Opioid Dependence Treatment and Guidelines

Lance Nicholls, PharmD; Lisa Bragaw, RPh; Charles Ruetsch, PhD

ABSTRACT

BACKGROUND: In response to the growing incidence of opioid dependence, guidelines have been created, and new treatments are being developed to assist physicians in treating dependence and withdrawal of opioids.

OBJECTIVE: To review treatment modalities and guidelines utilized in opioid dependence.

SUMMARY: Guidelines for the treatment of opioid dependence have been developed by organizations such as the American Society of Interventional Pain Physicians (ASIPP) and the American Psychiatric Association (APA). Current guidelines recommend comprehensive treatment with pharmacological agents such as methadone, buprenorphine, or buprenorphine combined with naloxone as well as psychosocial therapy. These guidelines stress the need for an integrated approach to treatment. Office-based opioid treatment is currently being utilized to treat opioid dependent patients in a physician's office setting with buprenorphine/naloxone replacement therapy as an alternative to entering patients into a methadone clinic. These office-based programs offer a breakthrough in access to care for dependent patients.

CONCLUSION: Physicians need to be aware of and adhere to currently accepted guidelines and recommendations for treating opioid dependent patients, including integrating psychosocial treatments and behavior modification strategies for optimal results. Clinicians must be educated on the new treatment modalities and regulations surrounding the use of these therapies.

J Manag Care Pharm. 2010;16(1-b):S14-S21

Authors

LANCE NICHOLLS, PharmD, is President, Lancer Solutions, LLC, New Milford, Connecticut. LISA BRAGAW, RPh, is the owner of Shoreline Pharmaceutical Associates, LLC, Niantic, Connecticut. CHARLES RUETSCH, PhD, is President and Chief Science Officer of Health Analytics, Columbia, Maryland.

AUTHOR CORRESPONDENCE: Lance Nicholls, PharmD, President, Lancer Solutions, LLC, New Milford, CT 06776. Tel.: 860.799.0523; Fax: 203.616.5137; E-mail: lancenicholls@lancersolutions.com.

DISCLOSURES

This activity was funded through an educational grant from Reckitt Benckiser Pharmaceuticals, Inc.

In response to the increased incidence of opioid abuse, the large degree of variance in patterns for prescribing opioids, and the many different medical specialties involved in treating patients with chronic pain, the American Society of Interventional Pain Physicians (ASIPP) has developed guidelines to help direct physicians who are treating chronic noncancer pain with opioids to better improve the treatment of these patients and reduce the rate of drug diversion. ASIPP notes that these guidelines are not intended to be a standard of care, as the body of evidence surrounding opioid use and misuse is constantly changing.[1,2] Physicians should be encouraged to develop and establish care plans for each of their patients based on that patients needs and risk factors.[1,2]

Wherever the treatment location or circumstances, some guidelines have suggested criteria to consider when treating opioid dependence. The following criteria were developed by the American Society of Addiction Medicine (ASAM) to consider in the treatment of dependence:[3]

1. acute intoxication and/or withdrawal potential
2. biomedical conditions and complications
3. emotional, behavioral, or cognitive conditions and complications
4. readiness to change
5. relapse, continued use, or continued problem potential
6. recovery/living environment

The American Psychiatric Association (APA) guideline identified the following 3 treatment modalities to be effective strategies for managing opioid dependence and withdrawal. (Please also refer to Table 1).[4,5]

1. opioid substitution with methadone or buprenorphine, followed by a gradual taper
2. abrupt opioid discontinuation with the use of clonidine to suppress withdrawal symptoms
3. clonidine-naltrexone detoxification

Anesthesia-assisted rapid opioid detoxification is no longer recommended due to a high incidence of adverse events (including severe pulmonary edema and aspiration pneumonia) that do not outweigh the benefit of treatment.[6,7]

The APA guideline stresses that psychosocial treatments are an essential component of a comprehensive treatment program. As one of the recommended psychosocial treatments, the guideline indicates that the community reinforcement approach (CRA) has been effective in alcohol dependence and, in theory, may help with opioid dependence. The basis of CRA is that patients with substance use disorders (SUD) lack positive reinforcement in their environment regarding finding activities that are pleasurable when sober, and that reinforcers for substance use may perpetuate SUD. CRA is geared at providing alternative positive reinforcers and rewarding community and familial involvement. Friends and family members serve to reinforce positive behaviors

TABLE 1 Common Medications for Opioid Dependence

Medication	Action	Indication	Dosage	Frequency	Adverse Effects
Buprenorphine	Partial opioid agonist	Withdrawal & maintenance	2-32 mg sublingual	Daily or 3 times per week	Respiratory depression, headache, constipation
Clonidine	α2-adrenergic antagonist	Withdrawal	0.1-0.3 mg orally	Every 6 hours	Bradycardia, hypotension, dry mouth, drowsiness
Levomethadyl acetate	Opioid agonist	Maintenance	25-100 mg orally	3 times per week	QT prolongation, Constipation
Methadone	Opioid agonist	Withdrawal & maintenance	20-100 mg orally	Daily	Constipation, respiratory depression, dizziness, nausea, sedation
Naltrexone	Opioid antagonist	Withdrawal & maintenance	50-100 mg orally	Daily or 3 times per week	Anxiety, nausea, myalgia

Adapted from: Fiellin DA, O'Connor PG. Office-based treatment of opioid-dependent patients. New Eng J Med. 2002;347:817-23.[4] Lexi-Comp (Lexi-Drugs, comp + specialties) [computer program]. Lexi-Comp; Mar 28, 2009.[5] For more information, please refer to the prescribing information for these drugs.

and promote a sober lifestyle in order to enable the patient to remain abstinent. Patients in CRA programs are also provided with job counseling and training, marriage counseling, and incentives like vouchers for recreation or food to promote and reward sober behaviors.[6]

Treatment Modalities

Treatment for Acute Opioid Intoxication

Mild to moderate acute opioid intoxication does not usually require treatment, but a severe opioid overdose requires emergency medical management to treat respiratory depression induced by naloxone.[6,8] Once acute symptoms are resolved, patients should be treated for opioid withdrawal and enrolled in a long-term treatment plan or program.[8]

Clonidine. Clonidine is generally considered a safe, non-narcotic medication used to help patients withdraw from opioids. It is a centrally acting alpha-2 adrenergic agonist and works to minimize the noradrenergic hyperactivity seen in opioid withdrawal.[6,9] Clonidine is not currently approved as a treatment for opioid withdrawal in the United States but has been studied in other countries extensively.[8] For opioid withdrawal, clonidine is typically dosed at 0.1 mg to 0.3 mg orally up to every 6 hours.[4,5,6] The use of clonidine in opioid withdrawal is limited because of its hypotensive and sedative adverse effects. It also does not manage withdrawal symptoms such as cravings and general malasia.[9] One benefit of clonidine is that it does not produce tolerance or dependence like opioid medications and can be immediately given with naltrexone (an opioid antagonist) if warranted.[6]

Contraindications to clonidine use include renal dysfunction, cardiac disorders, and hypotension.[6] Clonidine-assisted opioid detoxification is typically done in the inpatient setting, so physicians can best monitor the patient. If treatment is going to be administered in the outpatient setting, it is generally recommended that it should be under the guidance of experienced staff and that patients should not be given more than a 3-day supply of medication.[6]

Some clinicians will rapidly withdraw patients from opioids using a combination of clonidine and naltrexone. The patient is pretreated with clonidine to avoid some of the abrupt withdrawal symptoms caused by the naltrexone. This regimen is sometimes used to transition patients into narcotic antagonist therapy.[6]

Naltrexone. Naltrexone is a mu-receptor antagonist. It also antagonizes the kappa-receptor, and weakly antagonizes the delta-receptor. The mu- and kappa-receptors are responsible for analgesia, sedation, respiratory depression, euphoria, and dependence. Stimulation at the delta receptor provides analgesia and possibly psychomimetric and dysphoric effects. Naltrexone's active metabolite is 6-β-naltrexol, which provides the opioid antagonism.[1] When used in conjunction with clonidine for opioid withdrawal, naltrexone is usually dosed between 50 mg and 100 mg daily and can also be dosed 3 times weekly.[4,5,6]

Patients given clonidine and naltrexone must be monitored closely throughout the withdrawal process, especially during the first 8 hours of therapy, due to the potential severe withdrawal symptoms and risk of hypotension.[6]

Opioid Substitution Therapies

Methadone or buprenorphine maintenance therapy is appropriate for use in patients who have a history of dependence lasting more than 1 year.[6] Methadone replacement therapy became the first treatment modality for opioid dependence, and its use became widely available in the late 1960s.[10] Buprenorphine is a newer treatment modality that became available for office-based opioid treatment in 2000.[11]

Methadone. The use of methadone in opioid dependence dates back to 1950, when oral methadone was being used by U.S. Public Health Service hospitals in the treatment of opioid abstinence syndrome. In 1968, in response to the rising rates of heroin addiction, Drs. Marie Nyswander and Vincent Dole began research that led to the use of once daily dosing of methadone to prevent symptoms of opioid withdrawal and cravings.[10,12]

Though originally developed in 1939, methadone was not widely used as a pain reliever until World War II, possibly because initial doses were too high which resulted in intolerable adverse effects. In 1947, Eli Lilly bought the commercial rights for methadone for $1 and coined the brand name "Dolophine" from the Latin words "dolor" (pain) and "finis" (end).[10,12]

By 1971, an estimated 25,000 patients were enrolled in a methadone maintenance treatment (MMT) program.[10] Following the enactment of federal regulations (21 CFR Part 291) in 1972 and the Narcotic Addict Treatment Act of 1974, methadone use became restricted to a closed system requiring that doctors and pharmacies be registered to provide methadone treatment (regardless of the indication), resulting in the creation of federal- and state-licensed methadone clinics.[10,13] In 1976, the American Pharmaceutical Association (now known as the American Pharmacists Association) won a lawsuit to allow pharmacies to dispense methadone solely for treatment of pain, not to treat dependence.[9] Currently, methadone for the use of outpatient maintenance and detoxification may only be provided by Opioid Treatment Programs (OTP) certified by the Federal Substance Abuse and Mental Health Services Administration (SAMHSA) and registered by the Drug Enforcement Administration (DEA). However, exceptions may be made to allow a patient to continue with methadone maintenance treatment if admitted to the hospital for conditions other than opioid dependence and requires temporary methadone maintenance during the hospital stay (in accordance with 21 CFR 1306.07(c).[14]

Pharmacology of Methadone. Methadone hydrochloride is available commercially in 5 mg and 10 mg scored tablets and should be stored at controlled room temperature.[14] Methadone is an opioid receptor agonist at the mu-receptor. It is also an antagonist at the N-methyl-D-aspartate (NMDA) receptor. The commercial drug is a synthetic racemic mixture. The R isomer (R-methadone) is believed to be responsible for its analgesic properties, while the S isomer (L-methadone) is the NMDA antagonist and may be responsible for toxicities, including prolonged QTc (corrected QT interval). The NMDA antagonism is beneficial in severe neuropathic and "opioid-resistant" pain. The NMDA receptor mediates opioid tolerance, thus antagonism at this receptor may reverse opioid tolerance.[15] The S-isomer inhibits the reuptake of norepinepherine and serotonin as well.[1,14]

The bioavailability of methadone following oral administration is highly variable and ranges from 36% to 100%, with peak plasma concentrations being reached between 1 to 7.5 hours.[14] It is a highly lipophilic drug which binds predominantly to α1-acid glycoprotein. It is 85% to 90% protein bound in plasma. Metabolism is primarily via N-demethylation to the inactive metabolite 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidene (EDDP), which is excreted in the urine. Methadone is primarily metabolized by CYP3A4 and secondarily by CYP2D6. It is also metabolized through CYP2B6, CYP2C19, CYP2C9.[14] Therefore, enzyme inducers such as carbamazepine, nevirapine, phenobarbital, phenytoin, rifampin, saquinavir, and St John's Wort may decrease levels of methadone, which could potentiate withdrawal symptoms. Inhibitors of these enzymes, such as macrolide antibiotics (such as erythromycin), ketoconazole, fluvoxamine, clopidogrel, itraconazole, raloxifene, sertraline, and ticlopidine may increase methadone levels, enhancing its effects and toxicities.[1,14] Patients should be counseled to notify their physicians about any over-the-counter or herbal products they are taking to assess for interactions.[15] Clinicians should be advised to evaluate each patient's medication list to identify potential drug interactions and evaluate response to therapy before adjusting methadone dosages.[14]

The half-life is highly variable, ranging from 8 to 59 hours, and is thought to be due to a bi-exponential model.[1] The initial decline in plasma levels occurs within 2 to 3 hours, followed by the terminal phase of 15 to 60 hours. The analgesic effects of methadone are typically much shorter than its half-life. Analgesic dosing every 8 hours may lead to drug accumulation and potential adverse effects such as Torsades de Pointes.[1]

Methadone is indicated by the U.S. Food and Drug Administration (FDA) for the treatment of moderate to severe pain that is unresponsive to non-narcotic pain medications, for the detoxification of opioid addiction, and for maintenance treatment of opioid dependence in conjunction with social and medical services.[14] It is contraindicated in patients with respiratory depression, acute bronchial asthma, or hypercarbia (high blood levels of carbon dioxide). The peak respiratory depression caused by methadone persists longer than its analgesic action, especially in the initial dosing period. Therefore, iatrogenic overdose is often seen during the initiation of treatment or when titrating methadone doses.[14] A black-box warning has been added to the prescribing information stating the risk of cardiac and respiratory-related deaths after the initiation of methadone treatment.[14] Clinicians are strongly advised to review and understand the pharmacokinetics of methadone when initiating therapy and converting patients to methadone from other opioid analgesics. Careful attention is required especially at the initiation of treatment and when titrating doses. Most cases of respiratory depression, QT prolongation, and cardiac arrhythmias (including Torsades de Pointes) have occurred in patients on high doses of methadone, but these adverse events have been observed in doses used for maintenance of opioid dependence as well.[14,16]

Patients who are concomitantly on other opioids, benzodiazepines, other sedatives, and other CNS depressants are at increased risk of respiratory depression, hypotension, sedation, or coma.[14] Due to the potential risks of prolonging the QT interval, caution should be used when co-administering other agents with known risk of QT prolongation, including some neuroleptics, tricyclic antidepressants, and calcium channel blockers.[14]

As a Schedule II narcotic, methadone has an abuse potential similar to morphine and carries the risk of misuse, abuse, or

criminal diversion. Physicians should be aware of tools used to assess risk of abuse in order to best treat patients who require methadone for the management of pain. Abuse and misuse of methadone increases patients' risk for overdose and death, especially when consumed concurrently with alcohol and other substances such as benzodiazepines.[14] Tolerance and physical dependence are commonly seen during chronic therapy, and methadone treatment should not be stopped abruptly. Withdrawal symptoms of methadone consist of restlessness, yawning, perspiration, myalgia, chills, lacrimation, anxiety, irritability, joint pain, weakness, abdominal cramps, nausea, vomiting, diarrhea, hypertension, and increased respiratory or heart rate.[14]

For management of opioid dependence and detoxification, the treatment standards cited in 42 CFR Section 8.12 for methadone administration should be followed.[14] Medication-assisted methadone treatment usually lasts at least 12 months and can continue for 2 years or more. The length of treatment usually depends on individual patient needs, accounting for past instability (past dysfunction related to work, relationships, and behavior) and chronicity (length of opioid misuse/abuse and previous response to treatment). The typical initial dose is 20-30 mg once daily and should not exceed 30 mg; this dose is usually sufficient to suppress withdrawal symptoms. The typical maintenance dose range is 80-120 mg per day, with dosing adjustments being made over the first week based on withdrawal symptoms.[14]

Patients may choose short-term detoxification (a shorter period of withdrawal under medical supervision) or opt for maintenance treatment.[14] When and if patients are ready to taper off methadone after a prolonged period of maintenance, it should be under medical supervision. Dose reductions should be less than 10% of the maintenance dose and there should be a period of 10 to 14 days between dose reductions. Patients should be monitored for signs of relapse when withdrawing from methadone maintenance treatment.[14] Common side effects of methadone are similar to other opioids and include constipation, dizziness, sedation, lightheadedness, nausea and vomiting; less common side effects include itching, dry mouth, headache, weakness, and hypotension.[14] Patients should be informed of the risk of addiction and abuse associated with methadone use, as well as contraindications and side effects, including signs and symptoms of respiratory depression and cardiac problems potentially associated with methadone use. A baseline and follow-up ECG may be warranted. Patients should be educated to prevent theft and misuse and advised to avoid illicit drugs and alcohol.[14] Patients should be encouraged to seek other services, such as psychological counseling and pain management for their underlying pain condition.

Office-Based Opioid Treatment

Treatment for opioid dependence has different approaches such as pharmacologic, psychosocial or behavioral counseling and other options. Office-based opioid treatment evolved after passage of the Drug Addiction Treatment Act of 2000 (DATA 2000), allowing physicians to use some Schedule III-IV drugs such as buprenorphine and combinations thereof.[13,17] Physicians who wish to treat opioid dependence with buprenorphine and buprenorphine/naloxone in their offices must qualify for a waiver under DATA 2000 by meeting 1 or more of the following criteria in addition to holding a valid and current state medical license and DEA registration number:[13,17]

- subspecialty board certification in addiction psychiatry from the American Board of Medical Specialties
- addiction certification from the American Society of Addiction Medicine
- subspecialty board certification in addiction medicine from the American Osteopathic Association
- completion of at least 8 hours of training with respect to the treatment and management of opioid-addicted patients, sponsored by an organization authorized in the DATA 2000 legislation, or by another organization that the Secretary of the Department of Health and Human Services deems appropriate
- has participated as an investigator in clinical trials leading to the approval of a Schedule III, IV, or I narcotic drug for maintenance or detoxification treatment[17]

The DEA will issue qualified physicians a second DEA number beginning with an "X" after the physician has notified the Center for Substance Abuse Treatment (CSAT) that they have met the above criteria. When the program first started, physicians were limited to treating only 30 patients; however, in 2007, that limit was raised, allowing physicians to treat up to 100 patients for opioid dependence.[13,17]

Buprenorphine and Naloxone Replacement Therapy—Pharmacology and Pharmacokinetics. Buprenorphine is a partial mu-receptor agonist and an antagonist at the kappa-receptor. Buprenorphine has a high affinity for the mu-receptor, but at low efficacy, thus exhibiting opioid agonist activity and producing a dose-related response, but producing no additional effect beyond a certain point (it has a ceiling effect with regards to opioid response).[11,13,18] A ceiling effect is where the analgesic effect plateaus and no additional benefit is seen by increasing the dose, but an increase in the adverse opioid effects is anticipated. The activity expressed at the kappa-receptor provides analgesic activity, and also provides benefits for use in opioid deterrence, maintenance, and detoxification.[13,15,18] Also, because of the partial activation of the mu-receptor, patients are less likely to abuse buprenorphine. The high affinity for the mu-receptor coupled with the slow rate of disassociation from the receptor may block the effects of other opioids by displacing those other agents from the receptor. However, this same action may cause withdrawal symptoms in patients who have consumed opioids recently.[19] For this reason, patients are typically initiated on buprenorphine or buprenorphine/naloxone therapy under medical supervision and

after they have already started to exhibit signs and symptoms of withdrawal, with the goal of transitioning the patient from a state of physical dependence on opioids to an opioid-free state, while aiming to minimize withdrawal symptoms in the patient.[18]

Naloxone is a competitive antagonist at the mu- and kappa-receptors, though it exhibits most of its action at the mu-receptor.[1,13] The bioavailability after oral and sublingual dosing is low, but parenteral administration leads to a rapid onset of action leading to rapid reversal of opioid effects. It is added as an abuse deterrent; adding naloxone to buprenorphine reverses the opioid effects if a patient were to crush and inject buprenorphine/naloxone.[1,13] Buprenorphine is roughly 96% protein bound to alpha- and beta- globulin, while naloxone is about 45% bound primarily to albumin. Buprenorphine is metabolized by glucoronidation and by N-dealkylation via the cytochrome P450 3A4 isoenzyme to the active metabolite norbuprenorphine. Norbuprenorphine may also undergo further glucoronidation. Naloxone is metabolized by direct glucoronidation to naloxone 3-glucoronide and by N-dealkylation.[11] The mean elimination half-life of buprenorphine and naloxone is 37 hours and 1.1 hours, respectively.[11]

Buprenorphine undergoes significant first-pass metabolism, yet due to high lipid solubility, has excellent sublingual bioavailability, with an onset of action being seen within 30 to 60 minutes, and peak effect between 90 and 100 minutes.[13] Approximately two-thirds of buprenorphine is eliminated in the feces, the remaining third is excreted in the urine. Because of the extensive hepatic metabolism of both buprenorphine and naloxone, dosage adjustments should be considered in patients with decreased liver function, and patients should be monitored for signs and symptoms of opioid withdrawal due to the potential for elevated levels of naloxone. No dosage adjustments are required for renal failure.[11,13]

Due to the metabolism through the CYP 3A4 isoenzyme, patients receiving agents that are CYP 3A4 inhibitors (azole antifungals, macrolide antibiotics, and HIV protease inhibitors) should be closely monitored, and dose adjustments may need to be made. Additionally, patients receiving a concomitant CYP 3A4 inducer (phenobarbital, carbamazepine, phenytoin, and rifampin) should also be monitored, and dose adjustments may need to be made.[11] As buprenorphine can alter the level of liver enzymes, liver function should be monitored periodically depending upon any recent symptoms or history of hepatitis.[20]

Buprenorphine is available as 2 mg and 8 mg sublingual tablets as a single agent, and in combination with naloxone, in 2 mg buprenorphine/0.5 mg naloxone or 8 mg buprenorphine/2 mg naloxone sublingual tablets.[11] The single agent is primarily used in the initial phase of detoxification from long-acting opioids (methadone, sustained-release morphine, or sustained-release oxycodone), as the naloxone may precipitate withdrawal symptoms in the beginning of replacement therapy in patients withdrawing from these agents.[18] The sublingual buprenorphine and sublingual buprenorphine/naloxone are only approved dosage forms of buprenorphine for office-based opioid treatment.[13]

The typical dose range for buprenorphine is 2-32 mg per day, with the average dose being 16 mg, where 96% of opioid receptor coverage is achieved. The most common side effects include constipation and nonspecific headache.[11]

Phases of Office-Based Opioid Treatment

With regards to buprenorphine, there are 3 phases in treating the patient. They are induction, stabilization, and maintenance.[18] During the induction phase, patients must be experiencing mild withdrawal symptoms and to have avoided opiates for at least 6 hours.[9] Clinicians can use the Clinical Opiate Withdrawal Scale (COWS) or the Adjective Rating Scale for Withdrawal (ARSW) to determine withdrawal status.[9] The goal of this phase is to determine the minimum dose of buprenorphine required to prevent further withdrawal symptoms, reduce cravings, and provide minimal adverse effects.[18] When patients are no longer experiencing withdrawal symptoms, they have entered the stabilization phase of treatment. At this time, patients should be following up frequently with their physicians, and dose adjustments may be needed to obtain levels adequate to reduce cravings, yet minimize adverse drug effects.[18,19] This phase typically lasts one to two months.[19]

The maintenance phase is the longest phase of treatment. Medication-assisted buprenorphine treatment usually lasts at least 6 months and can continue for 2 years or more. Similar to methadone treatment, the length of buprenophine treatment usually depends on individual patient needs considering past instability (past dysfunction related to work, relationships, and behavior) and chronicity (length of opioid misuse/abuse and previous response to treatment).[20] If the patient regularly has negative urine toxicology screens and receives a stable dose of buprenorphine, the doctor may extend the intervals between visits to up to 30 days.[18] During the maintenance stage, psychosocial and family issues must be addressed to help the patient be successful in avoiding opioids and managing dependence.[18]

Methadone Versus Buprenorphine Replacement Therapy

Helm et al.[13] reviewed several studies including a randomized, double blind, parallel group study conducted by Johnson et al. that found buprenorphine (16 to 32 mg) to be as effective as high-dose methadone (60 to 100 mg) in reducing opioid use in short-term maintenance (at 17 weeks) compared with low-dose methadone (20 mg per day).[21] In 2003, Mattick et al. determined that both buprenorphine and methadone are effective in opioid dependence treatment.[22] A total of 405 opioid dependent individuals (as defined by DSM-IV criteria) were randomized into 2 treatment groups. One group received sublingual buprenorphine, while the other received oral methadone. A flexible dosing schedule was utilized, individualized to the patient's needs in each arm of the study. Minimum and maximum doses of therapy were 2 mg/32 mg for buprenorphine and 20 mg/150 mg for methadone,

respectively. The outcomes measured were retention in treatment, negative urine samples, and measures of illicit drug use and risk behavior utilizing the Opiate Treatment Index and Symptom Checklist. Social functioning, physical and mental status were also evaluated. Over the 13-week trial period, 54.8% of patients completed the trial. The trial did not find a statistically significant difference between treatments in the percentage of patients retained for the full 13 weeks of treatment (59% of the methadone group vs. 50% of the buprenorphine group; $P=0.061$).[13,22]

The American Academy of Family Physicians (AAFP) has issued clinical recommendations based on the Strength of Recommendation Taxonomy (SORT) evidence rating system.[23] The strength of SORT evidence ratings are ranked as A, B, or C ratings. An A rating is given when there is "consistent, good quality patient-oriented evidence," a B rating is assigned where there is "inconsistent or limited quality patient-oriented evidence," and a C rating denotes "consensus, disease-oriented evidence, usual practice, expert opinion, or case series."[23] The AAFP clinical recommendations state that "buprenorphine should be used to effectively manage opioid dependence" and have assigned an A rating for this recommendation.[19]

Buprenorphine's long-acting properties and partial agonism at the mu-opioid sites results in a plateau where no additional effect is observed with additional dosing.[11,19] Therefore, higher doses have a lower risk of toxicity, and there is less potential for abuse. Methadone is a full agonist, and additional dosing results in greater receptor activation, increasing the risk of abuse and potential for adverse effects.[11,19] The biggest advantage is the increased accessibility to treatment, as patients may go to a doctor's office for treatment and avoid the stigma and other negative feelings associated with going to a methadone clinic.[19] The stigma of going to an inpatient detoxification center or to a methadone clinic is removed in the office-based opioid treatment setting. Patients can continue with their normal activities (like continuing to work) while undergoing treatment for opioid dependence.[24]

In comparing conventional methadone maintenance to a stepped-care strategy using buprenorphine/naloxone with escalation to methadone if needed, Kakko et al. found both drug regimens that included intensive behavioral treatment to be equally efficacious.[25] Based on data from prior studies regarding the safety of buprenorphine Kakko et al. concluded that broad implementation of strategies using buprenorphine as a first-line treatment should be considered due to the advantageous safety profile of buprenorphine.[25]

Marsch et al. conducted a study of opioid-dependent adolescents to evaluate the relative efficacy of both buprenorphine- and clonidine-assisted withdrawal. Both medications were provided with 3 times weekly behavioral counseling and incentives contingent on opiate abstinence during the detoxification. A greater number of adolescents who received buprenorphine remained in treatment (72% versus 39%, $P<0.05$), and achieved markedly greater levels of abstinence from opioids (determined by negative urine tests) compared with those receiving clonidine (64% vs. 32%; $P=0.01$).[13,26]

Effective alternatives to long waiting lists for entry into methadone maintenance treatment have been studied.[27] Schwartz et al. compared the effectiveness of interim methadone maintenance (i.e., consisting of an individually determined methadone dose and emergency counseling only for up to 120 days) with that of the usual waiting list condition and found that interim methadone maintenance resulted in a substantial increase in the likelihood of entry into comprehensive treatment.[27]

Adherence and persistence to treatment protocols are also very low. A retrospective drug use evaluation was conducted on patients receiving buprenorphine-naloxone in a managed care population.[28] Persistence was determined by examining prescription claims data and defined as a gap of 30 days or less between expected refill date and the actual refill date. A total of 84 patients met study inclusion criteria; among these patients, the study found persistence rates of 47.6% at 1 month, 27.4% at 6 months, and 20.2% at 12 months. Utilization of opioids decreased by 18.8% from the pre-treatment to post-treatment period (1.49 opioid prescriptions PMPM vs. 1.21 opioid prescriptions PMPM; $P=0.031$). The actual drug cost of opioids including buprenorphine-naloxone appeared to be 26.9% lower ($156.24 PPPM) in the post period compared with $213.74 PPPM in the pre period, but the difference was not statistically significant ($P=0.254$). Currently no studies have evaluated gaps in therapy greater than one month, which may indicate relapse and restarts of treatment, so it is challenging to identify true rates of relapse.[28] Results showed that almost one-half (47.5%) of patients requiring opioid detoxification did not receive prescription opioids through an outpatient pharmacy during the 6-month period preceding opioid detoxification, suggesting that patients in need of buprenorphine-naloxone therapy obtain opioids illicitly, or use other illicit drugs, such as heroin. It is difficult to evaluate true cost savings of therapy as administrative claims databases do not capture the cost of illicit opioid use.[28] In a retrospective chart review, Caldiero et al. reported that patients had an average of 3.4 prior substance use treatments prior to receiving induction of buprenorphine.[29]

One recent study found the cost of providing 1 month of treatment per patient was $147 in methadone clinic treatments, $220 in methadone office treatments, and $336 buprenorphine office treatments ($P<0.001$).[30] Mean monthly medication cost was $93, $86, and $257, respectively ($P<0.001$). The cost to patients was $92, $63, and $38, respectively ($P=0.102$), demonstrating that while the overall cost of buprenorphine is higher, the cost to the patient for buprenorphine therapy is lower.[30] Another analysis of 259 published articles of economic evaluations of treating opiate dependence found that most studies used narrow treatment perspectives and surrogate outcome measures, concluding that the quantity and quality of economic evaluations are limited, evidence on cost-effectiveness of psychosocially-assisted pharmacotherapy is virtually nonexistent, and that most economic evaluations of treatment options are limited in terms of the range of costs and benefits considered.[31]

Conclusion

Office-based treatment programs are a breakthrough in access to care for patients who find it difficult to attend an outpatient program daily and who are not able to travel long distances to obtain treatment.[6] These programs also allow for better integration of health care needs for patients and thus serve to improve the quality of care provided. Buprenorphine and buprenorphine/naloxone have a better safety profile in cases of overdosing than methadone and can be given every 2 to 3 days as tolerated rather than every day as is the case for methadone. Prescriptions can be filled at the local pharmacy rather than visiting a clinic daily.[6,11]

REFERENCES

1. Trescot AM, Boswell MV, Atluri SL, et al. Opioid guidelines in the management of chronic noncancer pain. *Pain Physician*. 2006;9(1):1-39. Available at: http://www.painphysicianjournal.com/2006/january/2006;9;1-40.pdf. Accessed January 24, 2010.

2. Trescot AM, Helm S, Hansen H, et al. Opioids in the management of chronic noncancer pain: an update of American Society of the Interventional Pain Physicians' (ASIPP) guidelines. *Pain Physician*. 2008;11(2 Suppl):S5-S62. Available at: http://www.painphysicianjournal.com/2008/march/2008;11;S5-S62.pdf. Accessed January 20, 2010.

3. DHHS. Substance Abuse and Mental Health Services Administration. Center for Substance Abuse Treatment. Detoxification and substance abuse treatment training manual—based on a treatment improvement protocol (TIP) Series 45. DHHS Publication No. (SMA) 08-4331. 2008. Available at: http://www.kap.samhsa.gov/products/trainingcurriculums/pdfs/tip45_curriculum.pdf. Accessed January 25, 2010.

4. Fiellin DA, O'Connor PG. Office-based treatment of opioid-dependent patients. *New Eng J Med*. 2002;347(11):817-23. Available at: http://content.nejm.org/cgi/reprint/347/11/817.pdf. Accessed January 23, 2010.

5. Lexi-Comp (Lexi-Drugs, comp + specialties) [computer program]. Lexi-Comp; July 2, 2009.

6. American Psychiatric Association. Practice guideline for the treatment of patients with substance use disorders, 2nd ed. 2006. Available at: http://www.psych.org. Accessed January 19, 2010.

7. Collins ED, Kleber HD, Whittington RA, et al. Anesthesia-assisted vs. buprenorphine or clonidine-assisted heroin detoxification and naltrexone induction a randomized trial. *JAMA*. 2005;294(8):903-13. Available at: http://jama.ama-assn.org.lp.hscl.ufl.edu/cgi/reprint/294/8/903. Accessed January 24, 2010.

8. Magellan Health Services. Introduction to Magellan's adopted clinical practice guidelines for the assessment and treatment of patients with substance use disorders. December 2008. Available at: http://www.magellanprovider.com/MHS/MGL/providing_care/clinical_guidelines/clin_prac_guidelines/substance_abuse.pdf. Accessed January 26, 2010.

9. Amass L, Ling W, Freese TE, et al. Bringing buprenorphine-naloxone detoxification to community treatment providers: the NIDA clinical trials network field experience. *Am J Addict*. 2004(Suppl 1):S42-S66.

10. Gouldin WM, Kennedy DT, Small RE. American Pain Society. Methadone: History and recommendations for use in analgesia. APS Bulletin. 2000;10(5). Available at:. http://www.ampainsoc.org/pub/bulletin/sep00/upda1.htm. Accessed January 24, 2010.

11. Suboxone (buprenorphine HCl and naloxone HCl dihydrate sublingual tablets) prescribing information. September 2006. Reckitt Benckiser Pharmaceuticals, Inc. Available at: http://www.suboxone.com/hcp/pi/. Accessed January 26, 2010.

12. Anonymous. The history of methadone. Available at: http://www.drug-text.org/library/books/methandbook/history.htm. Accessed January 26, 2010.

13. Helm S, Trescot AM, Colson J, et al. Opioid antagonists, partial agonists, and agonists/antagonists: the role of office-based detoxification. *Pain Physician*. 2008;11(2):225-35. Available at: http://www.painphysicianjournal.com/2008/march/2008;11;225-235.pdf. Accessed January 24, 2010.

14. Dolophine hydrochloride (Methadone hydrochloride tablets) prescribing information. October 2006. Roxane Laboratories, Inc. Available at: http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM142842.pdf. Accessed January 24, 2010.

15. American Chronic Pain Association. ACPA chronic pain medications supplement 2008. Available at: http://www.theacpa.org/documents/ACPA%20Chronic%20Pain%20Medications%20Supplement%202008.pdf. Accessed January 24, 2010.

16. Ancherson K, Clausen T, Gossop M, et al. Prevalence and clinical relevance of corrected QT interval prolongation during methadone and buprenorphine treatment: a mortality assessment study. *Addiction*. 2009;104(6):993-99.

17. DHHS. Substance Abuse and Mental Health Services Administration. Center for Substance Abuse Treatment. Drug addiction treatment act of 2000 (DATA 2000). Title XXXV, Section 3502. Available at: http://buprenorphine.samhsa.gov/titlexxxv.html. Accessed January 19, 2010.

18. DHHS. Substance Abuse and Mental Health Services Administration. Center for Substance Abuse Treatment. Treatment Improvement Protocol (TIP) Series 40. DHHS Publication No. (SMA) 04-3939. 2004. Available at: http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=hssamhsatip&part=A72248. Accessed January 24, 2010.

19. Donaher PA, Welsh C. Managing opioid addiction with buprenorphine. *Am Fam Physician*. 2006;73(9):1573-78.

20. National Institute on Drug Abuse. Drugs, brains, and behavior: the science of addiction. NIH Publication # 07-5605. Reprinted February 2008. Available at: http://www.nida.nih.gov/scienceofaddiction/sciofaddiction.pdf. Accessed January 26, 2010.

21. Johnson RE, Chutuape MA, Strain EC, et al. A comparison of levomethadyl acetate, buprenorphine, and methadone for opioid dependence. *N Engl J Med*. 2000;343(18):1290-97. Available at: http://content.nejm.org/cgi/reprint/343/18/1290.pdf. Accessed February 2, 2010.

22. Mattick RP, Ali R, White J, et al. Buprenorphine versus methadone maintenance therapy: a randomized double-blind trial with 405 opioid-dependent patients. *Addiction*. 2003;98(4):441-52.

23. American Academy of Family Physicians. Strength of recommendation taxonomy (SORT). Available at: http://www.aafp.org/online/etc/medialib/aafp_org/documents/news_pubs/afp/afpsort.par.0001.File/dat/sortdef07.pdf. Accessed January 24, 2010.

24. Glabman M. Multiple therapies help curb opioid dependence. *Manag Care*. 2009;1(1):14-20. Available at: http://www.managedcaremag.com/supplements/0812_opioids_workplace/opioids_in_the_workplace.pdf. Accessed January 19, 2010.

25. Kakko J, Grönbladh L, Svanborg KD, et al. A stepped care strategy using buprenorphine and methadone versus conventional methadone maintenance in heroin dependence: a randomized controlled trial. *Am J Psychiatry*. 2007;164(5):797-803. Available at: http://ajp.psychiatryonline.org/cgi/reprint/164/5/797. Accessed January 24, 2010.

26. Marsch LA, Bickel WK, Badger GJ, et al. Comparison of pharmacological treatments for opioid-dependent adolescents: a randomized controlled trial. *Arch Gen Psychiatry*. 2005;62(10):1157-64.

27. Schwartz RP, Highfield DA, Jaffe JH, et al. A randomized controlled trial of interim methadone maintenance. *Arch Gen Psychiatry*. 2006;63(1):102-09.

28. Kaur AD, McQueen A, Jan S. Opioid drug utilization and cost outcomes associated with the use of buprenorphine-naloxone in patients with a history of prescription opioid use. *J Manag Care Pharm.* 2008;14(2):186-94. Available at: http://www.amcp.org/data/jmcp/JMCPMaga_March%2008_186-194.pdf.

29. Caldiero RM, Parran TV, Adelman CL, et al. Inpatient initiation of buprenorphine maintenance vs. detoxification: can retention of opioid-dependent patients in outpatient counseling be improved? *Am J Addict.* 2006;15(1):1-7.

30. Jones ES, Moore BA, Sindelar JL, et al. Cost analysis of clinic and office-based treatment of opioid dependence: results with methadone and buprenorphine in clinically stable patients. *Drug Alcohol Depend.* 2009;99(1-3):132-40.

31. Doran CM. Economic evaluation of interventions to treat opiate dependence: a review of the evidence. *Pharmacoeconomics.* 2008;26(5):371-93.