



## Medical Policy Manual

**Topic:** Opioid Antagonists Under Heavy Sedation or General Anesthesia as a Technique of Opioid Detoxification    **Date of Origin:** August 1999

**Section:** Mental Health

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### IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

**PLEASE NOTE:** Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

### DESCRIPTION

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.

### Background

The traditional treatment of opioid addiction involves substituting the opioid (i.e., heroin) with an equivalent dose of a longer acting opioid antagonist, i.e., 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 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 people on methadone maintenance. Detoxification is associated with acute symptoms followed by a longer period of protracted symptoms (i.e., six 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 an opioid antagonist (i.e., naloxone) 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 is associated with patient discomfort, such that many may be unwilling to attempt detoxification. Additionally, detoxification is only the first stage of treatment. Without ongoing medication and psychosocial support after detoxification, there is a low probability that any detoxification procedure alone will result in lasting abstinence. Opioid antagonists, such as naltrexone, may also be used as maintenance therapy to reduce 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 nalmefene under deep sedation with benzodiazepine or general anesthesia. This strategy has been referred to as "rapid", "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 to 48 hours. Since the patient is under anesthesia, there is no patient discomfort or memory of the symptoms of acute withdrawal, although protracted symptoms of withdrawal may still be present post anesthesia. 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 Centers, and Center for Research and Treatment of Addiction (CITA) are examples. These programs typically consist of three 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, demerol, dilaudid, fentanyl, oxycodone, hydrocodone, or butorphanol. Once acute detoxification is complete, the opioid antagonist naltrexone is often continued to decrease drug craving, thus hopefully reducing the incidence of relapse.

## MEDICAL POLICY CRITERIA

Opioid antagonists under heavy sedation or general anesthesia (i.e., ultra-rapid detoxification) are considered **investigational** as a technique for opioid detoxification.

## SCIENTIFIC EVIDENCE<sup>[1,2]</sup>

### Background

Evaluation of the safety and effectiveness of ultra-rapid treatment of opioid withdrawal using sedation or general anesthesia involves consideration of a variety of outcomes. For example, one might consider the numbers of patients enrolling in detoxification programs. Many opioid addicts may be fearful of prolonged detoxification programs and thus may only seek treatment in an accelerated detoxification program. Advocates of ultra-rapid detoxification point out that an increasing enrollment in detoxification programs is and of itself an important outcome.<sup>[3,4]</sup> In addition, proponents suggest that the procedure is a rapid and painless method of detoxification. Therefore, an important outcome is the comparison of the duration and severity of withdrawal symptoms associated with ultra-rapid detoxification and other detoxification strategies.

The completion rate of a detoxification program is another possible outcome. As noted by Scherbaum, up to 30% of patients may drop out of traditional inpatient detoxification programs.<sup>[5]</sup> Using sedation or anesthesia, one is assured of 100% completion of detoxification. However, as is commonly pointed out, detoxification is only the first step in treating opiate addiction, and ultra-rapid detoxification programs may offer different types of long-term follow-up care, based on ongoing psychosocial support with or without additional medication, such as naltrexone. Therefore, the rate of abstinence during both the short-term six-month period of protracted withdrawal symptoms and longer-term abstinence are also important outcomes. For example, traditional methods of withdrawal (i.e., tapering doses of methadone or buprenorphine) require the patient to be in a therapeutic environment for a prolonged period of time, potentially reducing the risk of long-term relapse.

In addition, the success of any detoxification program must be evaluated according to the patient populations treated. For example, patients addicted to heroin may respond differently than those addicted to oxycodone, and response may vary according to duration of addiction or prior attempts at traditional detoxification. Also, ultra-fast detoxification may be offered to patients on methadone maintenance, in a final effort to render these patients drug free. These patients may have been in a therapeutic environment for a prolonged period of time, and may have more stable personal lives than those attempting initial detoxification from heroin use. However, symptoms associated with methadone withdrawal are thought to be more severe than those associated with heroin or codeine withdrawal. The major safety considerations regarding ultra-rapid detoxification are the risks associated with general anesthesia in combination with opioid antagonists. While patients are generally intubated and ventilated, eliminating the risk of choking, intravenous naloxone has been associated with cardiovascular complications such as cardiac arrest and pulmonary edema. These potential safety issues are particularly important, since opioid withdrawal itself is not associated with life-threatening complications. In contrast, advocates of ultra-rapid detoxification point out that detoxification is a painful procedure, and that the risk of anesthesia has generally been considered acceptable when used to relieve pain.<sup>[6]</sup>

### Literature Appraisal

Given the above considerations, assessment of ultra-rapid opioid detoxification will focus 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.

## Cochrane Reviews

Regarding severity and duration of withdrawal symptoms, a review conducted by Gowing and colleagues for the Cochrane Library suggests that most patients did experience moderate withdrawal symptoms lasting a few days post anesthesia or sedation, including nausea, vomiting, diarrhea and sleep disturbances.<sup>[7]</sup> In addition, withdrawal severity may also be related to the anesthetic used. However, without a controlled trial, no conclusion can be made regarding the duration or severity of withdrawal symptoms compared to other techniques of detoxification.

This Cochrane review was updated in 2006<sup>[8]</sup> and 2010<sup>[9]</sup> by the same authors who 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 anaesthesia is not supported.” This conclusion was based on eight randomized controlled trials and one nonrandomized controlled trial. Few pooled analyses could be conducted due to differences in study designs (e.g., antagonist and anesthesia or sedation regimens, comparison interventions, outcome variables, etc.) such as:

- Four studies compared the intervention to conventional approaches of withdrawal
- Five studies compared different regimes of antagonist-induced withdrawal
- Five of the studies involved participants withdrawing from heroin or other short-acting opioids
- Three of the studies involved participants using heroin and/or methadone
- One of the studies involved participants withdrawing from methadone

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 in the conventional treatment group (relative risk [RR]: 4.28, 95% confidence interval [CI]: 2.91-6.30). Overall, 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).

Most of the studies did not report short or long term follow-up of abstinence, and those studies that did include follow up reported conflicting results. For example, Seoane and colleagues reported that 279 of the 300 patients treated were abstinent after one month,<sup>[10]</sup> while in Cucchia's study of 20 patients, 16 reported some resumption of heroin in the six months following detoxification, with 60% considered to have relapsed.<sup>[11]</sup> Albanese assessed relapse at six months in 120 patients. Relapse data were available for 111 patients; 55% were relapse free.<sup>[12]</sup> Again, without controlled studies in similar populations of patients, no conclusions can be drawn about the relative long-term efficacy of ultra-rapid detoxification compared with other treatment strategies.

A variety of adverse events have been reported in small numbers of patients, including vomiting while under anesthesia or sedation, various cardiac rhythm disturbances, pulmonary dysfunction, and renal insufficiency.<sup>[7,9]</sup> 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. One study reported adverse effects in patients who received octreotide during the anesthetic procedure; 7 out of the 11 patients (64%) experienced vomiting and/or diarrhea. The third study reported 3 serious adverse events, all of which occurred in the anesthesia group. Several deaths occurring either during anesthesia or immediately afterward have been reported.<sup>[13-16]</sup> Also, deaths subsequent to ultra-rapid detoxification have been

reported.<sup>[17]</sup> Of particular concern is the fact that the use of opioid antagonists results in loss of tolerance to opioids, rendering the patients susceptible to overdose if the patient returns to his/her pre-detoxification dosage of illicit drugs.<sup>[18]</sup>

### Randomized Controlled Trials (RCTs)

Three RCTs focused on treatment regimens that varied only in the level of sedation used.<sup>[10,19,20]</sup> Interpretation is limited due to the lack of a conventionally treated control group for comparison. For example, De Jong and colleagues randomized 272 opioid-dependent patients attending methadone clinics to rapid detoxification without anesthesia (RD) or rapid detoxification with general anesthesia (RD-GA). All patients were treated for seven days at an addiction treatment center. The patients randomized to RD-GA received four hours of general anesthesia and the opioid antagonist. They were monitored another four hours and discharged back to the treatment center. Opioid abstinence was monitored in both groups with urinalysis and the intensity of the signs and symptoms of withdrawal during and after treatment was assessed in both groups using subjective and objective measures. One month following rapid detoxification 62.8% of the RD-GA patients and 60.0% of the RD group were abstinent from opioids ( $p=0.71$ ). No adverse events or complications occurred during RD; however, in the RD-GA group five serious adverse events occurred, necessitating hospital admission. According to subjective reports the RD-GA group experienced more craving and withdrawal distress. However, the differences were not significant at one week. The authors also conducted a cost analysis and found that the cost of treatment with general anesthesia was much higher than RD without anesthesia. Because both treatments showed an equivalent efficacy in this study, the authors concluded that rapid detoxification without general anesthesia is the most cost-effective treatment.

Collins and colleagues randomized heroin-addicted patients to one of three study arms: rapid detoxification with general anesthesia, buprenorphine followed by naltrexone induction beginning on day two, or clonidine plus a variety of supportive medications for one week followed by naltrexone induction beginning day seven.<sup>[21]</sup> Following discharge all patients were treated with naltrexone for 12-weeks and relapse-prevention psychotherapy. Mean withdrawal severities and treatment retention at 12-weeks did not differ significantly across the three groups (20% RD-GA group, 24% buprenorphine group and 9% in the clonidine group). By week three more than 50% of patients had dropped out of each treatment arm. Three patients in the RD-GA group experienced significant life-threatening events immediately following general anesthesia which included pulmonary edema and aspiration pneumonia in one patient, diabetic ketoacidosis in another, and mixed bipolar episode with suicidal ideation that required hospitalization at five days in one patient. During the outpatient phase, no group differences occurred in number of urine samples positive for opiates. The authors conclude that general anesthesia for rapid detoxification for rapid antagonist induction does not currently have a meaningful role to play in the treatment of opioid dependence.

A randomized trial from a European center reported that the initial improvement in rate of opiate detoxification and abstinence with anesthesia was not maintained with longer-term follow-up.<sup>[22]</sup> Both cohorts (36 patients treated with anesthesia and 34 with classical clonidine detoxification) showed less than 5% abstinence after 12 months.

In 2011, Nasr et al. compared ultra-rapid detoxification under general anesthesia with and without dexmedetomidine.<sup>[23]</sup> Sixty male patients who were addicted to opioids were assigned to either the first group of patients who were treated with dexmedetomidine during anesthesia and for 6 days after recovery from anesthesia; or assigned to the control group who were treated after recovery from anesthesia with oral dose of lefoxidine 0.2 mg three times daily. Authors concluded from their results

that dexmedetomidine decreased withdrawal symptoms when used during ultra-rapid opiate detoxification under general anesthesia, and the patients reported being more satisfied. There were no long-term outcomes reported in this study.

## **Clinical Practice Guidelines**

No clinical practice guidelines or position statements were found that recommend use of rapid or ultra-rapid opiate detoxification.

### American Psychiatric Association (APA)<sup>[24]</sup>

The 2007 practice guideline from the APA Work Group on Substance Use includes the following recommendation: “Anesthesia-assisted rapid opioid detoxification (AROD) is not recommended because of lack of proven efficacy and adverse risk-benefit ratios.”

### Substance Abuse and Mental Health Services Administration (SAMHSA)<sup>[25]</sup>

- The 2006 Treatment Improvement Protocol (TIP) Series 45 concluded that, “Although the ultrarapid procedure under anesthesia has received wide publicity, controlled studies that would make it possible to evaluate the risk/benefit ratio are absent. The procedure is still unproven and controversial.”

### American Society of Addiction Medicine (ASAM)<sup>[26]</sup>

In 2005, the ASAM revised their 2000 public policy statement regarding opiate detoxification under sedation or anesthesia<sup>[18]</sup> which considered this treatment appropriate for selected patients. The updated statement calls for further research for both rapid and ultra-rapid opioid detoxification with the following 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 is needed into the physiology and consequences of ROD should be supported so that patients may be directed to the most effective treatment methods and practices.

## **Summary**

The small number of controlled trials, the consistent recommendations against these techniques in clinical practice guidelines, and the lack of a standardized approach to rapid and ultra-rapid detoxification do not permit scientific conclusions regarding the safety or efficacy 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. Therefore, rapid or ultra-rapid detoxification as an opioid detoxification technique is considered investigational.

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## CROSS REFERENCES

None

CODES	NUMBER	DESCRIPTION
CPT	01999	Unlisted anesthesia procedures(s)
	90899	Unlisted psychiatric service or procedure
HCPCS	None	