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Pharmacology Consult

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Making the Journey from Opioid and Heroin Addiction

One Map for the Clinical Nurse Specialist

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Pharmacology consult: I am a CNS in a busy community hospital emergency room. Increasingly, we are receiving patients with prescription and heroin overdose. The suffering, guilt, and hopelessness some days are overwhelming. Can you describe some of the current options for opioid addiction?

Nearly 2% percent of the US population or 5 million adults use or have used heroin.[1] Prescription opioid abuse is more difficult to quantify. However, the number of persons seeking treatment for nonheroin opioid abuse is increasing. Opioid abuse is has no racial, geographic, or social markers.

Elements of opioid dependence include some or all of the following elements: tolerance, intense desire for opioids, difficulty controlling use, neglect of the demands of life and relationships, withdrawal symptoms, and continued use despite harmful consequences. Repeated use modifies the neuronal connections for memory, motivation, and behavior.[2]

Rather than a character defect, opioid dependence is a medical condition, a brain disorder with complex sociobehavioral factors. With continued use, quality of life decreases rapidly because so much time is spent either intoxicated or drug seeking. High rates of depression also contribute to the downward spiral of broken relationships, unemployment, and premature death. For intravenous illicit drug users, unsafe injection practices may account for 90% of new hepatitis C infections.[2]

Treatment goals for opioid addiction include the following: reduce or stop opioid use, prevent future use, and improve quality of life to provide hope and a foundation for change.[2] Current pharmacological options for opioid dependence include methadone (full μ-opioid receptor agonist), buprenorphine (partial μ-opioid receptor agonist), and buprenorphine/naloxone (combination of partial μ-opioid receptor agonist and opioid receptor antagonist). The efficacy of these agents for the treatment of opioid dependence is not problematic. However, all of these agents have associated risks for abuse and diversion. As a result, significant prescribing restrictions including complete prohibition have been placed on these agents worldwide.[3]

Another option is naltrexone (naltrexone hydrochloride). Naltrexone is a μ-opioid receptor antagonist that blocks the euphoric effects of opioids without inducing tolerance or addiction. However, poor adherence to oral treatment has limited the effectiveness of naltrexone.

PATHWAYS FOR THERAPY

First-line agents for treatment include methadone and buprenorphine. Methadone (DEA Schedule II) is a full μ agonist that blocks the ability of other opioids to bind to μ receptors and reduces craving and is dispensed within highly regulated treatment programs. Buprenorphine (DEA Schedule III) is a partial opioid agonist with less risk for respiratory depression with the usual side effects of opioids, including sedation, nausea, and constipation. Buprenorphine can be prescribed in the outpatient setting only with special training and can be combined with naloxone to stop potential intravenous abuse of buprenorphine because opioid effects are blocked. Buprenorphine can displace full opioid agonists resulting in withdrawal symptoms.[1]

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Agonist maintenance treatment provides a daily opioid agonist (eg, methadone) or partial agonist (eg, buprenorphine) to promote a "stable" opioid effect that is not experienced as withdrawal or as a "high" like shorter-acting opioids such as heroin. Methadone is often preferred to buprenorphine related to cost. However, evidence supporting this pathway is slim and recidivism remains high. When, who, and how to withdraw opioid agonist maintenance treatment are essentially not known. However, agonist maintenance treatment, when combined with psychosocial assistance, appears more effective compared with detoxification or no treatment in reducing drug use, risky and criminal behavior, and all-cause mortality and keeps more patients in treatment.[2]

For some, immediate cessation of opioids is attractive for inpatient settings related to agonist treatment costs and ability to begin naltrexone treatment sooner rather than later. Immediate opioid cessation can be facilitated using α-2 adrenergic agonists (clonidine) to relieve withdrawal symptoms, daily naltrexone or naloxone infusions with continuous monitoring for delirium, vomiting, and diarrhea. Often, aggressive fluid replacement is required. Patients with a history of cardiac or renal disease, dependence on alcohol, or benzodiazepines or stimulants *should not* be with withdrawn from opioids via this accelerated path.[2] As for pregnant women and older adults, limited evidence suggests that methadone maintenance treatment may be the preferred option.[1]

AFTER OPIOID WITHDRAWAL

To prevent relapse in those who have withdrawn from opioids and desire to abstain from opioids, persons should be counseled to consider naltrexone. Treatment can be started within 1 week of cessation of short-acting opioids and buprenorphine and 10 to 14 days after cessation of methadone because naltrexone can precipitate severe withdrawal symptoms if administered to an individual using opioids.[2]

Naltrexone does not produce any opioid effects.[2] The efficacy of this opioid receptor antagonist compared with an opioid receptor agonist is unknown. However, evidence suggests that antagonist treatment may be more effective than placebo if the patient adheres to abstinence from opioids and has been detoxified to prevent withdrawal symptoms. Naltrexone is also an important option for patients who have work-related contraindications for opioid agonist treatment, such as healthcare and law enforcement workers, commercial drivers, and pilots.[1] Treatment also provides an alternative therapy without the metabolic, cognitive, and cardiovascular side effects and is pharmacologically analogous to abstinence.[4]

An oral dose of naltrexone of 50 mg effectively reverses and blocks methadone and heroin for 24 hours.[2] Although limited evidence suggests that naltrexone is effective compared with placebo after opioid withdrawal in reducing heroin use and criminal activity, adherence to treatment and relapse were not significantly improved with naltrexone. Limited evidence from observational studies also suggests that there are higher rates of opioid overdose after ceasing naltrexone treatment.[2,4]

In an analysis of 13 clinical trials with 1158 persons with opioid addiction receiving outpatient treatment of oral naltrexone, with and without psychotherapy, treatment was no better than placebo with regard to adherence, substance abuse, or side effects. The only significant outcome was a reduction in re-incarcerations by about a half in 2 of 13 studies. Naltrexone was also found not superior to benzodiazepines or buprenorphine. Less than a third remained in treatment, with a mean duration of therapy of 6 months (range, 1-10 months). Based on the evidence from this limited number of studies, further information is needed to further evaluate the efficacy of oral naltrexone treatment in opioid dependence.[5]

When the patient ceases naltrexone with the intention to use opioids such as heroin, determining the right dose is difficult because naltrexone effects gradually decline. Therefore, the opioid dose can be blocked or fatal. The result is a greater risk for unintentional drug overdoses. Therefore, naltrexone should only be prescribed to persons with the goal of complete abstinence from opioids and the patient has the motivation to stop related to risk of losing employment or risk of jail time. Naltrexone therapy appears more successful when a caregiver, companion, friend, or even employer administers and monitors adherence to therapy.[2]

ANOTHER OPTION

Nonadherence to oral naltrexone is a significant contributing factor to therapeutic failure.[4] To overcome this obstacle, injectable extended-release naltrexone (XR-NTX; Vivitrol or naltrexone for extended-release injectable suspension) was developed (Alkermes, Dublin, Ireland). Vivitrol appears highly effective at producing extended pharmacological abstinence from opioids, even if patients continue to crave or use opioids.[4]

In a recent clinical trial of treatment adherence in fully detoxified heroin-dependent subjects (n = 32), extended-release Vivitrol therapy was well tolerated without subject attrition due to side effects. Subjects who stayed in treatment remained abstinent from opioid use even 2 weeks after the expected cessation of the pharmacological effects and over half the sample remained abstinent from opioid drugs. Furthermore, subjects displayed reductions in cue-induced craving responses and, for some, a decrease in measures of depression. However, also observed in this trial was an increasing trend in opioid positive urine test results *near the end* of the last dosing interval. This finding suggests that injectable naltrexone may require

supplemental oral naltrexone with enhanced psychobehavioral support as the dosing interval is ending.[4]

Additional evidence from a 1-year open-label extension study of 114 subjects receiving injectable Vivitrol for the prevention of relapse in opioid dependence indicates 62.3% of patients completed the phase and 50.9% were abstinent from opioids. Injection site reactions occurred in 6.1% of the patients, of which most were graded as mild. Nearly 17% of the subjects had elevations in liver function tests. However, none of the elevations were deemed significant. No patients died, overdosed, or discontinued as a result of adverse events.[6]

Finally, in a randomized trial of criminal justice offenders (308 subjects), 153 received extended-release naltrexone and 155 received usual treatment to prevent opioid relapse. The group that received extended-release naltrexone had a lower rate of relapse compared with usual treatment. However, opioid prevention effects waned after treatment was discontinued.[7]

DRUG CONSIDERATIONS

Vivitrol is an extended-release, microsphere formulation of naltrexone designed to be administered by intramuscular gluteal injection every 4 weeks or once a month. After intramuscular injection, the naltrexone plasma concentration time profile is described as a transient initial peak, which occurs approximately 2 hours after injection, followed by a second peak observed approximately 2 to 3 days later. Beginning approximately 14 days after dosing, concentrations slowly decline, with measurable levels for greater than 1 month.[8–10]

Preparation of the injection requires precise interventions. It is recommended that the drug be administered *immediately* once the diluent is added to the Vivitrol microspheres has been suspended and transferred into the syringe. Administration in the gluteal region requires use of the needle provided with the drug.[8,9]

Patients must be instructed when receiving medical treatment to notify the treating healthcare provider that they are receiving Vivitrol and the date of the last dose. Patients and caregivers need to know that Vivitrol can block the effects of opioid-containing medicines for pain, cough or colds, or diarrhea.[8–10] Carrying an information card at all times can help drive effective and safe interventions during an emergency.

Perhaps the most important medication teaching for Vivitrol therapy is self-monitoring for a depressed mood or suicidal ideas, which should be reported immediately. It is important that the patient tell family members and close friends that he/she is receiving Vivitrol to assist with this monitoring. In addition, patients should immediately report shortness of breath, wheezing, or a cough that does not go away because some persons receiving Vivitrol have developed an allergic-type pneumonia.[8–10] Finally, the safety and efficacy of Vivitrol have not been established in the pediatric population nor have pharmacokinetics of Vivitrol been evaluated in a pediatric population.[2]

Risk of liver injury and dysfunction has been noted in clinical trials with and in the postmarketing period with naltrexone. Patients with elevated transaminases often had other comorbid conditions such as alcoholic liver disease and hepatitis B and or C infection. Consider discontinuation of naltrexone with signs and symptoms of hepatitis. If reversal of naltrexone is needed for pain management, options include regional analgesia, conscious sedation with a benzodiazepine, and use of nonopioid analgesics or general anesthesia.[11]

In summary, the outcomes of naltrexone, whether oral (naltrexone hydrochloride) or long-acting injectable (Vivitrol), are also a function of careful management of comorbid conditions, counseling therapy, support groups, and patient compliance with medication therapy.[2,11]

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