
**Systematic review of the safety of buprenorphine,
methadone and naltrexone**

**Dr Andy Gray
Department of Therapeutics and Medicines
Center for the AIDS Programme of Research in South Africa
Congella, South Africa**

**BACKGROUND DOCUMENT PREPARED FOR THIRD MEETING OF TECHNICAL
DEVELOPMENT GROUP (TDG) FOR THE
WHO "GUIDELINES FOR PSYCHOSOCIALLY ASSISTED PHARMACOTHERAPY
OF OPIOID DEPENDENCE"**

**17-21 SEPTEMBER 2007
GENEVA, SWITZERLAND**

TABLE OF CONTENTS

SYSTEMATIC REVIEW OF THE SAFETY OF BUPRENORPHINE, METHADONE AND NALTREXONE	1
1 TERMS OF REFERENCE	3
2 BUPRENORPHINE	4
2.1 INTRODUCTION	4
2.2 SEARCH STRATEGY	5
2.3 RESULTS	5
2.3.1 Evidence from Cochrane Reviews	5
2.3.2 Evidence from recent controlled trials	9
2.3.3 Evidence from other sources	11
2.3.4 Evidence from spontaneous ADR reports	12
2.3.5 Summary	14
3 METHADONE	15
3.1 INTRODUCTION	15
3.2 SEARCH STRATEGY	16
3.3 RESULTS	17
3.3.1 Evidence from Cochrane Reviews	17
3.3.2 Evidence from recent controlled trials	18
3.3.3 Evidence from other sources	19
3.3.4 The issue of cardiotoxicity	21
3.3.5 The issue of dental caries	23
3.3.6 Evidence from spontaneous ADR reports	24
3.3.7 Summary	25
4 NALTREXONE	26
4.1 INTRODUCTION	26
4.2 SEARCH STRATEGY	28
4.3 RESULTS	28
4.3.1 Evidence from Cochrane Reviews	28
4.3.2 Evidence from recent controlled trials	30
4.3.3 Evidence from other sources	30
4.3.4 Evidence from spontaneous ADR reports	31
4.3.5 Summary	31
5 SUMMARY TABLE AND CONCLUSIONS	32
6 ACKNOWLEDGEMENTS	33
7 REFERENCES	34

1 Terms of reference

The terms of reference of this consultancy were to:

1. perform a comprehensive review of safety of buprenorphine, methadone and naltrexone in the treatment of opioid dependence, including systematic literature search (limited to English language only) and analysis of database(s) and other information sources provided by WHO, in consultation with International Drug Monitoring Centre.
2. To perform meta-analysis of the data available, if appropriate.
3. To submit a draft of the review to WHO as an electronic copy.
4. To submit an electronic database of identified references.
5. To incorporate comments provided by WHO into the final draft and submit revised products to WHO.

This safety assessment forms part of the input process for the Technical Guideline Development Group for Treatment of Opioid Dependence. The consultant was also provided with the following documents from that process:

- Report on the 1st Consultation on Technical Guidelines for Treatment of Opioid Dependence
- WHO Guidelines for psychosocially assisted pharmacological treatment of persons dependent on opioids, prepared as a background paper for the above meeting by Uchtenhagen et al.
- An overview of Cochrane systematic reviews of pharmacological and psychosocial treatment of opioid dependence, prepared as a background paper for the above meeting by Amato et al.
- Overview of “Non Cochrane” systematic reviews of pharmacological and psychosocial treatment of opioid dependence, prepared as a background paper for the above meeting by Minozzi et al.

A first draft report was thus directed at ToRs 1 to 3. The document seeks to complement the work already done in the background papers to the 1st Consultation, rather than to repeat work already done. An electronic database of the references cited, in the form of an Endnote v9 file, is attached, together with .rtf files of the listing of the references cited as well as the composite sets of literature retrieved for all 3 agents. This final report takes into account requests for a summary table and conclusions section, as well as additional attention to the problems of dental caries in methadone users.

The methods followed and the results of the systematic review are presented for each of the 3 drugs in the order stated.

2 Buprenorphine

2.1 Introduction

Buprenorphine is an opioid partial agonist/antagonist. It has high affinity but low intrinsic activity at the μ (mu) receptor. It is also capable of binding at the κ (kappa) receptor. The rate of dissociation from the μ receptors is slow, which results in an antagonistic effect to any other opioids that may be co-administered. In addition, buprenorphine exhibits a ceiling effect, in that higher doses do not produce additional effects in terms of both positive mood and respiratory depression. It would therefore be expected that buprenorphine would be well tolerated and relatively safer than the full μ agonists, such as methadone.

When taken orally, buprenorphine undergoes first-pass hepatic metabolism with N-dealkylation and glucuroconjugation in the small intestine. The use of the sublingual route is therefore appropriate. After sublingual administration, peak plasma concentrations are achieved in 90 minutes. A linear dose-concentration relationship is evident between 2 mg and 16 mg.

Distribution is rapid and the half-life is 2 to 5 hours. Buprenorphine is oxidatively metabolised by cytochrome P450 CYP3A4 and by glucuroconjugation of the parent molecule and the dealkylated metabolite (norbuprenorphine). It has a long terminal elimination phase of 20 to 25 hours, due in part to reabsorption of buprenorphine after intestinal hydrolysis of the conjugated derivative, and in part to the highly lipophilic nature of the molecule. The conjugated metabolites are excreted mostly in the faeces by biliary excretion (80%), but also in the urine.

Standard drug monographs provide the following as the expected adverse effects for buprenorphine:

- constipation
- headaches
- insomnia
- asthenia
- drowsiness
- nausea and vomiting
- fainting and dizziness
- orthostatic hypotension
- sweating

More rarely, the following have been noted:

- respiratory depression
- hepatic necrosis and hepatitis
- hallucinations
- bronchospasm
- angioneurotic oedema
- anaphylactic shock

In cases where the substance is misused by intravenous injection, local reactions, sepsis and hepatitis have been reported.

As is expected from the partial agonist mechanism of action and the slow dissociation from these receptors, patients with marked opioid dependence may experience withdrawal effects

when administered buprenorphine. Conversely, abrupt cessation of buprenorphine administration can result in a slower onset of withdrawal symptoms and a less pronounced withdrawal syndrome in patients chronically dosed with this drug.

The expected manifestations of acute overdose would include pinpoint pupils, sedation, hypotension, respiratory depression and death.

2.2 Search strategy

Buprenorphine has been the subject of two Cochrane Reviews (Mattick, Kimber et al. 2003; Gowing, Ali et al. 2006), and these were used as the basis for the search strategy. Details of safety data considered in the Cochrane Reviews were gathered, where possible from the original references included in the reviews. More recent randomised controlled trials (RCTs) and controlled trials (CTs) in the management of opioid dependence, published after the Cochrane Reviews, were obtained by searching Medline and the Cochrane CENTRAL database. The PubMed Clinical Query utility was employed, using the following search strategy:

- (buprenorphine) AND ((clinical[Title/Abstract] AND trial[Title/Abstract]) OR clinical trials[MeSH Terms] OR clinical trial[Publication Type] OR random*[Title/Abstract] OR random allocation[MeSH Terms] OR therapeutic use[MeSH Subheading])

The bibliographies of such references were also hand searched for any additional sources. A broad, sensitive search of Medline was also conducted using the following strategies:

- "Buprenorphine"[MeSH] AND "adverse effects"[Subheading]
- "Buprenorphine"[MeSH] AND "Drug Toxicity"[MeSH]
- "Buprenorphine"[MeSH] AND "toxicity"[Subheading]
- "Buprenorphine"[MeSH] AND "Overdose"[MeSH]

The results of these searches are provided as additional Endnote Libraries, combined and with duplicates removed. This strategy was used to identify additional reviews, observational studies and programmatic reports, case series and significant case reports.

The evidence is presented from each of the categories identified above:

- Evidence from Cochrane reviews
- Evidence from randomised controlled trials and controlled trials published after the Cochrane Reviews
- Evidence from other sources (observational studies and programmatic reports, case series and significant case reports)

Lastly, data from the Uppsala Monitoring Centre are presented, representing spontaneous adverse event reports from member countries.

2.3 Results

2.3.1 Evidence from Cochrane Reviews

Mattick, Kimber et al (2003) reviewed RCTs of buprenorphine maintenance therapy versus either placebo or methadone for opioid dependence. The most recent substantive amendment was on 5 February 2003. Thirteen studies were included, all but one of which was double blind in design. Only two of the studies included (Johnson, Chutuape et al. 2000; Petitjean, Stohler et al. 2001) specifically included adverse effects as outcome measures. Not surprisingly, these data

could not be subjected to any quantitative analysis. In contrast, “retention in treatment” was considered as an efficacy measure. In the management of opioid dependence, retention in treatment cannot be considered to be a reliable measure of participants’ experience of adverse effects, because of the very nature of the condition being treated. Poor retention in two of the studies included was considered to be due to overly slow induction of buprenorphine treatment, rather than adverse effects due to the drug. It was also considered possible that participants who had recently ingested heroin would experience a mild withdrawal syndrome on induction of buprenorphine, as the partial agonist replaced the full agonist at opioid receptors. This could result in withdrawal from treatment.

Johnson et al (2000) assessed side effects every 4 weeks using an open-ended questionnaire, and then applied the COSTART coding system. This was a 4-arm study, involving levomethadyl acetate (n=55), buprenorphine (n=55) and two doses of methadone, 20mg daily (n=55) and 60-100mg daily (n=55). The lower dose methadone was considered minimally effective and thus provided a placebo-like comparison. The percentage of patients reporting at least one side effect was similar among all groups, including the minimally effective methadone group - levomethadyl acetate (55%), buprenorphine (49%), high-dose methadone (45%) and low-dose methadone (40%). The most common adverse effect reported was constipation (21% of all reports), followed by nausea (8%) and dry mouth (6%). The authors reported that “no toxic interactions associated with illicit-drug use were observed in any of the groups”. However, no tabulation of the individual prevalence rates of the adverse effects noted per group was provided.

Petitjean et al (2001) compared the use of buprenorphine (n=27) and methadone (n=31), but did not exclude patients receiving co-medication (including antidepressants) except for those on anticonvulsants and neuroleptics. However, as is common in RCTs, patients with serious medical conditions (such as liver or cardiovascular diseases) were excluded. The authors noted that “All doses of the buprenorphine tablet were tolerated well by all patients and no serious adverse events occurred during the study”. They recorded that the frequency of the following self-reported adverse events did not differ between the groups: insomnia, sweats, headache, somnolence, depression, anorexia, back pain, constipation, nervousness, vomiting, nausea, asthenia, rhinitis, dizziness, pain, and tremor. However, it was noted that the participants in the buprenorphine group reported more serious headaches (33 vs. 23%; which was not statistically significant) whereas the patients in the methadone group reported significantly more sedation (58 vs. 26%; p=0.014). No tabular recording of the prevalence of the other adverse effects noted was provided.

Though not specifically mentioned in the Cochrane report, the paper by Schottenfeld and colleagues (Schottenfeld, Pakes et al. 1997) did note that “no patient in any of the 4 maintenance treatments reported adverse effects that required dose reduction or termination from the study”. Two papers by Ling and colleagues (Ling, Wesson et al. 1996; Ling, Charuvastra et al. 1998) also made some reference to adverse effects. In the first of these, safety data were tabulated over 52 weeks on a symptom checklist and rated as mild, moderate or severe. The reporting of data was, unfortunately, minimal, with only a statement that “adverse effects were about equally represented in all three groups, and no clustering of type of event was apparent”. The authors commented that “[t]here was no expectation of serious adverse effects and none were found”. The 1998 paper, which compared 16 mg/day of buprenorphine to 8, 4 and 1mg/day over 16 weeks in 162 participants, is a good example of the problem of teasing out adverse events related to the medication and the problems of withdrawal. Only 51% of participants completed the 16 week trial. The authors noted 51 “serious medical events”, equally distributed in the 16mg (12 events out of 110 completers), 8mg (14/98), 4mg (13/93) and 1mg (12/74) groups.

Although a complete listing was not provided, it was stated that “serious medical events” included depression, cardiovascular events and accidents. The authors noted that “[a] host of minor complaints/adverse events was reported. Many of these were those frequently seen in patients treated with methadone or other opioids. Other complaints were those commonly associated with the opioid withdrawal syndrome”. For example, 31% of all participants complained of headache at some point, 26% of insomnia, 25% of pain, 24% of withdrawal and 22% of infections. Only constipation and diarrhoea seemed to be dose-related, the former more prevalent in the 8mg and the latter more prevalent in the 1mg groups. No deaths occurred during the study. Also not mentioned by the Cochrane authors was the study by Pani and colleagues (Pani, Maremmani et al. 2000), which noted 74 adverse events occurring in 7/38 (21%) on buprenorphine and 10/34 (31%) on methadone, but stated that these were related to “pre-existing conditions” or “pathological conditions typical of the addict population”.

The largest of the studies included was by the Cochrane Review’s author and his group (Mattick, Ali et al. 2003), involving 405 participants randomized to buprenorphine or methadone maintenance. In the buprenorphine group, 3 participants were reported to have withdrawn due to adverse effects. However, no statistical analysis of the serious adverse event (SAE) data was attempted, and these were rare. One case of allergic reaction was noted with buprenorphine. Other SAEs noted in the buprenorphine group were assault on the patient, motor vehicle accident, overdose on heroin or heroin plus benzodiazepines, pneumonia and suicide attempt. A table of “treatment-emergent adverse events” was provided, but showed predominantly those expected in this population, such as headache, sweating, insomnia and nausea. Palpitations were noted in 12/192 (6%) on buprenorphine, compared to 9/202 (5%) on methadone.

The second Cochrane Review, by Gowing et al (2006), sought controlled trials comparing buprenorphine in opioid withdrawal management with reducing doses of methadone, alpha 2 adrenergic agonists, symptomatic medications or placebo. The most recent substantive amendment was on 26 July 2004. Of the included studies comparing buprenorphine and clonidine, 5 studies recorded adverse effect data (Nigam, Ray et al. 1993; Cheskin, Fudala et al. 1994; Janiri, Mannelli et al. 1994; Lintzeris, Bell et al. 2002; Umbricht, Hoover et al. 2003). Only one of the studies comparing buprenorphine to reducing doses of methadone reported adverse effect data (Seifert, Metzner et al. 2002). Two of those reporting other comparisons also made some reference to adverse effects (Liu, Cai et al. 1997; Schneider, Paetzold et al. 2000). Two studies which measured the impact of different rates of buprenorphine dose reduction made some mention of adverse effects (Wang and Young 1996; Assadi, Hafezi et al. 2004). As with Mattick et al (2003), no meta-analysis of the adverse effect data was attempted, though the authors did conclude that “[b]uprenorphine is associated with fewer adverse effects than clonidine”.

Nigam et al (1993) also reported that “[n]o untoward side-effects of buprenorphine were reported”, but did note that 3/22 participants were withdrawn from the clonidine-treated group because of hypotension (<90/60 mmHg). They reported giddiness (80%), dry mouth (48%) and constipation (33%) as being most common in the clonidine-treated group, and nausea (17%), vomiting (17%) and constipation (13%) as most common in the buprenorphine-treated group (n=22). The Cochrane authors expressed the opinion that: “As nausea and vomiting are typical features of the opioid withdrawal syndrome, this comparison suggests minimal adverse effects among the buprenorphine-treated group”.

Cheskin et al (1994) also noted significantly more effects on blood pressure in the clonidine-treated group compared to the buprenorphine-treated group for the first three days of treatment.

Respiratory rate, by area under the curve values, was significantly lower for the buprenorphine group. This was a small study, with analysis based on only 18 participants who completed treatment.

The Cochrane authors noted that Janiri et al (1994) stated there was no significant difference between groups in blood pressure or heart rate, but otherwise did not discuss adverse effects.

Lintzeris et al (2002) was an RCT comparing up to 5 days of buprenorphine (n=58) to a control group (n=56) given up to 8 days of clonidine and other symptomatic medication. Data were collected at day 35. No severe adverse effects were recorded, and 16/58 treated with buprenorphine and 13/56 treated with clonidine reported no adverse events at all. Headache (15/58 vs. 2/56) and precipitated withdrawal (4/58 vs. 0/56) were more common in the buprenorphine group. Drowsiness (4/58 vs. 6/56), lethargy/tiredness (3/58 vs. 12/56), dry mouth (2/58 vs. 7/56) and light-headed, dizziness, hypotension (1/58 vs. 15/56) were more common in the clonidine group.

Umbricht et al (2003) also reported that 2/16 in the clonidine group, but none in the buprenorphine group (n=21), were discontinued from the study because of low systolic blood pressure (<90mmHg) and bradycardia.

In the methadone comparisons, Seifert et al (2002) reported no adverse effects in either group (comparing an 11-day low-dose buprenorphine plus carbamazepine to an 11-day methadone plus carbamazepine “detoxification” regimen). In the remaining comparisons, while Liu et al (1997) noted that all participants complained of dry mouth, Schneider et al (2000) reported no severe adverse effects in any participants.

Wang and Young (1996) merely reported that no adverse effects were reported. Assadi et al (2004) is a good example of a common problem with adverse effect reporting. Each of the 40 patients randomized to two buprenorphine treatment regimens were systematically examined each day and rated by a score sheet for symptoms typically related to the expected side effects of buprenorphine, including headache, sedation, constipation and dizziness. Each item was rated as absent (0) or present (1). The total side effect score was the sum of the scores on each item. Liver function tests (AST and ALT) were performed on day 8. The authors reported that there was “no significant difference between the two protocols in terms of total side effect profile” or for any specific side effect assessed on the score sheet. However, the prevalence of individual adverse effects was not reported. They did, however, note some differences in liver enzymes: patients treated with the conventional protocol showed significantly more increase in ALT levels from baseline (17.44 ± 22.10 U/liter vs. -2.47 ± 24.34 U/liter, $t = 2.53$, $p = 0.01$). While 1/20 participants patient in the experimental group had an ALT level above the upper limit of normal at the baseline, 0/20 had abnormal ALT at the end of the study. In the conventional group, 2/20 participants at baseline and 5/20 at the end of the study had ALT levels above the upper limit of normal (Fisher exact test, $p = 0.03$). The authors did note, however, that ALT levels never exceeded twice the upper limits of normal.

While the Cochrane Reviews mentioned are limited in their treatment of adverse effects, as would be expected from reviews of RCTs in the main, they do provide some evidence that buprenorphine is associated with few serious adverse events, whether used in the form of maintenance or as part of the management of withdrawal. None of the more serious adverse effects that could be predicted from an opioid agonist (such as respiratory depression, hepatic necrosis and hepatitis, hallucinations, bronchospasm, angioneurotic oedema or anaphylactic shock) were noted in any of the studies included in these reviews.

2.3.2 Evidence from recent controlled trials

Five more recent controlled studies looking at buprenorphine maintenance therapy in various settings were retrieved.

Chawarski and colleagues (Chawarski, Moody et al. 2005) investigated the pharmacokinetics of buprenorphine sublingual tablets and sublingual liquid preparations in 57 opiate-dependent volunteers. Although designed as a bioequivalence study, daily ratings of withdrawal symptoms were also taken. No relationship of “adverse” experiences to the buprenorphine formulation could be demonstrated.

Although this systematic review was limited to English language literature, it was noted that an article in Norwegian (Kristensen, Espegren et al. 2005) has reported on a randomized trial in 50 participants allocated to either buprenorphine (n=25) or methadone (n=25) maintenance therapy. The English abstract noted that “only those on buprenorphine reported significant improvement in physical health”.

Two studies have specifically looked at the problems of maintenance therapy in pregnant addicts (Jones, Johnson et al. 2005; Fischer, Ortner et al. 2006). Jones et al. Transitioned 18 pregnant opioid-dependent women from short-acting morphine to either buprenorphine or methadone under double-blind, double-dummy conditions, having first moved all patients from methadone to the short-acting morphine treatment. A wide range of ancillary medications were permitted, including paracetamol, antacids, various antimicrobials (including cotrimoxazole), antihistamines, indometacin and topical lidocaine for toothache. The safety parameters monitored included foetal movement, oral temperature, heart rate, respiratory rate and blood pressure. Measurements were done every 8 hours for 3 days. A battery of adverse effects was also logged, but recorded as evidence of withdrawal symptoms and scored as not present (0) to severe (3) for 10 items (maximum score 30). Mean scores were computed and the differences between the short-acting morphine period and the induction phase reported for each symptom. For buprenorphine the symptoms logged were nausea/vomiting, sweats, anxiety, agitation, rhinorrhoea/lacrimation, chills, abdominal cramps, muscle jerks/cramps, body aches and diarrhoea. Although abusers of alcohol and benzodiazepines were excluded, some women had used cocaine before entering the study and might have experienced withdrawal from this drug. The net result was that the transition reported as being both comfortable and safe. Fischer et al. also randomly assigned 18 women to receive either buprenorphine or methadone in a double-blind, double-dummy fashion during weeks 24-29 of pregnancy. Before entering the treatment phase, all participants were maintained on slow-release morphine. Follow-up was until 30 days after delivery. Apart from the small sample size, the results of this study should be viewed with caution as the entry criteria were so strict that only 12% of those screened were deemed eligible. Only 14/18 completed the study. Apart from neonatal outcomes (all delivered healthy babies), no other specific safety data were reported.

One study has looked specifically at the driving-relevant psychomotor effects of buprenorphine and methadone (Soyka, Hock et al. 2005). In this study, 62 participants were randomly assigned to either buprenorphine or methadone and subjected to a standardized test battery. The authors reported a tendency towards better psychomotor performance in those receiving buprenorphine.

Seven recent studies of buprenorphine in the context of detoxification were retrieved (Collins, Kleber et al. 2005; Digiusto, Lintzeris et al. 2005; Ling, Amass et al. 2005; Marsch, Bickel et al. 2005; Oreskovich, Saxon et al. 2005; Raistrick, West et al. 2005; Ponizovsky, Grinshpoon et al. 2006). Each of these is described in some detail.

Collins et al. (2005) randomly assigned 106 heroin-dependent patients to either anaesthesia-assisted rapid detoxification with naltrexone induction, buprenorphine-assisted rapid detoxification with naltrexone induction (on day 2 after admission) or clonidine-assisted rapid detoxification with delayed (1 week after admission) naltrexone induction. Given the nature of the interventions, blinding was not possible. A range of co-medication was allowed. The only SAEs recorded were in the anaesthesia group. One patient developed pulmonary oedema, one developed a mixed bipolar state, and one developed diabetic ketoacidosis. All three episodes were related to prior conditions and experiences.

Digiusto et al. (2005) pooled the data from 5 detoxification trials. However, the two that involved buprenorphine were either included in the Cochrane Review or excluded from that analysis.

Ling et al. (2005) assigned 113 in-patients and 231 out-patients to buprenorphine-naltrexone or clonidine-assisted detoxification in a 2:1 ratio. This was a pragmatic, open-label study. The number of side effects reported was included as a secondary outcome. A large number of prescription and over-the-counter medications for the relief of withdrawal symptoms was provided, including benzodiazepines, Phenobarbital and zolpidem. SAEs (adverse events resulting in overnight hospitalization or death, immediately life-threatening, involving any permanent or substantially disabling event or congenital anomaly) were distinguished from “adverse events”. The mean number of adverse events per treatment day was recorded for each group and the total for each group also calculated. A significantly lower mean number of adverse events was reported for the in-patient buprenorphine-naltrexone group (1.3, SD 0.8) compared to the clonidine group (2.4, SD 1.6), when analysed in an intention-to-treat fashion. This difference was lost in the completer analysis. In the out-patient group, the same difference was seen in both the intention-to-treat (0.7, SD 0.8 vs. 1.2, SD 1.6) and completer analyses (0.6, SD 0.6 vs. 1.1, SD 0.8). In the in-patient group, 4 SAEs were recorded in each arm, with a death in each arm (neither related to study medication) and in the out-patient group, 18 SAEs were recorded. Fourteen of these were in the buprenorphine-naltrexone arm. Ten were continued substance abuse/overdose, 2 were depression and one each were severe vomiting and admission for spinal surgery.

Oreskovich et al. (2005) performed a randomized, double-blind study to compare two buprenorphine dosing schedules to clonidine. The two dosing schedules were 8mg per day on days 1 to 3, then dropped to 4 and 2mg on the next two days (referred to as higher dose) and 2-4-8-4-2mg per day on days 1 to 5 (referred to as lower dose). Ancillary medications were allowed. Adverse effects were assessed by posing the question “How are you feeling” when 6-hourly assessments were made. As medication was withheld if the diastolic blood pressure was below 60 mmHg or the heart rate below 56/minute, these were also measured every 6 hours. Clonidine or placebo was administered 6 hourly. The main adverse effect detected was postural hypotension, in all three arms of the study.

Raistrick et al. (2005) compared buprenorphine to lofexidine for community-based opiate detoxification in an open-label, randomized trial in 210 participants. The primary outcome measured was completion of detoxification. Safety reporting was limited to a single statement: “No major adverse reactions were reported”.

Marsch et al. (2005) conducted a double-blind, double-dummy, randomized trial of buprenorphine versus clonidine in 36 adolescents (aged 13 to 18 years). Measures of “medication effects” were designed to elicit primarily withdrawal symptoms and to detect the

effects of clonidine on blood pressure and heart rate. Those receiving buprenorphine reported more “positive effects”, ascribed to the partial agonist nature of the medication.

The paper by Ponizovsky et al. (2006) has recently been released as an e-publication. It specifically set out to measure well-being, psychosocial factors and side-effects in 200 participants randomly assigned to buprenorphine or clonidine detoxification. The Distress Scale for Adverse Symptoms was used on all who completed the protocol. It elicited responses on a 5-point scale (0 for none to 4 for extreme) for 22 frequently observed side effects seen with psychotropic medicine use. The responses were based on 10-day recall of symptoms. On this basis, participants using buprenorphine experienced significantly less adverse symptoms than did those receiving clonidine.

None of these studies would have altered the conclusions reached in the respective Cochrane Reviews, nor did they provide data that could be subjected to meta-analysis together with data included in the Cochrane Reviews.

2.3.3 Evidence from other sources

Although the original article could not be retrieved, it was noted that an open study in 10 patients had shown rapid tapering of buprenorphine to be effective when compared in a pseudo-experimental fashion to standard detoxification protocols (Palmstierna 2004). No safety data could be retrieved. Also not retrieved was a quality of life (QOL) study in which 3-year follow-up was obtained in 25/53 opioid-dependent subjects who had undergone methadone or buprenorphine maintenance (Giacomuzzi, Ertl et al. 2005). The abstract indicated that “opioid addicts improved their QOL and health status when treated with methadone or buprenorphine”.

It has been claimed that the safety of buprenorphine in HIV-positive opiate-dependent patients has been demonstrated in an 8-day detoxification programme (Montoya, Umbricht et al. 1995). However, this was based on data from only 2/26 patients on the programme.

Three significant case reports have been retrieved which involved causes other than the predictable (such as respiratory depression in overdose). A French group reported a case of myocardial infarction associated with nasal “snorting” of crushed sublingual tablets (an 8mg dose) (Cracowski, Mallaret et al. 1999). The patient, however, had established atherosclerosis, which may have contributed to the ischaemia seen after buprenorphine-induced coronary spasm. Also from France, a series of 7 cases of hepatolytic hepatitis was reported (Herve, Riachi et al. 2004). In 5/7 cases, the presentation was acute, with icteric hepatitis and abdominal pain or fever. Average ALT levels were 39 times the upper limit of normal. All cases were hepatitis C virus positive. All cases resolved rapidly, even though doses were not reduced in 4/7. Parenteral abuse of buprenorphine was reported to be linked with 4 cases of severe upper limb complications (2 vascular problems, 1 hand abscess, 1 median nerve injury) in Singapore (Loo, Yam et al. 2005). Another case reported rhabdomyolysis and compressive sciatic neuropathy (Seet and Lim 2006).

On the positive side, Krantz and colleagues have reported the successful induction of buprenorphine treatment in a patient who presented with methadone-related *torsade de pointes* arrhythmia (Krantz, Garcia et al. 2005). Although this requires validation in larger, preferably prospective clinical trials, it does point to an important safety consideration that may favour the use of buprenorphine.

Programmatic data have been reported for three countries – France (Auriacombe, Franques et al. 2001; Auriacombe, Fatseas et al. 2004), the United Kingdom (Schifano, Corkery et al. 2005) and India (Ray, Pal et al. 2004). The first French estimate showed that from 1994 to 1998 there were an estimated 1.4 times more buprenorphine-related deaths than methadone-related deaths in France. The authors pointed out that “14 times more patients received buprenorphine than methadone” and that “[t]he yearly estimated death rate related to methadone use was at least 3 times greater than the death rate related to buprenorphine use”. They concluded that “[i]f all patients in France who received either of these drugs had been treated only with methadone, the expected number of deaths would have been 288 instead of 46”. The 2004 report from France noted the widespread use of buprenorphine in that country - approximately 65,000 patients per year (about half of the estimated 150,000 problem heroin users). They noted that “[i]ntravenous diversion of BUP may occur in up to 20% of BUP patients and has led to various infections and relatively rare overdoses in combination with sedatives”, but that “[o]piate overdose deaths have declined substantially (by 79%) since BUP was introduced in 1995”. The UK experience noted 43 fatalities over the 1980-2002 period, of which 12 (28%) were judged to be suicides. Although most cases involved other substances (such as benzodiazepines and other opiates), buprenorphine was detected on its own in seven cases. The authors felt this was cause for concern. However, they did note that “[n]o positive correlation was found between the number of buprenorphine deaths over the years and either buprenorphine dispensings/prescriptions or seizures”. The report from India was based on a post-marketing surveillance study. A total of 5551 observations from ten addiction centres were received. It was noted that about 5% of observations recorded systolic hypertension. Laboratory data were only available for 55 subjects, and of these 12 showed raised levels of AST and 9 showed elevated ALT. A total of 12 “adverse events” were reported, and these included seizure, epistaxis, panic attacks, constipation and dyspnoea.

Lastly, a review of the safety profile of the combined buprenorphine/naloxone product was conducted for the US National Institute on Drug Abuse (Bridge, Fudala et al. 2003). The Institute supported the use of buprenorphine, alone or together with naloxone, as the first-line option for office-based management of opiate dependence. This support was based on three observations:

- “a reduced likelihood of diversion of the combination product for diversion to illicit parenteral misuse”
- “the established utility of the mono product for the treatment of opiate dependence”
- “the preferable safety profile of a partial mu-opiate receptor agonist such as buprenorphine compared with that of a full mu-opiate receptor agonist”

2.3.4 Evidence from spontaneous ADR reports

Summary data on spontaneous adverse events reported to the Uppsala Monitoring Centre (the WHO Collaborating Centre for International Drug Monitoring) were extracted from Vigibase on 17 December 2005.¹ A total of 6568 reactions were received from 1978 to 2005 in 3445 reports.

¹ The data are reported here with the usual caveat statement: The WHO Collaborating Centre for International Drug Monitoring, Uppsala, Sweden receives summary clinical reports about individual suspected adverse reactions to pharmaceutical products from National Centres in countries participating in a Collaborative Programme. Only limited details about each suspected adverse reaction are received at the Centre. It is important that the limitations and qualifications which apply to the information and its use are understood. The term “pharmaceutical product” is used instead of “drug” to emphasize that products marketed under one generic or trade name may vary in their content of active or other ingredients, both in time or from place to place. The reports submitted to the Collaborating Centre in many instances describe no more than suspicions which have arisen from observation of an unexpected or unwanted event. In most instances it cannot be proven that a pharmaceutical product or ingredient is the cause of an event. The reports, which are submitted to National Centres, come from both regulatory and

The full Excel spreadsheets are appended electronically to this report. Figure 1 shows the number of reactions reported each year, since 1978.

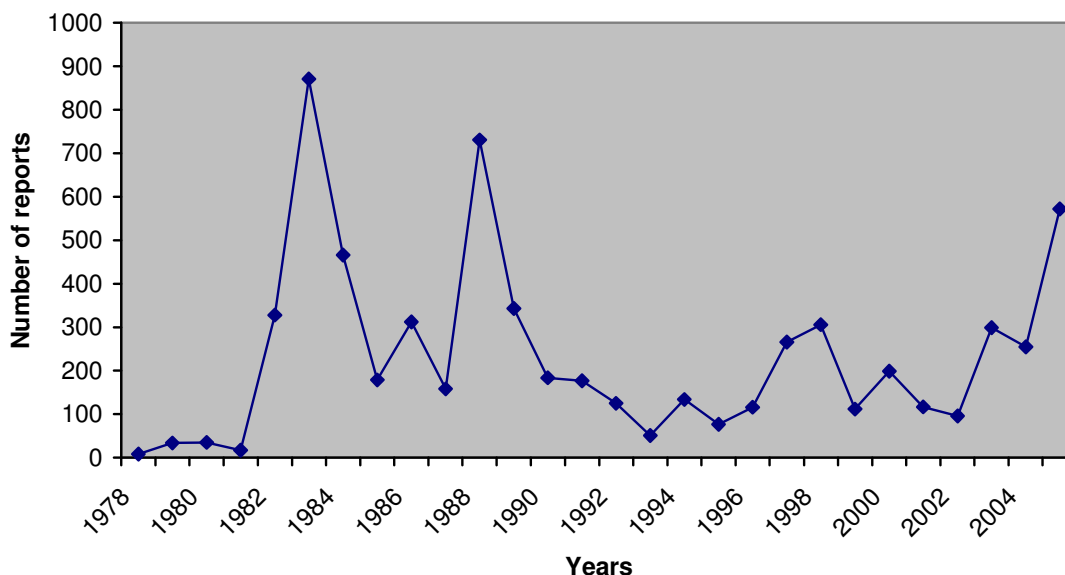


Figure 1: Buprenorphine adverse reactions noted by the Uppsala Monitoring Centre 1978-2005

Although the peak number of reactions reported was in 1983, the recent trend is upward. This may, however, reflect a greater number of reporting centres and improved reporting rates overall, rather than an increase in the true incidence of buprenorphine ADRs.

Of the 572 reactions recorded in 2005, the single largest category was accounted for by reports of “deaths” (n=65), followed by “drug abuse” (n=45). The only other categories in which more than 10 reports were received in the year were (in alphabetical order): “application site reaction” (n=11), “injection site infection (n=16), “withdrawal syndrome” (n=24), “dizziness” (n=12),

voluntary sources. Some national Centres accept reports only from medical practitioners; other National Centres accept reports from a wider spectrum of health professionals. Some National Centres include reports from pharmaceutical companies in the information submitted to the Collaborating Centre; other National Centres do not. The volume of reports for a particular pharmaceutical product may be influenced by the extent of use of the product, publicity, nature of reactions and other factors which vary over time, from product to product and country to country. Moreover, no information is provided on the number of patients exposed to the product. Thus the sources of reports accepted by National Centres vary, as do the proportions. A number of National Centres which contribute information to the Collaborating Centre make an assessment of the likelihood that a pharmaceutical product caused the suspected reaction. Other National Centres do not document such assessments on individual reports in the WHO data base. Processing time varies from country to country. Reporting figures obtained from the Collaborating Centre may therefore differ from those obtained directly from National Centres. For the above reasons interpretations of adverse reaction data, and particularly those based on comparisons between pharmaceutical products, may be misleading. The information tabulated in the accompanying printouts is not homogeneous with respect to the sources of the information or the likelihood that the pharmaceutical product caused the suspected adverse reaction. Some describe such information as "raw data". Any use of this information must take into account at least the above. Some National Centres which have authorized release of their information strongly recommend that anyone who intends to use it should contact them for interpretation. Any publication, in whole or in part, of the obtained information must have published with it a statement: (i) of the source of the information, (ii) that the information is not homogeneous at least with respect to origin or likelihood that the pharmaceutical product caused the adverse reaction, (iii) that the information does not represent the opinion of the World Health Organization. Omission of these 3 statements may exclude the responsible person or organization from further information from the system.

“tremor” (n=12), “nausea” (n=15), “vomiting” (n=15), “drug dependence” (n=14), “somnolence” (n=12), and “term under assessment for WHO-ART” (n=11).

Taken over the whole period, the highest number of reported reactions was coded as “vomiting” (n=678), followed by “nausea” (n=441), and then “dizziness” (n=320). Only 13 other categories accounted for more than 100 reported reactions each (in alphabetical order): “death” (n=118), “withdrawal syndrome” (n=134), “hypotension” (n=117), “headache” (n=124), “vertigo” (n=122), “hallucination” (n=157), “drug abuse” (n=223), “drug dependence” (n=138), “confusion” (n=132), “somnolence” (n=252), “hypoventilation” (n=121), “pruritis” (n=175), and “photosensitivity reaction” (n=148). Overall, the largest number of reactions were reported from the United Kingdom (n=2281), the United States (n=1350) and France (n=1334). Together with Germany (n=467) and Spain (n=265), these countries accounted for 87% of all reported reactions.

2.3.5 Summary

Although the recording of safety data in controlled trials included in the most recent Cochrane Reviews does not allow for meta-analysis, there is no reason to believe that buprenorphine is commonly associated with serious adverse effects. The frequency and severity of side effects seem to be similar for both methadone and buprenorphine patients, although there has been a claim that quality of life is better on buprenorphine. The reported reactions in the Uppsala database are consistent with the expected adverse reactions or the complications of managing this patient type.

3 Methadone

3.1 Introduction

Methadone is a potent synthetic opiate μ -agonist. It is a racemic mixture, with the l-isomer responsible for the drug's analgesic effects. The d-isomer shows less analgesic action, lacks respiratory depression activity and addiction liability, but is an antitussive. Both isomers and the racemate have low affinities for delta and kappa receptors. The principal actions of methadone are thus analgesia and sedation. It has been used in detoxification and maintenance in opioid addiction. The methadone abstinence syndrome, although similar to that of morphine, is slower in onset, and more prolonged, but the symptoms are less severe.

The oral bioavailability of methadone ranges between 36-100% and peak plasma concentrations are achieved between 1-7.5 hours after dosing. Methadone is a lipophilic drug and is therefore widely distributed. The steady-state volume of distribution ranges between 1.0-8.0 L/kg. In plasma, methadone is predominantly bound to α_1 -acid glycoprotein (85-90%). Methadone is primarily metabolized by N-demethylation to an inactive metabolite by the cytochrome P450 enzymes. The isozymes predominantly involved are CYP3A4, CYP2B6, and CYP2C19 and to a lesser extent CYP2C9 and CYP2D6. This has major implications for drug-drug interactions. The inactive metabolites are excreted mainly in urine.

Although respiratory depression is the chief hazard associated with methadone administration, more recently concern has been expressed about the potential for adverse cardiac conduction effects such as prolongation of the QT interval. Methadone can also cause severe hypotension in patients whose ability to maintain normal blood pressure is compromised.

Overdosage of may result in respiratory depression (characterised by a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration and cyanosis), extreme somnolence (eventually progressing to stupor or coma), maximally constricted pupils, skeletal-muscle flaccidity, cold and clammy skin, and, sometimes, bradycardia and hypotension. In severe overdosage, particularly by the intravenous route, this may result in apnoea, circulatory collapse, cardiac arrest, and death.

Intoxication may be reversed by the intravenous administration of opioid antagonists, such as naloxone.

Standard drug monographs provide the following as the expected adverse effects for morphine:

- lightheadedness
- dizziness
- sedation
- nausea
- vomiting
- sweating
- asthenia (weakness)
- oedema
- headache
- abdominal pain
- anorexia

- biliary tract spasm
- constipation
- dry mouth
- glossitis
- hypokalemia
- hypomagnesemia
- weight gain.
- confusion
- seizures
- disorientation
- dysphoria
- euphoria
- insomnia.
- pulmonary oedema.
- pruritus
- urticaria
- other skin rashes (rarely, hemorrhagic urticaria)
- visual disturbances
- antidiuretic effect
- amenorrhea
- urinary retention or hesitancy
- reduced libido and/or potency.

3.2 Search strategy

Methadone has been the subject of three Cochrane Reviews related to opioid dependence (Clark, Lintzeris et al. 2002; Faggiano, Vigna-Taglianti et al. 2003; Amato, Davoli et al. 2005), and these were used as the basis for the search strategy. Details of safety data considered in the Cochrane Reviews were gathered, where possible from the original references included in the reviews. More recent randomised controlled trials (RCTs) and controlled trials (CTs) in the management of opioid dependence, published after the Cochrane Reviews, were obtained by searching Medline and the Cochrane CENTRAL database. The PubMed Clinical Query utility was employed, using the following search strategy:

- (methadone) AND ((clinical[Title/Abstract] AND trial[Title/Abstract]) OR clinical trials[MeSH Terms] OR clinical trial[Publication Type] OR random*[Title/Abstract] OR random allocation[MeSH Terms] OR therapeutic use[MeSH Subheading])

The bibliographies of such references were also hand searched for any additional sources. A broad, sensitive search of Medline was also conducted using the following strategies:

- "Methadone"[MeSH] AND "adverse effects"[Subheading]
- "Methadone"[MeSH] AND "Drug Toxicity"[MeSH]
- "Methadone"[MeSH] AND "toxicity"[Subheading]
- "Methadone"[MeSH] AND "Overdose"[MeSH]

The results of these searches are provided as additional Endnote Libraries, combined and with duplicates removed. This strategy was used to identify additional reviews, observational studies and programmatic reports, case series and significant case reports. Given the interest in this safety aspect, specific attention was paid to retrieving reports concerning the cardiac safety of

methadone and this is reported as a separate section. On request, specific attention was paid to the issue of dental caries, and this is also reported separately.

The evidence is presented from each of the categories identified above:

- Evidence from Cochrane reviews
- Evidence from randomised controlled trials and controlled trials published after the Cochrane Reviews
- Evidence from other sources (observational studies and programmatic reports, case series and significant case reports)

Lastly, data from the Uppsala Monitoring Centre are presented, representing spontaneous adverse event reports from member countries.

3.3 Results

3.3.1 Evidence from Cochrane Reviews

Faggiano et al. (2003) reviewed the efficacy of different doses of methadone in the form of maintenance therapy. The most recent substantive amendment to this review was on 2 May 2003. The reviewers sought to gather data on the type and number of “undesired pharmacological effects” caused by the medication, based on self reports or clinical records. Of the 21 studies included, only 3 included adverse effects as an outcome (Ling, Charuvastra et al. 1976; Rhoades, Creson et al. 1998; Johnson, Chutuape et al. 2000). One other (van Ameijden, Langendam et al. 1999) reported on overdose mortality. Only the data from Johnson et al. (2000) were commented upon in the review, which stated that “no significant differences were evident for side effects ... for high doses compared to low”. No meta-analysis could be done for safety data.

Ling et al. (1976) reported no serious adverse reactions. They did note that 4 patients receiving 80mg of methadone 3 times a week terminated due to an inability to ejaculate. Other withdrawals were also noted to be linked to “decreased sexual interest, nausea and vomiting, tiredness and dizziness, and pruritic maculopapular rash. The authors tried to distinguish between symptoms of under-dosing, symptoms of over-dosing and those related to the patients’ somatic state. Despite heroic amounts of data, they still felt that the safety data were deficient in that only those who remained on therapy could be followed up. They did conclude, however, that “there were no deaths, serious adverse reactions or compelling trends in the laboratory or side effects data”. Van Ameijden et al. (1999) reported on a large prospective cohort of injecting drug users, providing 1 969 person-years of follow-up. During this period, 44 died, 15 of these due to overdose, 7 due to suicide, 7 due to sepsis and/or endocarditis, 5 due to liver failure, 4 due to accidents or violence and 6 due to other causes. The adjusted relative risk of death due to overdose was greatest in those receiving lower doses of methadone (5-55mg) (relative risk 0.35, 95% CI 0.11 to 1.08) than in those receiving higher doses (55-70mg and 75mg and more, RR 0.13, 95% CI 0.02-1.13 and RR 0.11, 95% CI 0.01-0.93, respectively). The data on dosing and deaths was considered to be of good quality, but it had to be accepted that the overdose data relied on only 15 deaths, so detailed data analysis was not possible. The authors did, however, point out that doses of more than 50mg were associated with a threefold lower risk of overdose death.

Though not mentioned by the Cochrane authors, the paper by Strain et al. did report some adverse effect data, but only on the extent of constipation, “sleepiness” or “grogginess”(Strain,

Bigelow et al. 1999). No differences were seen between the methadone doses compared (40-50mg versus 80-100mg per day).

Clark et al. (2002) reviewed the data on comparisons between levomethadyl acetate (LAAM) and methadone, when used for maintenance therapy. These data are of limited utility given the withdrawal of LAAM in the European Union. The most recent substantive amendment of this review was on 5 February 2002. Data were presented on “drop-outs” due to side effects. These were obtained from Johnson et al. (2000) and from a very old paper by Savage et al. (Savage, Karp et al. 1976). A separate analysis was done of data from patients on methadone before entry into the study (Ling, Klett et al. 1978; Karp-Gelernter, Savage et al. 1982). In both meta-analyses, the relative risk of drop-out was greater for LAAM than for methadone.

A more recent Cochrane Review has considered the issue of tapered doses of methadone for opioid withdrawal (Amato, Davoli et al. 2005). This was last updated on 18 May 2005. Of the 16 studies included, 10 reported on side effects. Despite this, the ways in which these data were reported precluded quantitative analysis. As expected, where the control arm was an alpha adrenergic agonist (such as clonidine), the blood pressure was lower in that group. For example, Bearn and colleagues (Bearn, Gossop et al. 1996) reported that no patients on the methadone experienced postural hypotension, compared to 2/44 given lofexidine. Data from a prison-based trial (Howells, Allen et al. 2002) also showed no difference in sitting blood pressure between those on methadone and those on lofexidine. No SAEs were reported. The only minor adverse effect noted was depression (1 case in each arm, out of a total of 74 participants). In a clonidine versus methadone comparison (Kleber, Riordan et al. 1985), it was reported that more patients on clonidine experienced side effects. Comparison with other studies was complicated by the fact that Kleber et al. reported mean side effect scores (scored on a scale of 0 to 4 in 5 areas). In Cami et al. (Cami, de Torres et al. 1985), the denominator for the adverse effect data reported is unclear, as 3 participants who commenced on clonidine were transferred to the methadone arm. Tennant et al., who compared methadone and propoxyphene, reported that “at least a few patients in both groups reported every side effect except hallucinations and seizures (Tennant, Russell et al. 1975). Guanfacine was shown to be associated with a greater bradycardic effect, compared to methadone (San, Fernandez et al. 1994). Mention has already been made of the study by Ubricht et al. (2003), who compared methadone and buprenorphine, showing that systolic blood pressure was lowered by buprenorphine not methadone, but that only patients in the clonidine group discontinued for such reasons. Of relevance to the issue of cardiac toxicity, an old study by Drummond et al. showed that methadone was associated with more bradycardia than chlordiazepoxide in the first days of treatment (Drummond, Turkington et al. 1989).

3.3.2 Evidence from recent controlled trials

Given the more recent date of the Cochrane Review on tapered doses in withdrawal, it is not surprising that the non-included controlled trial data found related to maintenance instead. The general studies are considered as a group, before specific attention is given to data on cardiac conduction issues.

The acute effects of intravenous methadone or heroin compared to placebo were studied in 25 opioid-dependent patients (Stoermer, Drewe et al. 2003). The focus was on ECG, respiratory movements and measurements and EEG effects. Methadone was associated with less respiratory depression than heroin. No bradycardia was noted.

Safety reporting was the specific target of a 29-week out-patient study of behavioural interventions in patients maintained on methadone (Schroeder, Schmittner et al. 2005). Adverse

event data were collected weekly and coded using MedDRA. A total of 884 adverse events were noted, of which 136 (15.4%) were considered to be opiate-related. The most common were coded as “gastrointestinal disorders” (which included dental problems) and “general disorders and administration-site conditions”, responsible for 57 events each. The latter category included withdrawal syndromes. These accounted for 55/57 considered opiate-related. The gastrointestinal events included constipation (39/57), nausea (8/57), vomiting (8/57) and abdominal pain “not otherwise stated” (2/57). Other AEs considered opiate-related were dizziness and somnolence, insomnia, sweating, pruritis and detoxification NOS.

The effect of switching from racemic to L-metahdone or vice versa was assessed in a stratified randomized, 2x2 crossover study (Verthein, Ullmann et al. 2005). Patient’s reporting of opioid effects, which can be described as the side effects of methadone maintenance therapy, were not influenced by the switch. As in so many studies, these were captured as scores, rated on a 4-point scale (not at all, slightly, moderately, strong) and then summed. The individual symptoms elicited were tiredness (within 2 hours of dosing), sweating, uneasiness, disturbance of virility/sexual arousal, constipation and difficulty in urinating.

Methadone was compared to slow-release morphine as an opioid maintenance therapy in a 14-week, randomized, double-blind, double-dummy study in 64 participants (Eder, Jagsch et al. 2005). Although extensive laboratory data were gathered, only elevated liver enzymes, explained by the high level of hepatitis C infection, were noted as abnormal. Reported side effects were similar in both groups, with at least 1 side effect reported by 82% of those receiving morphine and 76% of those receiving methadone. The most common side effect for methadone was toothache (22%), followed by vomiting (17%), headache (14%) and stomach ache (12%). Insomnia and sleep disturbance were the only side effects reported with methadone but not morphine. No SAEs were reported.

It could be argued that the positive effects of methadone are more likely to result in abuse than are those associated with partial agonists, such as buprenorphine. This was investigated in a very small double-blind, placebo-controlled inpatient study, involving self-administration of either intravenously buprenorphine or methadone (Comer, Sullivan et al. 2005). The authors concluded that “under these experimental conditions, buprenorphine and methadone were equally effective in producing reinforcing and subjective effects”.

Overall, these data would not have altered the conclusion of either Cochrane Review. The data retrieved were, similarly, inappropriate for meta-analysis.

3.3.3 Evidence from other sources

Cardiorespiratory function was assessed in 50 stable methadone maintenance patients, but the only abnormalities seen were considered due to either ongoing tobacco or cannabis smoking (Teichtahl, Wang et al. 2004).

The impact of higher doses of methadone in pregnant patients was assessed retrospectively in 81 mothers who received methadone (McCarthy, Leamon et al. 2005). No impact of higher doses on neonatal abstinence syndrome was demonstrated, but higher doses were associated with a greater impact on maternal drug abuse.

A cross-sectional study was conducted in 92 opioid-dependent men recruited from a methadone maintenance programme, to assess the impact of methadone on male sexual function (Brown, Balousek et al. 2005). Based on patient completion of a standardized research instrument, 14%

reported some sexual dysfunction. Increasing methadone dose was correlated with increased orgasm dysfunction. However, sexual dysfunction did not correlate with measured plasma testosterone or prolactin levels.

The link between methadone use and central sleep apnea was investigated in a study involving 50 patients on methadone maintenance (consisting of equal numbers of male and female subjects) and 20 controls matched for age, sex and body mass index (Wang, Teichtahl et al. 2005). It was shown that 30% of the methadone maintenance patients had demonstrable central sleep apnea. However, a simple cause-effect relationship was not shown, and the authors did not claim this to be the cause of mortality in methadone-maintained patients. In a multivariate analysis, methadone blood concentration could only explain a minority of the central sleep apnea noted. Although this review was limited to English language literature, it was noted that an article in French had reported a case of sleep apnea in a woman on opiate replacement therapy with methadone (Durst, Palazzolo et al. 2005).

Long-term follow-up data on 60 patients included in a methadone programme between 1994 and 2002 showed that 10 “failed” (Rhodin, Gronbladh et al. 2006). The causes of “failure” were cited as intractable nausea (n=4), drug diversion (n=4), methadone related arrhythmia (n=1) and insufficient analgesia (n=1).

Recent case reports have been published of desquamating rashes in patients on methadone treatment in New South Wales, Australia, and have stimulated an exchange of correspondence in the medical literature (Currie, Wallman et al. 2005; Heazlewood 2005; Kordjian, Donaldson et al. 2005; Sinclair 2005). There is as yet uncertainty about the exact aetiology and various differential diagnoses have been offered, including secondary syphilis and vasculitis.

The US Center for Substance Abuse Treatment, Substance Abuse and Mental Health Services Administration, produced a report on methadone-related mortality in 2004 (Anon. 2004). It noted that, in the States that have collected, analyzed, and reported relevant data, “methadone-associated mortality appears to be increasing, although the absolute number of cases remains a relatively modest portion of the total number of drug-related deaths” and found that the increased mortality was related to use outside of opioid-dependence management. An example of the data available is provided by a report on deaths among methadone clients in Texas over the period 1994 to 2002 (Maxwell, Pullum et al. 2005). Data on 776 deaths were analysed, showing a greater risk in methadone clients of death from overdose, liver disease, respiratory disease, homicide and AIDS compared to the general population in that State. A bimodal distribution was seen, with an older cohort dying of chronic diseases rather than traumas (including overdose). Data from Utah showed that most of the increase in drug-poisoning deaths over the 1991 to 2003 period was accounted for by non-illicit prescription drugs, notably methadone and other prescription narcotics (Anon. 2005).

Two other recent programmatic reviews have reported on methadone maintenance programmes. Mortality in the Swiss canton of Vaud was shown to be low, at 1% per year among those on methadone maintenance (Pelet, Doll et al. 2005). Similarly, a low threshold programme in Barcelona, Spain, reported a declining mortality over the period from 1992 to 1999 (based on a cohort created over the period 1992 to 1997), from 5.9 per 100 person-years to 1.6 per 100 person-years. The most important factor explaining overdose mortality was **not** being in a maintenance programme (relative risk 7.1).

3.3.4 The issue of cardiotoxicity

There are numerous case reports and case series in the literature that have noted the temporal link between ventricular arrhythmias, and in particular the variant described as *torsade de pointes* (TdP), and methadone administration for both opioid dependence and as an analgesic. Cases have been reported in methadone maintenance programmes (Mokwe and Ositadinma 2003; Decerf, Gressens et al. 2004; Ostvold and Topper 2005; Sanchez Hernandez, Atienza Fernandez et al. 2005), during detoxification with methadone (Ashwath, Ajjan et al. 2005), in relation to “high dose methadone” (Krantz, Lewkowicz et al. 2002; Vodoz, Jaquier et al. 2003; Walker, Klein et al. 2003; Al-Shakarshi, Bent-Hansen et al. 2004), in HIV-infected patients (Gil, Sala et al. 2003; Sala, Anguera et al. 2003; Hrovatin, Zardo et al. 2004), in the management of chronic pain (Porter, Coyne et al. 2005), in a case series from both pain and methadone maintenance programmes (Krantz, Kutinsky et al. 2003), particularly in patients also treated with drugs likely to enhance this effect (Piguet, Desmeules et al. 2004; Rademacher, Dietz et al. 2005), linked to cocaine use (Krantz, Rowan et al. 2005), in a patient sedated with continuous infusion methadone (Karir 2002), in a patient abusing methadone (Indik 2004) and in cases of acute methadone intoxication (De Bels, Staroukine et al. 2003; Almehmi, Malas et al. 2004). TdP has also been associated with the long-acting methadone derivate LAAM (Deamer, Wilson et al. 2001).

Contrary evidence has also been presented. A retrospective analysis of data from 520 cancer patients receiving methadone, in which ECG data were available for 11%, showed no effect on methadone on the QTc interval (based on the mean interval in 30 ECGs recorded before methadone dosing and 26 recorded after methadone) (Reddy, Fisch et al. 2004) The authors, however, did point out that the methadone doses used (median 30mg, range 2-480mg with only 3/520 receiving more than 300mg/day) were somewhat lower than is commonly seen in opioid dependence management.

A prospective cohort study in 132 heroin-dependent patients starting methadone maintenance showed that, regardless of the methadone dose, a statistically significant increase in QTc interval was seen during the first 2 months of methadone treatment (Martell, Arnsten et al. 2003). The authors noted that none of these patients experienced an increase of more than 40 milliseconds, which they referred to as “the generally accepted threshold for an increase that should prompt clinical concern”. A QTc interval greater than 500 milliseconds is also considered a definite risk for *torsade de pointes*, regardless of sex. The mean QTc interval seen in this study was below this threshold (428±21 ms). Similarly, the effect of methadone on QTc interval and “dispersion” (the difference between maximal and minimal QT values at that time point) was prospectively assessed in 118 patients newly admitted to a methadone maintenance facility and repeated at 6 months (Krantz, Lowery et al. 2005). A modest effect on both QTc (increased by 14.1ms) and QT dispersion (increased by 9.5ms) was seen between baseline and 6 months. If defined as values greater than 430ms in men and 450ms in women, then the percentage with “increased QTc” was seen to increase from baseline (14%) to 6 months (31%).

The incidence of prolonged QTc intervals was assessed in 83 patients on “long-term” methadone maintenance (defined for this study as at least 6 months) (Maremmani, Pacini et al. 2005). The mean methadone dose was 87±76mg/day (range 10 to 600mg/day). Prolonged QTc intervals than the reference values for sex and age were shown in 83% of these participants, with no correlation seen between QTc values and methadone dose. A similar study looked prospectively at 104 patients treated with 20mg or more of methadone per day for chronic pain or opioid dependence for 2 weeks or more (defined as “chronic”) (Cruciani, Sekine et al. 2005). The median methadone dose was 100mg/day (range 20-1200mg/day). Using the standard

definition (greater than 430ms in men and 450ms in women), 33% had QTc prolongation, but none had an interval in excess of 500ms. A significant dose-response relationship was observed in males on methadone for less than 12 months.

A prospective study in 44 participants free of structural heart disease sought to correlate QTc interval and methadone serum concentrations (Martell, Arnsten et al. 2005). All participants were newly admitted to a maintenance programme and were assessed at 6 months and 12 months. Mean (SD) increases from baseline to 6 months (12.4 ± 23 ms) and from baseline to 12 months (10.7 ± 30 ms) were demonstrated. At 12 months the change was shown to correlate with both the trough and peak serum methadone concentrations.

QTc changes associated with intravenous methadone (of a formulation containing chlorbutanol, registered only for sc and IM administration in the US) in cancer patients (n=190) were assessed from available ECG traces (for 47/190 patients, providing 169 traces on methadone and 202 off methadone) over a period of 20 months. (Kornick, Kilborn et al. 2003). These were compared to a control group given IV morphine (n=301, with 35 having ECG data, providing 95 traces on morphine and 135 off morphine). The median (SE) methadone dose was 17.8 ± 20.6 mg/hr (range 0.1 to 97.1mg/hr), which is comparable to the doses given to opioid-dependent patients. Methadone, in this formulation, was associated with a greater mean (SE) increase in QTc (41.7 ± 7.8 ms) than was morphine (9.0 ± 6.1 ms), and this correlated with methadone dose. *In vitro* data from the same paper showed that methadone and chlorbutanol independently blocked the cardiac potassium currents involved in a concentration-dependent manner, and that chlorbutanol potentiated methadone's effect.

The dose-dependent nature of methadone's effect has, however, been questioned. A detailed analysis was performed on 5503 methadone-associated adverse events reported to the FDA's Medwatch programme from 1996 to 2002 (Pearson and Woosley 2005). Of these, 43 (0.78%) noted the occurrence of TdP and 16 (0.29%) of QT prolongation. The doses administered were reported in 42/59 (71%) cases. The median dose was 345mg/day, with a range from 29 to 1680mg/day. The authors noted that 29% of cases occurred in patients given 60-100mg/day of methadone, which they regarded as "within the recommended range for methadone maintenance treatment". In 75% of cases, risk factors for TdP (female gender, interacting medication, hypokalaemia, hypomagnesaemia, structural heart disease) were present. While most required hospitalization or prolongation of hospitalization (47%), only 8% were fatal. The authors concluded that "prolonged QT and TdP can occur over a wide range of dosages including those recommended for addiction treatment".

The issue of methadone-associated cardiotoxicity has also been the subject of reviews and commentaries, as well as correspondence in the medical literature. Advice has varied. Some would suggest that baseline ECGs (and QTC determinations) are done before using methadone, together with a clinical evaluation to identify other possible causes of TdP (such as electrolyte disturbances or interacting drugs) (Lucchini, Barbaro et al. 2004; Sticherling, Schaer et al. 2005), while others reject the need for routine ECGs but emphasise the avoidance of other risk factors (Krook, Waal et al. 2004). The simple dose-dependent effect was questioned, particularly at higher and more effective doses (above 100mg/day) (Krantz and Mehler 2004).

Though not from the peer-reviewed literature, documents published by the Addiction Treatment Forum have provided useful reviews of the issue of methadone safety, and are cited by others (Stimmel 2003). In one of these (Does methadone maintenance treatment affect heart health? By S.B. Leavitt, dated June 2001; accessible at http://www.atforum.com/SiteRoot/pages/addiction_resources/Methadone%20&%20Heart%20H

ealth.pdf), Leavitt has comprehensively reviewed the science of QT prolongation, the risk factors in methadone maintenance patients and the scientific literature. An updated version has been produced (Cardiac considerations during MMT by S.B Leavitt and M.J. Krantz, dated October 2003' accessible at http://www.atforum.com/SiteRoot/pages/addiction_resources/CardiacPaper.pdf) and a comprehensive and fully referenced guide to methadone drug interactions (Methadone-drug interactions by S.B Leavitt, dated November 2005, accessible at http://www.atforum.com/SiteRoot/pages/addiction_resources/Drug_Interactions.pdf) was recently updated. The authors of the October 2003 document concluded that "methadone remains an effective and well-tolerated therapy for the treatment of opioid addiction when prescribed appropriately. They provided practical suggestions for safe use of methadone, but emphasized that these were not intended to deter the use of methadone in any patient who would otherwise benefit.

Despite such views, a case has been made that methadone should be abandoned and replaced with buprenorphine, based predominantly on safety in overdose (Luty, O'Gara et al. 2005). The authors noted that methadone was associated with 167 drug-related deaths in the United Kingdom in 2003, of which just more than half were associated with diverted methadone. In contrast, buprenorphine had not been implicated by coroners in any deaths since 1999. Seven deaths had been recorded in the UK's adverse event database in which buprenorphine was noted, but not specifically identified as the causative agent. The authors did, however, concede that buprenorphine was 4 times more expensive than methadone. This article stimulated at least two responses (Bakker and Sibanda 2006; Byrne and Hallinan 2006). Both disagreed with the proposal, arguing that both agents were necessary. The issue of injecting buprenorphine was raised. It was also pointed out that 75% of the methadone-related deaths recorded in the UK in 2003 involved multiple drugs. The highest death rate was in a part of the country where methadone provision was considered to be poor. Overall, opiate overdose deaths were decreasing. This is consistent with data from other countries (Shah, Lathrop et al. 2005).

This is a complex issue and one in which a clear picture has perhaps yet to emerge. There are, however, comprehensive resources that can help clinicians identify interacting drugs that may enhance methadone's ability to prolong the QTc interval and put patients at increased risk of life-threatening arrhythmias. One such resource has been identified above. For the particular problems seen with HIV-positive patients on antiretroviral agents (where the non-nucleoside reverse transcriptase inhibitors and the protease inhibitors may interact, particularly at the level of CYP 3A4), well-referenced resources are available at:

- The Liverpool HIV Pharmacology group's web site (<http://www.hiv-druginteractions.org/>)
- The University of California, San Francisco's centre for HIV Information web site (<http://hivinsite.org/arvdb?page=ar-00-02>)
- The well-known "Flockhart" chart web site (<http://medicine.iupui.edu/flockhart/table.htm>)

3.3.5 The issue of dental caries

Concern has been expressed about the risk of dental caries in users of methadone. A case series reporting "several cases of advanced tooth destruction from widespread severe carious lesions" was reported in the Australian dental literature in 1996 (Sheedy 1996). Although the original paper could not be retrieved for this review, it was noted that the abstract made a link between such cases and the use of methadone syrup in drug rehabilitation programmes. The possibility of

a causal link was, however, questioned at the same time. Zador et al. reported on a dietary analysis of 86 women attending a methadone maintenance clinic in Sydney, Australia (Zador, Lyons Wall et al. 1996). They found that the diet of this group was characterized by low energy intake, high sugar intake and low dietary fibre, concluding that “this eating pattern may contribute to the high incidence of dental caries and chronic constipation observed in the group”. A more recent commentary on the dental management of patients taking methadone has also pointed to the possible role of xerostomia, but cautioned that “many drug abusers have poor oral health”(Graham and Meechan 2005).

A recent review has also emphasized the view that the high incidence of dental caries in opioid users is “due to a complex, dynamic relationship between multiple factors” (Titsas and Ferguson 2002). The factors listed included general personal neglect and poor dental hygiene, a diet based on high-sugar convenience foods, increased palatability and rewarding aspects of sweet substances (a taste preference, in other words), xerostomia (particularly when opioids are co-administered with antidepressants), prolonged contact with sucrose-based methadone syrups (for example, in those wishing to prolong absorption time or even degurgitate later for parenteral administration or sale), masking of dental pain, high use of alcohol and tobacco, bruxism, and, possibly, altered microbial profiles and immune suppression related to opioid use.

Although published in French, the English abstract of a paper reporting on a case-control study looking at the buccal-dental health of opioid users was retrieved (Madinier, Harrosch et al. 2003). In this study, two groups of intravenous and non-intravenous drug addicts were compared with two age-matched control groups of non-addicted subjects. Compared to non-users, addicts had more decayed teeth, reduced masticatory function and lower periodontal health, which the authors reported to be “correlated with inadequate dental hygiene”. Intravenous heroin use was, however, associated with rapidly progressive dental decay, even in those with satisfactory dental hygiene (n=4).

A direct causal link between oral methadone use and markedly poorer dental health in thus difficult to demonstrate. Illicit opioid users are likely to present with many factors associated with dental caries and poor periodontal health.

3.3.6 Evidence from spontaneous ADR reports

Summary data on spontaneous adverse events reported to the Uppsala Monitoring Centre (the WHO Collaborating Centre for International Drug Monitoring) were extracted from Vigibase on 17 December 2005. A total of 6824 reactions were received from 1968 to 2005 in 3071 reports.

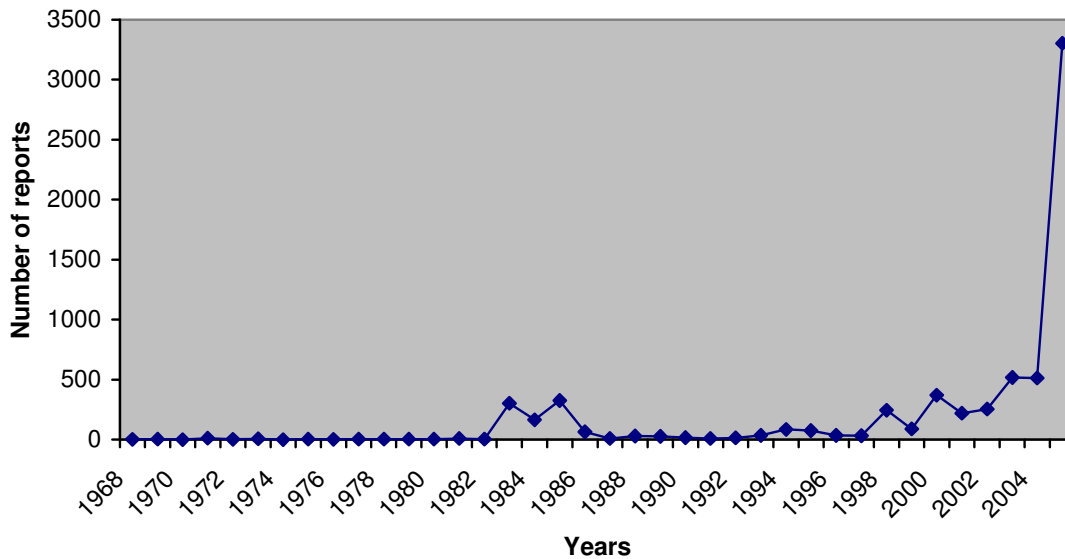


Figure 2: Methadone adverse reactions noted by the Uppsala Monitoring Centre 1968-2005

Almost half of all reported reactions were received in 2005. Assessment is complicated by the fact that almost a sixth of all reactions were coded as “term not accepted in WHO-ART” (n=700) and “term under assessment for WHO-ART” (n=377). Almost all of these (n=652 and n=374 respectively) were received from the United States, which accounted for 5543 (81%) reactions in total over the period under review. The next most prevalent reaction coded was “withdrawal syndrome” (n=380), followed by “death” (n=333), “suicide attempt (n=220), “medication error” (n=200), “drug abuse” (n=169), “cardiac arrest” (n=168) and “somnolence” (n=133). Together these accounted for 39% of reported reactions. Only 32 instances of *torsade de pointes* were reported over this period, all in the last 6 years and mostly (n=23) from the United States. In addition 32 instances of QT prolongation were reported over the same time period, 25 from the United States. All “heart rate and rhythm disorders” accounted for 367 reported reactions, of which 320 were from the USA and 224 were reported in 2005 only. In the preceding three years, 32, 25 and 25 such reactions were reported respectively. The most prevalent over the period was “cardiac arrest” (n=168).

Overall, the second most reports were from Australia (n=397), followed by France (n=293), Switzerland (n=109), Germany (n=101) and the United Kingdom (n=100). Together with the USA, these countries accounted for 95.9% of all reactions reported.

3.3.7 Summary

Methadone has been available for more than 35 years and has been used by millions of patients in a variety of settings. Although this review has not been able to provide suitable data for a meta-analysis of safety data, it would seem that the increased number of adverse events reported in recent years to the Uppsala Monitoring Centre may be due to increased awareness rather than an increase in the incidence of serious, previously unrecognised problems. As a full opioid agonist, it is associated with the full spectrum of effects of that class, but it is well-known and the means for safe and effective application in opioid dependence are available. Recent studies have pointed to how individual dose determinations can be made (Trafton, Minkel et al. 2006).

4 Naltrexone

4.1 Introduction

Naltrexone is a specific, high affinity, long acting competitive antagonist at opioid receptors. It has negligible opioid agonist activity. Importantly, tolerance does not develop with prolonged use. Naltrexone blocks the effects of opioids by competitive binding

Naltrexone is rapidly absorbed after oral administration, but significant first pass metabolism. Estimates of oral bioavailability range from 5-40%. It is metabolised by the liver to an active metabolite. Peak plasma levels of naltrexone and the active metabolite (6- β -naltrexol) occur within 1 hour of dosing. Both naltrexone and its metabolites are excreted primarily by the kidney (53-79% of the dose). Less than 5% is excreted in the faeces. The mean elimination half-life values for naltrexone and the active metabolite are 4 hours and 13 hours respectively. The systemic clearance exceeds liver blood flow, suggesting that naltrexone is a highly extracted drug (>98% metabolized) and that extra-hepatic sites of drug metabolism exist. Naltrexone and its metabolites are also conjugated to form additional metabolic products.

It is widely distributed, with 21% bound to plasma proteins. over the therapeutic dose range. Naltrexone and its metabolites may undergo enterohepatic recycling.

Standard drug monographs provide the following as the expected adverse effects for Naltrexone. Those occurring at an incidence rate of more than 10% include:

- difficulty sleeping
- anxiety
- nervousness
- abdominal pain/cramps
- nausea and/or vomiting
- low energy
- joint and muscle pain
- headache

Those occurring less frequently, at an incidence rate of less than 10% include:

- loss of appetite
- diarrhoea
- constipation
- increased thirst
- increased energy
- feeling down
- irritability
- dizziness
- skin rash
- delayed ejaculation
- decreased potency
- chills.

The following are reported to occur in less than 1% of subjects:

- nasal congestion
- itching
- rhinorrhea

- sneezing
- sore throat
- excess mucus or phlegm
- sinus trouble
- heavy breathing
- hoarseness
- cough
- shortness of breath
- nose bleeds
- phlebitis
- oedema
- increased blood pressure
- non-specific ECG changes
- palpitations
- tachycardia
- excessive gas
- haemorrhoids
- diarrhoea
- ulcer
- painful shoulders, legs or knees
- tremors
- twitching
- increased frequency of, or discomfort during, urination
- increased or decreased sexual interest
- oily skin
- pruritus
- acne
- athlete's foot
- cold sores
- alopecia
- depression
- paranoia
- fatigue
- restlessness
- confusion
- disorientation
- hallucination
- nightmares
- bad dreams
- burred, burning, light sensitive, swollen, aching, strained eyes
- "clogged" ears, aching or tinnitus
- increased appetite
- weight loss or weight gain
- yawning
- somnolence
- fever
- dry mouth
- head "pounding"

- inguinal pain
- swollen glands
- "side" pains
- cold feet
- "hot spells"

4.2 Search strategy

Naltrexone has been the subject of 4 Cochrane Reviews and these were used as the basis for the search strategy (Kirchmayer, Davoli et al. 2003; Gowing, Ali et al. 2006; Gowing, Ali et al. 2006; Minozzi, Amato et al. 2006). Details of safety data considered in the Cochrane Reviews were gathered, where possible from the original references included in the reviews. More recent randomised controlled trials (RCTs) and controlled trials (CTs) in the management of opioid dependence, published after the Cochrane Reviews, were obtained by searching Medline and the Cochrane CENTRAL database. The PubMed Clinical Query utility was employed, using the following search strategy:

- (naltrexone) AND ((clinical[Title/Abstract] AND trial[Title/Abstract]) OR clinical trials[MeSH Terms] OR clinical trial[Publication Type] OR random*[Title/Abstract] OR random allocation[MeSH Terms] OR therapeutic use[MeSH Subheading])

The bibliographies of such references were also hand searched for any additional sources. A broad, sensitive search of Medline was also conducted using the following strategies:

- " Naltrexone"[MeSH] AND "adverse effects"[Subheading]
- " Naltrexone"[MeSH] AND "Drug Toxicity"[MeSH]
- " Naltrexone"[MeSH] AND "toxicity"[Subheading]
- " Naltrexone"[MeSH] AND "Overdose"[MeSH]

The results of these searches are provided as additional Endnote Libraries, combined and with duplicates removed. This strategy was used to identify additional reviews, observational studies and programmatic reports, case series and significant case reports.

The evidence is presented from each of the categories identified above:

- Evidence from Cochrane reviews
- Evidence from randomised controlled trials and controlled trials published after the Cochrane Reviews
- Evidence from other sources (observational studies and programmatic reports, case series and significant case reports)

Lastly, data from the Uppsala Monitoring Centre are presented, representing spontaneous adverse event reports from member countries.

4.3 Results

4.3.1 Evidence from Cochrane Reviews

Kirchmayer et al. (2003) evaluated the effects of naltrexone maintenance therapy in preventing relapse in opioid addicts after detoxification. The most recent substantive amendment to this review was on 14 February 2003. The authors noted that only 13 studies met the criteria for inclusion and that most involved small numbers of participants. Six of the studies included had set out to record data on adverse effects or toxicity of naltrexone (Brahen, Capone et al. 1977; Hollister, Schwin et al. 1977; Brahen, Capone et al. 1979; San, Pomarol et al. 1991; Shufman,

Porat et al. 1994; Cornish, Metzger et al. 1997). No meta-analysis of side effect data was attempted.

Brahen et al. (1997) reported the number of side effects with the trial drug (naltrexone or cyclazocine) after subtracting the number of placebo responses. In this way a “preponderance” of side effects for cyclazocine (n=298) was shown over naltrexone (n=67). No patient on naltrexone discontinued treatment because of adverse effects. The most prevalent side effect noted was loss of appetite, but weight changes in both directions was noted in this group.

Brahen et al. (1979) found no significant difference in side effects between naltrexone and cyclazocine, but a trend in favour of the former.

Cornish et al (1997) noted that “the safety of naltrexone has now been repeated demonstrated”, and accordingly found that “complaints were few”.

The study by San et al (1991) was significant in that it showed no difference in efficacy or side effects between naltrexone and placebo over a 1 years study period. This study included only 50 participants.

Shufman et al. (1994) also showed no difference in adverse effects between naltrexone and placebo. The most common adverse effects noted were headaches, depression, “stomach/belly aches”, vomiting and diarrhoea. In this study, if the adverse effects noted by one participant in the placebo arm was included, that arm was associated with more adverse effects. This single participant was responsible for 30% of all adverse effects noted. This is a notable problem with such small studies, in which loss to follow-up is high. In this case, the study commenced with 32 participants and only 17 completed the programme.

The Cochrane Review by Minozzi et al. (2006) was completed more recently, and last amended on 27 October 2005. It also set out to evaluate the effects of naltrexone maintenance treatment versus placebo or other treatments in preventing relapse in addicts after detoxification. A secondary outcome measure included was the “number of participants with at least one side effect”. Ten studies with 696 participants were included in the review. Because of the way in which the outcome measure was constructed, some limited meta-analyses were possible. Of the studies that considered naltrexone versus placebo and naltrexone plus psychosocial therapy versus placebo plus psychosocial therapy, 3 studies (with 139 participants) could be analysed. No statistical difference was seen (RR 1.21, 95% CI 0.81 to 1.81), but the authors felt there was a trend in favour of placebo. If only the drug intervention studies only were included (2 studies, 87 participants), the result was similar (RR 0.96, 95% CI 0.65 to 1.42). The remaining study, which combined the drug trial with psychosocial therapy (52 participants) also showed the same result (RR2.47, 95%CI 0.74 to 8.28), again interpreted as showing a trend in favour of placebo plus psychosocial therapy. One study compared naltrexone versus psychosocial therapy, and again no difference could be detected (RR 0.83, 95% CI 0.34 to 2.02). Given the small numbers involved, the authors questioned the external validity of this review.

One of the studies included in this review that was not considered in the previous Cochrane Review by Kirchmayer et al. (2002), was published in 2004 (Krupitsky, Zvartau et al. 2004). This was a randomized, double blind study in 52 participants. The extent of side effect reporting is typical of clinical trials reports in this area. Of the 27 participants randomized to naltrexone, only 12 completed 6 months of therapy. Five reported side effects at 2 weeks and 3 at 1 month. In contrast, 2 patients on the placebo reported side effects at 2 weeks and 1 each at 6 weeks and 14 weeks. One placebo patient died of an overdose after dropping out of the study and one

active arm participant tried to commit suicide after being diagnosed HIV positive but failed (attributed to the naltrexone blockade). The side effects noted with naltrexone were abdominal discomfort and nausea, and one had a rash which responded to anti-allergic medication.

Two Cochrane Reviews by Gowing et al. (2006) have considered the use of naltrexone and other antagonists in withdrawal, together with either heavy sedation/anaesthesia or minimal sedation. The first of these was last updated on 11 December 2001, while the second was updated on 8 November 2005. Given the range of drugs administered and the withdrawal effects seen, teasing out adverse effects due to naltrexone alone is not easy. Vomiting during sedation or anaesthesia is significant, particularly if the airway is not adequately protected. Tied to this is the risk of cardiotoxicity, perhaps linked to hypokalaemia. Where minimal sedation is employed, the link between adverse effects and naltrexone should be somewhat easier to discern. The authors of the Cochrane Review noted that in one study (O'Connor, Waugh et al. 1995), 4/68 treated with clonidine-naltrexone, compared to 0/57 treated with clonidine only, experienced mild to moderate delirium on the first day of therapy. This effect may have been blunted in other studies where adjunctive medication had an antipsychotic effect.

4.3.2 Evidence from recent controlled trials

Two recent RCTs have considered the safety of naltrexone. Noting that dysphoria and depression had been cited as side effects, a randomized controlled study was designed to compare naltrexone (n=42) versus methadone (n=38) maintenance (Dean, Saunders et al. 2006). When analysed according to intention-to-treat principles there were no changes overall and no differences between the groups, as measured by the Beck Depression Index. A limitation of the study is that data on antidepressant use was available for only 36% of participants, although the extent of use was not different between groups (16 in the naltrexone group and 7 in the methadone group). What was, however, demonstrated was that patients adherent to naltrexone had less severe depressive symptoms than those who were non-adherent. The authors concluded that “depression need not be considered a common adverse effect of naltrexone treatment or a contraindication”.

The efficacy and safety of a sustained-release injectable formulation of naltrexone was assessed in an 8-week double-blind, placebo-controlled trial in 60 heroin-dependent adults (Comer, Sullivan et al. 2006). In the placebo group, 9/18 (50%) patients experienced an adverse event, compared to 13/20 (65%) in the 192mg naltrexone group and 15/22 (68%) in the 384mg naltrexone group. There were no significant differences in total AEs experienced, in treatment-related AEs and in the rates of discontinuation due to AEs. However, the numbers in each case were small. The majority of AEs noted were fatigue, injection site induration and injection site pain. Two SAEs were recorded, but were not treatment related (diabetes and an incident hepatitis C infection).

4.3.3 Evidence from other sources

A non-Cochrane review of naltrexone as maintenance therapy for opioid dependence has recently been published (Johansson, Berglund et al. 2006). The intended focus was on efficacy, not safety, and 15 RCTs (1071 participants) were included. Only out-patient studies involving 20 or more participants and with a duration of at least 4 weeks were included. Some studies included in the corresponding Cochrane Reviews were thus excluded. No safety data were reported.

The only other material evidence retrieved was a case series of 3 fatalities associated with naltrexone regimen changes (Oliver, Horspool et al. 2005). In each of the 3 cases, patients who

had been managed with naltrexone implants were changed to oral tablets, became non-adherent to this treatment, and then fatally overdosed on heroin. Loss of tolerance to usual heroin doses was considered responsible.

4.3.4 Evidence from spontaneous ADR reports

Summary data on spontaneous adverse events reported to the Uppsala Monitoring Centre (the WHO Collaborating Centre for International Drug Monitoring) were extracted from Vigibase on 31 January 2006. A total of 1507 reactions were received from 1985 to 2005 in 681 reports. Six reactions were logged in January 2006.

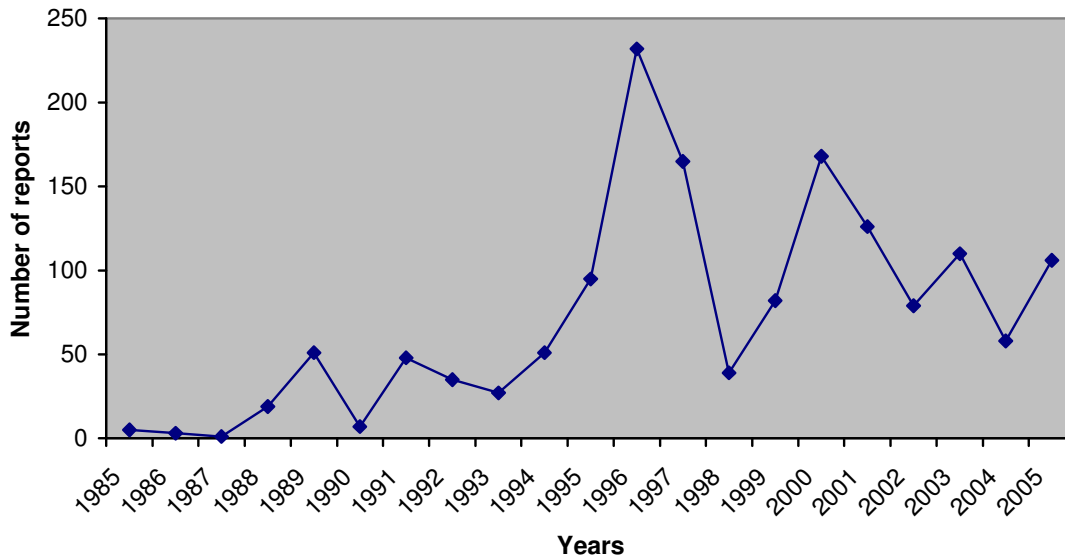


Figure 3: Naltrexone adverse reactions noted by the Uppsala Monitoring Centre 1985-2005

If anything, a stabilising trend could be deduced from these data. More than half (n=881) of the total reactions reported were from the United States, followed by Australia (n=134), the United Kingdom (n=119) and Finland (n=94). Together these countries accounted for 81.2% of all reactions reported.

The most prevalent reaction reported over the period was “vomiting” (n=61), followed by “nausea” (n=55), “abdominal pain” (n=44), “dizziness” (n=41), “withdrawal symptoms (n=39), “diarrhea” (n=37) and “headache” (n=34). Together these accounted for only 20.6% of reactions reported.

4.3.5 Summary

Although the data extracted, including that included in the various Cochrane Reviews, does not allow for meta-analysis, there is not reason to believe that naltrexone is commonly associated with serious adverse effects. The reported reactions in the Uppsala database are consistent with the expected adverse reactions or the complications of managing this patient type.

5 Summary table and conclusions

The sources of data for this review are shown in the summary table below. “Other” study designs refers to observational studies (cohorts, case-control, case series), as well as to commentaries and programmatic reports.

Agent	Cochrane Reviews	Non-Cochrane reviews	Controlled studies	Other studies	Spontaneous adverse event reports
Buprenorphine	2	-	12	11	3445
Methadone	3	-	5	57	3071
Naltrexone	4	1	2	1	681

The summary conclusions reached were as follows:

- Although the recording of safety data in controlled trials included in the most recent Cochrane Reviews does not allow for meta-analysis, there is no reason to believe that buprenorphine is commonly associated with serious adverse effects. The frequency and severity of side effects seem to be similar for both methadone and buprenorphine patients, although there has been a claim that quality of life is better on buprenorphine. The reported reactions in the Uppsala database associated with buprenorphine are consistent with the expected adverse reactions or the complications of managing this patient type.
- Although this review has not been able to provide suitable data for a meta-analysis of safety data, it would seem that the increased number of adverse events involving methadone reported in recent years to the Uppsala Monitoring Centre may be due to increased awareness rather than an increase in the incidence of serious, previously unrecognised problems. As a full opioid agonist, it is associated with the full spectrum of effects of that class, but it is well-known and the means for safe and effective application in opioid dependence are available. Recent studies have pointed to how individual dose determinations can be made. The question of methadone and cardiotoxicity is complex. A clear picture has perhaps yet to emerge. There are, however, comprehensive resources that can help clinicians identify interacting drugs that may enhance methadone’s ability to prolong the QTc interval and put patients at increased risk of life-threatening arrhythmias. A direct and exclusive causal link between oral methadone use and increased risk of dental caries cannot be supported by the available literature.
- Although the data extracted, including that included in the various Cochrane Reviews, does not allow for meta-analysis, there is not reason to believe that naltrexone is commonly associated with serious adverse effects. The reported reactions in the Uppsala database associated with naltrexone are consistent with the expected adverse reactions or the complications of managing this patient type.

6 Acknowledgements

I would like to acknowledge the assistance provided by the staff of the Uppsala Monitoring Centre, particularly Kristina Star, and also the assistance provided by Janet van Maarsdyk in accessing hard copies of the literature retrieved. The feedback provided by Dr Vladimir Poznyak and Dr Sue Hill is also acknowledged with thanks.

7 References

- Al-Shakarshi, J. S., L. Bent-Hansen, et al. (2004). "[Life-threatening, recurrent arrhythmia in patients on high-dose methadone treatment: torsade de pointes]." Ugeskr Laeger **166**(36): 3104-5.
- Almehmi, A., A. M. Malas, et al. (2004). "Methadone-induced torsade de pointes in a patient with normal baseline QT interval." W V Med J **100**(4): 147-8.
- Amato, L., M. Davoli, et al. (2005). "Methadone at tapered doses for the management of opioid withdrawal." Cochrane Database Syst Rev(3): CD003409.
- Anon. (2004). Methadone-Associated Mortality: Report of a National Assessment. Rockville, MD, Center for Substance Abuse Treatment, Substance Abuse and Mental Health Services Administration.
- Anon. (2005). "Increase in poisoning deaths caused by non-illicit drugs--Utah, 1991-2003." MMWR Morb Mortal Wkly Rep **54**(2): 33-6.
- Ashwath, M. L., M. Ajjan, et al. (2005). "Methadone-induced bradycardia." J Emerg Med **29**(1): 73-5.
- Assadi, S. M., M. Hafezi, et al. (2004). "Opioid detoxification using high doses of buprenorphine in 24 hours: a randomized, double blind, controlled clinical trial." J Subst Abuse Treat **27**(1): 75-82.
- Auriacombe, M., M. Fatseas, et al. (2004). "French field experience with buprenorphine." Am J Addict **13 Suppl 1**: S17-28.
- Auriacombe, M., P. Franques, et al. (2001). "Deaths attributable to methadone vs buprenorphine in France." Jama **285**(1): 45.
- Bakker, A. and V. Sibanda (2006). "Is methadone too dangerous for opiate addiction? Issue is one of toxicity v acceptability." Bmj **332**(7532): 53.
- Bearn, J., M. Gossop, et al. (1996). "Randomised double-blind comparison of lofexidine and methadone in the in-patient treatment of opiate withdrawal." Drug Alcohol Depend **43**(1-2): 87-91.
- Brahen, L. S., T. Capone, et al. (1977). "Naltrexone and cyclazocine. A controlled treatment study." Arch Gen Psychiatry **34**(10): 1181-4.
- Brahen, L. S., T. Capone, et al. (1979). "The double-blind crossover trial design: how good is it for psychoactive drugs?" Am J Drug Alcohol Abuse **6**(2): 189-96.
- Bridge, T. P., P. J. Fudala, et al. (2003). "Safety and health policy considerations related to the use of buprenorphine/naloxone as an office-based treatment for opiate dependence." Drug Alcohol Depend **70**(2 Suppl): S79-85.
- Brown, R., S. Balousek, et al. (2005). "Methadone maintenance and male sexual dysfunction." J Addict Dis **24**(2): 91-106.
- Byrne, A. and R. Hallinan (2006). "Is methadone too dangerous for opiate addiction? Methadone is still needed in addiction treatments." Bmj **332**(7532): 53.
- Cami, J., S. de Torres, et al. (1985). "Efficacy of clonidine and of methadone in the rapid detoxification of patients dependent on heroin." Clin Pharmacol Ther **38**(3): 336-41.
- Chawarski, M. C., D. E. Moody, et al. (2005). "Buprenorphine tablet versus liquid: a clinical trial comparing plasma levels, efficacy, and symptoms." J Subst Abuse Treat **29**(4): 307-12.
- Cheskin, L. J., P. J. Fudala, et al. (1994). "A controlled comparison of buprenorphine and clonidine for acute detoxification from opioids." Drug Alcohol Depend **36**(2): 115-21.
- Clark, N., N. Lintzeris, et al. (2002). "LAAM maintenance vs methadone maintenance for heroin dependence." Cochrane Database Syst Rev(2): CD002210.

- Collins, E. D., H. D. Kleber, et al. (2005). "Anesthesia-assisted vs buprenorphine- or clonidine-assisted heroin detoxification and naltrexone induction: a randomized trial." Jama **294**(8): 903-13.
- Comer, S. D., M. A. Sullivan, et al. (2005). "Comparison of intravenous buprenorphine and methadone self-administration by recently detoxified heroin-dependent individuals." J Pharmacol Exp Ther **315**(3): 1320-30.
- Comer, S. D., M. A. Sullivan, et al. (2006). "Injectable, sustained-release naltrexone for the treatment of opioid dependence: a randomized, placebo-controlled trial." Arch Gen Psychiatry **63**(2): 210-8.
- Cornish, J. W., D. Metzger, et al. (1997). "Naltrexone pharmacotherapy for opioid dependent federal probationers." J Subst Abuse Treat **14**(6): 529-34.
- Cracowski, J. L., M. Mallaret, et al. (1999). "Myocardial infarction associated with buprenorphine." Ann Intern Med **130**(6): 536; author reply 536-7.
- Cruciani, R. A., R. Sekine, et al. (2005). "Measurement of QTc in patients receiving chronic methadone therapy." J Pain Symptom Manage **29**(4): 385-91.
- Currie, J. N., L. Wallman, et al. (2005). "A syndromic rash in patients attending methadone clinics in New South Wales." Med J Aust **182**(2): 73-5.
- De Bels, D., M. Staroukine, et al. (2003). "Torsades de pointes due to methadone." Ann Intern Med **139**(2): E156.
- Deamer, R. L., D. R. Wilson, et al. (2001). "Torsades de pointes associated with high dose levomethadyl acetate (ORLAAM)." J Addict Dis **20**(4): 7-14.
- Dean, A. J., J. B. Saunders, et al. (2006). "Does naltrexone treatment lead to depression? Findings from a randomized controlled trial in subjects with opioid dependence." J Psychiatry Neurosci **31**(1): 38-45.
- Decerf, J. A., B. Gressens, et al. (2004). "Can methadone prolong the QT interval?" Intensive Care Med **30**(8): 1690-1.
- Digiusto, E., N. Lintzeris, et al. (2005). "Short-term outcomes of five heroin detoxification methods in the Australian NEPOD Project." Addict Behav **30**(3): 443-56.
- Drummond, D. C., D. Turkington, et al. (1989). "Chlordiazepoxide vs. methadone in opiate withdrawal: a preliminary double blind trial." Drug Alcohol Depend **23**(1): 63-71.
- Durst, P., J. Palazzolo, et al. (2005). "[Methadone and sleep apnea syndrome]." Can J Psychiatry **50**(3): 153-8.
- Eder, H., R. Jagsch, et al. (2005). "Comparative study of the effectiveness of slow-release morphine and methadone for opioid maintenance therapy." Addiction **100**(8): 1101-9.
- Faggiano, F., F. Vigna-Taglianti, et al. (2003). "Methadone maintenance at different dosages for opioid dependence." Cochrane Database Syst Rev(3): CD002208.
- Fischer, G., R. Ortner, et al. (2006). "Methadone versus buprenorphine in pregnant addicts: a double-blind, double-dummy comparison study." Addiction **101**(2): 275-81.
- Giacomuzzi, S. M., M. Ertl, et al. (2005). "Sublingual buprenorphine and methadone maintenance treatment: a three-year follow-up of quality of life assessment." ScientificWorldJournal **5**: 452-68.
- Gil, M., M. Sala, et al. (2003). "QT prolongation and Torsades de Pointes in patients infected with human immunodeficiency virus and treated with methadone." Am J Cardiol **92**(8): 995-7.
- Gowing, L., R. Ali, et al. (2006). "Buprenorphine for the management of opioid withdrawal." Cochrane Database Syst Rev(2): CD002025.
- Gowing, L., R. Ali, et al. (2006). "Opioid antagonists under heavy sedation or anaesthesia for opioid withdrawal." Cochrane Database Syst Rev(2): CD002022.
- Gowing, L., R. Ali, et al. (2006). "Opioid antagonists with minimal sedation for opioid withdrawal." Cochrane Database Syst Rev(1): CD002021.

- Graham, C. H. and J. G. Meechan (2005). "Dental management of patients taking methadone." Dent Update **32**(8): 477-8, 481-2, 485.
- Heazlewood, V. J. (2005). "A syndromic rash in patients attending methadone clinics in New South Wales." Med J Aust **182**(12): 653; author reply 654.
- Herve, S., G. Riachi, et al. (2004). "Acute hepatitis due to buprenorphine administration." Eur J Gastroenterol Hepatol **16**(10): 1033-7.
- Hollister, L. E., R. L. Schwin, et al. (1977). "Naltrexone treatment of opiate-dependent persons." Drug Alcohol Depend **2**(3): 203-9.
- Howells, C., S. Allen, et al. (2002). "Prison based detoxification for opioid dependence: a randomised double blind controlled trial of lofexidine and methadone." Drug Alcohol Depend **67**(2): 169-76.
- Hrovatin, E., F. Zardo, et al. (2004). "[Long QT and torsade de pointes in a patient with acquired human immunodeficiency virus infection in multitherapy with drugs affecting cytochrome P450]." Ital Heart J Suppl **5**(9): 735-40.
- Indik, J. H. (2004). "A 38-year-old woman with dizziness." Cardiol Rev **12**(2): 63-4.
- Janiri, L., P. Mannelli, et al. (1994). "Opiate detoxification of methadone maintenance patients using lefetamine, clonidine and buprenorphine." Drug Alcohol Depend **36**(2): 139-45.
- Johansson, B. A., M. Berglund, et al. (2006). "Efficacy of maintenance treatment with naltrexone for opioid dependence: a meta-analytical review." Addiction **101**(4): 491-503.
- Johnson, R. E., M. A. Chutuape, et al. (2000). "A comparison of levomethadyl acetate, buprenorphine, and methadone for opioid dependence." N Engl J Med **343**(18): 1290-7.
- Jones, H. E., R. E. Johnson, et al. (2005). "Randomized controlled study transitioning opioid-dependent pregnant women from short-acting morphine to buprenorphine or methadone." Drug Alcohol Depend **78**(1): 33-8.
- Karir, V. (2002). "Bradycardia associated with intravenous methadone administered for sedation in a patient with acute respiratory distress syndrome." Pharmacotherapy **22**(9): 1196-9.
- Karp-Gelernter, E., C. Savage, et al. (1982). "Evaluation of clinic attendance schedules for LAAM and methadone: a controlled study." Int J Addict **17**(5): 805-13.
- Kirchmayer, U., M. Davoli, et al. (2003). "Naltrexone maintenance treatment for opioid dependence." Cochrane Database Syst Rev(2): CD001333.
- Kleber, H. D., C. E. Riordan, et al. (1985). "Clonidine in outpatient detoxification from methadone maintenance." Arch Gen Psychiatry **42**(4): 391-4.
- Kordjian, N., A. D. Donaldson, et al. (2005). "A case of desquamating rash associated with methadone use." Med J Aust **182**(2): 76-7.
- Kornick, C. A., M. J. Kilborn, et al. (2003). "QTc interval prolongation associated with intravenous methadone." Pain **105**(3): 499-506.
- Krantz, M. J., J. A. Garcia, et al. (2005). "Effects of buprenorphine on cardiac repolarization in a patient with methadone-related torsade de pointes." Pharmacotherapy **25**(4): 611-4.
- Krantz, M. J., I. B. Kutinsky, et al. (2003). "Dose-related effects of methadone on QT prolongation in a series of patients with torsade de pointes." Pharmacotherapy **23**(6): 802-5.
- Krantz, M. J., L. Lewkowicz, et al. (2002). "Torsade de pointes associated with very-high-dose methadone." Ann Intern Med **137**(6): 501-4.
- Krantz, M. J., C. M. Lowery, et al. (2005). "Effects of methadone on QT-interval dispersion." Pharmacotherapy **25**(11): 1523-9.
- Krantz, M. J. and P. S. Mehler (2004). "Methadone and QT prolongation: a dose-dependent effect?" Am J Cardiol **93**(7): 952.
- Krantz, M. J., S. B. Rowan, et al. (2005). "Cocaine-related torsade de pointes in a methadone maintenance patient." J Addict Dis **24**(1): 53-60.
- Kristensen, O., O. Espegren, et al. (2005). "[Buprenorphine and methadone to opiate addicts--a randomized trial]." Tidsskr Nor Laegeforen **125**(2): 148-51.

- Krook, A. L., H. Waal, et al. (2004). "[Routine ECG in methadone-assisted rehabilitation is wrong prioritization]." Tidsskr Nor Laegeforen **124**(22): 2940-1.
- Krupitsky, E. M., E. E. Zvartau, et al. (2004). "Naltrexone for heroin dependence treatment in St. Petersburg, Russia." J Subst Abuse Treat **26**(4): 285-94.
- Ling, W., L. Amass, et al. (2005). "A multi-center randomized trial of buprenorphine-naloxone versus clonidine for opioid detoxification: findings from the National Institute on Drug Abuse Clinical Trials Network." Addiction **100**(8): 1090-100.
- Ling, W., C. Charuvastra, et al. (1998). "Buprenorphine maintenance treatment of opiate dependence: a multicenter, randomized clinical trial." Addiction **93**(4): 475-86.
- Ling, W., C. Charuvastra, et al. (1976). "Methadyl acetate and methadone as maintenance treatments for heroin addicts. A veterans administration cooperative study." Arch Gen Psychiatry **33**(6): 709-20.
- Ling, W., C. J. Klett, et al. (1978). "A cooperative clinical study of methadyl acetate. I. Three-times-a-week regimen." Arch Gen Psychiatry **35**(3): 345-53.
- Ling, W., D. R. Wesson, et al. (1996). "A controlled trial comparing buprenorphine and methadone maintenance in opioid dependence." Arch Gen Psychiatry **53**(5): 401-7.
- Lintzeris, N., J. Bell, et al. (2002). "A randomized controlled trial of buprenorphine in the management of short-term ambulatory heroin withdrawal." Addiction **97**(11): 1395-404.
- Liu, Z. M., Z. J. Cai, et al. (1997). "Rapid detoxification of heroin dependence by buprenorphine." Zhongguo Yao Li Xue Bao **18**(2): 112-4.
- Loo, H. W., A. K. Yam, et al. (2005). "Severe upper limb complications from parenteral abuse of Subutex." Ann Acad Med Singapore **34**(9): 575-8.
- Lucchini, A., G. Barbaro, et al. (2004). "Methadone and QT prolongation in HIV-infected patients." Am J Cardiol **94**(1): 147-8.
- Luty, J., C. O'Gara, et al. (2005). "Is methadone too dangerous for opiate addiction?" Bmj **331**(7529): 1352-3.
- Madinier, I., J. Harrosch, et al. (2003). "[The buccal-dental health of drug addicts treated in the University hospital centre in Nice]." Presse Med **32**(20): 919-23.
- Maremmani, I., M. Pacini, et al. (2005). "QTc interval prolongation in patients on long-term methadone maintenance therapy." Eur Addict Res **11**(1): 44-9.
- Marsch, L. A., W. K. Bickel, et al. (2005). "Comparison of pharmacological treatments for opioid-dependent adolescents: a randomized controlled trial." Arch Gen Psychiatry **62**(10): 1157-64.
- Martell, B. A., J. H. Arnsten, et al. (2005). "Impact of methadone treatment on cardiac repolarization and conduction in opioid users." Am J Cardiol **95**(7): 915-8.
- Martell, B. A., J. H. Arnsten, et al. (2003). "The impact of methadone induction on cardiac conduction in opiate users." Ann Intern Med **139**(2): 154-5.
- Mattick, R. P., R. Ali, et al. (2003). "Buprenorphine versus methadone maintenance therapy: a randomized double-blind trial with 405 opioid-dependent patients." Addiction **98**(4): 441-52.
- Mattick, R. P., J. Kimber, et al. (2003). "Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence." Cochrane Database Syst Rev(2): CD002207.
- Maxwell, J. C., T. W. Pullum, et al. (2005). "Deaths of clients in methadone treatment in Texas: 1994-2002." Drug Alcohol Depend **78**(1): 73-81.
- McCarthy, J. J., M. H. Leamon, et al. (2005). "High-dose methadone maintenance in pregnancy: maternal and neonatal outcomes." Am J Obstet Gynecol **193**(3 Pt 1): 606-10.
- Minozzi, S., L. Amato, et al. (2006). "Oral naltrexone maintenance treatment for opioid dependence." Cochrane Database Syst Rev(1): CD001333.
- Mokwe, E. O. and O. Ositadinma (2003). "Torsade de pointes due to methadone." Ann Intern Med **139**(4): W64.

- Montoya, I. D., A. Umbricht, et al. (1995). "Buprenorphine for human immunovirus-positive opiate-dependent patients." Biol Psychiatry **38**(2): 135-6.
- Nigam, A. K., R. Ray, et al. (1993). "Buprenorphine in opiate withdrawal: a comparison with clonidine." J Subst Abuse Treat **10**(4): 391-4.
- O'Connor, P. G., M. E. Waugh, et al. (1995). "Primary care-based ambulatory opioid detoxification: the results of a clinical trial." J Gen Intern Med **10**(5): 255-60.
- Oliver, P., M. Horspool, et al. (2005). "Fatal opiate overdose following regimen changes in naltrexone treatment." Addiction **100**(4): 560-1.
- Oreskovich, M. R., A. J. Saxon, et al. (2005). "A double-blind, double-dummy, randomized, prospective pilot study of the partial mu opiate agonist, buprenorphine, for acute detoxification from heroin." Drug Alcohol Depend **77**(1): 71-9.
- Ostvold, C. and M. Topper (2005). "[Methadone-induced heart arrhythmia]." Tidsskr Nor Laegeforen **125**(15): 2021-2.
- Palmstierna, T. (2004). "Effects of a high-dose fast tapering buprenorphine detoxification program on symptom relief and treatment retention." J Psychoactive Drugs **36**(2): 273-7.
- Pani, P. P., I. Maremmani, et al. (2000). "Buprenorphine: a controlled clinical trial in the treatment of opioid dependence." Drug Alcohol Depend **60**(1): 39-50.
- Pearson, E. C. and R. L. Woosley (2005). "QT prolongation and torsades de pointes among methadone users: reports to the FDA spontaneous reporting system." Pharmacoepidemiol Drug Saf **14**(11): 747-53.
- Pelet, A., S. Doll, et al. (2005). "Methadone maintenance treatment in the Swiss Canton of Vaud: demographic and clinical data on 1,782 ambulatory patients." Eur Addict Res **11**(2): 99-106.
- Petitjean, S., R. Stohler, et al. (2001). "Double-blind randomized trial of buprenorphine and methadone in opiate dependence." Drug Alcohol Depend **62**(1): 97-104.
- Piguet, V., J. Desmeules, et al. (2004). "QT interval prolongation in patients on methadone with concomitant drugs." J Clin Psychopharmacol **24**(4): 446-8.
- Ponizovsky, A. M., A. Grinshpoon, et al. (2006). "Well-being, psychosocial factors, and side-effects among heroin-dependent inpatients after detoxification using buprenorphine versus clonidine." Addictive Behaviors(Mar 2006): epub.
- Porter, B. O., P. J. Coyne, et al. (2005). "Methadone-related Torsades de Pointes in a sickle cell patient treated for chronic pain." Am J Hematol **78**(4): 316-7.
- Rademacher, S., R. Dietz, et al. (2005). "QT prolongation and syncope with methadone, doxepin, and a beta-blocker." Ann Pharmacother **39**(10): 1762-3.
- Raistrick, D., D. West, et al. (2005). "A comparison of buprenorphine and lofexidine for community opiate detoxification: results from a randomized controlled trial." Addiction **100**(12): 1860-7.
- Ray, R., H. Pal, et al. (2004). "Post-marketing surveillance of buprenorphine." Pharmacoepidemiol Drug Saf **13**(9): 615-9.
- Reddy, S., M. Fisch, et al. (2004). "Oral methadone for cancer pain: no indication of Q-T interval prolongation or torsades de pointes." J Pain Symptom Manage **28**(4): 301-3.
- Rhoades, H. M., D. Creson, et al. (1998). "Retention, HIV risk, and illicit drug use during treatment: methadone dose and visit frequency." Am J Public Health **88**(1): 34-9.
- Rhodin, A., L. Gronbladh, et al. (2006). "Methadone treatment of chronic non-malignant pain and opioid dependence--a long-term follow-up." Eur J Pain **10**(3): 271-8.
- Sala, M., I. Anguera, et al. (2003). "Torsade de pointes due to methadone." Ann Intern Med **139**(4): W64.
- San, L., T. Fernandez, et al. (1994). "Efficacy of methadone versus methadone and guanfacine in the detoxification of heroin-addicted patients." J Subst Abuse Treat **11**(5): 463-9.
- San, L., G. Pomarol, et al. (1991). "Follow-up after a six-month maintenance period on naltrexone versus placebo in heroin addicts." Br J Addict **86**(8): 983-90.

- Sanchez Hernandez, A. M., F. Atienza Fernandez, et al. (2005). "[Torsades de pointes during methadone treatment]." Rev Esp Cardiol **58**(10): 1230-2.
- Savage, C., E. G. Karp, et al. (1976). "Methadone/LAAM maintenance: a comparison study." Compr Psychiatry **17**(3): 415-24.
- Schifano, F., J. Corkery, et al. (2005). "Buprenorphine mortality, seizures and prescription data in the UK, 1980-2002." Hum Psychopharmacol **20**(5): 343-8.
- Schneider, U., W. Paetzold, et al. (2000). "Buprenorphine and carbamazepine as a treatment for detoxification of opiate addicts with multiple drug misuse: a pilot study." Addiction Biology **5**: 65-69.
- Schottenfeld, R. S., J. R. Pakes, et al. (1997). "Buprenorphine vs methadone maintenance treatment for concurrent opioid dependence and cocaine abuse." Arch Gen Psychiatry **54**(8): 713-20.
- Schroeder, J. R., J. P. Schmittner, et al. (2005). "Adverse events among patients in a behavioral treatment trial for heroin and cocaine dependence: effects of age, race, and gender." Drug Alcohol Depend **80**(1): 45-51.
- Seet, R. C. and E. C. Lim (2006). "Intravenous use of buprenorphine tablets associated with rhabdomyolysis and compressive sciatic neuropathy." Ann Emerg Med **47**(4): 396-7.
- Seifert, J., C. Metzner, et al. (2002). "Detoxification of opiate addicts with multiple drug abuse: a comparison of buprenorphine vs. methadone." Pharmacopsychiatry **35**(5): 159-64.
- Shah, N., S. L. Lathrop, et al. (2005). "Unintentional methadone-related overdose death in New Mexico (USA) and implications for surveillance, 1998-2002." Addiction **100**(2): 176-88.
- Sheedy, J. J. (1996). "Methadone and caries. Case reports." Aust Dent J **41**(6): 367-9.
- Shufman, E. N., S. Porat, et al. (1994). "The efficacy of naltrexone in preventing reabuse of heroin after detoxification." Biol Psychiatry **35**(12): 935-45.
- Sinclair, R. D. (2005). "A syndromic rash in patients attending methadone clinics in New South Wales." Med J Aust **182**(12): 653-4; author reply 654.
- Soyka, M., B. Hock, et al. (2005). "Less impairment on one portion of a driving-relevant psychomotor battery in buprenorphine-maintained than in methadone-maintained patients: results of a randomized clinical trial." J Clin Psychopharmacol **25**(5): 490-3.
- Sticherling, C., B. A. Schaer, et al. (2005). "Methadone-induced Torsade de pointes tachycardias." Swiss Med Wkly **135**(19-20): 282-5.
- Stimmel, B. (2003). "Methadone and affairs of the heart and of the brain." J Addict Dis **22**(3): 1-5.
- Stoermer, R., J. Drewe, et al. (2003). "Safety of injectable opioid maintenance treatment for heroin dependence." Biol Psychiatry **54**(8): 854-61.
- Strain, E. C., G. E. Bigelow, et al. (1999). "Moderate- vs high-dose methadone in the treatment of opioid dependence: a randomized trial." Jama **281**(11): 1000-5.
- Teichtahl, H., D. Wang, et al. (2004). "Cardiorespiratory function in stable methadone maintenance treatment (MMT) patients." Addict Biol **9**(3-4): 247-53.
- Tennant, F. S., Jr., B. A. Russell, et al. (1975). "Heroin detoxification. A comparison of propoxyphene and methadone." Jama **232**(10): 1019-22.
- Titsas, A. and M. M. Ferguson (2002). "Impact of opioid use on dentistry." Aust Dent J **47**(2): 94-8.
- Trafton, J. A., J. Minkel, et al. (2006). "Determining Effective Methadone Doses for Individual Opioid-Dependent Patients." PLoS Med **3**(3): e80.
- Umbricht, A., D. R. Hoover, et al. (2003). "Opioid detoxification with buprenorphine, clonidine, or methadone in hospitalized heroin-dependent patients with HIV infection." Drug Alcohol Depend **69**(3): 263-72.
- van Ameijden, E. J., M. W. Langendam, et al. (1999). "Dose-effect relationship between overdose mortality and prescribed methadone dosage in low-threshold maintenance programs." Addict Behav **24**(4): 559-63.

- Verthein, U., R. Ullmann, et al. (2005). "The effects of racemic D,L-methadone and L-methadone in substituted patients--a randomized controlled study." Drug Alcohol Depend **80**(2): 267-71.
- Vodoz, J. F., F. Jaquier, et al. (2003). "[Torsade de pointes: a severe and unknown adverse effect in a patient taking methadone]." Schweiz Rundsch Med Prax **92**(41): 1748-50.
- Walker, P. W., D. Klein, et al. (2003). "High dose methadone and ventricular arrhythmias: a report of three cases." Pain **103**(3): 321-4.
- Wang, D., H. Teichtahl, et al. (2005). "Central sleep apnea in stable methadone maintenance treatment patients." Chest **128**(3): 1348-56.
- Wang, R. I. and L. D. Young (1996). "Double-blind controlled detoxification from buprenorphine." NIDA Research Monograph **162**: 114.
- Zador, D., P. M. Lyons Wall, et al. (1996). "High sugar intake in a group of women on methadone maintenance in south western Sydney, Australia." Addiction **91**(7): 1053-61.