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Treatment of Heroin (Diamorphine) Addiction

Current Approaches and Future Prospects

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Abstract

New pharmacological treatments for heroin (diamorphine) addiction include drugs that reduce opiate withdrawal symptoms and agents that are given during the maintenance phase of treatment. A variety of different types of pharmacological agents (opioid agonists, partial opioid agonists, opioid antagonists and α_2-adrenoreceptor agonists) are reviewed and the evidence of their use during managed withdrawal and maintenance are presented.

Experimental approaches attempting to reduce the time of opiate withdrawal and to accelerate the transition to abstinence are being developed. The combination tablet of buprenorphine and naloxone that is to be introduced for office-based maintenance is currently undergoing intense evaluation in the US. This new approach may facilitate the expansion of treatment while reducing the potential for medication diversion and intravenous use.

The use of heroin continues to increase and is estimated that eight million people in the world (0.14%) abuse opiates. The regions with the highest annual prevalence (2%) are South East and South West Asia,[1] and based on the National Household Survey,[2] the annual prevalence of heroin use in the US is 0.3% with a rising trend of heroin use in the last 2 years.[3]

Comprehensive treatments for heroin dependence include environmental changes, psychosocial interventions and pharmacotherapy. Recent advances in pharmacotherapy are aimed at reducing problems associated with persistent heroin use and expanding the accessibility of long-term treatment. For example, the introduction of the combination tablet of buprenorphine and naloxone into drug abuse treatment in an office-based setting should expand available treatment slots and facilitate general medical care of individuals who are addicted.[4,5] This review focuses on the rationale, indications and limitations of medications that either facilitate the reduction of withdrawal symptoms during detoxification or improve the overall psychosocial stabilisation during maintenance, and briefly discusses potential future directions for opiate dependence treatments.

1. Opiate Receptor Agonists

1.1 Methadone

Methadone is a synthetic, potent opiate μ-receptor agonist that is not related to morphine. The slow onset and long duration of action of methadone results in a blunted euphoric effect. Methadone is well absorbed when taken orally and 80% is bound to blood proteins. It has a long elimination half-life of 24 to 36 hours.[6] Methadone is currently used for managed withdrawal and for opiate agonist maintenance in the treatment of heroin dependence.

1.1.1 Managed Withdrawal

One treatment strategy employs the general principle of initially stabilising the patient who is dependent on a short-acting opiate, such as heroin, on methadone and then slowly decreasing the methadone dose over several days or even months. Induction onto methadone may start with 20mg as the physical signs of abstinence begin to appear. However, larger methadone doses (40mg over the first 24 hours) have been required in starting patients who use heroin of greater purity or healthcare professionals who have more severe opiate dependence.

Once a stabilising dose has been reached, methadone is tapered by 20% per day for inpatients on a schedule that may last 2 weeks. Alternatively, the dose may be slowly tapered to a gradual cessation lasting as long as 6 months.[7] Senay and colleagues[8] studied the effects of moderate (reductions of 10% of initial dose per week) and slow (3% per week) outpatient cessation under double-blind conditions, and found that the 10% weekly decrements were associated with higher drop-out rates, increased illicit opioid use and elevated levels of subjective distress; thus, they recommended the slow dose-tapering rate. On such a slow regimen, successful detoxification is still only achieved by 40% of outpatients when success is measured by completion of detoxification and a withdrawal-free naloxone challenge test, although more rapid inpatient tapering (e.g. 10 days) can have an 80% success rate.[7]

1.1.2 Methadone Maintenance

Methadone maintenance is currently the gold standard for pharmacotherapy of heroin dependence and is based on the principle of substituting a long acting opiate for a short acting opiate. This substitution reduces the fluctuations of opiate receptor stimulation, decreases withdrawal symptoms and thereby decreases the probability of relapsing. The administration of methadone also increases the tolerance to opioid effects through cross-tolerance and, therefore, reduces the euphoric and reinforcing effects of further heroin consumption.

Methadone maintenance programmes continue to be the most effective treatment for opiate dependence, in spite of public controversies about their usefulness.[9,10] These programmes have been associated with decreases in intravenous drug use

and a decline in HIV infection.[11] They also improve social functioning through increased employment and decreased criminal activity.[12] Several studies[13-16] have shown decreased mortality correlated with prolonged participation in methadone maintenance programmes. On the basis of the 12-fold reduction of death risk described in the Gronbladh study,[14] Barnett[17] showed an increment of 14 770 additional years of life for those patients who participated in prolonged treatment compared with those who did not connect with treatment.

Pharmacological factors associated with better treatment outcomes include maintaining the patient on an optimal daily dose and having a slow reduction regimen for well-stabilised patients who decide to become abstinent from methadone therapy. The optimal dose starts with induction onto methadone at 20 to 30mg with increments of 5 to 10mg every other day as clinically tolerated. Whereas most patients will require a maintenance methadone dosage of between 60 and 100 mg/day to become stable and be free of withdrawal and craving symptoms, others may need to receive dosages of over 100 mg/day, in particular patients receiving protease inhibitors for infection with HIV.[18,19]

Once the optimal dosage has been achieved and the patient has improved in most psychosocial areas of functioning, current treatment recommendations are to encourage long-term maintenance on methadone. This recommendation is based on the high rate of relapse associated with discontinuation from methadone maintenance, and the increased risk of various infections and even death linked to intravenous heroin use. The length of time necessary before a patient can be safely transitioned to complete abstinence is still a matter of controversy.[14]

Some of the limitations that have been identified in methadone maintenance programmes are the need for daily attendance by clients, the need for intense involvement by clinicians early in treatment and the limited availability of treatment slots in accessible programmes. Later in treatment an excessive amount of resources are mandated by law to maintain long- term stable patients who only need methadone dispensed and do not need ancillary services. The strategy of authorising take-home methadone doses to patients as a way to reduce excessive resource utilisation has not been fully successful because of methadone diversion to the black market and fatalities as a result of accidental ingestion by minors. Methadone maintenance in physician's offices or 'medical maintenance' is another alternative that has the potential to expand methadone maintenance services for those individuals who are psychosocially stable.[20-22]

Finally, the creation of a new regulatory system based on an accreditation model (e.g. Commission on Acreditation of Rehabilitation Facilities [CARF]) and a shift of the administrative responsibility and oversight from the US Food and Drug Administration (FDA) to the Substance Abuse and Mental Health Services Administration (SAMHSA)[23] may also allow expansion of methadone maintenance treatment services across the US as a result of less restrictive regulations and more emphasis on indicators of treatment outcomes.[24]

1.2 Levacetylmethadol (LAAM)

Levacetylmethadol (L-α-acetylmethadol; LAAM) is a derivative of methadone with a longer elimination half-life and slower onset of action, which provides the advantage of suppressing opiate withdrawal symptoms for more than 72 hours. The long duration of action is probably related to the presence of two active metabolites, L-α-noracetylmethadol (norlevacetylmethadol) and L-α-dinor-acetylmethadol (dinor-levacetylmethadol). LAAM is available in parental and oral forms; this latter preparation is currently approved for opiate maintenance. However, the FDA has concerns about the association of symptomatic arrhythmia with prolongation of the QT interval in patients maintained on LAAM. Thus, the use of LAAM is contraindicated in patients with known or suspected QT prolongation, and should not be used as the first option for opiate substitution, but rather limited to patients who

have failed maintenance with methadone.[25] These potential cardiovascular complications from the use of LAAM also resulted in its being withdrawn from the European market.

1.2.1 LAAM Maintenance

The pharmacological characteristics of LAAM allow this oral solution to be administered on a less than daily schedule, usually on a Monday-Wednesday-Friday schedule. The build-up phase usually starts at 20mg with increments every other day as clinically tolerated by the patient for the following 4 to 6 weeks.

Treatment retention with LAAM has been considered a problem that is thought to be related to the prolonged time that is required for LAAM to achieve a steady state blood concentration, as the patient is stabilised onto an effective maintenance dose. However, Judson et al.[26] showed that 51% of those who participated in a rapid induction schedule (20, 30, 40, 40 and 50mg) remained in treatment compared with only 23% of those who received a slower induction schedule (20, 20, 30, 30, 40, 40, 50, 50, 60, 60, 70, 70 and 75mg). Similarly, in a randomised, double-blind trial, Ling et al.[27] showed that medium (50, 50 and 70mg) and high (100, 100 and 140mg) induction doses were well tolerated by most patients with no differences between groups in retention (overall retention was 83%). Both studies suggest that a 1-week rapid induction on to medium to high doses may be tolerable to most patients and perhaps improve treatment retention. Furthermore, Jones et al.[28] demonstrated that an induction regimen which achieved three different target maintenance doses (low, medium and high) were all well tolerated and had 80% retention, but noticed that the high dose induction (100mg) was associated with more dropouts and agonist side effects. Thus, a medium dose induction schedule using LAAM 30, 40 and 50mg on the second, third and fourth active dose administration days was the best tolerated, whereas the high-dose induction using LAAM 30mg on the second active dose administration day followed by dose increases of 10mg every other day may have benefited from clinical assessments before continuing to increase the dose to the 100 mg/day target. Finally, a 2-week stabilising induction onto methadone can be used before starting LAAM followed by direct transition to LAAM using a 1.2 to 1.3 conversion ratio.

In terms of a dosage for LAAM maintenance, Eissenberg et al.[29] showed that while there were no significant differences in retention among the different dosages, 34% of those assigned to high-dose (100, 100, 140mg) LAAM were able to achieve 4 consecutive weeks of opiate free urine tests, compared with 14% assigned to medium (50, 50, 70mg) or 11% assigned to the low (20, 20, 30mg) doses.

Potential advantages of LAAM over methadone are its slower onset of action and the fact that it can be dispensed three times weekly rather than daily as needed for methadone. However, this characteristic may also increase the risk of the patient for overdose, especially during the induction phase. During induction, patients may use other opiates in conjunction with LAAM and this may facilitate an overdose. In one study,[30] two documented deaths occurring during the induction phase of treatment were associated with the use of non-prescription opiates.

LAAM produces a characteristic opiate withdrawal syndrome. However, in a double-blind comparison study, Judson et al.[31] showed that there were no retention differences between patients receiving abrupt and or gradual discontinuation from LAAM.

2. Partial Opiate Receptor Agonists

2.1 Buprenorphine

Buprenorphine is a high affinity, partial opioid μ-receptor agonist which has been used as opioid substitution therapy for opiate dependence in France since 1996.[32] It is awaiting approval in the US as a sublingual combination tablet with naloxone.[33] Buprenorphine and its metabolite norbuprenorphine achieve steady state concentration in approximately 8 to 10 days.[34] As a partial μ-receptor agonist, buprenorphine has a ceiling to its

pharmacological effects, minimising complications of overdose such as full respiratory depression. Higher dosages of buprenorphine appear to increase the duration of its effects, which is probably related to plasma concentrations of buprenorphine, and the high affinity and slow dissociation of buprenorphine from the μ-receptor.[35] Because of its long duration of action, buprenorphine can be effectively administered in alternate day dose administration and as infrequently as three times per week.[36,37] In addition, the combination form of buprenorphine in doses containing up to 6mg of sublingual naloxone with 24mg of buprenorphine can be delivered without adverse reactions.[36,38] The ceiling effect of buprenorphine on agonist activity decreases the danger of overdose, may limit its abuse liability[39,40] and results in low toxicity even at high intravenous doses.[41,42]

2.1.1 Managed Withdrawal

The pharmacological profile of buprenorphine makes it suitable for managing different durations of opiate withdrawal treatment. Gowing et al.[43] reviewed controlled studies in which the short-term use of buprenorphine was compared to other treatments in the management of opiate withdrawal, and found five studies that showed the superiority of buprenorphine to other pharmacotherapies for opiate detoxification[44-48] using randomised or quasi-randomised prospective designs. Ongoing detoxification studies through the US National Institute on Drug Abuse (NIDA) Clinical Trials Network are evaluating the combination tablet for managed withdrawal in different settings (in-patient or outpatients) and using different lengths of time for detoxification from opiate dependence, and should provide added guidance for the use of buprenorphine in the future.

Patients with heroin dependence who are candidates for transitioning onto buprenorphine should have had their last dose of heroin use 6 hours before starting the induction and show objective signs of opiate withdrawal. An induction onto buprenorphine[36,38,49] using the combination tablet can start with buprenorphine/naloxone 4mg/1mg twice a day for the first day, 8mg/2mg on the second day and then increase to 16mg/4mg or 24mg/6mg over successive days as clinically indicated.

Some controlled studies have shown that buprenorphine may be superior to clonidine alone in reducing opiate withdrawal symptoms. For instance, O'Conner et al.[48] used a randomised, double-blind design in a primary care setting to compare three detoxification protocols (clonidine alone, clonidine and naltrexone, and buprenorphine) in 162 heroin-dependent patients. They showed that 81% of both the buprenorphine and the clonidine plus naltrexone groups were successfully detoxified compared with 65% of the clonidine alone group. A second study[45] compared buprenorphine to clonidine in 44 opiate-dependent patients and showed that buprenorphine was more effective than clonidine in reducing opiate withdrawal symptoms. Janiri et al.[46] also compared the efficacy of buprenorphine to clonidine and to lefetamine in reducing opiate withdrawal symptoms among 39 patients who were being detoxified from methadone 10mg, and showed that buprenorphine had a greater reduction of withdrawal symptoms than both clonidine and lefetamine on day 5 of the 8-day detoxification protocol ($p < 0.05$). However, one controlled study[47] did not show a significant difference between buprenorphine and clonidine in 25 patients during a rapid inpatient detoxification.

Although these studies have compared buprenorphine with clonidine or clonidine plus naltrexone, Umbricht et al.,[44] in a randomised placebo-controlled design, evaluated buprenorphine taper alone to buprenorphine taper followed by naltrexone in a rapid detoxification. They showed that by adding naltrexone on day 2 of the buprenorphine taper, the withdrawal symptoms would subside after day 5, relative to the buprenorphine taper alone, where the withdrawal symptoms increased over these 5 days. This more rapid symptom resolution suggests that naltrexone in combination with buprenorphine may be useful

in reducing withdrawal symptoms and shortening the length of detoxification.

In conclusion, the use of buprenorphine in managed withdrawal appears to be promising, but data on the clinical effectiveness for longer duration detoxifications (e.g. beyond 2 weeks) are still limited.[50,51]

2.1.2 Buprenorphine Maintenance

Patients inducted on to buprenorphine will usually be stabilised with dosages of less than 32 mg/day sublingually. In a multicentre, randomised clinical trial, Ling et al.[52] showed that patients maintained on buprenorphine 8 or 16 mg/day during a 16-week trial were more likely than patients maintained on buprenorphine 1 mg/day to remain in treatment, increase the percentage of opiate-free urine tests and report reduced opiate craving. Other studies evaluating buprenorphine as a maintenance agent using daily doses from 1.5 to 16mg[53-55] have shown that these doses are as efficacious as methadone for treatment retention and suppressing withdrawal symptoms. However, Kosten and colleagues[56] compared daily sublingual doses of buprenorphine at 2 and 6mg with methadone at 35 and 65mg and found that the groups receiving these low doses of buprenorphine were more likely to drop out of treatment, have fewer opioid-free urine tests and less self-reported heroin use than the group receiving methadone. In a comparison between different opiate substitution agents (methadone, LAAM and buprenorphine) with methadone 20mg, Johnson and colleagues[57] showed that high-dose methadone (60 to 100 mg), LAAM (75 to 115mg) and buprenorphine (16 to 32 mg) were all effective and superior to low-dose methadone.

Buprenorphine, in a high dosage (8mg tablets) for sublingual administration, has been available in France since 1996 for ambulatory prescription by all physicians for maintenance of opiate-dependent patients. This policy included office-based general practitioners who may be as effective as addiction specialists in prescribing buprenorphine and helping opiate-dependent patients improve their social and medical status.[58,59] Furthermore, Thirion and colleagues,[60] using data from an annual French survey, showed an important decline of heroin use from 74 to 25% during 1995 to 1997. This decline perhaps was associated with the availability of buprenorphine since 1996 and with the freedom of its prescription which allowed an expansion of its use in 1 year (36 to 49%). However, 12% of clients who reported only taking buprenorphine admitted to using intravenous drugs compared with 4% of those receiving methadone. Similarly, in a cross sectional study in South-Eastern France, Obadia et al.[32] surveyed 343 intravenous poly-drug users and showed that 57% (n = 198) had used buprenorphine intravenously at least once during the previous 6 months, and that among those patients who were receiving buprenorphine maintenance (n = 112), 70.5% had used buprenorphine intravenously during the previous 6 months. Finally, at least two studies [61,62] in France have reported deaths associated with intravenous injection of crushed tablets and concomitant use of psychotropics, mostly benzodiazepines and antipsychotics.

In order to minimise the risk of diversion and intravenous use of buprenorphine, a combination tablet containing buprenorphine and naloxone (4 : 1) has been developed that allows good sublingual absorption of buprenorphine, but a full opiate antagonist effect of naloxone if the tablet is dissolved in water and injected.[63] Thus, maintenance with the buprenorphine/naloxone tablet would retain the advantage of facilitating expanding access to opiate substitution while hopefully reducing the potential for misuse.

3. α_2-Agonists

3.1 Clonidine and Lofexidine

Clonidine and lofexidine are α_2-adrenergic receptor agonists and are the most commonly used non-opiate drugs for detoxification from opiates in the US and the UK, respectively. Activation of the presynaptic α_2-receptors results in the inhibition of the sympathetic outflow associated with the opiate withdrawal syndrome. Whereas a significant limitation of clonidine is that it may induce hypoten-

sion, several studies have shown that lofexidine in the dose range of between 0.2 and 3.2mg is without significant hypotensive effects and yet effectively reduces opiate withdrawal symptoms.[64-67]

3.1.1 Managed Withdrawal

Gold et al.[68] reported amelioration of opioid withdrawal symptoms by use of clonidine and postulated that both morphine and clonidine blocked activation of the locus ceruleus, a major noradrenergic nucleus which shows increased activity during opioid withdrawal. Whereas opioids exert their effect through opiate receptors, clonidine activates α_2-adrenergic receptors. Consequently, clonidine does not produce the opioid-associated physical dependence or have the same abuse potential.

In a subsequent study, clonidine was reported to 'reduce or eliminate most of the commonly reported withdrawal symptoms,' including lacrimation, rhinorrhoea, restlessness, muscle pain, joint pain and gastrointestinal symptoms. However, symptoms such as lethargy and insomnia persisted.[69] Sedation and dizziness secondary to orthostatic hypotension were reported as the most significant adverse effects of clonidine.

This early protocol involved administration of clonidine 0.1mg every 4 to 6 hours as needed for withdrawal discomfort on the first day, followed by an increase in clonidine of 0.1 or 0.2 mg/day, to a maximum of 1.2 mg/day, according to the blood pressure of each patient and withdrawal symptoms. The average maximum dosage used in the study was 0.8 mg/day. Toward the end of the detoxification period (days 5 to 7 in heroin detoxification) the clonidine dose was tapered by 0.1 to 0.2 mg/day to avoid rebound hypertension, headaches and the re-emergence of withdrawal symptoms. Success was defined as becoming opiate-free in 10 days and undergoing a naloxone administration without precipitating opioid withdrawal. In this study,[69] 80% of methadone-maintained patients (taking 5 to 40 mg/day) but only 36% of heroin-dependent patients were successfully detoxified. Charney et al.[70] confirmed the 80% completion rate for clonidine-assisted methadone detoxification, but found that withdrawal symptoms of anxiety, restlessness, insomnia and muscle aches were the most resistant to clonidine treatment. In another outpatient study comparing a slow methadone taper (at 1mg decrements starting from a 20 mg/day methadone dosage) to clonidine detoxification over 10 to 13 days, Kleber et al.[71] demonstrated equal effectiveness and 40% successful completion of detoxification. In a 6-month follow-up, about one third of each group had maintained abstinence. However, the authors noted that clonidine offered some advantages for outpatient detoxification, in that it poses minimal risk of diversion to illicit use, it is not a controlled substance and, therefore, is more widely available to general physicians, and it shortens the detoxification period from 20 days (for the methadone taper) to 10 to 13 days.

Some reports indicate clonidine does not induce euphoria,[68] while other reports indicate reinforcing properties associated with this drug in animals.[72] The reinforcing properties are relatively weak[73] and are not morphine-like in animals. Although there have been case reports of street abuse of clonidine,[74] this has not become a widespread problem.

Recently lofexidine, an analogue of clonidine which is also an agonist at the α_2-noradrenergic receptor, has shown promise as a detoxification agent and has mainly been used for opiate detoxification in some countries in Europe. In general, lofexidine is reported to be equally effective as clonidine,[66,75,76] but to be more economical and have fewer adverse effects. For instance, an Italian study [77] compared lofexidine to clonidine in a 3-day detoxification regimen, and showed that lofexidine significantly lowered the levels of withdrawal symptoms, and recipients had fewer mood problems and less sedation and hypotension. This drug is not available in the US but is currently being evaluated in clinical trials as an opiate detoxification agent.

4. Opiate Receptor Antagonists

4.1 Naltrexone

Naltrexone is an oral, long-acting competitive antagonist at the opiate μ-receptor. A daily dose of naltrexone 50mg will block the pharmacologic effects of intravenous heroin 25mg for as long as 24 hours. Doubling the dose of naltrexone provides blockade for 48 hours and tripling the dose provides blockade for up to 72 hours. Naltrexone can either displace opiate agonists from binding at these receptors or prevent opiate binding. Naltrexone is employed to accelerate opiate detoxification by displacing opiate agonists and as a maintenance agent for detoxified formerly opiate-dependent patients who want to remain opioid-free. The major problem of naltrexone maintenance therapy is poor compliance compared with methadone, which has agonist effects to enhance its compliance. Further studies examining other formulations (e.g. biweekly injectable depot naltrexone) may lead to new naltrexone dose administration strategies that can surmount this compliance barrier.

4.1.1 Managed Withdrawal

Rapid Opiate Detoxification (ROD)

Although clonidine alone reduces some of the symptoms of opiate withdrawal, it does not alter the time course of the withdrawal.[78] The addition of the opioid antagonist naltrexone to the treatment of opiate withdrawal with an adrenergic agonist may shorten the duration of withdrawal without increasing patient discomfort.[79] Some controlled studies have compared naltrexone plus clonidine to clonidine alone or to methadone tapering, and found that the former approach was well tolerated and reduced the withdrawal period while improving retention.[48,80-82] Another study also showed that naltrexone combined with buprenorphine was a well tolerated intervention which shortened opioid detoxification.[44] Finally, an Italian study showed equal efficacy for clonidine compared with lofexidine when combined with naloxone and naltrexone for a 3-day rapid detoxification.[77] However, lofexidine had fewer adverse effects, thereby making it more suitable for outpatient settings. This study also allowed oxazepam, baclofen and ketoprofen to be added during the detoxification, which complicates the interpretation.

Induction onto naltrexone may start with naltrexone 12.5mg on the first day, 25mg on the second day and 50mg on the third day.[48,80] The dose of clonidine typically is individually determined each day and is based on the severity of the withdrawal symptoms. For instance, clonidine 0.1 to 0.2mg every 4 hours has been given as needed to control withdrawal symptoms.

Vining et al.[83] compared two rapid outpatient opioid detoxifications using clonidine plus naltrexone, and found that the combined clonidine plus naltrexone group had a completion rate of 75% compared with 40% for methadone or clonidine alone. Diazepam 10mg twice a day on days 1 and 2 was found to be very effective for persistent restlessness and muscle aches. Similarly, in a randomised, double-blind clinical trial, O'Connor et al.[48] showed that 81% of the group receiving the combination of naltrexone plus clonidine were detoxified successfully in comparison with 65% of the participants who received clonidine alone. These findings suggest that naltrexone is an effective and well tolerated addition to clonidine in the management of opiate withdrawal. Thus, the use of opiate antagonists during the detoxification phase of treatment not only may reduce the length of the detoxification intervention safely and comfortably, but also may facilitate the acceptance and compliance with these antagonists during the maintenance phase.

Ultra-Rapid Opiate Detoxification (UROD)

A recent controversial development, which has grown from the clonidine plus naltrexone combination, is ultra-rapid inpatient detoxification (UROD) from opiates using sedatives and anaesthetics in combination with opiate antagonists. Ultra-rapid detoxification was first described in a study of 12 opioid-dependent patients who were given naloxone while under general anaesthesia.[84] Loimer and associates[85] also reported a

protocol involving barbiturate anaesthesia with methohexital (methohexitone; 100mg intravenously pre-treatment, then 400mg intravenously) plus naltrexone (10mg intravenously). This protocol successfully detoxified patients from opiates in 48 hours but required intensive medical treatment (intubation, artificial ventilation). Because of the risks of anaesthesia, the utility of UROD is controversial.

Subsequent studies of this technique have used various other approaches to sedation or general anaesthesia.[86,87] These studies have generally been small and methodologically limited, have not compared UROD to other methods, and have provided little long-term follow-up as reviewed by O'Conner and Kosten.[86] One study in which detoxified patients were followed up by telephone interview, found that only 10% continued naltrexone maintenance therapy for 7 months.[88] As reviewed by O'Conner and Fiellin,[89] two studies have demonstrated that substantial withdrawal symptoms persist well beyond detoxification.[87,90] In addition, the expense of this procedure (up to $US7500, 1999 values), the additional risk associated with general anaesthesia, and other safety concerns[91,92] limit its usefulness in clinical practice.[86] General anaesthesia with intubation avoids the significant risk of vomiting and aspiration which may occur with sedation, but in at least one instance, safety concerns led to the termination of a clinical programme that provided ultra-rapid detoxification.[93]

Although many investigators have suggested that the procedure should be limited to clinical trials until its safety and efficacy can be further established,[94] interest in this procedure and consumer demand remain intense and some studies are ongoing. Albanese et al.[95] evaluated 6-month outcome data of 93 men and 27 women receiving with UROD followed by naltrexone maintenance and an aftercare programme. Outcome was relapse-free status by urine drug screen, significant other report and/or therapist report. One hundred percent were reported to be relapse free. However, this study is limited by lack of a prospective, randomised, controlled design. Another recent study by Hensel and Kox[96] reported follow-up data from 72 opioid (morphine, codeine, heroin, methadone)-dependent patients detoxified using the UROD method with propofol general anaesthesia, and subsequently administered long-term naltrexone maintenance and a supportive psychotherapy programme. After 12 months, 49 patients (68%) were abstinent from opiates, 17 had relapsed and six were lost to follow-up. It was noted that methadone patients had more withdrawal symptoms than other addicts. This study has similar design limitations of being nonblind with no random assignment to a comparison group. A recent study[97] included the design strength of comparison of UROD to an alternative method of 30-day inpatient detoxification, but found that UROD was less effective. Eighty-one of 87 patients who underwent 30-day detoxification, and 82 of 139 patients who underwent UROD (93 *vs* 55%) were interviewed by telephone 12 to 18 months after programme participation. Results suggested UROD was more expensive and less effective than traditional treatment. This study was limited by its retrospective design and non-randomised assignment, but supports longer-term biopsychosocial treatment alternatives over rapid pharmacological detoxification.

In conclusion, UROD remains a controversial but still investigated new treatment approach for opioid dependence. It may be the only treatment acceptable to certain otherwise healthy patients unwilling to interrupt their work or personal schedules for a more comprehensive treatment commitment. It may also provide rapid induction to and maintenance on naltrexone. Nevertheless, the risks remain considerable and much research remains to be done on long-term outcome issues.

4.1.2 Naltrexone Maintenance

Suggested regimens for naltrexone maintenance include the initial administration of 25 or 50mg followed by one of the following dosage schedules: (i) 50 mg/day; (ii) 100mg on Monday, 100mg on Wednesday and 150mg on Friday; and (iii) 150mg on Monday and 200mg on Thursday.

While Marrazzi et al.[98] found that high dosages of naltrexone (200mg twice daily) used to treat eating disorders were not associated with adverse effects or laboratory changes in liver function, naltrexone has been associated with hepatotoxicity at these high daily doses of above 200mg. Thus, it is common clinical practice to evaluate liver function before starting patients on naltrexone. Although the pharmacological properties of naltrexone make it promising for long-term maintenance of abstinence in formerly opiate dependent patients, the expansion of its clinical use across different settings has not been impressive.

In a review and meta-analysis of randomised, controlled studies evaluating the use of naltrexone as a maintenance agent, Kirchmayer et al.[99] found a tendency in favour of naltrexone but concluded that there is not sufficient evidence to evaluate the efficacy of naltrexone treatment for opioid dependence. For example, Shufman et al.[100] in a double-blind, controlled design evaluated the efficacy of naltrexone in reducing opioid positive urine tests during a 12-week trial and found naltrexone to be superior to placebo. Similarly, in a multicentre, randomised, controlled trial, Hollister[101] examined 170 opiate-dependent patients at 9-month follow-up, and found that the group treated with naltrexone had more opiate-free urine tests and reduced attrition rates. However, other studies did not show significant difference between treatment groups.[102-104] Finally, Hulse and Basso[105] evaluated treatment outcome at 6 months for 100 heroin-dependent patients maintained on naltrexone. They used two different definitions of success, that is, periodic heroin use and complete abstinence, and found that using the former criterion 60% of the participants were still receiving naltrexone and 28% had returned to periodic heroin use. Complete abstinence was not characteristic of many of those patients continuing on naltrexone, in spite of its complete blocking of heroin reinforcement. Thus, periodic heroin use during naltrexone maintenance may occur but this periodic use did not prevent successful outcomes for those maintained on naltrexone.

5. Conclusion

The heroin epidemic has been escalating over the last decade but new pharmacotherapies are developing, including buprenorphine and rapid clonidine or lofexidine plus naltrexone detoxification to augment the proven efficacy of methadone. The long acting form of methadone, LAAM, has some cardiac complications (QT interval prolongation) that have limited its utility. One of the most promising new developments in the US is an improvement in the delivery system for opioid maintenance using office-based buprenorphine plus naloxone. This approach has been successfully used in France to reduce overdose deaths, to improve public health related to the transmission of HIV and viral hepatitis, and to replace criminal activity with more pro-social activities by former heroin addicts. Thus, new treatments are available for this worldwide epidemic of heroin dependence and its associated complications including AIDS.

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