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

Policy #: 091       Latest Review Date: January 2014
Category: Mental Health/Pharmacology       Policy Grade: B

Background/Definitions:  
As a general rule, benefits are payable under Blue Cross and Blue Shield of Alabama health plans only in cases of medical necessity and only if services or supplies are not investigational, provided the customer group contracts have such coverage.

The following Association Technology Evaluation Criteria must be met for a service/supply to be considered for coverage:

1. The technology must have final approval from the appropriate government regulatory bodies;
2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes;
3. The technology must improve the net health outcome;
4. The technology must be as beneficial as any established alternatives;
5. The improvement must be attainable outside the investigational setting.

Medical Necessity means that health care services (e.g., procedures, treatments, supplies, devices, equipment, facilities or drugs) that a physician, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury or disease or its symptoms, and that are:

1. In accordance with generally accepted standards of medical practice; and
2. Clinically appropriate in terms of type, frequency, extent, site and duration and considered effective for the patient’s illness, injury or disease; and
3. Not primarily for the convenience of the patient, physician or other health care provider; and
4. Not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient’s illness, injury or disease.
**Description of Procedure or Service:**
Two new approaches for detoxification have been developed. A rapid opioid detoxification (RD) technique is designed to shorten detoxification by precipitating withdrawal through the administration of opioid antagonists such as naloxone hydrochloride or naltrexone in awake individuals. This approach gets patients through detoxification rapidly to minimize the risk of relapse, and quickly initiate treatment with naltrexone maintenance and psychosocial intervention.

Ultra-rapid opioid detoxification (URD) uses relatively high doses of opioid antagonists, such as naltrexone, naloxone, or nalmefene, under deep sedation with a benzodiazepine or general anesthesia. The use of opioid antagonists accelerates the acute phase of detoxification, which can be completed in 24 to 48 hours. Patients have no discomfort or memory of the symptoms of acute withdrawal. A variety of other medications may be used to control acute withdrawal symptoms: prochlorperazine (anti-emetic), benzodiazepine (to induce sleep), ibuprofen (an analgesic), and clonidine (to attenuate sympathetic and hemodynamic effects of withdrawal). The procedure is done as an inpatient if general anesthesia is used or possibly as an outpatient if heavy sedation is used.

Initial detoxification is followed by ongoing support for the protracted symptoms of withdrawal. In addition, naltrexone may be continued to discourage relapse.

URD may be offered by specialized facilities such as psychiatric centers or drug addiction treatment centers. These programs typically consist of three phases: a comprehensive evaluation, inpatient detoxification under anesthesia, and mandatory post detoxification care and follow up. URD may be offered by Neuraad™ treatment Centers, Nutmeg Intensive Rehabilitation and center for Research and Treatment of Addiction (CITA).

**Policy:**
Blue Cross and Blue Shield of Alabama will treat the techniques of rapid opioid detoxification (RD) and ultra-rapid opioid detoxification (URD) and related services, using opioid antagonists under heavy sedation or anesthesia, as investigational.

Blue Cross and Blue Shield of Alabama does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Cross and Blue Shield of Alabama administers benefits based on the member’s contract and corporate medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

**Key Points:**
The opioid drugs include morphine, codeine, heroin, hydromorphone, and oxycodone. All of these substances are capable of producing euphoria as well as psychological and physical dependence when taken in high enough doses over prolonged periods of time. Opiate tolerance,
dependence and withdrawal are considered to be related phenomena and may involve a number of neurochemical systems and psychological processes.

The acute withdrawal symptoms can last up to eight days and include anxiety, apprehension, irritability, chills, nausea, diarrhea, coughing, sneezing, lacrimation, rhinorrhea, sweating, yawning, muscular and abdominal pains, general weakness and insomnia. Protracted withdrawal symptoms can last up to six months and include change in pupillary size, autonomic dysfunction, change in sleep pattern, a general feeling of reduced well-being and drug craving. Relapse is common during this period.

The traditional treatment of opioid addiction involves substituting the opioid, i.e., heroin, with an equivalent dose of a long-acting opioid antagonist, i.e., methadone, and tapering to a maintenance dose. Methadone maintenance therapy does not cure opiate addiction, but provides a substitute drug that is legal and safe. Methadone maintenance, along with education and counseling, has been shown to result in improved general health, retention of patients in treatment, and a decrease in the risk of transmitting HIV or hepatitis. However, critics of methadone maintenance point out that this strategy substitute’s one drug for another.

Other methods of detoxification include treatment with buprenorphine, an opioid agonist-antagonist; or naloxone or naltrexone, opioid antagonists. Clonidine, an alpha-2 adrenergic agonist, can be used to treat sympathetic nervous system overactivity.

In a review article in 1998, Patrick G. O’Connor looked at twelve studies on RD and nine studies on URD. The twelve RD studies enrolled a total of 641 subjects: 478 received RD and 163 were controls. Most studies enrolled heroin users and were performed in inpatient settings—typically psychiatric facilities with specialized substance abuse services. Medication protocols and outcomes assessed varied in all studies. Only three studies provided long-term follow up data. The nine URD studies enrolled a total of 424 subjects, all treated as inpatients. The medications used included naloxone and naltrexone, but the doses varied. The methods of sedation or general anesthesia varied across studies. Five studies used general anesthesia with intubation and mechanical ventilation, and four used sedation without intubation. Only three studies included a control group. Most studies reported only short-term outcomes.

Detoxification represents only a first step in substance abuse treatment and relapse rates without follow-up are extremely high. In these 21 studies, only four provided follow-up beyond detoxification. Longer-term treatment outcomes are needed to provide a more complete assessment of the role of these protocols in the management of opioid dependence.

An additional limitation is the lack of control groups in most studies, so direct comparisons of the effectiveness of these new techniques to more traditional detoxification approaches, e.g., methadone taper, is not possible. One question is whether a more prolonged detoxification using alternative techniques such as a methadone taper or clonidine might allow more time for a therapeutic alliance with the clinician and treatment program as opposed to the rapidity and intensity of the newer RD and URD techniques, for a better long-term outcome.
Another question regarding URD concerns the risks and cost of general anesthesia. There are few data on the impact of opioid dependence and the comorbid problems commonly seen in this population (e.g., human immuno deficiency syndrome or cocaine use) on anesthesia risk. There may be respiratory or cardiovascular problems associated with general anesthesia. Heavy sedation without intubation also carries the potential risk of vomiting with aspiration and sedative overdose. The high cost of general anesthesia may contribute to the potentially high cost of URD and limit its use.

In a review article in 2000, L. Gowing reviewed 35 reports of studies involving the administration of opioid antagonists with concomitant sedation or anesthesia. They noted that there have been no published studies comparing anesthesia-assisted opioid withdrawal with other approaches to detoxification. The lack of controlled studies comparing anesthesia-assisted withdrawal with other approaches makes it difficult to determine the effectiveness of this method. They also noted that treatment regimens varied considerably in the opioid antagonist used, the dose and mode of administration, the anesthetic agent, duration of anesthesia, and adjunct medication used. This complexity and diversity of anesthesia based regimens as well as different approaches to the assessment and reporting of outcomes makes it difficult to compare studies. Most studies did not report follow-up information.

Adverse events varied greatly in the studies, and included diarrhea, vomiting, respiratory depression, brachycardia, fever, transient psychotic episode, venous thrombosis and catheter-related sepsis, hypokalemia, transient renal insufficiency, EKG abnormalities, and a few reports of deaths. Larger scale epidemiological studies are necessary to accurately estimate the risk of serious adverse events.

Another consideration is the high cost of the technique due to the requirement of a hospital setting with a high level of care. This high cost may be offset by a shorter duration of treatment or a higher proportion of patients achieving and maintaining abstinence post-detoxification. However, there is limited information on referral to ongoing treatment or relapse, so it is impossible to draw adequate comparisons.

In a study by Scherbaum of Germany, 22 patients underwent URD with general anesthesia. Many patients suffered intense withdrawal symptoms during the first seven days of treatment, which were significantly more than during baseline.

In 2000, the American Society of Addiction Medicine published a public policy statement regarding opiate detoxification under sedation or anesthesia. This policy statement includes the following:

Opioid antagonist agent detoxification under sedation or anesthesia (OADUSA) can be an appropriate withdrawal management intervention for selected patients, provided that such services are performed by adequately trained staff with access to appropriate emergency medical equipment.

Although there is medical literature describing various techniques of OADUSA, more research is needed to better define its role in opioid detoxification. Further studies of outcome are needed,
including both the safety and efficacy of OADUSA as compared to other opioid detoxification modalities, as well as any differential effects on the long-term rehabilitation of opioid addicts."

**March 2008 Update**
A randomized trial from a European center reported that the initial improvement in rate of opiate detoxification and abstinence (three month) with anesthesia was not maintained with longer-term follow-up; both groups (36 patients treated with anesthesia and 34 with classical clonidine detoxification) showed less than 5% abstinence after 12 months. In addition, a Cochrane review on heavy sedation or anesthesia for opioid withdrawal concluded that “Heavy sedation compared to light sedation does not confer additional benefits in terms of less severe withdrawal or increased rates of commencement on naltrexone maintenance treatment. Given that the adverse events are potentially life-threatening, the value of antagonist-induced withdrawal under heavy sedation or anesthesia is not supported. Anesthesia for rapid opiate detoxification is considered to be investigational.

**March 2010 Update**
A literature search did not identify any randomized controlled trials for this technique. This therapy is investigational for the treatment of opioid detoxification given the insufficient evidence to evaluate the impact on net health outcomes. The policy statement remains unchanged.

**December 2010 Update**
In 2010, an updated Cochrane review by Gowing et al on opioid antagonists under heavy sedation or anesthesia for opioid withdrawal was published. A total of nine studies including 1109 participants were eligible for inclusion; there were eight randomized controlled trials (RCTs) and one non-randomized controlled trial. Four studies compared the intervention to conventional approaches of withdrawal and five compared different regimes of antagonist-induced withdrawal. In five of the studies, all participants were withdrawing from heroin or other short-acting opioids, in three studies, they were using heroin and/or methadone and, in one 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 three 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 conventional treatment (relative risk [RR] = 4.28, 95% confidence interval [CI] =2.91 to 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 to 5.61). Safety data from these three studies were not pooled. One of the studies reported no adverse effects and one only reported adverse effects in patients who received octreotide during the anesthetic procedure; seven out of these 11 patients (64%) experienced vomiting and/or diarrhea. The third study reported three serious adverse events, all of which occurred in the anesthesia group. There were no pooled analyses of the results of studies evaluating the efficacy differing opioid antagonist withdrawal regimens. One meta-analysis of safety data from two 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 to 9.12). Other adverse events included high rates of vomiting in several studies and, in one 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.”

Collins et al reported on the results of a trial of 106 heroin addicts who were randomized to undergo detoxification with an anesthesia-assisted rapid opioid detoxification, buprenorphine-assisted rapid opioid detoxification, or clonidine-assisted opioid detoxification. All patients received an additional 12 weeks of outpatient naltrexone maintenance. Mean withdrawal severities were similar among the three groups, and treatment retention in the 12-week follow-up period was also similar. However, the anesthesia procedure was associated with three potentially significant life-threatening adverse events. The authors concluded that the data did not support the use of general anesthesia for heroin detoxification.

Favrat et al published a randomized controlled trial in 2006 from a European center. The trial reported that the initial improvement in rate of opiate detoxification and abstinence (three months) with anesthesia was not maintained with longer-term follow-up; both groups (36 patients treated with anesthesia and 34 with classical clonidine detoxification) showed less than 5% abstinence after 12 months.

Among the published randomized controlled trials are two that focused on treatment regimens that varied only in the level of sedation used and did not include a conventionally treated control group. For example, Seoane et al compared rapid intravenous detoxification treatment under either monitored light intravenous sedation or unmonitored deep intravenous sedation. In 2011, Nasr and colleagues in Egypt compared ultra-rapid detoxification under general anesthesia with and without dexmedetomidine. Thus, no conclusions can be drawn about the relative efficacy of rapid detoxification and standard methods.

2013 Update
Literature review through November 4, 2013 did not reveal any additional information. Policy statement remains unchanged.

Summary
Ultra-rapid detoxification is an opioid detoxification technique that uses relatively high doses of opioid antagonists under deep sedation or general anesthesia. The paucity of controlled trials and lack of a standardized approach to ultra-rapid detoxification does not permit scientific conclusions regarding the safety or efficacy of ultra-rapid detoxification compared to other approaches that do not involve deep sedation or general anesthesia. Moreover, there are concerns about adverse effects, including life-threatening or potentially life-threatening events. Thus, this technology remains investigational.

Practice Guidelines and Position Statements
In 2007, the National Institute for Health and Clinical Excellence issued clinical practice guideline on “drug misuse, opioid detoxification.” The guidelines include the following
statement regarding ultra-rapid detoxification. “Ultra-rapid detoxification under general anesthesia or heavy sedation (where the airway needs to be supported) must not be offered. This is because of the risk of serious adverse events, including death.” The guideline was reviewed in 2011 and it was determined to be up-to-date.

In 2007, the American Psychiatric Association Work Group on Substance Use disorders released a practice guideline for the treatment of patients with substance use disorders. The practice guideline includes the following recommendation “anesthesia-assisted rapid opioid detoxification (AROD) is not recommended because of lack of proven efficacy and adverse risk-benefit ratios.”

In 2005, the American Society of Addiction Medicine published a public policy statement regarding opiate detoxification under sedation or anesthesia (update of their 2000 statement). It included the following position statements:

“Opioid detoxification alone is not a treatment of opioid addiction. ASAM does not support the initiation of acute opioid detoxification interventions unless they are part of an integrated continuum of services that promote ongoing recovery from addiction.

Ultra-Rapid Opioid Detoxification (UROD) is a procedure with uncertain risks and benefits, and its use in clinical settings is not supportable until a clearly positive risk-benefit relationship can be demonstrated. Further research on UROD should be conducted.

Although there is medical literature describing various techniques of Rapid Opioid Detoxification (ROD), further research into the physiology and consequences of ROD should be supported so that patients may be directed to the most effective treatment methods and practices.”

**Key Words:**
Detoxification, opioids, opioid agonist and antagonist, naloxone, naltrexone, buprenorphine, clonidine, methadone, rapid opioid detoxification (RD), ultra-rapid opioid detoxification (URD), general anesthesia, opioid antagonist agent detoxification under sedation or anesthesia (OADUSA), one day detox

**Approved by Governing Bodies:**
Not applicable

**Benefit Application:**
Coverage is subject to member’s specific benefits. Group specific policy will supersede this policy when applicable.

ITS: Home Policy provisions apply

*Proprietary Information of Blue Cross and Blue Shield of Alabama*
Medical Policy #091
FEP contracts: Special benefit consideration may apply. Refer to member’s benefit plan. FEP does not consider investigational if FDA approved and will be reviewed for medical necessity.

**Coding:**

CPT codes: 01999  Unlisted anesthesia procedure

**References:**

15. Hensel, M., Kox, W.J. Safety, efficacy, and long-term results of a modified version of rapid opiate detoxification under general anesthesia: A prospective study in methadone, heroin,


**Policy History:**

Medical Policy Group, January 2003 (3)
Medical Policy Administration Committee, January 2003
Available for comment February 19-April 7, 2003
Medical Policy Group, March 2006 (3)
Medical Policy Administration Committee, March 2006
Available for comment March 14-April 27, 2006
Key Points updated, references updated March 2008 (1)
Medical Policy Group, March 2010 (1): Key points updated, references added
Medical Policy Group, January 2011 Key points updated, references added
Medical Policy Group, March 2012 (3): 2012 Literature review, References updated
Medical Policy Group, October 2013 (3): Removed ICD-9 Diagnosis codes; no change to policy statement.
Medical Policy Panel, December 2013
Medical Policy Group, January 2014 (3): 2013 Updates to Key Points and References; no change in policy statement.
This medical policy is not an authorization, certification, explanation of benefits, or a contract. Eligibility and benefits are determined on a case by case basis according to the terms of the member’s plan in effect as of the date services are rendered. All medical policies are based on (i) research of current medical literature and (ii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.

This policy is intended to be used for adjudication of claims (including pre-admission certification, pre-determinations, and pre-procedure review) in Blue Cross and Blue Shield’s administration of plan contracts.