

# A comparison of rapid (opioid) detoxification with clonidine-assisted detoxification for heroin-dependent persons

Diane E. Arnold-Reed, PhD  
Gary K. Hulse, PhD

## ABSTRACT

*This study compares two methods of detoxification available to heroin users in Western Australia: clonidine-assisted detoxification (CD) or clonidine-naloxone precipitated withdrawal under sedation (rapid opioid detoxification [ROD]). Oral naltrexone was made available to all participants following detoxification. Eighty heroin-dependent persons were randomly assigned to either ROD or CD. Most undertaking ROD commenced and completed this treatment. Less than one-third undertaking CD completed this treatment. There was no significant difference in those treated by CD or ROD in subjective assessment of degree or duration of pain, severity of withdrawal and craving, nor was there an increase in the withdrawal sequelae after treatment. Induction of oral naltrexone following ROD was greater, but oral naltrexone compliance levels and abstinence from heroin four weeks following detoxification were similar between ROD and CD groups. The level of patient satisfaction between the two treatments was also similar. The authors discuss why ROD is considered more effective than CD.*

*Key words: rapid opioid detoxification, naloxone/naltrexone, clonidine-assisted withdrawal*

## INTRODUCTION

The heroin withdrawal syndrome is well-documented, with symptoms including insomnia, irritability, restlessness, malaise, pain, fatigue, and gastrointestinal hypermotility, which extend over a seven- to 10-day withdrawal period. The objective of managed withdrawal or detoxification is to suppress withdrawal symptoms. Clonidine-assisted detoxification (CD) has commonly involved the use of adrenergic agonists and adjunctive medication to mitigate withdrawal symptoms. For example, the use of clonidine, a centrally active  $\alpha$ -2 agonist, can reduce some of the autonomic symptoms but not craving or anxiety. Regardless of the type of withdrawal approach used, patients still experience a significant degree of withdrawal symptomatology over the seven- to 10-day withdrawal period.<sup>1</sup>

Unfortunately, a high proportion of patients fail to complete CD procedures—25 to 50 percent for inpatients and up to 80 percent for outpatient programs.<sup>2</sup> The primary reasons for failing to complete CD include difficulty tolerating the duration and severity of withdrawal symptoms. Cravings in patients undergoing protracted managed withdrawal are also considered to be a significant factor in relapse.<sup>3</sup>

One response to these difficulties has been to accelerate the process of detoxification using opioid antagonists, while sedating (or anesthetizing) the patient to minimize discomfort. This procedure is most commonly known as rapid opioid detoxification (ROD). The ROD procedure is designed to significantly reduce the time required for detoxification through the use of opioid antagonists such as naloxone and naltrexone to precipitate withdrawal, thus shortening the duration of patient discomfort.<sup>1,4,5</sup> During the ROD procedure, sedation or general anesthesia, along with antiemetics, antidiarrheals, and centrally acting sympathetic antagonists are employed to mitigate withdrawal symptoms.<sup>6</sup> Immediate induction of naltrexone, which more often than not follows ROD, may also distinguish ROD from CD in reducing craving.<sup>7</sup> However, in the current study, the majority of subjects desired detoxification so as to initiate naltrexone maintenance.

The current study was commissioned by the Department of Health (Western Australia) to evaluate the effectiveness of two detoxification programs available in Perth, Western Australia: one using CD (inpatient and outpatient) and the other ROD with induction of oral naltrexone.

## METHODS

### Subject selection

Heroin-using adults with a desire to enter a detoxification program were recruited over the period of July 2000 to October 2001 in Perth, Western Australia. The study was advertised through selected general practitioners, hospital emergency departments, psychologists, the Perth Needle Exchange Programme, community and private alcohol,

**Table 1. Inclusion and exclusion criteria for the study**

<b>Inclusion criteria:</b>
resident within the Perth metropolitan area
willing and able to provide written informed consent
current heroin user and dependent on heroin as defined by DSM-IV criteria
have a stated goal of abstinence from opiates
considered willing and able to participate in either of the randomly allocated detoxification procedures
completion of prestudy clinical screening to the satisfaction of the study investigators
<b>Exclusion criteria:</b>
previous enrollment in the study
current enrollment in any other research project relating to the treatment of opiate dependence
pregnancy or unable to complete the study protocol, e.g., four-week period due to, for example, pending incarceration
contraindications due to naltrexone, e.g., chronic hepatitis with associated liver damage or pain that requires narcotic treatment
history of adverse reactions to medication likely to be used in the study
suffering from medical conditions potentially exacerbated by opiates
suffering from a major psychiatric condition that would prevent giving informed consent
<b>Subject study withdrawal criteria:</b>
a subject could withdraw from the study at any time or for any reason without being obliged to divulge their reason for doing so to the investigators or clinic staff
noncooperation with clinic staff and/or noncompliance with study clinic regulations
unacceptable adverse events including distress due to effects of any study procedure or medication

drug, and other advisory services, the West Australian Alcohol and Drug Information Service, newspapers, television reports, and pharmacies.

All subjects were assessed for dependence using the *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition* (DSM-IV) criteria. Potential subjects underwent screening to determine study eligibility (Table 1) and, upon initial contact, were given general information as to the nature of the study. Within 24 hours of initial contact

during weekdays, all subjects were interviewed in person at the study center. Subjects were fully informed of the study and given the opportunity to ask questions and discuss their participation. Eligible subjects were randomly assigned to one of two detoxification treatment groups. One group was assigned to undergo ROD during day surgery at a private, community-based treatment facility. A second group was assigned to undergo CD as an inpatient or as an outpatient, as determined following clinical assessment at a community-based public facility. Subjects were also provided with a summary of the possible risks and discomforts of using naltrexone if randomized to ROD. All subjects were offered the chance to undergo oral naltrexone maintenance. Both treatments were cost-neutral to the participants.

Clinical assessment of whether the subject was considered suitable for the assigned treatment was determined by the clinician at the treatment service. No treatment arm considered a patient to be unsuitable for treatment. Persons who were interested in participating and fulfilled study inclusion criteria were required to provide informed consent in accordance with the University of Western Australia Human Ethics Research Committee guidelines.

### Study participants

A total of 80 subjects entered the study. Of these, 41 were randomized to ROD and 39 were randomized to CD.

### Detoxification regimens

Patients undergoing ROD received clonidine-naloxone precipitated withdrawal and were inducted onto oral naltrexone during day surgery. The exact treatment regimen depended on the length of time since last opioid use. Generally, patients were given premedication with subcutaneous octreotide ( $\approx 0.1$  mg) for abdominal pain and intravenous (IV) ondansetron ( $\approx 2$  mg) for nausea 30 to 45 minutes prior to commencement of detoxification and an IV line inserted into the peripheral vein of the arm. Depending on the level of opioid use in the days before treatment, an oral flunitrazepam also was administered immediately prior to detoxification. Then patients were administered IV naloxone ( $\approx 800$   $\mu$ g) over a period of five to eight minutes in titred IV doses interspersed with IV doses of clonidine hydrochloride (150  $\mu$ g in 10 ml saline) and a sedative hypnotic (midazolam hydrochloride), depending on the level of arousal and discomfort experienced by the patient. When no significant withdrawal signs appeared, patients were allowed to rest for 20 to 30 minutes before oral doses of 4, 8, 15, and 23 mg naltrexone were gradually dispensed at 30-minute intervals.

Patients undergoing detoxification underwent CD over five to seven days (inpatient) or seven to 10 days (outpatient), as described by Palmer.<sup>8</sup> CD involved a two-step procedure. First, a medical assessment was conducted. Second, prescribed pharmaceuticals were dispensed from the clinic pharmacy for use on an outpatient basis at home over the seven- to 10-day withdrawal period. Patients were considered to have commenced CD only after accessing prescribed pharmaceuticals. Prescribed pharmaceuticals involved the use of 75 to 150 µg oral clonidine reviewed daily, daily dispensing of 10 to 20 mg temazepam, and additional medications (e.g., hyosine butylbromide, quinine bisulphate, and metaclopramide hydrochloride) at doses indicated for symptomatic relief.

The study did not provide or require any alteration to the standard detoxification procedures offered by the clinical services.

### Study plan

The following data were collected:

**Post-screening.** Information on general drug use, medical (including treatment history), and general demographics were collected using the Opioid Treatment Index.<sup>9,10</sup>

**Immediately prior to detoxification.** Self-reports of withdrawal history, preference for withdrawal procedures, and expectations of treatment and physical withdrawal (Part 1, Severity of Dependence Questionnaire [SODQ])<sup>11</sup> and craving<sup>12</sup> were made.

**Immediately post-detoxification.** Self-reports of the duration of detoxification procedure and level of discomfort, together with physical withdrawal (Part 1, SODQ<sup>11</sup>) and craving<sup>12</sup> were made.

**Four weekly follow-ups.** Over a four-week post-detoxification follow-up period, subjects were contacted weekly either in person or by telephone to verify whether they were taking daily oral naltrexone or had used heroin.

**Statistical analysis.** Subjects were classified for analysis on whether detoxification treatment was completed. The categorization is more detailed in the results section (Table 2) but to summarize: Subjects were compared on whether detoxification was commenced and completed (i.e., detoxification completed) or not commenced or not completed (i.e., unsuccessful detoxification).

Generalized mixed liner models were used to test significance where repeated measures were made for the same group of study subjects (e.g., for comparing discrete time point measures within the same detoxification

group when comparing before-and-after outcomes). Mann Whitney U-tests were used for comparisons between detoxification treatments. In all instances, significance was ascribed at the 5 percent level.

## RESULTS

### Study population

Eighty heroin users were assigned to either CD or ROD. There was no significant difference in the population randomized to the respective treatment services in relation to age, gender, socioeconomic status, or total length of heroin use.

### General demographics

The general age range of the study population was 16 to 50 years, with the average ( $\pm$  SE) age of  $30.6 \pm 1.04$  years. Sixty-four percent of the population was male, and 36 percent was female.

Ninety-nine percent of the population were nonaboriginal, and 82.5 percent were born in Australia. All received a secondary education to at least year 10, 49 percent received a tertiary education qualification, and 57.5 percent were known to be unemployed. Of those who were born in a country other than Australia, all had been residing in Australia for at least 14 years. Fifty-five percent of the population was classified in the high-medium disadvantage or lower category, as determined by their residential postcode from the Socio-Economic Indices for Areas 96 Disadvantage Index (Australian Bureau of Statistics).

There were no significant differences in the age, gender, place of birth, aboriginality, and levels of education and employment between the two treatment populations.

### Heroin and other drug use

Only 6.2 percent of the study population reported using opioids other than heroin in addition to heroin.

Sixty-six percent of the study population had used heroin for more than five years, with 47 percent using heroin on a regular basis (i.e., daily) for more than five years. Nearly 57 percent of the study population had spent more than 75 percent of their total heroin use period as regular heroin users.

In the month prior to deciding to seek treatment, 95 percent ( $n = 76$ ) of the study population used heroin daily or more than once a day.

In the month prior to seeking treatment, tobacco (91 percent), cannabis (64 percent), alcohol (51 percent), tranquilizers (45 percent), and amphetamines (26 percent) were the other most frequently used drugs reported among the study population. Cannabis was reported to have

**Table 2. Status of study subjects by clinic**

Treatment	Status	Percent frequency	Classification	Percent frequency
ROD	Commenced and completed	87.8 (n = 36)	Successful completion	87.8 (n = 36)
	Attended clinic but did not commence detoxification	7.32 (n = 3)	Unsuccessful completion	10.53 (n = 5)
	Did not attend clinic at all	2.4 (n = 1)		
	Self-detoxified (prison)	2.4 (n = 1)		
	Total	100 (n = 41)		100 (n = 41)
CD	Commenced and completed	28.2 (n = 11)	Successful completion	28.2 (n = 11)
	Commenced but did not complete	23.1 (n = 9)	Unsuccessful completion	71.8 (n = 28)
	Crossover to ROD	5.1 (n = 2)		
	Self-detoxified	5.1 (n = 2)		
	Attended clinic but did not commence detoxification	33.3 (n = 13)		
	Did not attend clinic at all	11.0 (n = 2)		
	Total	100 (n = 39)		100 (n = 39)

ROD = Rapid opiate detoxification; CD = Clonidine-assisted detoxification; actual numbers of patients are shown in parentheses.

been used most frequently—more than once a day, while alcohol, tranquilizers, and amphetamines were reported to have been used most frequently—more than once a week. Only one person reported using cocaine, and three persons reported using hallucinogens once a week or less often. Of the 91 percent who reported tobacco use, the average ( $\pm$  SE) number of cigarettes smoked per day was  $19 \pm 4$ .

**Previous treatments**

Sixty-seven percent (n = 54) of the study population had previously undergone treatment for addiction (predominantly heroin addiction). Forty-nine percent (n = 39) of those who had previously undergone treatment had been in receipt of more than one type.

**Incentive to be treated**

During the pretreatment interview, 96 percent (n = 77) of the study population stated that it was their choice to enter treatment, while 4 percent (n = 3) stated it was suggested to them. All subjects stated that their reason for seeking treatment was to cease heroin use. Forty-four

percent (n = 45) of the study population had reduced heroin intake prior to entering detoxification. Ninety-six percent (n = 77) of the population stated that they were considering entering naltrexone maintenance after detoxification, 2.5 percent (n = 2) stated that they did not want naltrexone maintenance, and one participant was unsure.

**Treatment assessment**

**Number of subjects commencing treatment.** Table 2 shows the classification used for the analyses based on the study subjects' detoxification status. Of the 41 subjects assigned to ROD, 88 percent (n = 36) commenced and completed treatment, while 46 percent (n = 18) of the 39 subjects assigned to CD commenced, but only 28.2 percent (n = 11) completed treatment. Of the 39 patients assigned to CD, 10 patients attended as inpatients. Of these 10 patients, three did not complete detoxification, and one crossed over to ROD. Of those who never started treatment, a higher proportion of those assigned to CD (33.3 percent, n = 13 vs. 7.32 percent, n = 3) attended the clinic but failed to commence detoxification. Two subjects commenced CD but did not complete and crossed over to ROD. For the purpose of assessing detoxification,

**Table 3. Oral naltrexone and absence of heroin use in the four weeks post-detoxification**

		Oral naltrexone compliance			Absence of heroin use
		Over entire four weeks	At some time in four weeks	Not at all over four weeks	
ROD	Of the 36 persons who commenced	56% (20)	86% (31)	14% (5)	39% (14)
	Of the 36 persons who completed	56% (20)	86% (31)	14% (5)	39% (14)
CD	Of the 20 who commenced	40% (8)	50% (10)	50% (10)	30% (6)
	Of the 11 who completed	73% (8)	90% (10)	9% (1)	55% (6)

ROD = Rapid opiate detoxification; CD = Clonidine-assisted detoxification; actual numbers of patients are shown in parentheses.

procedure assessment has been restricted to the 47 subjects who completed detoxification.

**Assessment of detoxification.** Of the 47 subjects who started and completed detoxification, information on detoxification assessment was collected from only 92 percent of those who underwent ROD and 82 percent of those who underwent CD. The remainder was lost to follow-up. Of those who were questioned, 22 percent (n = 2/9) of those who underwent CD felt the procedure was too long compared to 15 percent (n = 5/33) of those who underwent ROD. There was no significant difference in the proportion of subjects undergoing ROD (30 percent, n = 10/33) and those undergoing CD (22 percent, n = 2/9) who felt the degree of pain experienced was too great. Similarly, there was no significant difference between subjects' perception of pain duration associated with the two procedures (ROD: 21.9 percent, n = 7/32; CD: 22 percent, n = 2/9). Fifty-four percent (n = 18/33) and 78 percent (n = 7/9) of those questioned who were undergoing ROD and CD, respectively, stated that they would undergo the treatment again. Of those questioned following ROD, 81 percent (n = 26/32) stated that the presence of support in the form of a "salient other" had been helpful during detoxification.

**Assessment of physical withdrawal.** It should be noted that average ( $\pm$  SE) physical withdrawal scores, as measured by Part 1 of the SODQ<sup>11</sup> immediately before CD commenced, were not significantly different in those who completed detoxification compared to those who were unsuccessful in completing detoxification (3.4  $\pm$  0.76 vs. 5  $\pm$  1.97, respectively).

The change in physical withdrawal scores ( $\pm$  SE) before and after detoxification was not significantly different for ROD (13.09  $\pm$  1.24, n = 35 before vs. 12.39  $\pm$  1.16, n = 33 after) or CD (3.4  $\pm$  0.76, n = 10 before vs. 5.63  $\pm$  1.47, n = 8 after).

**Assessment of craving.** Craving levels before detoxification were the same for both groups whether assigned to ROD or CD. There was no significant difference in craving scores ( $\pm$  SE) before and after detoxification, regardless of whether it was through ROD (3.25  $\pm$  0.23, n = 35 before vs. 2.71  $\pm$  0.3, n = 33 after) or CD (3.23  $\pm$  0.59, n = 35 before vs. 2.21  $\pm$  0.46, n = 9 after). Neither was there any significant difference in craving levels after detoxification between the two groups. Craving was not different in those who commenced but did not complete CD, compared to those who commenced and completed detoxification.

**Assessment of oral naltrexone maintenance and absence of heroin use four weeks post-detoxification.** Results of assessment through self-report of oral naltrexone compliance and absence of heroin use are presented in Table 3.

## DISCUSSION

Managed withdrawal can and should be assessed on three major criteria: first, the percentage of those seeking treatment compared to those who commence withdrawal; second, the percentage of those who commence treatment compared to those completing managed withdrawal; and third, the severity of withdrawal sequelae and

patient satisfaction associated with the procedure. It could also be argued that a fourth criterion should be post-withdrawal abstinence from heroin.

Of the 41 patients assigned to ROD, only five failed to complete compared with 28 of the 39 assigned to CD. This occurred despite the majority of patients stating that they wished to undertake opioid detoxification in order to enter oral naltrexone maintenance (96 percent) and/or to cease heroin use (100 percent), and that the risk of attrition was similar between treatments, as the majority of patients attended both treatments on an outpatient basis.

Clearly, some feature of ROD facilitated a significantly greater proportion of patients who attended for withdrawal assessment to undertake treatment, as only three of the 41 patients attended the clinic but failed to commence ROD compared with 13 of the 39 patients randomized to CD. One likely possibility is the nature of ROD, which involved the prompt administration of an opioid antagonist as a medically supervised nonambulatory day procedure and provided little avenue for treatment avoidance. In contrast, patients undergoing CD were expected to self-supervise detoxification over a seven- to 10-day period through pharmacy-dispensed medications. It is also possible that despite subjects' initial agreement to be randomized to either ROD or CD, many patients had an undisclosed preference for ROD, which influenced their motivation to collect medications and ultimately commence conventional withdrawal.

ROD was also associated with a higher rate of detoxification completion than CD (89 percent commenced and completed ROD vs. 30 percent completing CD). This outcome is not surprising since ROD was initiated and completed as a medically supervised nonambulatory day procedure, while CD was completed over a seven- to 10-day period, largely on an outpatient basis. However, even three of the 10 CD patients managed as inpatients failed to complete their inpatient withdrawal regimen. Similar proportions have been reported previously for those completing CD<sup>13</sup> or ROD under sedation and receiving their first dose of naltrexone.<sup>14</sup> The above finding shows, as it has in previous studies,<sup>1</sup> that accelerating the process of detoxification, while sedating/anesthetizing the patient to minimize discomfort, overcomes some of the problems of patient adherence to treatment. In fact, studies have shown that rapid withdrawal proves successful in instances where protracted withdrawal has been unsuccessful<sup>15</sup> and may even increase the uptake of abstinence-based maintenance programs.<sup>16</sup>

The current study's findings suggest that there was no more of an increase in patient discomfort before and after treatment due to withdrawal symptoms associated with ROD than there was with CD. Current study results are contrary to previous reports in which patients undergoing ROD under sedation<sup>4,5,17</sup> or anesthesia<sup>18</sup> reported increased

levels of discomfort compared to more conventional withdrawal methods.

The difference between our results and those of other published ROD procedures more than likely lies in the amount and duration of action of the opioid antagonist used. In studies that report significant withdrawal sequelae over ROD, the use of repeated 1.2 mg naloxone IV every 30 minutes until no or little withdrawal sequelae were observed<sup>5</sup> or the single administration of 50 mg oral naltrexone<sup>4,17</sup> would have caused chronic high-level antagonism to opioids and accounted for the reported symptoms. This contrasts dramatically with the current protocol in which naloxone was used in titred doses, with recuperation times between doses, before small, but increasing doses of oral naltrexone were administered over 120 minutes. Given that naloxone has a half-life of one hour<sup>19</sup> and is metabolized rapidly on its first passage through the liver so it retains only one-fiftieth of its potency,<sup>20</sup> it is likely that this low-dose naloxone delivery produced significant withdrawal for only minutes. This low-level precipitation of withdrawal, alleviation of withdrawal symptoms with clonidine and sedative hypnotics, and recuperation time prior to the administration of the competitive antagonist naltrexone in a low oral dose may be an important component in the current study, providing a safe and relatively comfortable ROD. In fact, Gerra et al.<sup>21</sup> provided support for this in a comparison of patients detoxified with clonidine over five days, with patients undergoing ROD over two days. It was reported that there were fewer withdrawal symptoms, cravings, and mood problems in the ROD group than in the clonidine-only group.

The authors suggest that ROD is more effective than CD on a number of grounds. First, the majority of patients randomized to ROD were successfully withdrawn, while only the highly self-motivated few completed CD. It is evidenced in the high dropout rate between commencement and completion of CD. Second, ROD is a better method of inducting patients onto naltrexone maintenance, in that a higher proportion of patients who undertook ROD entered oral naltrexone immediately and sometime over a four-week post-withdrawal follow-up period, than those who undertook CD. However, this disparity in uptake was not translated into compliance with oral naltrexone or a reduction in relapse to heroin use over the four-week follow-up. This suggests that while ROD has the ability to induct persons onto oral naltrexone, there still remains a deficit in the ability to maintain oral naltrexone compliance. The shorter periods of detoxification associated with ROD would infer that should a relapse to dependent opioid use occur, ROD may provide the ability to quickly and effectively again withdraw patients with minimal loss during the withdrawal process. Given that heroin dependence is a chronic relapsing condition, this feature of ROD to opportunistically take a

relapse-dependent patient at the commencement of the day and successfully withdrawn him or her by the evening should not be overlooked.

We have already suggested that given the longer duration of CD, completion of this procedure probably was achieved by only a highly motivated few. Given the transient nature of motivation, it is therefore not unreasonable that these latter few would be more compliant, even though all participants said it was their desire to enter naltrexone maintenance. The authors argue that rather than reflecting a deficit in ROD, which clearly has the ability to induct persons onto naltrexone maintenance, more needs to be done to improve methods of naltrexone delivery to increase compliance.

## CONCLUSION

In conclusion, this study dispels some of the commonly held views within the heroin treatment arena. The disparity in results between the current and previous ROD studies raises questions about the use of large doses of opioid antagonist during ROD and whether this practice should be avoided. Clearly, further studies that directly compare the two approaches are required. The study shows that ROD is more effective in detoxifying a greater number of clients than CD, and, more importantly, 96 percent of all randomized subjects indicated that they wished to withdraw in order to enter naltrexone maintenance. As the ROD detoxification procedure included induction of oral naltrexone, it follows that in terms of naltrexone maintenance uptake, this ROD procedure is more likely to show greater success than CD. Comparison of our results with other studies also suggests that not all ROD procedures produce equitable results, and that a best practice for ROD needs to be established.

## ACKNOWLEDGMENTS

The authors acknowledge the assistance of Dr. Sean Murray and Ms. Eveline Durkin with data collection and the willing helpfulness of medical, nursing, and ancillary staff at the treatment clinics. This research was supported by funds from the Department of Health (Western Australia) and was carried out with approval from the University of Western Australia Human Research Ethics Committee.

Diane E. Arnold-Reed, PhD, Research Fellow, Unit for Research and Education in Drugs and Alcohol, School of Psychiatry and Clinical Neurosciences, The University of Western Australia, Crawley, Australia.

Gary K. Hulse, PhD, Coordinator of Alcohol and Drug Education and Training, Unit for Research and Education in Drugs and Alcohol, School of Psychiatry and Clinical Neurosciences, The University of Western Australia, Crawley, Australia.

## REFERENCES

1. Mattick RP, Hall W: Are detoxification programmes effective? *Lancet*. 1996; 347: 97-100.
2. Lipton DG, Maranda MJ: Detoxification from heroin dependency: An overview of methods of effectiveness. *Adv Alcohol Subst Abuse*. 1983; 2: 31-55.
3. Weinstein A, Wilson SC, Bailey J, et al.: Imagery of craving in opiate addicts undergoing detoxification. *Drug Alcohol Depend*. 1997; 48: 25-31.
4. Bell JR, Young MR, Masterman SC, et al.: A pilot study of naltrexone-accelerated detoxification in opioid dependence: *Med J Aust*. 1999; 171: 26-30.
5. Resnick RB, Kestenbaum RS, Washton A, et al.: Naloxone-precipitated withdrawal: A method for rapid induction onto naltrexone. *Clin Pharmacol Ther*. 1977; 21: 409-413.
6. O'Connor PG, Kosten TR: Rapid and ultrarapid opioid detoxification techniques. *JAMA*. 1998; 279(3): 229-234.
7. Lerner A, Sigal M, Bacalu A, et al.: A naltrexone double blind placebo controlled study in Israel. *Isr J Psychiatry Relat Sci*. 1992; 29: 36-43.
8. Palmer B: *Alcohol and Drug Withdrawal: A Practical Approach. A Manual for Doctors to Assist in Treatment of Patients Withdrawing from Alcohol and Other Drugs*. Mount Lawley, Australia: Next Step Specialist Drug and Alcohol Services, 2000.
9. Darke S, Ward J, Hall W, et al.: *The Opiate Treatment Index (OTI) Researchers' Manual*. Sydney: National Drug and Alcohol Research Centre, 1991.
10. Darke S, Hall W, Wodak A, et al.: Development and validation of a multi-dimensional instrument for assessing outcome of treatment among opiate users: The Opiate Treatment Index. *Br J Addict*. 1992; 87: 733-742.
11. Sutherland G, Edwards G, Taylor C, et al.: The measurement of opiate dependence. *Br J Addict*. 1986; 81: 485-494.
12. Tiffany ST, Field L, Singleton E, et al.: *The development of a heroin craving questionnaire*. 1997 (in preparation).
13. Rawson RA, McCann MJ, Shoptaw S, et al.: Naltrexone for opioid dependence: Evaluation of a manualized psychosocial protocol to enhance treatment response. *Drug Alcohol Rev*. 2001; 20: 67-80.
14. McGregor C, Ali R, White JM, et al.: A comparison of antagonist-precipitated withdrawal under anesthesia to standard inpatient withdrawal as a precursor to maintenance naltrexone treatment in heroin users: Outcomes at 6 and 12 months. *Drug Alcohol Depend*. 2002; 68: 5-14.
15. Seoane A, Carrasco G, Cabre L, et al.: Efficacy and safety of two new methods of rapid intravenous detoxification in heroin addicts previously treated without success. *Br J Psychiatry*. 1997; 171: 340-345.
16. Tucker TK, Ritter A, Maher C, et al.: Naltrexone maintenance for heroin dependence: Uptake, attrition, and retention. *Drug Alcohol Depend*. 2004; 23: 299-300.
17. Cucchia AT, Monnat M, Spagnoli J, et al.: Ultra-rapid opiate detoxification using deep sedation with oral midazolam: Short and long-term results. *Drug Alcohol Rev*. 1998; 52: 243-250.
18. Ali R, Thomas P, White J, et al.: Antagonist-precipitated heroin withdrawal under anaesthetic prior to maintenance naltrexone treatment: Determinants of withdrawal severity. *Drug Alcohol Rev*. 2003; 22: 425-431.
19. Misra, AL: Metabolism of opiates. In Aldler ML, Manara L, Samanin R (eds.): *Factors affecting the action of narcotics*. New York: Raven Press, 1978.
20. Nutt JG, Jasinski DR: Methadone-naloxone mixtures for use in methadone maintenance programs. I. An evaluation in man of their pharmacological feasibility. II. Demonstrations of acute physical dependence. *Clin Pharmacol Ther*. 1974; 15: 156-166.
21. Gerra G, Zaimovic A, Rustichelli P: Rapid opiate detoxification in outpatient treatment: Relationship with naltrexone compliance. *J Subst Abuse Treat*. 2000; 18: 185-191.