone is taken orally, it is less likely to produce the sharp increases in plasma levels required to elicit a "high" such as that accompanying the injection of heroin or other opioids. Since methadone also has a long half-life compared to heroin or morphine, once-daily administration of methadone produces plasma opioid levels that remain relatively constant over time and, therefore, mitigate cravings and prevent the emergence of withdrawal signs and symptoms. Methadone also produces cross-tolerance to other opioids, so that a patient who injects heroin or another opioid while taking methadone experiences a reduced effect of the injected drug. However, methadone has significant abuse liability, and there is a risk of death from respiratory depression when methadone is overdosed or combined with another opioid or CNS depressant. For these reasons, methadone should be dispensed for opioid maintenance treatment only under controlled circumstances in government-licensed programs.

In a related agonist-based approach, injectable diacetylmorphine (heroin) maintenance was compared with oral methadone maintenance therapy in patients with opioid dependence that were refractory to treatment (18). The finding of superiority of diacetylmorphine in this study is highly controversial, but represents an extreme example of harm reduction. Harm reduction is a set of practical strategies that are not abstinence-based but intended to reduce negative

consequences of drug use. A spectrum of strategies are employed to allow safer drug use, e.g., needle sharing, so that users can stay within the law and have their healthcare needs met, thereby reducing the public health expenditures associated with criminalization.

Based upon observation that antagonist (e.g., naltrexone) based treatment of opioid dependence suffers from poor adherence and that full agonists with advantageous pharmacokinetic properties (e.g., methadone) can nevertheless be diverted from medical care and abused, partial agonist medications have been developed for the treatment of opioid dependence. The partial agonist action of buprenorphine at mu-opioid receptors and antagonism at kappa-opioid receptors alleviates withdrawal symptoms associated with decreases in plasma levels of abused opioids. Buprenorphine also reduces opioid cravings by increasing mesolimbic dopaminergic neurotransmission. Thus, buprenorphine not only facilitates opioid detoxification but also can be employed for maintenance treatment. Since it is not a full agonist, buprenorphine carries a relatively low risk of respiratory depression from overdose. Also, since it antagonizes the reinforcing effects of full opioid agonists such as heroin, it reduces the likelihood of relapse. The partial agonist properties and relatively long half-life of buprenorphine (compared to most abused opioids), result in mild to absent withdrawal symptoms from buprenorphine per se. To minimize abuse in the outpatient setting, buprenorphine is usually administered daily or on alternate days as a sublingual preparation (Suboxone®) that also contains the opioid antagonist naloxone. If Suboxone® is diverted and administered parenterally, the naloxone present antagonizes the agonist effects of buprenorphine; but when administered sublingually, the naloxone is not absorbed sufficiently to be bioavailable and the full effect of buprenorphine is experienced. Outpatient use of buprenorphine will likely replace methadone-based treatment programs for opioid dependence in all but the most severely addicted patients. Treatment of other psychiatric diagnoses and psychotherapeutic support are important components of palliative replacement treatment with both methadone and buprenorphine. Despite the possibility of gradually discontinuing medication and replacing it with an opioid-free life through psychosocial support, most patients choose to continue on agonist treatment for opioid dependence. The availability of buprenorphine for office-based treatment of opioid dependent patients has significantly added to their quality of life (19). Patients on buprenorphine comment repeatedly about how they feel "normal" for the first time in years. (This is in contrast to feeling "drugged" when they were previously maintained on methadone.) Patients also comment on how liberating it is not to have to think of opioids from the moment they rise each morning to when they go to bed at night which allows them to "get on with the rest of my life".

A final approach to treatment of opioid dependence is to specifically treat co-occurring psychiatric symptoms that are highly prevalent in individuals diagnosed with drug-use disorders. Depressed mood, anxious affect, mood instability, and psychotic symptoms are frequently observed in patients whether on methadone, buprenorphine, or abstinence based treatment. A meta-analysis of antidepressant use in addicted patients found that these medications are not effective unless a patient is diagnosed with a co-occurring major depression (20). In fact, there is some evidence that selective serotonin reuptake inhibitors (SSRIs) may cause early-onset, antisocial addicts to become worse and drink more alcohol than those receiving a placebo. Treatment of abstinent addicts with bipolar or psychotic disorders, using mood stabilizers and antipsychotics, is generally viewed as beneficial. Nevertheless, most clinicians recognize that it may be difficult to accurately diagnose and treat co-occurring psychiatric disorders while individuals are actively using alcohol and other drugs. The misuse of sedative hypnotic agents frequently complicates opioid agonist therapy contributing significantly to morbidity and likelihood of death by overdose.

Of course, the standard of care for opioid dependent patients now typically comprises an integrated pharmacopsychosocial approach wherein administration of a pharmacological agent is used to complement long-accepted social and psychotherapeutic treatment modalities (21). Psychosocial treatment approaches—for example,

counseling techniques such as cognitive-behavioral therapy—have been effective when used alone or in combination with pharmacologic treatment. Often, the integrated use of both pharmacologic and psychosocial approaches increases the positive outcomes of treatment. In addition, participation in mutual support self-help programs (e.g., Narcotics Anonymous) often improves outcomes, either utilized alone or when self-help facilitation is incorporated into psychiatric treatment programs. These psychosocial strategies specifically address the role of social learning and motivation in the pathogenesis of drug-use disorders.

Importantly, recovery from opioid dependence is recognized to be much more than simply abstinence from the drug—and from alcohol and other substances of abuse—but also the capacity to have a balanced, productive, and fulfilling life. If a person can attain a healthy and balanced life with the assistance of prescribed opioid agonist medicine, this is as acceptable in the treatment of opioid dependence as is the life-long control of glucose levels with insulin therapy for the diabetic or antihypertensive medication for the patient with high blood pressure. No other chronic illness is expected to continue in remission when the treatment regime that facilitates a healthier, balanced life is discontinued (22). Any effort to lower the dose of opioid agonist therapy in a stable functioning addict should be negotiated using motivational techniques (23), never pressured, and always accompanied by enhanced, long-term therapy, monitoring, and social support for the patient's harm reduction or abstinence goals.

Confusion abounds when addiction is considered to be somehow self-inflicted and different from other chronic illnesses. Evidence is accumulating that it is good medical practice to manage opioid dependence within the principles of personalized, evidence-based medicine with non-punitive goals similar to any other chronic illness—to allow patients to achieve a balanced and fulfilling life. In future, a corrective neurobiological intervention to resolve dysfunctional reward pathway circuitry may be developed, or more intensive prolonged and acceptable psychosocial treatment monitoring may become practical and economically viable. Until then, opioid maintenance medication is available to effectively diminish the need for an opioid-focused life outside the law and typically produces improved outcomes when compared with repeated cycles of short-duration discontinuation. Opioid agonist maintenance treatment improves patient comfort and quality of life. The benefits include decreased illicit drug use, improved retention in treatment, decreased HIV risk behaviors and decreased criminal activity—in sum, better health. While regulations vary by country, these medications are becoming increasingly available internationally, and are being prescribed over the long term as decided by the physician-patient dyad, with less clinical bias and decreasing stigma.

REFERENCES

1. Koob GF, Le Moal M. Plasticity of reward neurocircuitry and the 'dark side' of drug addiction. Nat Neurosci 2005; 8:1442-1444.

2. Chen D, Liu F, Shang Q, Song X, Miao X, Wang Z. Association between polymorphisms of DRD2 and DRD4 and opioid dependence: Evidence from the current studies. Am J Med Genet B Neuropsychiatr Genet 2011; 156:661-670.

3. Weiss RD, Potter JS, Fiellin DA, Byrne M, Connery HS, Dickinson W, Gardin J, Griffin ML, Gourevitch MN, Haller DL, Hasson AL, Huang Z, Jacobs P, Kosinski AS, Lindblad R, McCance-Katz EF, Provost SE, Selzer J, Somoza EC, Sonne SC, Ling W. Adjunctive Counseling During Brief and Extended Buprenorphine-Naloxone Treatment for Prescription Opioid Dependence: A 2-Phase Randomized Controlled Trial. Arch Gen Psychiatry 2011; 68:1238-1246.

4. CDC. CDC Grand Rounds: Prescription Drug Overdoses — a U.S. Epidemic. Morbidity and Mortality Weekly (MMWR) 61[01], 10-13. 1-13-0012.

5. Tetrault JM, Fiellin DA. Current and potential pharmacological treatment options for maintenance therapy in opioid-dependent individuals. Drugs 2012; 72:217-228.

6. Braden JB, Sullivan MD, Ray GT, Saunders K, Merrill J, Silverberg MJ, Rutter CM, Weisner C, Banta-Green C, Campbell C, Von Korff M. Trends in long-term opioid therapy for noncancer pain among persons with a history of depression. Gen Hosp Psychiatry 2009; 31:564-570.

7. Kleber HD. Methadone maintenance 4 decades later. JAMA 2008; 300:2303-2305.

8. DuPont RL, McLellan AT, Carr G, Gendel M, Skipper GE. How are addicted physicians treated? A national survey of physician health programs. J Subst Abuse Treat 2009; 37:1-7.

9. Taxman FS, Henderson CE, Belenko S. Organizational context, systems change, and adopting treatment delivery systems in the criminal justice system. Drug Alcohol Depend 2009; 103 (Supp. 1):1-6.

10. Ward J, Hall W, Mattick RP. Role of maintenance treatment in opioid dependence. The Lancet 1999; 353:221-226.

11. Khantzian EJ, Mack JE, Schatzberg AF. Heroin use as an attempt to cope: clinical observations. Am J Psychiatry 1974; 131:160-164.

12. Dackis C, O'Brien C. Neurobiology of addiction: treatment and public policy ramifications. Nat Neurosci 2005; 8:1431-1436.

13. Leshner AI. Addiction is a brain disease, and it matters. Science 1997; 278:45-47.

14. Volkow N, Baler R, Goldstein R. Addiction: Pulling at the neural threads of social behaviors. Neuron 2011; 69:599-602.

15. O'Brien CP. Anticraving medications for relapse prevention: a possible new class of psychoactive medications. Am J Psychiatry 2005; 162:1423-1431.

16. Papaleo F, Ghozland S, Ingallinesi M, Roberts AJ, Koob GF, Contarino A. Disruption of the CRF2 Receptor pathway decreases the somatic expression of opiate withdrawal. Neuropsychopharmacology 2008; 33:2878-2887.

17. Gastfriend DR. Intramuscular extended-release naltrexone: current evidence. Ann N Y Acad Sci 2011; 1216:144-166.

18. Oviedo-Joekes E, Brissette S, Marsh DC, Lauzon P, Guh D, Anis A, Schechter MT. Diacetylmorphine versus methadone for the treatment of opioid addiction. N Engl J Med 2009; 361:777-786.

19. Fudala PJ, Bridge TP, Herbert S, Williford WO, Chiang CN, Jones K, Collins J, Raisch D, Casadonte P, Goldsmith RJ, Ling W, Malkerneker U, McNicholas L, Renner J, Stine S, Tusel D. Office-based treatment of opiate addiction with a sublingual-tablet formulation of buprenorphine and naloxone. N Engl J Med 2003; 349:949-958.

20. Nunes EV, Levin FR. Treatment of co-occurring depression and substance dependence: using meta-analysis to guide clinical recommendations. Psychiatr Ann 2008; 38:730-738.

21. Martin PR, Weinberg BA, Bealer BK. Healing Addiction: An Integrated Pharmacopsychosocial Approach to Treatment. Hoboken, New Jersey: John Wiley & Sons Inc., 2007.

22. McLellan AT, Lewis DC, O'Brien CP, Kleber HD. Drug dependence, a chronic medical illness: implications for treatment, insurance, and outcomes evaluation. JAMA 2000; 284:1689-1695.

23. Hettema J, Steele J, Miller WR. Motivational interviewing. Annu Rev Clin Psychol 2004; 1:91-111.