Opioid Antagonists Under Heavy Sedation or General Anesthesia as a Technique of Opioid Detoxification

Archived Medical Policy

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Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the “Company”), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers opioid antagonists under heavy sedation or anesthesia as a technique for opioid detoxification (i.e., ultra-rapid detoxification) to be investigational.*

Background/Overview
The use of relatively high doses of opioid antagonists under deep sedation or general anesthesia is a technique for opioid detoxification and is known as ultra-rapid detoxification. It is a potential alternative to standard detoxification that allows patients to avoid the acute symptoms associated with initial detoxification. Ultra-rapid detoxification is used in conjunction with maintenance treatments e.g., oral opioid antagonists and psychosocial support.

The traditional treatment of opioid addiction involves substituting the opiate (i.e., heroin) with an equivalent dose of a longer-acting opioid antagonist, e.g., methadone, followed by tapering to a maintenance dose. Methadone maintenance therapy does not resolve opioid addiction but has been shown to result in improved general health, retention of patients in treatment, and a decrease in the risk of transmitting human immunodeficiency virus (HIV) or hepatitis. However, critics of methadone maintenance point out that this strategy substitutes one drug of dependence for the indefinite use of another. Detoxification followed by abstinence is another treatment option, which can be used as the initial treatment of opioid addiction or offered as a final treatment strategy for patients on methadone maintenance. Detoxification is associated with acute symptoms followed by a longer period of protracted symptoms (i.e., 6 months) of withdrawal. Although typically not life-threatening, acute detoxification symptoms include irritability, anxiety, apprehension, muscular and abdominal pains, chills, nausea, diarrhea, yawning, lacrimation, sweating, sneezing, rhinorrhea, general weakness, and insomnia. Protracted withdrawal symptoms include a general feeling of reduced well-being and drug craving. Relapse is common during this period.

Detoxification may be initiated with tapering doses of methadone or buprenorphine (an opioid agonist-antagonist), treatment with a combination of buprenorphine and naloxone (an opioid antagonist), or discontinuation of opioids and administration of oral clonidine and other medications to relieve acute symptoms. However, no matter what type of patient support and oral medications are offered, detoxification
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is associated with patient discomfort, and many patients may be unwilling to attempt detoxification. In addition, detoxification is only the first stage of treatment. Without ongoing medication and psychosocial support after detoxification, the probability is low that any detoxification procedure alone will result in lasting abstinence. Opioid antagonists, such as naltrexone, may also be used as maintenance therapy to reduce drug craving and thus reduce the risk of relapse.

Dissatisfaction with current approaches to detoxification has led to interest in using relatively high doses of opioid antagonists, such as naltrexone, naloxone, or nalmefone under deep sedation with benzodiazepine or general anesthesia. This strategy has been referred to as "ultra-rapid," "anesthesia-assisted," or "one-day" detoxification. The use of opioid antagonists accelerates the acute phase of detoxification, which can be completed within 24–48 hours. Since the patient is under anesthesia, the patient has no discomfort or memory of the symptoms of acute withdrawal. Various other drugs are also administered to control acute withdrawal symptoms, such as clonidine (to attenuate sympathetic and hemodynamic effects of withdrawal), ondansetron (to control nausea and vomiting), and somatostatin (to control diarrhea). Hospital admission is required if general anesthesia is used. If heavy sedation is used, the program can potentially be offered on an outpatient basis. Initial detoxification is then followed by ongoing support for the protracted symptoms of withdrawal. In addition, naltrexone may be continued to discourage relapse.

Ultra-rapid detoxification may be offered by specialized facilities. Neuraad™ Treatment Centers, Nutmeg Intensive Rehabilitation, and Center for Research and Treatment of Addiction (CITA) are examples. These programs typically consist of 3 phases: a comprehensive evaluation, inpatient detoxification under anesthesia, and finally, mandatory post-detoxification care and follow-up. The program may be offered to patients addicted to opioid or narcotic drugs such as opium, heroin, methadone, morphine, meperidine, hydromorphone, fentanyl, oxycodone, hydrocodone, or butorphanol. Once acute detoxification is complete, the opioid antagonist naltrexone is often continued to decrease drug craving, with the hope of reducing the incidence of relapse.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)
In October 2002, Reckitt Benckiser received U.S. FDA approval to market a buprenorphine monotherapy product, Subutex®, and a buprenorphine/naloxone combination product, Suboxone®, for use in opioid addiction treatment.

Centers for Medicare and Medicaid Services (CMS)
Medicare Coverage Issues Manual—Medical Procedures
Section 35-42, Withdrawal Treatment for Narcotic Addictions, states: "Withdrawal is an accepted treatment for narcotic addiction, and Part B payment can be made for these services if they are provided by the physician directly or under his personal supervision and if they are reasonable and necessary. In reviewing claims, reasonableness and necessity are determined with the aid of the contractor’s medical staff.
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Drugs that the physician provides in connection with this treatment are also covered if they cannot be self-administered and meet all other statutory requirements."

Section 35-22.2, Treatment of Drug Abuse (Chemical Dependency), states:
“We recognize that there are similarities in approach to treatment of drug abuse and alcohol detoxification. However, the intensity and duration of treatment for drug abuse may vary (depending on the particular substance(s), duration of use, and the patient’s medical and emotional condition) from the duration of treatment or intensity needed to treat alcoholism. Accordingly, when it is medically necessary for a patient to receive detoxification and/or rehabilitation for drug substance abuse as a hospital inpatient, coverage for that care is available. Coverage is also available for treatment services that are provided in the outpatient department of a hospital to patients who, for example, have been discharged from an inpatient hospital stay for the treatment of drug substance abuse or who require treatment but do not require the availability and intensity of services found only in the inpatient hospital setting. The coverage available for these services is subject to the same rules generally applicable to the coverage of an outpatient hospital. The services must be reasonable and necessary for the treatment of the individual’s condition. Decisions regarding reasonableness and necessity of treatment, the need for inpatient hospital level of care, and lengths of treatment should be made by intermediaries based on accepted medical practice with the advice of their medical consultant.”

Rationale/Source
This assessment of ultrarapid opioid detoxification, focuses on data reporting the severity and duration of withdrawal symptoms and the short- and long-term outcomes of maintenance of abstinence in distinct populations of patients, based on type and duration of addiction. Efficacy outcomes will be balanced against the safety considerations of deep sedation or general anesthesia in conjunction with naloxone.

In 2010, a Cochrane review by Gowing and colleagues on opioid antagonists under heavy sedation or anesthesia for opioid withdrawal was published. A total of 9 studies including 1,109 participants were eligible for inclusion; there were 8 randomized controlled trials (RCTs) and 1 non-randomized controlled trial. Four studies compared the intervention to conventional approaches of withdrawal, and 5 compared different regimens of antagonist-induced withdrawal. In 5 of the studies, all participants were withdrawing from heroin or other short-acting opioids; in 3 studies, they were using heroin and/or methadone and, in 1 study, all participants were withdrawing from methadone.

Due to differences in study designs (e.g., antagonist and anesthesia or sedation regimens, comparison interventions, outcome variables, etc.), few pooled analyses could be conducted. Findings from 3 trials (total n=240) comparing antagonist-induced and conventional withdrawal were pooled for several outcome variables. The number of participants completing maintenance treatment was significantly higher in the antagonist-induced group than in the conventional treatment group (relative risk [RR]: 4.28; 95% confidence interval [CI]: 2.91-6.30). The number of participants who continued maintenance treatment or were abstinent at 12 months also favored the antagonist-induced group (RR: 2.77; 95% CI: 1.37-5.61). Safety
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data from these 3 studies were not pooled. One of the studies reported no adverse effects, and 1 only reported adverse effects in patients who received octreotide during the anesthetic procedure; 7 out of these 11 patients (64%) experienced vomiting and/or diarrhea. The third study reported 3 serious adverse events, all of which occurred in the anesthesia group. There were no pooled analyses of the results of studies that evaluated the efficacy of differing opioid antagonist withdrawal regimens. One meta-analysis of safety data from 2 studies (total n=572) found a statistically significantly higher rate of adverse events with heavy sedation compared to light sedation (RR: 3.21; 95% CI: 1.13-9.12). Other adverse events included high rates of vomiting in several studies and, in 1 study, episodes of irregularities in respiratory patterns during withdrawal.

The authors of the Cochrane review commented that, due to variability among the trials, “it is not possible to identify ‘standard’ treatment regimens for antagonist-induced withdrawal in conjunction with heavy sedation or anesthesia.” They concluded that “the increased risk of clinically significant adverse events associated with withdrawal under heavy sedation or anesthesia make the value of anesthesia-assisted antagonist-induced withdrawal questionable.”

A representative RCT included in the Cochrane review was a 2005 trial by Collins et al. In this study, 106 persons addicted to heroin were randomly assigned to undergo detoxification with an anesthesia-assisted rapid opioid detoxification, buprenorphine-assisted rapid opioid detoxification, or clonidine-assisted opioid detoxification. All study participants received an additional 12 weeks of outpatient naltrexone maintenance. Mean withdrawal severities were similar among the 3 groups, and treatment retention in the 12-week follow-up period was also similar. However, the anesthesia procedure was associated with 3 potentially significant life-threatening AEs. The authors concluded that the data did not support the use of general anesthesia for heroin detoxification.

Among the AEs reported in the Cochrane review, vomiting under sedation is particularly worrisome due to the threat of aspiration. Techniques reported to minimize this risk include intubation, use of prophylactic antibiotics, and the use of medication to diminish the volume of gastric secretions. Several deaths occurring either during anesthesia or immediately thereafter have been reported. Also, deaths subsequent to ultrarapid detoxification have been reported. Of particular concern is the fact that the use of opioid antagonists results in loss of tolerance to opioids, rendering patients susceptible to overdose if they return to predetoxification dosage of illicit drugs.

Relapse after ultrarapid detoxification was examined in a 2014 study by Salimi et al. A total of 424 patients with self-reported opioid use entered a treatment program at a single institution in Iran. Treatment consisted of rapid detoxification under general anesthesia and naltrexone maintenance therapy. Four hundred of the 424 patients (94%) completed 2 years of follow-up. Among completers, 97 patients (24%) experienced at least 1 incident of relapse. Patients who relapsed had significantly lower rates of long-term compliance with naltrexone therapy, and all of the patients who relapsed had discontinued naltrexone use prior to relapse.
Mild AEs were common and did not differentiate between patients with successful abstinence versus relapse. For example, 52% of those with treatment success and 56% who relapsed (p>0.05) experienced mild muscle pain in the first 3 months after withdrawal. This study was uncontrolled and does not provide data on the relative efficacy of detoxification methods.

A follow-up study was done by Forozeshfard et al to evaluate relapse after ultrarapid detoxification. This prospective study, done in Iran, included 64 patients undergoing the procedure with general anesthesia, followed by outpatient treatment using naltrexone oral therapy, and free-of-charge monthly psychiatric visits. Of the 64 patients undergoing treatment, 48 (75%) patients suffered relapse within the first month, with 12 patients returning to opioid abuse at 3 months, and the remaining 4 patients by 6 months. Four (6%) patients had life-threatening complications during the procedure, including pulmonary edema, pneumothorax, bradycardia, and refractory delirium with hypertension and cardiac arrhythmia. None of these patients had a fatal event.

Ongoing and Unpublished Clinical Trials
A search of ClinicalTrials.gov in November 2015 did not identify any ongoing or unpublished trials that would likely influence this review.

Summary of Evidence
The evidence for ultrarapid detoxification under general anesthesia in individuals who have opioid addiction includes both randomized and nonrandomized clinical trials as well as prospective follow-up studies, which compare other approaches not involving deep or general anesthesia. Relevant outcomes are hospitalizations, medication use and treatment-related morbidity and mortality. There is a paucity of data in the controlled trials and a lack of standardized approaches to ultrarapid detoxification. Additionally, significant adverse effects, including life-threatening complications, are a concern using this treatment. Most patients subsequently return to daily use shortly after this technique. The evidence is insufficient to determine the effects of the technology on health outcomes.

References
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Policy History

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02/06/2014 Medical Policy Committee review
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09/15/2014 Coding update; deleting code J2315 from the coding section
02/05/2015 Medical Policy Committee review
02/18/2015 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
08/03/2015 Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
02/04/2016 Medical Policy Committee review
02/17/2016 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
01/01/2017 Coding update: Removing ICD-9 Diagnosis Codes
02/02/2017 Medical Policy Committee review. Recommend archiving.
02/15/2017 Medical Policy Implementation Committee approval. Archived.

Next Scheduled Review Date: Archived medical policy

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A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the FDA and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or

B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
   1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
   2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
   3. Reference to federal regulations.

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