

## REVIEWS AND COMMENTARIES

# From opioid maintenance to abstinence: a literature review

HEGE KORNØR & HELGE WAAL

Unit for Addiction Medicine, University of Oslo, Oslo, Norway

### Abstract

*It appears that the literature on agonist maintenance therapies for opioid dependence pays more attention to outcomes during, rather than after, treatment. This review aims to (a) estimate to what extent opioid abstinence can be expected from former maintenance patients, (b) examine possible relationships between patient and treatment characteristics and abstinence rates and (c) assess the need for research in the field of abstinence-orientated maintenance treatment in general, and time-limited buprenorphine maintenance treatment in particular. Database searches supplemented by cross-references resulted in 12 studies included in the review. The studies were mostly naturalistic follow-up studies of former methadone maintenance patients, authored by US researchers in the 1970s. Buprenorphine was used in only one of the studies, and then as a transition between methadone and abstinence. There were considerable variations in definition and assessment of abstinence. Pooled abstinence rates ranged from 22% to 86%. The single factor associated most frequently with abstinence was voluntary participation in detoxification programmes with eligibility criteria ('therapeutic detoxification'). When 'therapeutic detoxification' was compared to 'non-therapeutic detoxification' the pooled abstinence rates were 48% and 22%, respectively. Abstinence-orientated maintenance therapy may be suitable for a subgroup of patients, but there is a substantial need for research updates. [Kornør H, Waal H. From opioid maintenance to abstinence: a literature review. *Drug Alcohol Rev* 2005;24:267–274]*

**Key words:** abstinence orientated, buprenorphine, detoxification, maintenance, methadone, time-limited.

### Introduction

Almost four decades after the introduction of Dole & Nyswander's high-dose, long-term methadone maintenance treatment model [1], agonist replacement therapies have achieved a dominating position among treatment options for opioid dependence. The effectiveness in terms of reduction in illicit opioid use, crime and transmission of infectious diseases has been amply documented [2–8]. These are, however, in-treatment outcomes in line with a 'chronic disease' perspective of opioid dependence [9–12], as opposed to post-treatment results, which would be needed to estimate the effect of time-limited maintenance treatments.

In spite of the scientific support mainly for long-term treatment, time-limited programmes are not uncommon in many countries, such as the UK methadone reduction programmes [13,14], the US 90- or 180-day interventions [15,16] and the Australian abstinence-orientated programmes [17,18].

Compared to the in-treatment research on substitution treatment, the number of publications addressing post-treatment outcomes is modest. A follow-up study where subjects were interviewed 22 years after admission to methadone maintenance programmes found an increased risk of heroin use among subjects currently not maintained on methadone than those still in, or having returned to, treatment [19]. This trend was supported in a 1-year follow-up of participants in the Drug Abuse Treatment Outcome Study (DATOS) [20]. On the other hand, Maddux & Desmond's 10-year follow-up showed that individuals who had spent less than 1 cumulative year in methadone maintenance were significantly more likely to have been in continuous voluntary abstinence for 3 years or longer than those who had spent at least 1 year in treatment [21]. When comparing post-treatment outcomes of five methadone maintenance studies with those of six drug-free treatment studies, the same authors observed

---

Hege Kornør Cand Polit (psychology), Research Fellow, Unit for Addiction Medicine, University of Oslo, Norway, Helge Waal MD, Professor, Unit for Addiction Medicine, University of Oslo, Norway. Correspondence to Hege Kornør, Unit for Addiction Medicine, MARIO, Kirkevn 166, N-0407 Oslo, Norway. E-mail: hege.kornor@psykiatri.uio.no

Received 26 February 2004; accepted for publication 1 June 2004.

that the two treatment modalities had very similar abstinence rates [22].

In a 1988 review, Milby [23] assessed abstinence rates up to more than 24 months after treatment discontinuation. Studies were arranged according to publication year into three separate 5-year eras. Milby's tables show that in the 1970–75 era, 137 of 332 patients completing detoxification (41%) were abstinent at 6–12-month follow-up. When patients were categorized as either meeting or not meeting rehabilitation criteria, the abstinence rates were 51% and 10%, respectively. The tables for the 1976–80 and 1981–85 eras did not report corresponding abstinence rates. Milby suggested that psychotherapy during detoxification could enhance post-treatment outcomes, while no such effect was observed for the use of drugs such as naltrexone or clonidine to accelerate and/or ameliorate the withdrawal process.

Thirteen years later, Magura [24] reviewed the literature again, asking 'What are the observed consequences of patients leaving methadone maintenance?'. Here, Milby was criticized for overestimating abstinence rates by too-liberal definitions and calculations of abstinence. Magura reported lower abstinence rates among examples of more recent studies and concluded with warnings that a large proportion of patients will relapse to illicit opioid use, and death rates post-treatment are greatly increased. However, consistent with Milby's review, he also found that patients classified as having completed treatment appeared to have a better prognosis than patients detoxified prematurely or against their will.

Magura's review mainly addressed negative consequences of treatment discontinuation and the review by Milby, published in 1988, excludes more recent research. Also, the termination of buprenorphine maintenance is not included. Buprenorphine has been introduced as an alternative to methadone in most western countries, and has been described as less addictive than methadone, giving less protracted and milder withdrawal symptoms [25–28]. An updated review of the literature on the positive consequences of detoxification, in terms of abstinence from illicit and prescribed opioids, appears timely.

The aim of abstinence in replacement treatments can be justified for several reasons. First, the ethics of keeping people in treatment longer than necessary is always questionable. Secondly, time-limited treatment as opposed to indefinite maintenance would increase patient turnover and the total number of patients treated per year. Thirdly, a subgroup of treatment-seeking people might find an indefinite treatment perspective unattractive for different reasons. Some might want to get rid of opioid dependence as such, some might dislike enduring monitoring, and some might experience conflict between self-fulfilment or

ambitions and ongoing therapy. Finally, it has been demonstrated that selected individuals are able to detoxify from methadone and achieve long-term abstinence [23,24].

This review aims to (a) estimate to what extent opioid abstinence can be expected from former maintenance patients, (b) examine possible relationships between patient and treatment characteristics and abstinence rates and (c) assess the need for research in the field of abstinence-orientated maintenance treatment in general, and time-limited buprenorphine maintenance treatment in particular.

## Method

Two database (Medline, Pre-Medline and PsychInfo, 1966–July 2003) searches were performed. The purpose of the first search was to identify studies of treatment programmes with time-limited or abstinence-orientated policies, using every possible combination of 'buprenorphine' or 'methadone', and 'short-term', 'intermediate', 'time-limited' or 'abstinence-orientated'. In addition, key words 'buprenorphine reduction' and 'methadone reduction' were used separately. The second search objective was to identify studies of successful withdrawal from programmes without preset time limitation, this time combining 'buprenorphine maintenance' and 'methadone maintenance' with 'detoxification', 'withdrawal' and 'abstinence'. The searches were supplemented with cross-references from central publications, such as overview articles and textbooks.

Studies of detoxification per se defined as programmes of less than 30 days' duration were excluded. Patients had to be aged at least 18 years and studies were required to report post-treatment abstinence rates and length of follow-up interval. There were no methodological or design requirements. Article titles, abstracts and full text papers were screened by both authors independently. Key findings were summarized by pooled averages. For continuous variables pooled averages were calculated by multiplying sample means with respective sample sizes, and dividing the sum of these products by the sum of sample sizes. The corresponding calculations for categorical variables were to divide the sum of each study's prevalence by the sum of sample sizes.

## Results

### *Literature search*

The search for studies of time-limited, abstinence-orientated agonist therapies resulted in 220 references and that for terminated maintenance treatments in 110. The combined search result contained 239 references

after removal of 47 duplicates, 22 reviews or meta-analyses and 22 articles published in non-English languages. Seventy-nine were excluded as they addressed substance use or treatment in general, research on animals, treatments other than the therapeutic use of opioid agonists or various non-clinical aspects of opioid dependence. Among the remaining 160 references, 25 reported on opioid-dependent neonates and 34 on agonist-assisted detoxification of 30 days' duration or less. Another 83 contained in-treatment outcomes only. After this selection stage 18 apparently relevant papers remained. These were screened thoroughly in full text, resulting in another 14 exclusions. Seven failed to report post-detoxification abstinence rates, four lacked information on post-detoxification follow-up time, one was unavailable in full text and two were preliminary research reports updated in later publications. One of the four studies included originated from the search for time-limited, abstinence-orientated treatment and the remaining three from the search for terminated maintenance treatments. In addition, 31 relevant cross-references were identified, from which 10 were included. Thus a total of 14 studies were included in the review.

#### *Study characteristics*

Seven studies were published in the 1970s [29–35], three in the 1980s, two in the 1990s and two in this millennium. Authors' nationalities were US [29–39], Australian [40,41] and Swedish [42,43]. Apart from one study reporting from a time-limited, low-dose methadone programme for young heroin-addicts [31], and one study set in a general practice [41], all patient samples were selected from methadone maintenance treatment programmes. Buprenorphine was only used in one study [40], and then merely as a transition medication from methadone to abstinence. In general, the study designs were naturalistic follow-up studies, except in two cases [34,40], where study participants were selected from methadone maintenance programmes and assigned randomly to various detoxification conditions. In addition, one study was set as a natural experiment, where the experimental group comprised patients in a methadone maintenance programme that was forced to close down. The comparison group comprised patients in a continuing programme [39]. One study was represented with two articles describing complimentary features of the study [42,43].

#### *Assessments*

Patient characteristics were assessed by clinical records in all but two studies; one study [30] failed to report patients' age, gender and duration of opioid depen-

dence, and one [42] used the follow-up interview as assessment instrument. In addition, one study failed to present separate characteristics for patients who detoxified from methadone [44]. Patients' age was reported at entry to methadone maintenance treatment in six studies [31,33,35,38,39,41], at initiation of detoxification in three studies [29,34,40], at completion of detoxification in one study [32], and at follow-up in two studies [36,42]. Duration of opioid dependence or regular use at entry to methadone maintenance treatment was reported on the basis of clinical records in eight studies [29,31,33–35,39–41], in a standardized research interview in one case [36] and otherwise not available.

Most studies used urine samples, clinical records, official records and/or interviews as information sources at follow-up.

#### *Patient characteristics*

The total study population counted 9718 individuals, all methadone maintenance patients, from which samples were drawn for detoxification and post-treatment abstinence studies. Study samples totalled 1902 patients who initiated detoxification from methadone and were subjects to post-treatment follow-up.

The cross-study average age was 30.0 (19.0–35.6) years (Table 1). Seventy-nine per cent of the participants were male. The patients had been dependent on or using illicit opioids regularly for an average of 7.4 (1.7–11.5) years prior to entering methadone treatment, which had an average duration of 22.2 (1.0–48.1) months.

#### *Treatment characteristics*

Seven studies failed to describe maintenance or detoxification characteristics at all [30,35–39,42]. Where reported, mean daily methadone maintenance dose prior to detoxification was 20 mg [31], 30.2 mg [40], 31 mg [34], 77 mg [33] and 87.2 mg [32], respectively. In addition, Berger & Schwegler [29] reported a dose range of 30–120 mg, and median dose in Byrne was 50 mg [41].

Detoxification schemes were flexible in all studies that accounted for them [29,31–34,40], meaning that delays in dose reduction, temporary dose increases and return to maintenance treatment were allowed. Patients reached 0 mg in an average of 7 weeks [29,31] to 7 months [33], apparently dependent on original maintenance dose. Three studies distinguished themselves with advanced detoxification protocols. In Berger & Schwegler's study, patients were unaware of their dose during detoxification, which included a final month of placebo dosing [29]. Senay and colleagues randomized their detoxification patients into two double-blind

**Table 1.** Patient characteristics

Study no.	First author (publication year)	<i>n</i>	Age	Gender (males)	Dependence/ regular heroin use (years)	Months in maintenance treatment	
1	Berger (1973)	17	22.4	15	88%	4.9	1–11
2	DeAngelis (1973)	37	19.0	29	78%	1.7	2.8
3	Lowinson (1976)	63	27.8	50	79%		22.7
4	Riordan (1976)	38	31.4			8.6	30.1
5	Senay (1977)	63	33.0	55	87%	11.5	> 12
6	Cushman (1978)	225					
7	Stimmel (1978)	429	29.7			6.5	19.7
8	Judson (1980)*	112					20.1
9	Des Jarlais (1981)	528	28.6	428	81%		25.2
10	McGlothlin (1981)	94	30.7	55	59%	5.5	21.4
11	Ball (1991)	105	35.6	105	100%	10.3	24.0
12	Eklund (1994/5)	50	40.1	38	76%		
13	Byrne (2000)	86	29.2	62	72%	8.6	
14	Breen (2003)	55	35.2	32	58%	9.5	48.1
	Total	1902	30.0	869	79 %	7.4	22.2

\* Patient characteristics for detoxification sample omitted in original article.

conditions. In the rapid withdrawal condition, methadone doses were reduced by 10% per week for 10 weeks, and then placebo was given throughout the following 20 weeks [34]. The gradual withdrawal condition implied 3% weekly dose reductions for 30 weeks. Finally, in Breen and colleagues' trial, patients entering the detoxification programme on 30 mg or less were directly transferred to buprenorphine, while patients on higher doses (maximum 40 mg) were randomized to two conditions [40]. In one condition, methadone was replaced by buprenorphine when the methadone dose had been reduced to 30 mg, while the other group was transferred when 'uncomfortable'. After stabilization on buprenorphine, the dose was gradually reduced.

Where psychosocial services were described, patients were advised to report to the clinic for counselling after completion of detoxification [29,31,32,40].

#### *Abstinence definitions*

Definitions of abstinence varied in substances included, frequency of use and time perspective. Two studies excluded any drug or alcohol use in their abstinence definitions [32,42], two studies excluded any illicit drug use [31,33], one study defined abstinence as 'not relapsed to intravenous use' [36], while the remaining studies included opioids only in their definitions. In addition, six studies required that patients should not have returned to methadone maintenance or any other drug dependence treatment after detoxification [33,34,37,39,40,42]. With respect to time perspectives, the most frequent definition of abstinence was based on no opioid use during the entire follow-up period [30,31,33–36,40], while

sporadic post-detoxification use was accepted in one definition [29]. In one study abstinence was defined as at least 1 month during the follow-up period with no intense use [38]. One defined abstinence as no use the last 4 weeks prior to follow-up [39], one as no post-detoxification opioid use for a minimum of 3 consecutive months [41]. Two studies required abstinence the last year prior to follow-up in their definition [37,42].

#### *Abstinence rates*

Across the studies, 611 of the former 1902 methadone patients (33%) were abstinent (or had had extensive periods of abstinence) from at least opioids for an average of more than 2 years (1–103 months) after completing detoxification from methadone (Table 2). Abstinence rates ranged from 22% to 86%.

Eleven studies examined relationships between abstinence and patient/treatment characteristics. Of these, no statistical method was described in five [29,33,36–38]. The remaining six studies [30,34,35,38,39,43] applied the concept of statistical significance, including  $\chi^2$ , *t*-test and Cox's relative risk. Table 3 gives an overview of studies observing various characteristics and their respective findings in relation to abstinence rates.

#### *Abstinence rates and treatment characteristics*

The term 'therapeutic detoxification' refers to special detoxification programmes for methadone patients regarded as treatment completers according to certain criteria who detoxify according to their own decision. In order to be eligible for these detoxification pro-

grammes, patients were required to have been in treatment for at least 6 months, compliant to programme regulations and to be stable with respect to various relevant problem areas. Eligibility criteria varied somewhat from programme to programme, but were basically comparable. The term 'non-therapeutic detoxification', then, includes all other circumstances for termination. Such circumstances could be patients wishing to detoxify against staff recommendation or patients discharged from treatment against their will for different reasons. As opposed to therapeutic detoxifications, non-therapeutic detoxifications often had relatively fixed dose reduction plans.

**Table 2.** Follow-up intervals and abstinence rates

Study	n	Follow-up interval (months)	Abstinence rates	
Berger (1973)	17	6–11	9	53%
DeAngelis (1973)	37	3	29	78%
Lowinson (1976)	63	5.2	44	70%
Riordan (1976)	38	19.5	26	68%
Senay (1977)	63	1	16	25%
Cushman (1978)	225	32.4	49	22%
Stimmel (1978)	429	37.6	98	23%
Judson (1980)	112	> 12	37	33%
Des Jarlais (1981)	528	22.8	148	28%
McGlothlin (1981)	94	26	48	51%
Ball (1991)	105	7.2	54	51%
Eklund (1994/5)	50	7.5	25	50%
Byrne (2000)	86	103.2	31	86%*
Breen (2003)	55	1	17	31%
Total	1902	27.8	611	33 %

\* The percentage represents 31 out of 36 patients who completed detoxification.

Four studies addressed 'therapeutic detoxification', all finding a positive relationship with post-treatment abstinence [29,30,35,38]. When we divided the study samples into two groups, 'therapeutic' and 'non-therapeutic' detoxification, the pooled abstinence rates were 47% (25–70%) and 23% (6–78%), respectively (Table 4).

Other treatment characteristics examined were methadone maintenance dose (four studies) and psychosocial support (two studies). None of these were found related to abstinence rates [31,34,39,43].

#### *Abstinence rates and patients characteristics*

Among patient characteristics, positive relationships were found between abstinence rates and age [33,35], time in treatment [31,35], ethnicity (African American) [33] and employment/educational level [29] in some studies. However, these factors were unrelated in other studies (i.e. age in three studies [30,31,39], time in treatment in three studies [37,39,43] and the remaining two characteristics in two studies each [34,39]).

Negative relationships were found in some studies in relation to duration or severity of dependence [29,31,33], detoxification difficulties or time to reduce [33], pre-treatment social problem or polydrug use [29,33,39], criminal behaviour/prison sentences [29,39] and in-treatment substance use [29,36,39]. Again, other studies contradicted these findings. Two studies found duration or severity of dependence unrelated to post-treatment abstinence [34,39], detoxification difficulties or time to reduce in three studies [34,39,43] and the remaining characteristics each in one study [34,39]. Finally, only two studies examined

**Table 3.** Relationships between patient/treatment characteristics and abstinence rates

	Number of studies observing the characteristic			
	Positively related	Negatively related	Unrelated	Total
<b>Patient characteristics</b>				
Age	2	0	3	5
Duration or severity of dependence	0	3	2	5
Time in treatment	2	0	3	5
Detoxification difficulties or time to reduce	0	1	3	4
Pre-treatment social problem or polydrug use	0	3	1	4
Ethnicity	1	0	2	3
Criminal behaviour/prison sentences	0	2	1	3
Employment/education level	1	0	2	3
Substance use during treatment	0	3	1	4
Gender	0	0	2	2
<b>Treatment characteristics</b>				
Methadone maintenance dose	0	0	4	4
'Therapeutic detoxification'	4	0	0	4
Psychosocial support during detoxification	0	0	2	2

**Table 4.** 'Therapeutic' vs. 'non-therapeutic' detoxification

Study	N	'Therapeutic'				'Non-therapeutic'			
		n		Abstinence		n	Abstinence		Abstinence
Berger (1973)	17	17	100%	9	53%				
DeAngelis (1973)	37					37	100%	29	78%
Lowinson (1976)	63	63	100%	44	70%				
Riordan (1976)	38	38	100%	26	68%				
Senay (1977)	63	63	100%	16	25%				
Cushman (1978)	225	89	40%	41	46%	136	60%	8	6%
Stimmel (1978)	429	88	21%	50	57%	341	79%	48	14%
Des Jarlais (1981)	516	202	39%	88	44%	314	61%	56	18%
McGlothlin (1981)	94					94	100%	48	51%
Ball (1991)	105	23	22%	7	30%	82	78%	27	34%
Eklund (1994/5)	50	50	100%	25	50%				
Byrne (2000)	36					36	100%	21	58%
Breen (2003)	55	55	100%	17	31%				
Total	1728	688	40%	323	47%	1040	60%	237	23%

One study [36], which did not indicate whether detoxification was 'therapeutic' or 'non-therapeutic', was omitted from this table.

gender. None found this to influence post-treatment outcomes [34,39].

## Discussion

One of the aims of this review was to calculate the long-term abstinence rate after discontinued maintenance treatment. We calculated a pooled abstinence rate of 33%, which is lower than Milby's 41% [23]. However, Magura questioned Milby's abstinence definitions (such as 'staying off methadone') as too liberal [24]. Despite the variations of abstinence definitions across the studies in our review, our pooled abstinence rate appears to be more conservative than that of Milby. All the studies reviewed here met a minimum requirement that the abstinence definition should include both prescribed and illicit opioids, and most of the studies also included other substances in their definitions. In addition, the difference between our and Milby's abstinence rates may be explained by factors such as the number of studies included in the calculation (12 vs. seven) and the time frame from which studies were selected (1965–2003 versus 1970–75). Magura also remarked that Milby's abstinence rates contained a selection bias, in that they largely represented a selected subsample (estimated to 50%) of good treatment responders.

The pooled abstinence rate in the present review also encounters the problem of selection bias, as it represents a total sample of 1902 individuals selected from a total of 9718 patients in methadone maintenance treatment. With the exception of one natural experiment, where a clinic was closed down, the study samples mainly included self-selected treatment responders, patients who were discharged for administrative reasons and dropouts. Consequently, there is no basis for generalization.

The results of the search for possible prognostic factors were inconsistent, although we did find support for Milby's and Magura's observations of improved prognosis among rehabilitated patients selected for participation in so-called therapeutic detoxification programmes [23,24]. In this subgroup of patients, a rough estimate for expected post-detoxification opioid abstinence can be set to around 50%, which is in line with Milby's finding [23]. In comparison, the 'non-therapeutic' detoxification group showed a 22% abstinence rate, which is considerably higher than Milby's corresponding 10%. The difference is probably best explained by the fact that Milby's 'non-therapeutic' detoxification group consisted of only 78 patients, while our group counted 958 individuals. Meeting rehabilitation criteria appears to be rather strongly associated with post-detoxification success.

Among other possible prognostic factors we observed a negative relationship between severity of dependence and abstinence in three of five studies. Further, single studies indicate that younger patients with less severe dependence and better pre-treatment psychological and social functioning could be associated with improved prognoses. The heterogeneity of the studies makes it difficult to provide a reasonable conclusion about these prognostic factors.

If this review were to have any implications for practice, we have three recommendations. First, and most importantly, patients should not be detoxified against their will or too early. It should also be seen as problematic to close down maintenance programmes without treatment alternatives. Secondly, patients in indefinite maintenance who have achieved sufficient stabilization should be given the opportunity to make an informed choice on the continuation or discontinuation of treatment. If discontinuation is chosen, a flexible

detoxification scheme should be employed and patients should have the option of returning to maintenance. Thirdly, time-limited treatment programmes may be the right option for carefully selected patients. Again, flexible dose reduction protocols and the possibility to transfer to long-term maintenance treatment appear to be the most ethical treatment philosophy.

Our observed abstinence rates and suggested prognostic factors should, however, along with these recommendations, be seen in the light of several limitations. The selection bias has already been mentioned. More importantly, our study selection criteria did not prevent the inclusion of poor quality studies. Finally, the included studies represent great variations in patient characteristics, treatment practice, assessments, abstinence definitions, follow-up intervals and methodology. Our findings should therefore only be interpreted as indicators.

A striking feature of this review is the modest number of identified published empirical findings on abstinence-orientated or discontinued maintenance therapies. There is a widespread practice for such treatments and solid reasons to attempt this route, but in spite of a search strategy with liberal requirements to study design and methodology, the number of studies of post-treatment abstinence that could be located is remarkably low.

Moreover, the research literature has barely been updated the last 20–30 years and is probably not representative for current patient populations and treatment practices. For instance, changes over time is described in a US study showing that the percentage of patients receiving daily methadone doses of 60 mg or less decreased from 79.5% in 1988 to 35.5% in 2000. This considerable change in treatment practice is likely to influence retention rates, which again will presumably contribute to an increase in the number of rehabilitated patients eligible for detoxification.

With regard to research needs within the field of abstinence-orientated maintenance treatments, there is a particularly large void in the literature on buprenorphine. This partial agonist is regarded as less addictive than full agonists such as methadone [25,26] and may thus be more appropriate for an abstinence-orientated treatment approach. Future comparisons of the long-term outcomes of discontinued methadone versus buprenorphine treatment are necessary. Factors associated with abstinence do also represent research needs. There is every reason to elaborate the concept of patient selection and therapeutic detoxification. Finally, time-limited maintenance therapy as early intervention would be of great interest. In such studies, we suggest a comparison between less and more severely opioid-dependent patients with regard to detoxification completion rates and long-term outcomes.

## Acknowledgements

We gratefully acknowledge the librarians at the Norwegian Institute for Drug and Alcohol Research for the retrieval of articles.

## References

- [1] Dole VP, Nyswander M. A medical treatment for diacetylmorphine (heroin) addiction—a clinical trial with methadone hydrochloride. *JAMA* 1965;193:646.
- [2] Farrell M, Ward J, Mattick R *et al.* Fortnightly review—methadone-maintenance treatment in opiate dependence—a review. *Br Med J* 1994;309:997–1001.
- [3] Joseph H, Stancliff S, Langrod J. Methadone maintenance treatment (MMT): a review of historical and clinical issues. *Mt Sinai J Med* 2000;67:347–64.
- [4] Mattick RP, Breen C, Kimber J, Davoli M. Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence. *Cochrane Database of Systematic Reviews* 2003;(2):CD002209.
- [5] Mattick RP, Kimber J, Breen C, Davoli M. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. *Cochrane Database of Systematic Reviews* 2003;(2):CD002207.
- [6] Ward J, Mattick R, Hall W. Methadone maintenance treatment and other opioid replacement therapies. Amsterdam: Harwood Academic Publishers, 1998.
- [7] Farre M, Mas A, Torrens M, Moreno V, Cami J. Retention rate and illicit opioid use during methadone maintenance interventions: a meta-analysis. *Drug Alcohol Depend* 2002;65:283–90.
- [8] Ling W, Huber A, Rawson RA. New trends in opiate pharmacotherapy. *Drug Alcohol Rev* 2001;20:79–94.
- [9] Kreek MJ. Methadone-related opioid agonist pharmacotherapy for heroin addiction. History, recent molecular and neurochemical research and future in mainstream medicine. *Ann NY Acad Sci* 2000;909:186–216.
- [10] Kreek MJ, Laforge KS, Butelman E. Pharmacotherapy of addictions. *Nat Rev Drug Discov* 2002;1:710–726.
- [11] Leshner AI, Koob GF. Drugs of abuse and the brain. *Proc Assoc Am Physicians* 1999;111:99–108.
- [12] McLellan AT, Lewis DC, O'Brien CP, Kleber HD. Drug dependence, a chronic medical illness: implications for treatment, insurance, and outcomes evaluation. *JAMA* 2000;284:1689–95.
- [13] Gossop M, Marsden J, Stewart D, Rolfé A. Patterns of improvement after methadone treatment: 1 year follow-up results from the National Treatment Outcome Research Study (NTORS). *Drug Alcohol Depend* 2000;60:275–86.
- [14] Gossop M, Marsden J, Stewart D, Treacy S. Outcomes after methadone maintenance and methadone reduction treatments: two-year follow-up results from the National Treatment Outcome Research Study. *Drug Alcohol Depend* 2001;62:255–64.
- [15] Robles E, Stitzer ML, Strain EC, Bigelow GE, Silverman K. Voucher-based reinforcement of opiate abstinence during methadone detoxification. *Drug Alcohol Depend* 2002;65:179–89.
- [16] Sees KL, Delucchi KL, Masson C *et al.* Methadone maintenance vs 180-day psychosocially enriched detoxification for treatment of opioid dependence: a randomized controlled trial. *JAMA* 2000;283:1303–10.
- [17] Bell J, Chan J, Kuk A. Investigating the influence of treatment philosophy on outcome of methadone maintenance. *Addiction* 1995;90:823–30.

- [18] Caplehorn JRM. A comparison of abstinence-oriented and indefinite methadone maintenance treatment. *Int J Addict* 1994;29:1361–75.
- [19] Goldstein A, Herrera J. Heroin addicts and methadone treatment in Albuquerque: a 22-year follow-up. *Drug Alcohol Depend* 1995;40:139–50.
- [20] Hubbard RL, Craddock SG, Flynn PM, Anderson J, Etheridge RM. Overview of 1-year follow-up outcomes in the Drug Abuse Treatment Outcome Study (DATOS). *Psychol Addict Behav* 1997;11:261–78.
- [21] Maddux JF, Desmond DP. Ten-year follow-up after admission to methadone maintenance. *Am J Drug Alcohol Abuse* 1992;18:289–303.
- [22] Maddux JF, Desmond DP. Methadone-maintenance and recovery from opioid dependence. *Am J Drug Alcohol Abuse* 1992;18:63–74.
- [23] Milby JB. Methadone maintenance to abstinence. How many make it? *J Nerv Ment Dis* 1988;176:409–22.
- [24] Magura S, Rosenblum A. Leaving methadone treatment: lessons learned, lessons forgotten, lessons ignored. *Mt Sinai J Med* 2001;68:62–74.
- [25] Fudala PJ, Jaffe JH, Dax EM, Johnson RE. Use of buprenorphine in the treatment of opioid addiction. II. Physiologic and behavioral effects of daily and alternate-day administration and abrupt withdrawal. *Clin Pharmacol Ther* 1990;147:525–34.
- [26] Kosten TR, Krystal JH, Charney DS, Price LH, Morgan CH, Kleber HD. Opioid antagonist challenges in buprenorphine maintained patients. *Drug Alcohol Depend* 1990;25:73–8.
- [27] Leonard BE. *Fundamentals of psychopharmacology*. Chichester: John Wiley, 1992.
- [28] Lewis JW. Buprenorphine. *Drug Alcohol Depend* 1985;14:363–72.
- [29] Berger H, Schwegler MJ. Voluntary detoxification of patients on methadone maintenance. *Int J Addict* 1973;8:1043–7.
- [30] Cushman P Jr. Abstinence following detoxification and methadone maintenance treatment. *Am J Med* 1978;65:46–52.
- [31] DeAngelis GG, Lehmann WX. Adolescents and short term, low dose methadone maintenance. *Int J Addict* 1973;8:853–63.
- [32] Lowinson J, Berle B, Langrod J. Detoxification of long-term methadone patients: problems and prospects. *Int J Addict* 1976;11:1009–18.
- [33] Riordan CE, Mezritz M, Slobetz F, Kleber HD. Successful detoxification from methadone maintenance. Follow-up study of 38 patients. *JAMA* 1976;235:2604–7.
- [34] Senay EC, Dorus W, Goldberg F, Thornton W. Withdrawal from methadone maintenance. Rate of withdrawal and expectation. *Arch Gen Psychiatry* 1977;34:361–7.
- [35] Stimmel B, Goldberg J, Cohen M, Rotkopf E. Detoxification from methadone maintenance: risk factors associated with relapse to narcotic use. *Ann NY Acad Sci* 1978;311:173–80.
- [36] Ball JC, Ross A. *The effectiveness of methadone maintenance treatment: patients, programmes, services, and outcome*. New York: Springer-Verlag, 1991.
- [37] Judson BA, Ortiz S, Crouse L, Carney TM, Goldstein A. A follow-up study of heroin addicts five years after first admission to a methadone treatment programme. *Drug Alcohol Depend* 1980;6:295–313.
- [38] Des J, Joseph H, Dole VP. Long-term outcomes after termination from methadone maintenance treatment. *Ann NY Acad Sci* 1981;362:231–8.
- [39] McGlothlin WH, Anglin MD. Shutting off methadone. Costs and benefits. *Arch Gen Psychiatry* 1981;38:885–92.
- [40] Breen C, Harris SJ, Lintzeris N *et al*. Cessation of methadone maintenance treatment using buprenorphine: transfer from methadone to buprenorphine and subsequent buprenorphine reductions. *Drug Alcohol Depend* 2003;71:49–55.
- [41] Byrne A. Nine-year follow-up of 86 consecutive patients treated with methadone in general practice, Sydney, Australia. *Drug Alcohol Rev* 2000;19:153–8.
- [42] Eklund C, Melin L, Hiltunen A, Borg S. Detoxification from methadone maintenance treatment in Sweden: long-term outcome and effects on quality of life and life situation. *Int J Addict* 1994;29:627–45.
- [43] Eklund C, Hiltunen AJ, Melin L, Borg S. Factors associated with successful withdrawal from methadone maintenance treatment in Sweden. *Int J Addict* 1995;30:1335–53.
- [44] Judson BA, Ortiz S, Crouse L, Carney TM, Goldstein A. A follow-up study of heroin addicts five years after first admission to a methadone treatment programme. *Drug Alcohol Depend* 1980;6:295–313.