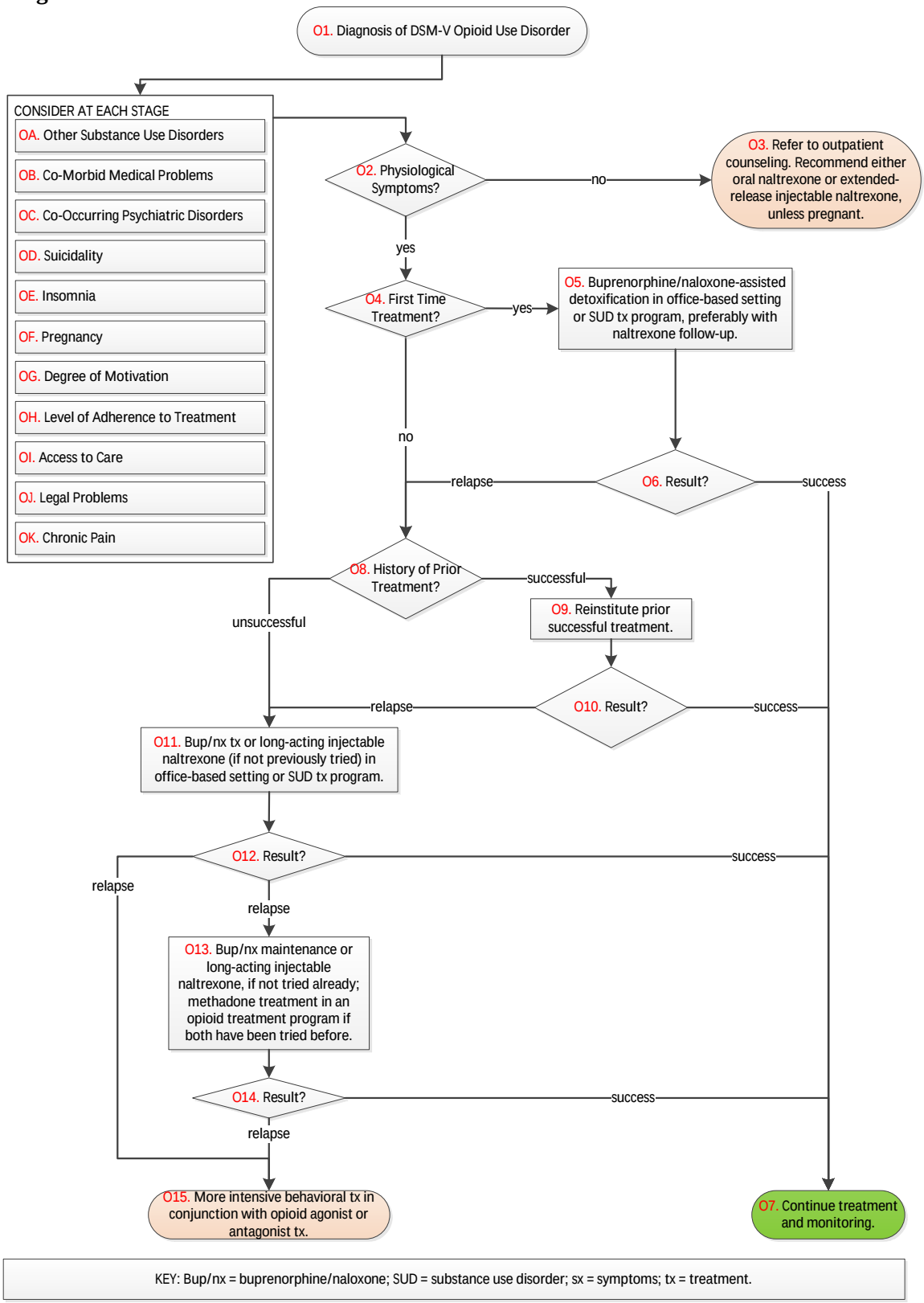
Opioid Algorithm

Diagram



Abbreviations: Bup = Buprenorphine, nx = Naloxone, SUD = substance use disorder, LOE = level of evidence, sx = symptoms, tx = treatment.

Node O1. Diagnosis.
The first consideration in assessing an individual with a suspected opioid use disorder is to conduct a diagnostic assessment to determine whether the patient fulfills criteria for a DSM-5 (American Psychiatric Association, 2013) diagnosis of opioid use disorder. At the same time the patient should be assessed with regard to the following considerations. These should be reassessed throughout the treatment.

Node OA. Other Substance Abuse Disorders.
Opioid use disorders occur frequently with other substance use disorders (McCabe et al., 2008; Williamson et al., 2007; Ross et al., 2005). Therefore, when diagnosing an opioid use disorder, it is useful to assess use of other substances of abuse; commonly abused substances include marijuana, cocaine, alcohol, nicotine and benzodiazepines. If there is another substance use disorder, consult the appropriate algorithm. In particular, a patient with opioid use disorder 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 use disorder, physiological 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. Co-Morbid Medical Problems.
Opioid use disorder 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 use disorder can be associated with accidental overdose, respiratory depression, and death. Moreover, many patients abusing opioid analgesics have chronic pain and have substantial medical comorbidity. Medical assessment is thus an essential component of initial evaluation and routine follow-up and will help determine appropriate pharmacotherapy, as the medications used to treat opioid use disorder may have medical warnings or interactions with other medications (e.g., methadone and rifampin). (Sullivan et al., 2008; Kresina et al., 2005; Bassetti et al., 2004; Doyon, 2004; Ball and Ross, 1991)

Node OC. Co-Occurring Psychiatric Disorders.
Opioid use disorder occurs frequently with co-occurring psychiatric disorders. Attempt to discern the likelihood that a co-occurring disorder is independent of the substance use disorder or a result of the substance use disorder. Evidence to support an independent psychiatric 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. Obtaining history from a collateral informant such as a family member may be very helpful in this process. For a presumptive independent psychiatric disorder, treat the disorder according to standard protocols. There is no evidence to suggest that opioid use disorder alters routine psychotropic medication selection for co-occurring psychiatric disorders; however, there is evidence that omitting appropriate pharmacotherapy for co-occurring independent psychiatric illness negatively affects an individual's capacity to achieve abstinence from opioid use. (Grella and Stein, 2006; Havassy et al., 2004; Carpenter et al., 2004;

Dean et al., 2002; Nunes et al., 1994)

Node OD. Suicidality.
Individuals with opioid use disorder 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 OE. Insomnia.
Insomnia is a common problem in people with opioid use disorder, 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 increase the risk of 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 doxepin, mirtazapine, hydroxyzine, diphenhydramine, and ramelteon; however, evidence supporting their efficacy is limited. (Amedt et al., 2007; Hajak et al., 2003; Hirst and Sloan, 2002) (***LOE IV***). Trazodone, an antidepressant with properties of serotonin antagonism and reuptake inhibition, has traditionally been one of the most prescribed medications for insomnia, especially in opioid dependent persons due to its non-addictive nature; however, a randomized, double blind, placebo-controlled trial found that trazodone did not improve sleep in opioid dependent patients receiving methadone maintenance treatment (***LOE II***) (Stein et al., 2012). Other alternative medications, specifically gabapentin and quetiapine, have been used widely for insomnia in this population, but have been noted to have abuse potential complicating their use (***LOE V***) (Recoppa et al, 2004; Sansone and Sansone, 2010; Schifano et al, 2011; Yargic and Caferov, 2011).

Node OF. Pregnancy.
The treatment of a pregnant woman with opioid use disorder warrants special consideration. In such cases, opioid maintenance rather than medically supervised withdrawal treatment is recommended (***LOE III***). Methadone maintenance has traditionally been the standard treatment in such a situation, although a number of reports have suggested that buprenorphine (the mono preparation, not the preparation with naloxone) may be an acceptable, and perhaps superior alternative (Minozzi et al., 2008; Winklbaur et al., 2008; Kleber et al., 2007). In a randomized, multi-center trial, the Maternal Opioid Treatment: Human Experimental Research (MOTHER) study compared methadone versus buprenorphine on neonatal outcomes (Jones et al, 2010). Neonates whose mothers received buprenorphine had fewer symptoms of neonatal abstinence and required less time in the hospital. No significant differences in maternal outcomes occurred between the groups, including Caesarean section rates, positive drug screens at delivery, or medical complications at delivery. However, pregnant women were more likely to drop out of the buprenorphine group. Buprenorphine (without naloxone) appears to be at least as effective and safe as methadone for the treatment of pregnant, opioid dependent women (***LOE II***).

Node OG. Degree of Motivation.
Individuals having low motivation for change frequently do not return for treatment. Counseling approaches that use motivational interviewing techniques and certain cognitive-behavioral and twelve-step facilitation 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 OH. Level of Adherence to Treatment.
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 that are contingent on active participation in a treatment program) (***LOE IA***) (Brooner et al., 2007; Pierce et al., 2006; Schottenfeld et al., 2005; Carroll et al., 2002; Dutra et al., 2008). For patients for whom naltrexone is an appropriate treatment, the use of the injectable, long-acting form of this medication may help mitigate poor adherence issues associated with the oral dose form.

Node OI. Access to Medical Care.
Access to medical care, particularly opioid agonist therapies such as buprenorphine and methadone stabilization or maintenance, is 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 OJ. Legal Problems.
Opioid-dependent individuals may experience legal problems, and may in fact seek 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 OK. Chronic Pain.
Chronic pain is quite common among those seeking treatment for opioid use disorders. Indeed, some such patients begin their use of opioids in response to a painful condition. Treating patients with co-occurring chronic pain and opioid use disorder is a significant challenge; 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 use disorder, recognizing that prolonged exposure to opioids may be associated with hyperalgesia (increased sensitivity to pain) that complicates treatment. (Ballantyne and LaForge, 2007)

Node O2. Physiological Symptoms?
Among individuals with opioid use disorder, it is important to assess for physiological dependence that would indicate a need for medical detoxification or induction onto agonist pharmacotherapy. 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. Patients who are physiologically dependent are recommended to receive pharmacotherapy for either opioid detoxification or maintenance treatment, categorized according to a variety of considerations, including treatment history and the presence of high-risk behaviors such as injection drug use (Mattick et al., 2008; Adi et al., 2007) (Node O8).(Mattick et al., 2008; Adi et al., 2007). 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 or induction onto agonist pharmacotherapy (Collins and Kleber, 2004; Tomkins et al., 2009). It is important to note that, 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.

Node O3. Refer to Outpatient Counseling.
If the patient meets criteria for opioid use disorder without physiological dependence, then the patient should be referred for outpatient counseling, and naltrexone treatment should be strongly 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. (Ross, 1995) Extended-release injectable naltrexone (available via once-monthly injections) can improve adherence rates and should be recommended for opioid-dependent patients who either do not adhere to oral naltrexone treatment or appear unlikely to do so.

It is important to note here that the treatment of a pregnant woman with opioid use disorder 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 as described above (node OG) recent evidence has suggested that buprenorphine (the mono preparation, not the preparation with naloxone) may be an acceptable and perhaps preferable alternative.

Node O4. First Treatment?
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. Buprenorphine/Naloxone Detox.
One common approach to a physiologically dependent patient seeking treatment for the first time (other than a pregnant woman, see above) would be to institute medically supervised withdrawal with sublingual buprenorphine/naloxone (either in tablet or film form) 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 or treatment stabilization (e.g., for poorly controlled diabetes). 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 on to buprenorphine/naloxone with an initial dose of 2/0.5 to 4/1 mg sublingually. Commonly, the dose for the first day will be 8/2 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. One study of patients dependent on prescription opioids showed what has been demonstrated with heroin-dependent patients previously, i.e., that the rate of successful opioid use outcomes (i.e., abstinence or near-abstinence) is far higher during buprenorphine stabilization treatment than during or after a taper (Weiss et al, 2011). If tapering occurs, it 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 commonly employed, 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 (Gowing et al., 2009). 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. (Ling et al., 2006; Gowing et al, 2009)

In addition to pregnancy, another clinical situation in which one might eschew detoxification and proceed immediately to buprenorphine maintenance treatment would occur if the patient presenting for treatment for the first time is engaging in 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 strongly 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 opioid use itself), and request maintenance treatment at that time. This should be seriously considered after a discussion with the patient of the risks and benefits of this approach. 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 strongly consider the use of 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 who 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).

One mechanism for improving adherence is through an extended-release injectable form of naltrexone initially available for the treatment of alcohol use disorder (as described above), and now approved for the treatment of opioid use disorder as well (Comer et al, 2006; Krupitsky et al, 2011). Although controlled trials have not compared the efficacy of long-acting injectable naltrexone with opioid agonist treatments (i.e.,., buprenorphine or methadone), data show improved adherence rates for injectable compared to oral naltrexone, a fact that might protect patients who would otherwise have stopped taking oral naltrexone and relapsed (Brooks et al, 2010). Similarly, naltrexone implants have been tested outside of the United States, but are not FDA-approved (Kunøe et al, 2010). Given the lack of comparison trials, the choice of route of naltrexone administration in such situations will often depend on patient choice.

Node O6. Successful Detoxification?

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. Continue Treatment and Monitoring.
For patients who respond well 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. The evidence for the optimal length of buprenorphine treatment is lacking, although a study of patients dependent upon prescription opioids found that tapering buprenorphine either initially or after three months of stabilization generally led to return to opioid use (Weiss et al., 2011). 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. History of Prior Treatments?
This section focuses on individuals who have had previous treatment for opioid use disorder and are now seeking treatment again. There are two potential presentations for such a patient. Node O9 is for those with a good history, but have had a relapse. Node O11 is for the others.

Node O9. Reinstitute Previously Successful Treatment.
In the first presentation, the patient has a history of sustained improvement 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 or long-acting injectable naltrexone) 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 a different treatment approach, while a lengthy period of abstinence and a brief, relatively contained relapse would favor reinstitution of the previously successful treatment regimen.

Node O10. Result?
After reinstitution of the previously successful treatment, one should assess whether this has been successful. If so, go to Node O7. If not, go to Node O11.

Node O11. Buprenorphine/Naloxone Treatment or Long-Acting Injectable Naltrexone.
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 a new strategy. If naltrexone had not been used previously (following buprenorphine detoxification), then either naltrexone or opioid maintenance treatment with buprenorphine/naloxone should be strongly considered (***LOE V***). As stated above, there have as of yet been no randomized trials comparing long-acting injectable naltrexone to buprenorphine maintenance treatment, so patient preference, likelihood of adherence, risk of diversion, medical issues, and access to treatment should all be considered in making this determination. In general, if maintenance treatment is chosen, 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 either naltrexone or buprenorphine by prescription in a 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 use disorder. Both injectable naltrexone and buprenorphine are more expensive than methadone, however. Optimal length of naltrexone treatment is unknown at this time. For some patients, 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. Maintenance pharmacotherapy 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 O12. Result?

After prescribing buprenorphine/naloxone or long-acting injectable naltrexone, the clinician should assess the degree to which this intervention is successful. If successful, go to Node O7. If not, then the next step depends upon which treatments have already been tried. If the patient has done poorly on both naltrexone and buprenorphine, then one should decide if Node O13 or Node O15 is the most appropriate next step. If the patient has tried naltrexone only, then buprenorphine-naloxone maintenance would be the next recommended step. If the patient has tried buprenorphine but not naltrexone, then naltrexone should be discussed in addition to Nodes O13 and O15. 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. The

buprenorphine/naloxone formulation in soluble film form (as compared to the tablet form) aims to improve adherence (via more rapid sublingual absorption time and improved taste), minimize diversion (via individually wrapped unit-dose packages with tracking numbers), and enhance accidental overdose protection (via child-resistant packaging) (Strain et al, 2011), and should be considered for patients in whom these factors are concerning (***LOE V***).

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 use disorder).

Node O13. Buprenorphine maintenance or long-acting injectable naltrexone, if not tried already.

For individuals who have responded poorly to long-acting injectable naltrexone, then buprenorphine maintenance would be a recommended treatment. Similarly, for those with recurrent relapses despite seemingly adequate buprenorphine treatment and associated psychiatric and psychosocial treatment, one should reconsider medically supervised withdrawal (inpatient if necessary) followed by naltrexone (particularly long-acting injectable naltrexone) if it has not been used before or if it has been used before with good success at times; considerations for naltrexone are discussed in Node O5. If the patient has already tried naltrexone without success, or if the patient declines this option, then 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; 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 O14. Result?
Individuals who receive methadone, buprenorphine, or naltrexone (e.g., extended-release naltrexone) maintenance treatment and do well should go to Node O7. If they are not doing well, one should reconsider naltrexone (particularly long-acting injectable naltrexone) if it has not been used before or if it has been used before with good success at times; considerations for naltrexone are discussed in Node O5. If the patient has already tried naltrexone without success, or if the patient declines this option, then one may need to add more psychosocial or psychiatric treatment, as in Node O15.

Node O15. Behavioral Treatments.
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.

References

Adi Y, Juarez-Garcia A, Wang D, Jowett S, Frew E, Day E, Bayliss S, Roberts T, Burls A. Oral naltrexone as a treatment for relapse prevention in formerly opioid-dependent drug users: a systematic review and economic evaluation. Health Technol Assess. 2007 Feb; 11 (6):iii-iv, 1-85.

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 5th Edition: DSM-5. American Psychiatric Publishing, Washington, DC: 2013

Arnedt JT, Conroy DA, Brower KJ. Treatment options for sleep disturbances during alcohol recovery. J Addict Dis. 2007;26(4):41-54.

Ball JC, Ross A. The Effectiveness of Methadone Maintenance Treatment: patients, programs, services, and outcome. New York, Springer Verlag, 1991.

Ballantyne JC, LaForge KS. Opioid dependence and addiction during opioid treatment of chronic pain. Pain. 2007 Jun;129(3):235-55.

Bassetti S, Battegay M. Staphylococcus aureus infections in injection drug users: risk factors and prevention strategies. Infection. 2004 Jun; 32(3):163-9.

Brooks AC, Comer SD, Sullivan MA, Bisaga A, Carpenter KM, Raby WM, Yu E, O'Brien CP, Nunes EV. Long-acting injectable versus oral naltrexone maintenance therapy with psychosocial intervention for heroin dependence: a quasi-experiment. J Clin Psychiatry. 2010 Oct;71(10):1371-8.

Brooner RK, Kidorf MS, King VL, Stoller KB, Neufeld KJ, Kolodner K. Comparing adaptive stepped care and monetary-based voucher interventions for opioid dependence. Drug Alcohol Depend. 2007 May;88 Suppl 2:S14-23.

Carpenter KM, Brooks AC, Vosburg SK, Nunes EV. The effect of sertraline and environmental context on treating depression and illicit substance use among methadone maintained opiate dependent patients: a controlled clinical trial. Drug Alcohol Depend 2004;74:123-134.

Carroll KM, Ball SA, Nich C, O'Connor PG, Eagan DA, Frankforter TL, Triffleman EG, Shi J, Rounsaville BJ. Targeting behavioral therapies to enhance naltrexone treatment of opioid dependence: efficacy of contingency management and significant other involvement. Arch Gen Psychiatry 2001;58:755-761.

Carroll KM, Sinha R, Nich C, Babuscio T, Rounsaville BJ. Contingency management to enhance naltrexone treatment

of opioid dependence: a randomized clinical trial of reinforcement magnitude. Exp Clin Psychopharmacol 2002;10:54-63.

Collins ED, Kleber H. Opioids: detoxification, in The American Psychiatric Publishing Textbook of Substance Abuse Treatment, 3rd edition. Edited by Galanter M, Kleber HD. Washington DC, American Psychiatric Publishing, 2004, pp 265-289.

Comer SD, Sullivan MA, Yu E, Rothenberg JL, Kleber HD, Kampman K, Dackis C, O'Brien CP. Injectable, sustained-release naltrexone for the treatment of opioid dependence: a randomized, placebo-controlled trial. Arch Gen Psychiatry. 2006 Feb;63(2):210-8.

Copenhaver MM, Bruce RD, Altice FL. Behavioral counseling content for optimizing the use of buprenorphine for treatment of opioid dependence in community-based settings: a review of the empirical evidence. Am J Drug Alcohol Abuse. 2007;33(5):643-54.

Dean AJ, Bell J, Mascord DJ, Parker G, Christie MJ. A randomized, controlled trial of fluoxetine in methadone maintenance patients with depressive symptoms. J Affect Disord 2002;72:85-90.

Doyon S. Opioids, in Emergency Medicine: A Comprehensive Study Guide, 6th edition. Edited by Tintinalli JE, Kelen GD, Stapczynski JS. New York, McGraw-Hill, 2004, pp 1071-1074.

Dunn KE, Sigmon SC, Strain EC, Heil SH, Higgins ST. The association between outpatient buprenorphine detoxification duration and clinical treatment outcomes: a review. Drug Alcohol Depend 2011; 119(1-2):1-9.

Dutra L, Stathopoulou G, Basden SL, Leyro TM, Powers MB, Otto MW. A meta-analytic review of psychosocial interventions for substance use disorders. Am J Psychiatry. 2008 Feb;165(2):179-87.

Gowing L, Ali R, White J. Buprenorphine for the management of opioid withdrawal. Cochrane Database Syst Rev. 2009 Jul 8;(3):CD002025.

Gowing L, Farrell M, Ali R, White JM. Alpha2-adrenergic agonists for the management of opioid withdrawal. Cochrane Database Syst Rev. 2009 Apr 15;(2):CD002024.

Grella CE, Stein JA. Impact of program services on treatment outcomes of patients with comorbid mental and substance use disorders. Psychiatr Serv. 2006 Jul;57(7):1007-15.

Hajak G, Müller WE, Wittchen HU, Pittrow D, Kirch W. Abuse and dependence potential for the non-benzodiazepine hypnotics zolpidem and zopiclone: a review of case reports and epidemiological data. Addiction. 2003 Oct;98(10):1371-8.

Havassy BE, Alvidrez J, Owen KK. Comparisons of patients with comorbid psychiatric and substance use disorders: implications for treatment and service delivery. Am J Psychiatry. 2004 Jan;161(1):139-45.

Hirst A, Sloan R. Benzodiazepines and related drugs for insomnia in palliative care. Cochrane Database Syst Rev. 2002;(4):CD003346.

Jones HE, Kaltenbach K, Heil SH, Stine SM, Coyle MG, Arria AM, O'Grady KE, Selby P, Martin PR, Fischer G. Neonatal abstinence syndrome after methadone or buprenorphine exposure. N Engl J Med. 2010; 363 (24): 2320-2331.

Kleber HD, Weiss RD, Anton RF Jr, George TP, Greenfield SF, Kosten TR, O'Brien CP, Rounsaville BJ, Strain EC, Ziedonis DM, Hennessy G, Connery HS, McIntyre JS, Charles SC, Anzia DJ, Cook IA, Finnerty MT, Johnson BR, Nininger JE, Summergrad P, Woods SM, Yager J, Pyles R, Cross CD, Peele R, Shemo JP, Lurie L, Walker RD, Barnovitz MA, Gray SH, Saxena S, Tonnu T, Kunkle R, Albert AB, Fochtmann LJ, Hart C, Regier D; Work Group on Substance Use Disorders; American Psychiatric Association; Steering Committee on Practice Guidelines. Treatment of patients with substance use disorders, second edition. American Psychiatric Association. Am J Psychiatry. 2007 Apr;164(4 Suppl):5-123.

Kresina TF. Medication assisted treatment of drug abuse and dependence: global availability and utilization. Recent Patents Anti-Infect Drug Disc. 2007 Jan;2(1):79-8.

Kresina TF, Eldred L, Bruce RD, Francis H. Integration of pharmacotherapy for opioid addiction into HIV primary care for HIV/hepatitis C virus-co-infected patients. AIDS. 2005 Oct;19 Suppl 3:S221-6.

Krupitsky E, Nunes EV, Ling W, Illeperuma A, Gastfriend DR, Silverman BL. Injectable extended-release naltrexone for opioid dependence: a double-blind, placebo-controlled, multicentre randomised trial. Lancet. 2011 Apr 30;377(9776):1506-13.

Kunøe N, Lobmaier P, Vederhus JK, Hjerkinn B, Hegstad S, Gossop M, Kristensen O, Waal H. Retention in naltrexone implant treatment for opioid dependence. Drug Alcohol Depend. 2010 Sep 1;111(1-2):166-9.

Ling W, Amass L, Shoptaw S, Annon JJ, Hillhouse M, Babcock D, Brigham G, Harrer J, Reid M, Muir J, Buchan B, Orr D, Woody G, Krejci J, Ziedonis D; Buprenorphine Study Protocol Group. A multi-center randomized trial of buprenorphine-naloxone versus clonidine for opioid detoxification: findings from the National Institute on Drug Abuse Clinical Trials Network. Addiction. 2005 Aug;100(8):1090-100.

Maloney E, Degenhardt L, Darke S, Mattick RP, Nelson E. Suicidal behaviour and associated risk factors among opioid-dependent individuals: a case-control study. Addiction. 2007 Dec;102(12):1933-41.

Mattick RP, Kimber J, Breen C, Davoli M. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. Cochrane Database Syst Rev. 2008 Apr 16;(2):CD002207.

McCabe SE, Cranford JA, West BT. Trends in prescription drug abuse and dependence, co-occurrence with other substance use disorders, and treatment utilization: Results from two national surveys. Addict Behav. 2008 Oct;33(10):1297-305

Minozzi S, Amato L, Vecchi S, Davoli M. Maintenance agonist treatments for opiate dependent pregnant women. Cochrane Database Syst Rev. 2008 Apr 16;(2):CD006318.

Nunes E, Quitkin F, Brady R, Post-Koenig T. Antidepressant treatment in methadone maintenance patients. J Addict Dis 1994;13:13-24.

Peirce JM, Petry NM, Stitzer ML, Blaine J, Kellogg S, Satterfield F, Schwartz M, Krasnansky J, Pencer E, Silva-Vazquez L, Kirby KC, Royer- Malvestuto C, Roll JM, Cohn A, Copersino ML, Kolodner K, Li R. Effects of lower-cost incentives on stimulant abstinence in methadone maintenance treatment: a National Drug Abuse Treatment Clinical Trials Network study. Arch Gen Psychiatry. 2006 Feb;63(2):201-8.

Recoppa L, Malcolm R, Ware M. Gabapentin abuse in inmates with prior history of cocaine dependence. Am J Addict. 2004; 13(3): 321-3.

Ross J, Teesson M, Darke S, Lynskey M, Ali R, Ritter A, Cooke R. The characteristics of heroin users entering treatment: findings from the Australian treatment outcome study (ATOS). Drug Alcohol Rev. 2005 Sep;24(5):411-8. Rounsaville BJ. Can psychotherapy rescue naltrexone treatment of opioid addiction?, in Integrating Behavior Therapies With Medication in the Treatment of Drug Dependence. NIDA Research Monograph 150. Edited by Onken LS, Blaine JD, Boren JJ. Rockville, MD. National Institute on Drug Abuse, 1995. pp 37-52.

Sansone RA, Sansone LA. Is Seroquel developing an illicit reputation for misuse/abuse? Psychiatry (Edgemont) 2010; 7(1): 13-16.

Schifano F, D'Offizi S, Piccione M, Corazza O, Deluca P, Davey Z, Di Melchiorre G, Di Furia L, Farre M, Flesland L, Mannonen M, Majava A, Pagani S, Peltoniemi T, Siemann H, SkutleA, Torrens M, Pezzolesi C, van der Kreeft P, Scherbaum N. Is there a recreational misuse potential for pregabalin? Analysis of anecdotal online reports in comparison with related gabapentin and clonazepam data. Psychother Psychosom 2011; 80: 118-122.

Schottenfeld RS, Chawarski MC, Pakes JR, Pantalon MV, Carroll KM, Kosten TR. Methadone versus buprenorphine with contingency management or performance feedback for cocaine and opioid dependence. Am J Psychiatry. 2005 Feb;162(2):340-9.

Strain EC, Bigelow GE, Liebson IA, Stitzer ML. Moderate- vs high-dose methadone in the treatment of opioid dependence: a randomized trial. JAMA 1999;281:1000-1005.

Strain EC, Harrison JA, Bigelow GE. Induction of opioid-dependent individuals onto buprenorphine and buprenorphine/naloxone soluble-films. Clin Pharmacol Ther. 2011; 89(3): 443-9.

Stein MD, Kurth ME, Sharkey KM, Anderson BJ, Corso RP, Millman RP. Trazodone for sleep disturbance during

methadone maintenance: a double-blind, placebo-controlled trial. Drug Alcohol Depend. 2012 Jan 1; 120(1-3): 65-73.

Sullivan LE, Moore BA, Chawarski MC, Pantalon MV, Barry D, O'Connor PG, Schottenfeld RS, Fiellin DA. Buprenorphine/naloxone treatment in primary care is associated with decreased human immunodeficiency virus risk behaviors. J Subst Abuse Treat. 2008 Jul;35(1):87-92.

Sullivan MA, Birkmayer F, Boyarsky BK, Frances RJ, Fromson JA, Galanter M, Levin FR, Lewis C, Nace EP, Suchinsky RT, Tamerin JS, Tolliver B, Westermeyer J. Uses of coercion in addiction treatment: clinical aspects. Am J Addict. 2008 Jan-Feb;17(1):36-47.

Tompkins DA, Bigelow GE, Harrison JA, Johnson RE, Fudala PJ, Strain EC. Concurrent validation of the Clinical Opiate Withdrawal Scale (COWS) and single-item indices against the Clinical Institute Narcotic Assessment (CINA) opioid withdrawal instrument. Drug Alcohol Depend. 2009 Nov 1;105(1-2):154-9.

Trémeau F, Darreye A, Staner L, Corrêa H, Weibel H, Khidichian F, Macher JP. Suicidality in opioid-dependent subjects. Am J Addict. 2008 May-Jun;17(3):187-94.

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 Dec;68(12):1238-1246.

Williamson A, Darke S, Ross J, Teesson M. The effect of baseline cocaine use on treatment outcomes for heroin dependence over 24 months: findings from the Australian Treatment Outcome Study. J Subst Abuse Treat. 2007 Oct;33(3):287-93.

Winklbaur B, Jung E, Fischer G. Opioid dependence and pregnancy. Curr Opin Psychiatry. 2008 May;21(3):255-9.

Yargic I, Caferov C. Quetiapine dependence and withdrawal: a case report. Subst Abus. 2011; 32(3): 168-9.