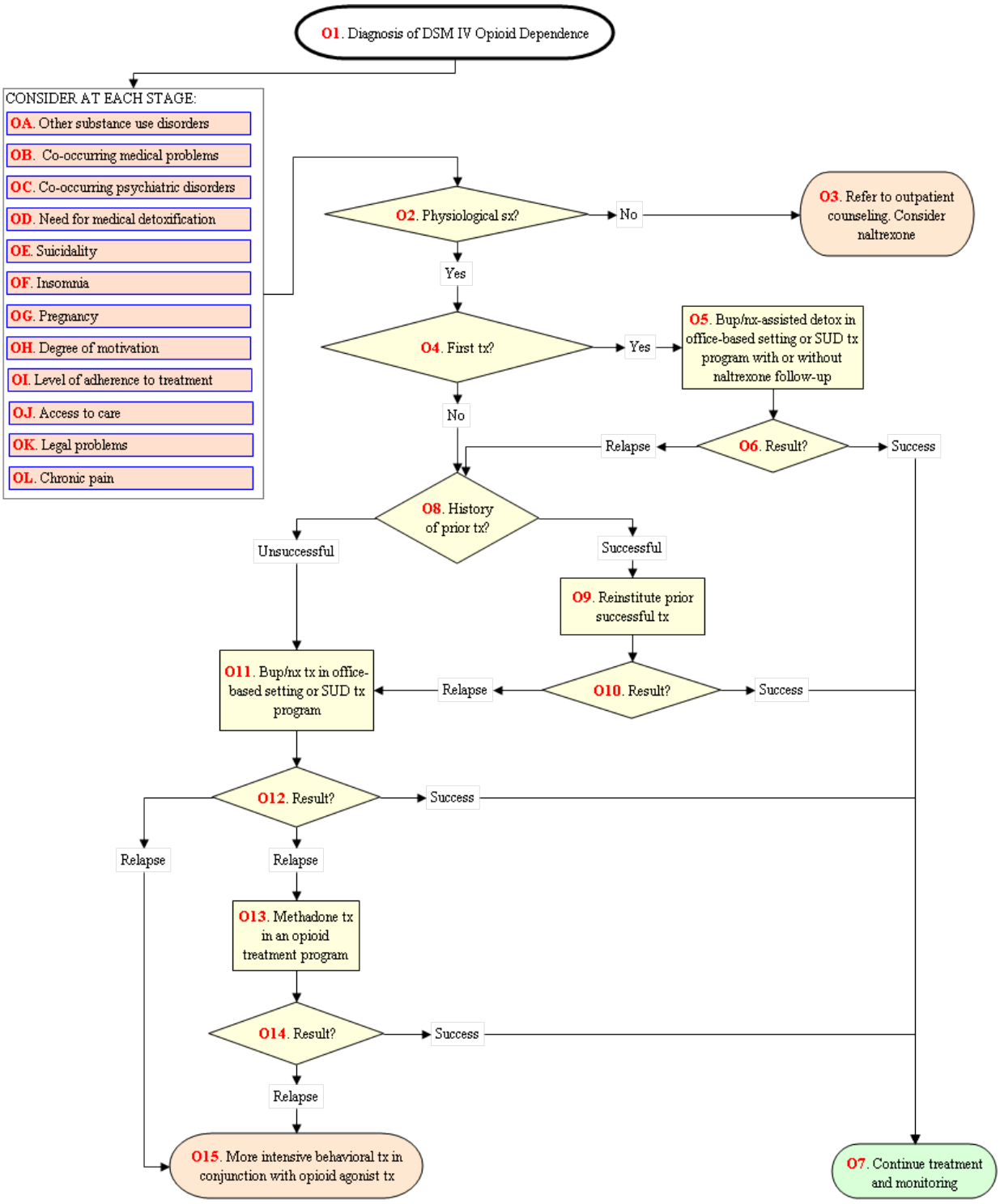
Opioid Algorithm



KEY: Bup/nx = buprenorphine/naloxone; OD = opioid dependence; SUD = substance use disorder; sx = symptoms; tx = treatment.

Node O1. The first consideration in assessing an individual with a suspected opioid dependence is to conduct a diagnostic assessment to determine whether the patient fulfills criteria for a DSM-IV diagnosis of opioid dependence (DSM-IV-TR, 1994).

At the same time the patient should be assessed with regard to the following considerations. These should be reassessed throughout the treatment.

Node OA. Opioid dependence occurs frequently with other substance use disorders (McCabe et al., 2008; Williamson et al., 2007; Ross et al., 2005). Therefore, when diagnosing opioid dependence, it is useful to ask about use of other substances of abuse; commonly abused substances include marijuana, cocaine, alcohol, nicotine and benzodiazepines. If there is dependence on another substance, consult the appropriate algorithm. In particular, a patient with opioid dependence should be evaluated for physiologic dependence on other substances, especially alcohol and/or sedative-hypnotics (e.g., benzodiazepines). Physiologic dependence on these non-opioid drugs may necessitate medical detoxification. When combined with opioid dependence, dependence on alcohol and/or sedative-hypnotics may be best treated in a more intensive level of care such as an inpatient service that can manage the treatment of such patients.

Node OB. Opioid dependence can cause serious medical problems, particularly when injection use is involved. Severe infections such as hepatitis B and C, HIV infection, and cellulitis resulting in soft tissue infections, endocarditis, or sepsis can occur. Injection users are at higher risk for methicillin-resistant Staphylococcus aureus (MRSA) infections as well as necrotizing lesions that further complicate soft tissue infections associated with injection drug use. Individuals using combination opioid analgesic drugs such as oxycodone/acetaminophen may experience acetaminophen toxicity with hepatic injury or failure. Opioid dependence can be associated with accidental overdose, respiratory depression, and death. Medical assessment is an essential component of initial evaluation and routine follow-up and will help determine appropriate pharmacotherapy, as the medications used to treat opioid dependence may have medical warnings or contraindications (e.g., patients with severe liver disease should not take naltrexone). (Sullivan et al., 2008; Kresina et al., 2005; Bassetti et al., 2004; Doyon, 2004; Ball and Ross, 1991)

Node OC. Opioid dependence occurs frequently with co-occurring psychiatric disorders. Attempt to discern the likelihood that a co-occurring Axis I or Axis II disorder is independent of the substance use disorder or a result of the substance use disorder. Evidence to support an independent Axis I or Axis II diagnosis includes a history that psychiatric symptoms preceded the onset of substance use, that psychiatric symptoms persist beyond early abstinence or recur during prolonged periods of abstinence, and a family history positive for psychiatric illness. For a presumptive independent Axis I or Axis II disorder, treat the disorder according to standard protocols. There is no evidence to suggest that opioid dependence alters routine psychotropic medication selection for co-occurring psychiatric disorders; however, there is evidence that omitting appropriate psychopharmacotherapy for co-occurring independent psychiatric illness negatively affects an individual's capacity to achieve abstinence from opiate use. (Grella and Stein, 2006; Havassy et al., 2004; Carpenter et al., 2004; Dean et al., 2002; Nunes et al., 1994)

Node OD. A patient with opioid dependence should be evaluated for physiological dependence that would indicate a need for medical detoxification. In general, individuals at risk for withdrawal are those who are using opioids daily or nearly every day. Physiological dependence on opioids can recur rapidly when an abstinent individual relapses to opioid use. Also, once detoxified, the risk of death from overdose (either intentional or accidental) is increased because of the loss of tolerance to the respiratory depressant actions of the opioids. Standardized assessment instruments, such as the Clinical Opiate Withdrawal Scale (COWS) or the Clinical Institute Narcotic Assessment (CINA), can help determine withdrawal symptom severity and the recommendation for medical detoxification. (Collins and Kleber, 2004)

Node OE. Individuals with opioid dependence are at significantly greater risk of suicide than those without this disorder. Screening for suicide risk at initial evaluation and routine follow-up is recommended in this population. (Tremeau et al., 2008; Maloney et al., 2007)Node OF. Insomnia is a common problem in people with opioid dependence, and sometimes a chronic problem. Commonly prescribed hypnotic medications in the general population include benzodiazepines, and GABA-receptor subtype agonists, e.g. zolpidem; unfortunately these medications have increased abuse potential in individuals with substance use disorders and may be used to augment the effects of opioids, and add to respiratory depression in the event of an overdose. Therefore, most addiction medicine specialists

do not recommend treatment with these medications for opioid-dependent patients. Alternative medications without reported abuse liability include trazodone, doxepin, gabapentin, mirtazapine, hydroxyzine, diphenhydramine, quetiapine, and ramelteon. Evidence supporting their efficacy is limited, however. (Amedt et al., 2007; Hajak et al., 2003; Hirst and Sloan, 2002)(LOE IV).

Node OG. The treatment of a pregnant woman with opioid dependence warrants special consideration. In such cases, opioid maintenance rather than medically supervised withdrawal treatment is recommended (LOE III). Methadone maintenance is the standard treatment in such a situation, although a number of clinical reports and some published trials have suggested that buprenorphine (the pure preparation, not the preparation with naloxone (i.e., Subutex)) may be an acceptable alternative (LOE IV). (Minozzi et al., 2008; Winklbaur et al., 2008; Kleber et al., 2007)

Node OH. Individuals having low motivation for change frequently do not return for treatment. Counseling approaches that use motivational interviewing techniques and certain cognitive-behavioral techniques can be helpful to enhance willingness to engage in treatment. Sometimes, the legal system or significant others may help to provide external incentives for treatment motivation while waiting for internal motivation to be bolstered. More intensive psychosocial interventions, including intensive outpatient programs or residential treatment, should be considered to help patients engage in the treatment process. (Dutra et al., 2008; Copenhaver et al., 2007; Carroll et al., 2001)

Node OI. Poor adherence to treatment is very common in opioid-dependent patients. Adherence can be improved both by reinforcing desired behaviors (e.g., providing take-home methadone doses to people who refrain from using illicit opioids) and by providing contingent reinforcers (e.g., probationary agreements are contingent on active participation in a treatment program).(Brooner et al., 2007; Pierce et al., 2006; Schottenfeld et al., 2005; Carroll et al., 2002)

Node OJ. Access to medical care, particularly opioid agonist therapies such as buprenorphine and methadone stabilization or maintenance, are not always readily available. Common barriers to treatment include lack of transportation, lack of health insurance and financial access to services, and lack of regional medical clinicians experienced in providing appropriate treatment. These issues should be considered when recommending a treatment approach. (Kresina, 2007)

Node OK. Opioid-dependent individuals may experience legal problems, and may in fact be seeking treatment as a result of these problems. This type of external motivating influence can sometimes be helpful in precipitating changes in drug use for this population. (Sullivan et al., 2008)

Node OL Chronic pain is quite common among those seeking treatment for opioid dependence. Indeed, some such patients begin their use of opioids in response to a painful condition. Treating patients with co-occurring chronic pain and opioid dependence is a significant challenge and working with a pain specialist is often useful to improve outcomes for this population. The clinician should assess and monitor pain as part of comprehensive treatment plan for opioid dependence, recognizing that prolonged exposure to opioids can be associated with hyperalgesia that complicates treatment. (Ballantyne and LaForge, 2007)

Node O2. Among individuals with opioid dependence, it is important to assess for physiological dependence. Physiological dependence usually occurs in the context of daily or near-daily use, and many physiologically dependent patients will report having experienced withdrawal symptoms after refraining from opioid use for a sufficient period of time. Pharmacotherapy for either opioid detoxification or maintenance treatment requires that the patient be physiologically dependent. Patients with physiological dependence are then categorized according to whether this is their first treatment episode (Node O4) or not (Node O8).(Mattick et al., 2008; Adi et al., 2007)

Node O3. If the patient meets criteria for opioid dependence without physiological dependence, then the patient should be referred for outpatient counseling, and naltrexone treatment should be considered in addition to counseling in order to help prevent relapse (LOE IB). Most opioid-dependent patients would be good candidates for naltrexone treatment if they accept it. Individuals with medical conditions that require opioid treatment (e.g., for pain) would not be good candidates. Liver function tests should be checked prior to initiation of naltrexone treatment, and, if satisfactory, should be monitored during treatment. (Rounsaville, 1995)

It is important to note here that the treatment of a pregnant woman with opioid dependence warrants special consideration. In such cases, opioid maintenance rather than medically supervised withdrawal treatment is

recommended (LOE III). Methadone maintenance is the standard treatment in such a situation, although a number of anecdotal reports and some published trials have suggested that buprenorphine (the pure preparation, not the preparation with naloxone) may be an acceptable alternative (LOE IV).

Node O4. For patients with opioid dependence with physiological dependence, the treatment approach can be affected by whether the patient is seeking treatment for the first time or not.

Node O5. The most common approach to a patient seeking treated for the first time (other than a pregnant woman, see above) would be to institute medically supervised withdrawal with sublingual buprenorphine/naloxone in an office-based setting or in a substance use disorder treatment program (LOE V). This can be accomplished safely and effectively on either an outpatient or an inpatient basis; inpatient treatment could be recommended if there are complicating features such as another substance use disorder requiring intensively supervised detoxification, another psychiatric illness requiring stabilization, or other medical conditions that would require more intensive monitoring. It may also be preferable for an individual whose immediate home environment will not support detoxification (due to proximity of other drug-using individuals or easy access to opioids). Such a patient can be inducted with buprenorphine/naloxone with an initial dose of 2/0.5 to 4/1 mg sublingually. Commonly, the dose for the first day will be 12/3 to 16/4 mg, depending on degree of dependence and opioid use; the speed of the taper can vary quite substantially, from several days to several months. Optimal rates of tapering buprenorphine have not been clearly determined, so this should be done in collaboration with the patient, depending on the patient's condition, preferences, and recovery resources.

Although the treatment approach described above is most commonly used, some exceptions may arise. For example, one may initiate a buprenorphine induction and discover that the patient has a higher than expected level of physiological dependence and is unable to achieve an adequate opioid agonist effect with buprenorphine. Alternatively, there may be limited access to buprenorphine treatment in an individual's geographic area. In such a case, patients can be detoxified from opioids by using methadone in an opioid treatment program or in a general substance use disorder treatment program that has a license to use methadone for detoxification. If neither buprenorphine nor methadone is readily available or if they are contraindicated, an alpha-2 adrenergic agonist can be used to treat opioid withdrawal symptoms. Although not approved by the FDA for this purpose in the United States, lofexidine has had good success treating opioid withdrawal outside of the US. In the US, clonidine is the most commonly used alpha-2 adrenergic agonist in the treatment of opioid withdrawal, although it is not approved by the FDA for this use; in a study comparing clonidine to buprenorphine for opioid detoxification, buprenorphine demonstrated clear superiority. (Kleber et al., 2007; Gowing et al., 2006)

In addition to pregnancy, another clinical situation in which one might avoid detoxification and proceed immediately to buprenorphine maintenance treatment would occur if the patient presenting for treatment for the first time is engaging in very high-risk behaviors such as injection drug use, needle-sharing, high-dose mixed opioid use, or repeated accidental overdosing. While detoxification could be considered in such a case, the likelihood that this will lead to stable good outcomes is low, and maintenance should be considered.

As in all aspects of this algorithm, another critical consideration in selecting treatment is patient preference. Some patients may enter treatment for the first time and seek opioid maintenance treatment. The clinician should educate the patient to make an informed choice in this matter, which might be maintenance treatment. It is not uncommon for individuals who are in the midst of an opioid taper to experience great difficulty (either severe craving or illicit opioid use itself), and request maintenance treatment at that time. This should be seriously considered after a discussion of the risks and benefits of this approach with the patient. Conversely, later in the algorithm, patients for whom one might recommend maintenance treatment may not want to accept this approach.

Following the completion of opioid detoxification, one should consider the use of oral naltrexone, as described in node O3 above (LOE IB). For those who were physiologically dependent upon opioids, it is recommended that the patient be opioid-free for at least one week before initiating naltrexone treatment, to avoid precipitating withdrawal symptoms. The major problem limiting the utility of oral naltrexone is its limited acceptability among opioid-dependent patients; relatively few people accept naltrexone, and among those who begin taking naltrexone, adherence rates are low (LOE IB). Adherence rates can be increased through external support (e.g., from family members, social

support networks, or significant others) or pressure (e.g., from the legal authorities, licensing boards, case managers, etc.) (LOE IV). Patients who have a family member or significant other that monitors administration of naltrexone maybe be better candidates for this medication, as are patients with contingencies for adherence (e.g., licensing boards requiring maintenance on naltrexone). An extended-release injectable form of naltrexone is FDA-approved for the treatment of alcohol dependence, and could someday be an excellent medication for opioid-dependent patients, since its long duration of action helps protect patients who might otherwise have stopped taking oral naltrexone and thus relapsed. However, it is not currently FDA-approved for the treatment of opioid dependence, and is not recommended here for the treatment of opioid dependence at this time. Similarly, naltrexone implants have been tested outside of the United States, but are not FDA-approved.

Node O6. The next step in the treatment process is influenced by whether the buprenorphine-assisted detoxification (with or without subsequent naltrexone treatment) was successful or not.

Node O7. For patients who have responded to treatment, the length of the ongoing treatment varies by modality and by individual. For example, many patients who enter methadone maintenance treatment do so for the rest of their lives, while this is generally not the case for naltrexone treatment, and the evidence for the optimal length of buprenorphine treatment is lacking. Ongoing monitoring is generally very helpful, in keeping with the conceptualization of addiction as a chronic medical illness with the possibility of relapse at any time. While the intensity of monitoring can be reduced over time, ongoing treatment and monitoring can often help patients maintain better outcomes.

Node O8. This section focuses on individuals who have had previous treatment for opioid dependence and are now seeking treatment again. There are two potential presentations for such a patient.

Node O9. In the first presentation, the patient has a history of sustained abstinence related to a previous treatment episode, and has recently relapsed. In such an instance, one should reinstitute the previously successful treatment unless there is an intervening reason not to do so (e.g., pregnancy, medical contraindication, etc.) (LOE V). Whether the patient should resume a previously successful treatment or change to another treatment (e.g., buprenorphine maintenance) can be a difficult decision, and depends to some extent on the length of abstinence obtained and the severity of the most recent relapse; a shorter period of abstinence (e.g., a few weeks or months), less successful overall functioning (e.g., variable adherence with the previous treatment episode), and greater severity of current relapse all would favor institution of maintenance treatment, while a lengthy period of abstinence and a brief, relatively contained relapse would favor reinstitution of the previously successful treatment regimen.

Node 10. After reinstitution of the previously successful treatment, one should assess whether this has been successful. If so, go to Node 7. If not, go to Node 11.

Node 11. If the patient did not have a period of sustained abstinence after the previous treatment episode (e.g., buprenorphine detoxification with or without subsequent naltrexone maintenance), or if reinstitution of a previously successful treatment was unsuccessful this time, then one should consider opioid maintenance treatment with buprenorphine/naloxone (LOE V). In general, buprenorphine/naloxone is recommended over buprenorphine alone because of its decreased risk for misuse and diversion (LOE IB). Buprenorphine/naloxone is recommended for initial maintenance treatment over methadone because it affords greater flexibility, since patients can be treated in a physician's office or in a substance use disorder treatment program, while methadone can only be used within an opioid treatment program (LOE V). In addition, patients can receive buprenorphine prescriptions episodically rather than needing frequent visits for on-site dosing, as is the case with methadone. Buprenorphine also has a greater safety profile than methadone, as a result of fewer drug-drug interactions, a lower risk of accidental or intentional overdose (LOE III), and possibly a lower risk of cardiac effects compared to very high dose methadone (LOE IV). The ability for patients to receive buprenorphine by prescription in a private physician's office rather in a more public clinic setting that exposes patients to other drug-dependent individuals may also lower the barrier to seeking treatment for opioid dependence. Buprenorphine is more expensive than methadone, however.

For some people, buprenorphine treatment may last for a matter of months, while for others, it will be indefinite. An initial target dose range that has been demonstrated to be effective for many opioid-dependent patients is 8/2 to 16/4 mg daily of buprenorphine/naloxone (LOE IB). However, there is great variability in the patients' response and

sensitivity to buprenorphine, and the prescribing physician should use clinical response, laboratory testing (i.e., urine screen data), and side effects to determine dose; in some cases, collateral informant data, i.e., information from family members or significant others, can be another source of information as well. Patients have been treated safely and effectively with buprenorphine/naloxone doses ranging between 4/1 and 32/8 mg per day (LOE IB). As described above, patient preference is an important consideration in determining the proper treatment approach at this juncture; some patients may not want to receive maintenance treatment. In such a case, the risks and benefits of maintenance vs. other treatments should be discussed thoroughly. In the case of someone who refuses maintenance treatment, other treatment strategies (e.g., naltrexone maintenance, intensive psychosocial treatment, residential treatment) should be considered.

Pharmacotherapy maintenance treatment should not be delivered in a vacuum. Providing access to psychosocial treatment, whether delivered by the prescribing physician, an outside counselor or therapist, or a substance use disorder treatment program, is recommended with medication (LOE IB). Self-help approaches such as Narcotics Anonymous or Alcoholics Anonymous can also play an important role for patients, but should not be the sole form of non-pharmacologic service provided – especially early in treatment.

Node 12. After prescribing buprenorphine/naloxone treatment, the clinician should assess the degree to which this intervention is successful. If successful, go to Node 7. If not, one should decide if Node 13 or Node 15 is the most appropriate next step. Some individuals who have taken buprenorphine previously and have resumed opioid use may be prescribed buprenorphine again before returning to physiological dependence. In such a case, the patient should be treated with a lower dose (e.g., half the original induction dose) of buprenorphine during the induction process.

For individuals who relapse or continue regular illicit opioid use while being prescribed buprenorphine/naloxone maintenance, the first step in such a situation is to conduct an assessment to ensure that the patient is receiving an adequate dose of buprenorphine/naloxone and is taking the medication as prescribed. In some instances, the problem may be that the person is not holding the medication under his or her tongue for an adequate period of time, preventing adequate absorption. In other instances, the patient may be diverting the medication. A second consideration is whether the patient should receive more intensive psychosocial services (Node O15). Examples of this would include individual and/or group drug counseling (including intensive outpatient or partial hospital treatment), attendance at self-help groups such as Narcotics Anonymous or Alcoholics Anonymous, sober housing, or residential treatment to ensure stabilization.

In some instances, the patient may have a co-occurring psychiatric illness that increases vulnerability to relapse. Psychiatric assessment should be conducted to see whether this might be the case. If so, proper psychiatric treatment, whether pharmacologic, psychological, or both should be instituted.

Co-occurring substance use may also make patients vulnerable to relapse to opioid use. Optimal treatment for other substance use disorders should be instituted, perhaps including substance-specific pharmacotherapy (e.g., disulfiram or acamprosate for alcohol dependence).

Node 13. For individuals with recurrent relapses despite seemingly adequate buprenorphine treatment and associated psychiatric and psychosocial treatment, opioid treatment programs using methadone may offer several advantages. These include the potential institution of supervised daily dosing, positive and negative contingencies for abstinence and continued substance use, respectively, the capacity to provide ancillary treatment for other psychosocial and medical problems, intensive urine collection and testing, and regular individual and group counseling that focuses on substance use.

The patient can be inducted onto methadone at the opioid treatment program. As with buprenorphine, the therapeutic dose of methadone can be variable. Doses above 60 mg a day are typically needed to significantly reduce opioid use, although some patients may respond to lower doses (LOE V). Conversely, some patients may need much higher doses, e.g., > 100 mg a day, to achieve optimal benefit (LOE IA). When patients are not responding well despite seemingly adequate doses, measurement of peak and trough methadone levels may be indicated to rule out the possibility of rapid methadone metabolism (LOE V). (Kleber et al., 2007; Gowing et al., 2006; Strain et al., 1999)

Patients receiving methadone maintenance treatment should receive regular medical attention, including checking liver function tests and monitoring cardiac electrical activity, since high-dose methadone has been shown in some instances to increase the QTc interval (LOE IV). Since methadone has a number of drug-drug interactions with the types of medications that opioid-dependent patients are frequently prescribed (e.g., HIV medications, antibiotics, and psychiatric medications), the physician should monitor these other medications carefully in people who are receiving methadone.

As described above, patient preference is a critical consideration in making a treatment plan. Many opioid-dependent patients may be reluctant to enter methadone maintenance treatment. In such situations, as described above when discussing buprenorphine maintenance treatment, the physician should discuss the risks and benefits of methadone maintenance and alternative treatments with the patient. If the patient refuses methadone maintenance treatment, and has not responded well to buprenorphine maintenance treatment, then alternatives such as naltrexone maintenance, intensive psychosocial treatment, and/or residential treatment should be considered.

Node 14. Individuals who receive methadone maintenance treatment and do well should go to Node 7. If they are not doing well, they may need additional psychosocial or psychiatric treatment, as in Node O15.

Node 15. The patient should receive more intensive psychosocial services. Examples of this would include individual and/or group drug counseling (including intensive outpatient or partial hospital treatment), attendance at self-help groups such as Narcotics Anonymous or Alcoholics Anonymous, sober housing, or residential treatment to ensure stabilization.

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