



GUIDELINES

The World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for the Biological Treatment of Substance Use and Related Disorders. Part 2: Opioid dependence

MICHAEL SOYKA^{1,2}, HENRY R. KRANZLER³, WIM VAN DEN BRINK⁴, JOHN KRYSZAL⁵, HANS-JÜRGEN MÖLLER¹ & SIEGFRIED KASPER⁶
The WFSBP Task Force on Treatment, Guidelines for Substance Use Disorders*

¹Department of Psychiatry, Ludwig-Maximilian University, Munich, Germany, ²Private Hospital Meiringen, Meiringen, Switzerland, ³Department of Psychiatry, University of Pennsylvania, Philadelphia, PA, USA, ⁴Amsterdam Institute for Addiction Research and Department of Psychiatry of the Academic Medical Center University of Amsterdam, The Netherlands, ⁵Department of Psychiatry, Yale University School of Medicine, Yale-New Haven Hospital, New Haven, USA, ⁶Department of Psychiatry and Psychotherapy, Medical University of Vienna, Austria

Abstract

Objectives. To develop evidence-based practice guidelines for the pharmacological treatment of opioid abuse and dependence. **Methods.** An international task force of the World Federation of Societies of Biological Psychiatry (WFSBP) developed these practice guidelines after a systematic review of the available evidence pertaining to the treatment of opioid dependence. On the basis of the evidence, the Task Force reached a consensus on practice recommendations, which are intended to be clinically and scientifically meaningful for physicians who treat adults with opioid dependence. The data used to develop these guidelines were extracted primarily from national treatment guidelines for opioid use disorders, as well as from meta-analyses, reviews, and publications of randomized clinical trials on the efficacy of pharmacological and other biological treatments for these disorders. Publications were identified by searching the MEDLINE database and the Cochrane Library. The literature was evaluated with respect to the strength of evidence for efficacy, which was categorized into one of six levels (A–F). **Results.** There is an excellent evidence base supporting the efficacy of methadone and buprenorphine or the combination of buprenorphine and naloxone for the treatment of opioid withdrawal, with clonidine and lofexidine as secondary or adjunctive medications. Opioid maintenance with methadone and buprenorphine is the best-studied and most effective treatment for opioid dependence, with heroin and naltrexone as second-line medications. **Conclusions.** There is enough high quality data to formulate evidence-based guidelines for the treatment of opioid abuse and dependence. This task force report provides evidence for the efficacy of a number of medications to treat opioid abuse and dependence, particularly the opioid agonists methadone or buprenorphine. These medications have great relevance for clinical practice.

Key words: Opioid dependence, buprenorphine, clonidine, heroin, lofexidine, methadone, naloxone, naltrexone, maintenance treatment

Preface and disclosure statement

These practice guidelines for the biological – mainly pharmacological – treatment of opioid dependence were developed by an international task force of the World Federation of Societies of Biological Psychiatry (WFSBP). The preparation of these guidelines was not supported by any commercial

organization. The guidelines were developed principally by psychiatrists and psychotherapists in active clinical practice, with some contributors primarily involved in research or other academic endeavours. Members of the task force were selected on the basis of their expertise and with the aim of including diverse practices. It is possible that through such

*Henry R. Kranzler (Chairman; USA), Mats Berglund (Co-Chairman; Sweden), Anne Lingford-Hughes (Co-Chairman; UK), Michael Soyka (Secretary; Switzerland), Hans-Jürgen Möller (Chairman of the WFSBP Committee on Scientific Publications), Edgard Belfort (Venezuela), Ihn-Geun Choi (Korea), Richard Frey (Austria), Markus Gastpar (Germany), David A. Gorelick (USA), Gerardo M. Heinze (Mexico), Victor Hesselbrock (USA), Thomas Kosten (USA), Phillipe Lehert (Belgium), Michel Lejoyeux (France), Walter Ling (USA), Carlos Mendoza (Peru), Michael Musalek (Austria), Toshikazu Saito (Japan), Manit Srisurapanont (Thailand), Hiroshi Ujike (Japan), and Ulrich Wittchen (Germany).

Correspondence: Michael Soyka, MD, Private Hospital Meiringen, PO Box 612, 3860 Meiringen, Switzerland. Tel: +41 339 728295. Fax +41 339 728291. E-mail: Michael.Soyka@privatklinik-meiringen.ch

activities some contributors have received income related to medicines discussed in this guideline (see author disclosures at the end of the manuscript). Some drugs recommended in the present guideline are not available in all countries, and approved dosages may vary among countries.

Introduction

The non-medical use of opioids, including heroin, represents a major public health problem, with a worldwide prevalence of 0.4% among individuals aged 15–64 years (United Nations Office on Drugs and Crime 2006). In Europe, the average prevalence of problematic opioid use is estimated to be 3.6–4.4 cases per 1000 population aged 15–64 years (EMCDDA 2010). This corresponds to approximately 1.35 million individuals. In the United States, approximately 3.7 million individuals have used heroin at least once in their lives and 750,000–1,000,000 individuals are currently heroin dependent (Kleber et al. 2007). Data from the annual US National Survey on Drug Use and Health indicate that in 2009 the rate of current illicit use among persons aged 12 or older was 8.7% (2008: 8.0%), including 200,000 heroin users (www.samsha.gov). Opioid abuse and dependence do not always follow from recreational use or the individual's social background and lifestyle. Recent data suggest that the prevalence of opioid dependence in chronic non-cancer pain patients is as high as 26% (Boscarino et al. 2010). Non-medical opioid use is often associated with multiple social and health problems, including acquisitive crime, violence, suicide, premature death from overdose and infection with HIV, hepatitis C, tuberculosis or other pathogens (Goldstein and Herrera 1995; Hulse et al. 1999; Darke and Ross 2002). The World Health Organization (WHO) estimates that the burden of harm from opioid use is 11.2 million disability-adjusted life-years (DALYs; World Health Organization 2004).

Long-term studies of groups of opioid dependent individuals indicate that sustained abstinence is uncommon and risk of mortality is high (Hulse et al. 1999; Hser et al. 2001; Termorshuizen et al. 2005; Degenhardt et al. 2010). While heroin is the most commonly abused opioid, other opioids are also frequently misused, including prescription pain relievers such as hydromorphone, morphine, oxycodone, codeine and propoxyphene (Boscarino et al. 2010; SAMSHA 2010). Agonist medications used to treat opioid dependence, such as methadone and buprenorphine, also have abuse potential. The types of drugs abused differ substantially among countries. For example, the prevalence rates of the abuse of

prescription opioids such as oxycodone and related deaths are higher in the United States than in Europe (Spiller et al. 2009; Manchikanti et al. 2010; Strassels 2010).

The opioid system

The endogenous opioid system is involved in a variety of brain functions, including the regulation of emotion and pain (Koob and Le Moal 2010). Opioid receptors are most commonly expressed in frontal and prefrontal brain regions, as well as the limbic system, including the ventral striatum, and can be visualized by positron emission tomography (PET) using ligands such as carfentanil and diprenorphine (Greenwald et al. 2007; Valotassoiu et al. 2008). The opioid system is linked to other neurotransmitter systems and modulates dopamine release in the limbic system (Koob and Le Moal 2006). There are three opioid receptor subtypes and all have been implicated in the risk of addiction: mu, kappa, and delta. Most opioids are mu-opioid receptor agonists – the mu-opioid receptor has been linked to analgesia, euphoria, respiratory depression and pupillary constriction. The kappa-opioid receptor subtype has been linked to analgesia, dysphoria and diuresis, and the reinforcing effects of drugs of abuse (Wee and Koob 2010). The delta-opioid receptor subtype has been linked to analgesia (Koob and Le Moal 2006).

Differences in receptor function may influence the abuse liability of opioids (Bond et al. 1998; Ikeda et al. 2005; Somogyi et al. 2007). Approximately 100 variants of the mu-opioid receptor gene have been identified (Lotsch and Geisslinger 2005; Somogyi et al. 2007). The most commonly studied single nucleotide polymorphism (SNP) is A118G, which results in an amino acid exchange of asparagine to aspartate (Asn40Asp) at position 40 (Bond et al. 1998). Although some studies have found an association of the Asn40Asp SNP with the risk of opioid dependence, meta-analyses have shown that such findings are not consistent and, overall, no statistically significant association appears to exist (Arias et al. 2006; Glatt et al. 2007). The clinical relevance of opioid receptor genes has not been demonstrated by genomewide approaches such as genome wide association studies (GWAS). The risk of developing opioid dependence may be lower in individuals who are rapid metabolizers due to variation in the CYP2D6 gene (Haile et al. 2008). In contrast, the risk for fatal methadone-related intoxications may be higher in the context of benzodiazepine intoxication in slow metabolizers due to variation at the CYP2B6 gene

the presence of an OPRM1 Asp40 allele (Bunten et al. 2010).

The moderating role of functional variants of the mu-opioid receptor gene in outcomes associated with opioid maintenance is unclear and, therefore, pharmacogenomics based tailoring of the treatment does not seem to be expedient (Bond et al. 1998; Ikeda et al. 2005; Somogyi et al. 2007). Some other gene variants such as the p-glycoprotein gene (ABCB1) or the dopamine D2 receptor gene (DRD2) may play a role (Crettol et al. 2008; Yuferov et al. 2010).

Methods

These guidelines are intended for use by clinicians in the diagnosis and treatment of patients with opioid use disorders. Although the guidelines are based on published evidence, the treating clinician is ultimately responsible to assess the patient and choose the best treatment for that patient. These guidelines do not establish a standard of care nor do they ensure a favourable clinical outcome if followed. The primary aim of the guidelines is to evaluate the role of pharmacological agents in the treatment and management of opioid use disorders, focusing on the treatment of adults. Because such treatments are not delivered in isolation, the role of specific psychosocial and psychotherapeutic interventions and service delivery systems is also covered, albeit briefly.

The guidelines were developed by the authors and arrived at by consensus with the WFSBP Task Force on Substance Use and Related Disorders, consisting of 22 international experts in the field. All experts received a written request for comments before publication. An extensive search of publications in peer-reviewed journals was conducted using the MEDLINE database and the Cochrane Library through January 2010 and supplemented by other sources, including published reviews. The evidence was summarized and categorized to reflect its susceptibility to bias (Shekelle et al. 1999). In addition, a number of national and international guidelines were reviewed (Lingford-Hughes et al. 2004; van den Brink and Haasen 2006; Connock et al. 2007; Kleber et al. 2007; NHS NICE Clinical Guidelines Nos 51, 52, NICE 2007a,b; Meili et al. 2008; Chou et al. 2009; Fareed et al. 2010; Nicholis et al. 2010; Perron et al. 2010).

To achieve uniform and – in the opinion of the Task Force – appropriate ranking of evidence, we adopted the same hierarchy of evidence-based rigor and level of recommendation as was recently

published in the WFSBP Guidelines for the Pharmacological Treatment of Anxiety, Obsessive-Compulsive and Post-Traumatic Stress Disorders (Bandelow et al. 2008) and those for Acute Mania (Grunze et al. 2009) (see Table I). Each recommendation for the treatment of opioid dependence was evaluated and discussed by the WFSBP Task Force on Treatment Guidelines for Substance Use Disorders with respect to the strength of evidence for its efficacy, safety, tolerability and feasibility and the strength of recommendation was rated (See Table 2). It should be noted that the strength of recommendation is based on the level of efficacy, safety, tolerability and feasibility, not necessarily on the treatment's importance.

Treatment goals and related strategies

There are several overall goals for the treatment of patients with opioid use and dependence. These can only be touched on briefly in these guidelines, which predominantly address biological treatments. Although the increasing use of agonist substitution treatments has caused mortality rates among opioid-abusing patients to decline, intoxication and overdose continue to account for most opioid-related deaths (Soyka et al. 2008a; Degenhardt et al. 2010). Thus, efforts to reduce the morbidity and mortality of opioid intoxication and overdose must continue, and can be enhanced by co-occurring rehabilitation efforts. There are two generally accepted primary treatment goals for opioid-dependent individuals (van den Brink and Haasen et al. 2006):

- a. Complete abstinence from all opioids and all illegal drugs. This may be achieved through the use of opioid antagonist treatments such as naltrexone.
- b. A substantial decrease in the use of opioids and illegal drugs. This may be achieved by maintenance treatment using opioid agonists such as methadone or buprenorphine.

Secondary goals of opioid treatment include better psychosocial integration; treatment of co-occurring somatic and psychiatric disorders such as major depression, bipolar disorder and chronic pain; and the prevention of infection with HIV, hepatitis C and other communicable diseases (by avoiding intravenous drug use and needle sharing). Although sustained abstinence in individuals with substance use disorders is not the rule, especially in opioid-dependent individuals (Berglund et al. 2003), it is

Table I. Categories of Evidence (CE) and recommendation grades (RG 3).

Category of evidence	Description
A	<p>Full Evidence From Controlled Studies is based on:</p> <p>2 or more double-blind, parallel-group, randomized controlled trials (RCTs) showing superiority to placebo (or in the case of psychotherapy studies, superiority to a ‘psychological placebo’ in a study with adequate blinding)</p> <p><i>and</i></p> <p>1 or more positive RCT showing superiority to or equivalent efficacy to established comparator treatment in a three-arm study with a placebo control or in a well-powered non-inferiority trial (only required if such a standard treatment exists)</p> <p>In the case of existing negative studies (studies showing non-superiority to placebo or inferiority to comparator treatment), these must be outweighed by at least 2 additional positive studies or a meta-analysis of all available studies showing superiority to placebo and non-inferiority to an established comparator treatment. Studies must fulfil established methodological standards. The decision is based on the primary efficacy measure.</p>
B	<p>Limited Positive Evidence From Controlled Studies is based on:</p> <p>1 or more RCTs showing superiority to placebo (or in the case of psychotherapy studies, superiority to a ‘psychological placebo’)</p> <p><i>or</i></p> <p>a randomized controlled comparison with a standard treatment without placebo control with a sample size sufficient for a non-inferiority trial</p> <p><i>and</i></p> <p>In the case of existing negative studies (studies showing non-superiority to placebo or inferiority to comparator treatment), these must be outweighed by at least 1 additional positive study or a meta-analysis of all available studies showing superiority to placebo or at least one more randomized controlled comparison showing non-inferiority to an established comparator treatment.</p>
C	Evidence from Uncontrolled Studies or Case Reports/Expert Opinion
C1	<p>Uncontrolled studies is based on:</p> <p>1 or more positive naturalistic open studies (with a minimum of 5 evaluable patients)</p> <p><i>or</i></p> <p>a comparison with a reference drug with a sample size insufficient for a non-inferiority trial</p> <p><i>and</i></p> <p>no existing negative controlled studies</p>
C2	<p>Case reports is based on:</p> <p>1 or more positive case reports</p> <p><i>and</i></p> <p>no existing negative controlled studies</p>
C3	Based on the opinion of experts in the field or clinical experience
D	Inconsistent results
E	<p>Positive RCTs are outweighed by an approximately equal number of negative studies</p> <p>Negative evidence</p> <p>The majority of RCTs or exploratory studies show non-superiority to placebo (or in the case of psychotherapy studies, non-superiority to a ‘psychological placebo’) or inferiority to comparator treatment</p>
F	<p>Lack of evidence</p> <p>Adequate studies proving efficacy or non-efficacy are lacking.</p>
Recommendation Grade (RG)	
Based on:	
1	Category A evidence <u>and</u> good risk-benefit ratio
2	Category A evidence <u>and</u> moderate risk-benefit ratio
3	Category B evidence
4	Category C evidence
5	Category D evidence

not as rare as many believe (Hser et al., 2001; Dutra et al. 2008).

Although detoxification and abstinence-oriented treatment are major goals for many clinicians, opioid detoxification should not routinely be offered to people who have a medical condition needing urgent

treatment, have presented to an acute emergency setting, or are in police custody or similar conditions. Under these circumstances, the primary emergent problem should be addressed and opioid withdrawal symptoms treated, with referral to further drug services as appropriate or feasible (NICE

Table II. Categories of evidence (CE) and grade of recommendation (RG) for pharmacological treatments in opioid dependence.

Medication	CE RG Typical recommended daily dose for adults
<i>Abuse and dependence</i>	
Methadone	A 1 40–100 mg
Buprenorphine	A 1 4–16 mg
Buprenorphine/naloxone	A 1 4–16 mg
Naltrexone	B 3 50 mg
Heroin	B 3 200–600 mg
<i>Withdrawal</i>	
Methadone	A 1 40–100 mg initial
Buprenorphine	A 1 4–16 mg initial
Buprenorphine/naloxone	A + 4–16 mg initial
Clonidine	B 3 0.3 mg
Lofexidine/clonidine	C 4 1.6–3.2 mg
Naltrexone under general anesthesia	D 5

Clinical Guideline No 52, NHS NICE 2007b). In addition, pregnant women who are opioid dependent should undergo detoxification only under exceptional circumstances (e.g., serious comorbid physical or mental health problems) and with great caution.

A Cochrane review (Amato et al. 2008) showed that the combination of psychosocial treatments and pharmacological treatments is more effective than pharmacotherapy alone for opioid detoxification. Berglund et al. (2003), in their scholarly meta-analysis, concluded that re-educative interventions and psychotherapies have significant effects on relapse to opioid use when compared to treated control groups. The effect sizes were moderate and supportive treatment measures had no effect.

In summary, the goals of opioid use and dependence treatment are:

1. Crisis intervention directed at immediate survival through resuscitation in the case of overdose
2. Stable abstinence from all legal and illegal opioid agonists (abstinence-oriented treatment) through the following processes
 - 2a. Evaluation and enhancement of motivation for recovery
 - 2b. Detoxification
 - 2c. Relapse prevention
3. Reduction or discontinuation of the use of all illegal opioid agonists and improvements in health and social function (harm avoidance)
 - 3a. Maintenance treatment
 - 3b. Harm avoidance (e.g., needle and syringe exchange)
 - 3c. Rehabilitation

Treatment settings

Treatment settings for opioid-related disorders include inpatient units and outpatient clinics and offices, opioid agonist substitution programmes, self-help groups and therapeutic communities (Kleber et al. 2007). The choice of treatment setting depends on the patient's preferences and treatment needs. In general, opioid withdrawal can be managed in both inpatient and outpatient settings (Day et al. 2005). Inpatient treatment is warranted for management of opioid-related overdose and other life-threatening emergencies, crisis intervention, abstinence-oriented detoxification, and homeless patients. In contrast, harm reduction approaches are usually offered in an outpatient setting. Following detoxification, treatment of opioid-dependent patients may include abstinence-oriented, drug-free programmes or self-help groups such as Narcotics Anonymous. The outcomes of opioid withdrawal alone are poor in the long term (Mattick et al. 2009).

Psychosocial treatments for opioid dependence include a number of different strategies and techniques that are often used in combination (Amato et al. 2008a,b; Dutra et al. 2008). Although psychotherapy is not provided for most patients in maintenance therapy (Salamina et al. 2010), options include cognitive-behavioural therapies (CBT, Woody et al. 1983, 1984, 1987, 1995; Dutra et al. 2008), behavioural therapies such as contingency management (Stitzer and Bigelow 1978; Grabowski et al. 1979; Stitzer et al. 1986, 1992; McLellan et al. 1993; Iguchi et al. 1996; Silverman et al. 1996, 1998; Preston et al. 1999; Carroll et al. 2001; Dutra et al. 2008), community reinforcement and other community treatments (Abbott 2009; Mardsen et al. 2009), family therapies and relapse prevention (Berglund et al. 2003; Dutra et al. 2008), self-help groups and 12-step-oriented treatments, and to a much lesser extent psychodynamic and interpersonal therapies (Woody et al. 1983, 1995; Khantzian et al. 1990). The evidence for psychosocial interventions is best for cannabis use and worst for polysubstance abuse, with contingency management interventions having the strongest effect (Dutra et al. 2008).

Intoxication and overdose

Intoxication following the inhalation or intravenous (i.v.) injection of an opioid has been described as having four sequential stages: euphoria, feeling "high," a state of escape ranging from sleepiness to virtual unconsciousness and finally "being straight" (Koob and Le Moal 2006). Overdose in i.v. opioid users is characterized by miosis, respiratory depression and unconsciousness/coma and is a frequent

reason for emergency treatments (Backmund et al. 2009). Patients at particular risk of overdose include youth, those relapsing after abstinence-oriented treatment and those recently released from prison (Cook et al. 1998, Darke and Hall 2003; Møller et al. 2010).

Intoxication and overdose should be assessed clinically and toxicologically. In many cases, patients are intoxicated from a variety of drugs, including other psychotropic drugs or alcohol. Mild or moderate intoxications (without clouding of the sensorium) do not require specific treatment. Since heroin has a short half-life, patients with an overdose of only heroin may be supervised in an emergency department until the intoxication is resolved. Overdoses with longer-acting opioids such as methadone may require hospital admission to permit observation for 24–48 h. Methadone-induced hypoxemia is caused by the drug's effects on the mu-opioid receptor, with modulation by the kappa opioid receptor (Chevallard et al. 2010). Severe opioid overdose is characterized by respiratory depression and CNS symptoms and requires hospitalization (Lingford-Hughes et al. 2004; Kleber et al. 2007).

Naloxone, a short-acting opioid antagonist that is pharmacologically active only after parenteral administration, can reverse respiratory and CNS depression (van Dorp et al. 2007). The drug is considered to be safe at a dosage of up to 10 mg (van Dorp et al. 2007). Naloxone should be titrated to have the desired effect and, given its short half-life, it should be continued until chances for the opioid agonist effects to return have diminished (Dahan et al. 2010). The drug can also be used as a diagnostic agent in cases of intoxication by unknown agents. An opioid with high receptor affinity (e.g., buprenorphine) requires greater naloxone concentrations and/or continuous infusion to antagonize opioid effects than opioids with lower affinity (Dahan et al. 2010). However, because buprenorphine causes limited respiratory depression (Dahan 2006) fatal intoxications with this compound alone are rare (Pirnay et al. 2004); when they occur they are often caused by intravenous misuse especially in combination with the use of benzodiazepines (Megarbane et al. 2006). In these cases a combination of naloxone and flumazenil can be life saving (Megarbane et al. 2006, 2010). The recent recommendation that buprenorphine be used with or without naloxone to treat cases of heroin overdose cannot be recommended (Nielsen and Lintzeris 2008; Welsh et al. 2008).

Recommendation. Despite the relative lack of controlled studies, naloxone seems to be a very effective and vital treatment for opioid overdose (3). However,

the short half-life of the drug means that the effects may end prematurely in the case of long-acting opioids (e.g., methadone, buprenorphine) (van Dorp et al. 2007), so that repeated dosing or a continuous infusion may be required to prevent the recurrence of signs and symptoms of overdose.

Abuse and dependence

Choice of treatment and allocation of patients

A Cochrane review of randomized controlled clinical trials that compared inpatient settings with other settings for opioid detoxification included only one study that met the pre-established inclusion criteria (Day et al. 2005). The authors concluded that there is not adequate research available in this area by which to choose the best setting for the treatment of opioid withdrawal. We would emphasize that, although the treatment of opioid withdrawal has an important role in the treatment of opioid dependence, in and of itself, it is not an effective treatment for opioid dependence.

The choice of medications to treat opioid dependence is often based upon patient or physician preference and an assessment of the patient's individual treatment history, health status and specific clinical needs, such as comorbid psychiatric or somatic disorders or other substance use (Mattick 2003a,b, 2009; Kleber et al. 2007; Amato et al. 2008a,b; Wittchen et al. 2008; Castells et al. 2009). Because methadone maintenance can be lifelong (Kleber et al. 2007), some clinicians avoid it as first-line treatment for adolescents. The same may be true for adult patients with a short "opioid-use career" or excellent social integration and sufficient personal resources. However, in most other cases, agonist maintenance treatment is the most effective and, therefore, dominant intervention with positive long-term outcomes. It should be noted, however, that the standard of care in opioid dependence and the indications for use of opioid maintenance varies among different countries (EMCDDA 2010).

Full mu-opioid receptor agonists: methadone, LAAM, slow-release oral morphine and heroin

Methadone

The main goals of methadone maintenance therapy are:

- to achieve stable methadone maintenance in order to suppress withdrawal, block the effects of illegal opioids, reduce opioid craving and stop the illicit use of opioids (and possibly other drugs), and

- to promote and facilitate patient engagement in psychosocial treatment programmes, thereby reducing drug use, promoting abstinence and supporting patients' psychosocial integration.

Maintenance treatment with opioid agonists such as methadone is one of the best studied treatment options available for opioid-dependent patients (Connock et al. 2007; Mattick et al. 2009). Its efficacy in reducing opioid consumption; criminal behaviour, psychosocial and medical morbidity, including rates of HIV and hepatitis B virus (HBV) infection; and mortality has been demonstrated in many randomized controlled and cohort studies (Soyka et al. 2006; McGowan et al. 2009; Kimber et al. 2010). However, a recent Cochrane review showed efficacy of methadone only for treatment retention and the reduction of illicit opioid use (Mattick et al. 2009). However, the authors acknowledge that these conclusions are probably the result of the review being based only on randomized, controlled trials (RCTs) and that criminality and mortality are better studied in large scale prospective cohort studies. Methadone maintenance has also been shown to increase retention rates and social functioning in opioid addicts (Prendergast et al. 2000, 2001; West et al. 2000; Farre et al. 2002; Mattick et al. 2003a,b; Amato et al. 2004; Sullivan et al. 2006).

Methadone is a synthetic mu-opioid receptor agonist with pharmacological activity similar to that of morphine. Because its structure includes an asymmetrical carbon atom, two enantiomeric forms exist: (*R*-) or levo- or *L*-methadone, and (*S*-) or dextro- or *D*-methadone. Both *L*-methadone and a racemic (i.e., a 50:50) mixture of the two enantiomers are used in the treatment of opioid dependence. The racemic mixture is the most commonly used form of methadone, though a "pure" *L*-form of methadone, which accounts for the majority of the opioid agonist effects of the drug, is marketed in Germany for the treatment of opioid dependence.

Differences in clinical efficacy and the effective dosage of methadone are based on the stereoselective binding of *L*-methadone to specific opioid receptors (Eap et al. 2002). Although the racemic form has only half of the pharmacological activity of the *L*-form at the mu-opioid receptor, it differs less systematically from the *L*-form in its activity at other neuroreceptors and in its effects on cardiac function. Most importantly, the *L*-form has no effect on the electrocardiographic QT interval and therefore does not create a risk for Torsade de pointes (see below). Thus, the *L*-form could be an alternate treatment for individuals who experience QT-elongation with racemic methadone; currently it is available

only in Germany (Soyka 2008 a,b; Soyka and Zingg 2009).

Both enantiomers of methadone antagonize the NMDA receptor and inhibit serotonin and norepinephrine uptake (Eap et al. 2002). There is substantial inter-individual variability in the pharmacodynamics of methadone (Foster et al. 2000, 2004; Kharasch et al. 2004). Recent studies also indicate substantial metabolic and pharmacogenetic differences for the enantiomers (Eap et al. 2002). CYP3A4 is the principal enzyme involved in the metabolism of both methadone enantiomers, but other enzymes (i.e. CYP2D6 and other cytochrome P450 enzymes) also play a role. About 5% of the population are poor metabolizers at the CYP2D6 enzyme and about half are extensive metabolizers (Jannetto and Bratanow 2009). After a standard dose, "poor metabolizers" at CYP3A4 and CYP2D6 have higher methadone concentrations than individuals with normal enzyme activity, and "extensive metabolizers" at CYP2D6 have lower concentrations (Crettol et al. 2005, 2006). For ultra-rapid metabolizers who do poorly on methadone, buprenorphine might be an alternative because it is not significantly metabolized by CYP2D6 (see below) (Haile et al. 2008).

Methadone is orally active and can be dosed once daily for maintenance treatment. Bioavailability does not differ between the tablet and liquid forms (Gourevitch and Friedland 2000). In adequate doses, methadone suppresses opioid withdrawal and blocks the effects of other opioids. In many countries, methadone for maintenance treatment is available only through specially licensed opioid treatment programmes. However, legislation related to methadone varies considerably among countries (see Farrell et al. 1996). Strictness of local laws and rules concerning maintenance treatment are usually driven by concerns about diversion of opioids to the black market, rather than treatment outcome considerations. The effects of the setting, the adequacy of dosing and the availability of concurrent psychosocial support are important determinants of treatment outcomes (Berglund et al. 2003; Connock et al. 2007; Dutra et al. 2008; Mattick et al. 2008; Wittchen et al. 2008).

A number of clinical studies and meta-analyses show that, overall, methadone treatment significantly reduces the excess morbidity and mortality associated with opioid dependence (Caplehorn et al. 1996; Langendam et al. 2001; Mattick et al. 2003b; Maxwell et al. 2005). Methadone is also a cost-effective treatment (Barnett et al. 2001).

The Cochrane database indicates that methadone is effective in the treatment of opioid withdrawal and for the maintenance of abstinence, especially in combination with psychosocial treatment (Amato et al.

2004; Mattick et al. 2003b; Gowing et al. 2006; Connock et al. 2007).

No randomized studies have compared the efficacy of the two methadone isoforms, and few studies have addressed the impact of switching from one form to the other (Judson et al. 1976; Scherbaum et al. 1996; de Vos et al. 1998; Soyka et al. 2009). Single-dose studies (Kristensen et al. 1996; Boulton et al. 2001) and studies under steady-state conditions (Kreek et al. 1979; Nakamura et al. 1982) suggest that (*R*-) methadone has a longer elimination half-life than (*S*-) methadone.

Dosing

Dosing is a key issue in methadone maintenance. Methadone is orally active, administered once daily and can be given in liquid or tablet form. Although it is possible to measure plasma levels of methadone, such assays are not commonly performed in maintenance therapy and there is no consensus as to what constitutes an optimal plasma concentration (Soyka 2008a,b). There is considerable inter-individual variation in the plasma concentration of methadone after a standard dose, probably partly due to the pharmacology of the drug and individual differences in metabolism, as mentioned above (Eap et al. 2002; Soyka 2008b). Therefore, dosing should be based on clinically guided dose titration. Although the usual maintenance dosage of methadone is 60–100 mg/day (Freed et al. 2010), some patients achieve abstinence or are free of withdrawal symptoms when treated with less than 40 mg/day of methadone. Generally, 40–60 mg of methadone will prevent the occurrence of the opioid withdrawal syndrome (Farre et al. 2002). Experimental studies suggest that methadone doses of 60–100 mg/day or higher are more effective than lower doses for reducing or stopping heroin self-administration in opioid-dependent patients (Strain et al. 1999; Faggiano et al. 2003; Donny et al. 2005; Fareed et al. 2010). Clinically, higher doses are associated with better treatment retention rates and outcomes (Ling et al. 1976; Strain et al. 1993a,b, 1999; Prendergast et al. 2000, 2001) and may be necessary in patients with comorbid psychiatric disorders (Maremmani et al. 2000a,b). However, no controlled treatment studies have demonstrated greater benefit for dosages higher than 100 mg/day. A higher dosage may be required in individual patients (for example rapid metabolizers of methadone or in patients using medications that induce the CYP3A system) and those with medical disorders such as hepatitis C infection (Okruhlica and Klem-pova 2000; Maxwell et al. 2002). Better results can be obtained if methadone maintenance treatment is

combined with contingency management. However, there are no indications that cognitive behavioural therapy adds to its efficacy (NICE 2010).

Safety

Risk associated with the use of methadone include respiratory depression (Darke et al. 2007), pharmacokinetic interactions with other drugs (Eap et al. 2002; Kharasch et al. 2004; Crettol et al. 2006) and cardiotoxicity (prolonged QT interval, risk of Torsade de pointes) (Ehret et al. 2006; Justo 2006).

Methadone maintenance is generally safe (Kleber et al. 2007). Results from large surveillance studies indicate that the 1-year mortality rate is approximately 1% and is mostly due to overdose or intoxication from multiple drugs that produce respiratory depression, e.g., alcohol and/or benzodiazepines or other sedatives (Soyka et al. 2006; Wittchen et al. 2008). Many of the deaths associated with the use of methadone, especially in the United States, are related to its use as an analgesic (Substance Abuse and Mental Health Services Administration (SAMHSA) 2001). Drug-drug interactions (both pharmacokinetic and pharmacodynamic) are an important consideration in the use of methadone (Corkery et al. 2004). Slow metabolizers may have a higher risk for methadone-associated deaths (Bunten et al. 2010). The most frequent adverse events associated with methadone are constipation, increased sweating and sexual dysfunction. Subtle-to-mild cognitive impairment has often been described (Darke et al. 2000; Mintzer and Stitzer 2002; Soyka et al. 2008a), but most patients receiving methadone maintenance do not show clinically relevant cognitive impairment (see below).

Methadone, especially at higher dosages, has been associated with cardiotoxicity and a risk of arrhythmias, including QT prolongation and Torsade de pointes (Krantz et al. 2002, 2003, 2007; Gil et al. 2003; Martell et al. 2005; Ehret et al. 2007). Ventricular arrhythmias are an uncommon but important problem (Hanson et al. 2010). There have been some official warnings of this risk in Germany and in Switzerland (Elsner 2005). The risk for cardiac complications is higher in patients with existing cardiac disorders, electrolyte imbalance (particularly hypokalemia) or liver dysfunction, and in individuals taking diuretics or medications that prolong the QT interval such as antipsychotics. There are multiple interactions with other drugs, especially those metabolized via CYP2D6 and CYP3A4 such as tricyclic antidepressants (Kosten 1990a,b), other psychotropic drugs and HIV medication (Eap et al. 2002; Neuman et al. 2006; Gruber

and McCance-Katz 2010). For a recent review of these interactions see McCance-Katz et al. (2010). In a retrospective case-control study of 167 methadone-treated patients, 16% had clinically relevant QT prolongation but only 3.6% showed Torsade de pointes on electrocardiogram (ECG) (Ehret et al. 2006), with no clear relationship between methadone dose and Torsade de pointes or QT prolongation. Moreover, many patients with Torsade de pointes were also being treated with other medications, which could have contributed to the development of this arrhythmia. Although Backmund et al. (2005a) reported a QT prolongation in 24% of 49 patients, Maremmani et al. (2005) found that only two of 83 patients (2.5%) showed such an effect. Although some authors recommend a cardiac evaluation with at least an ECG before starting methadone treatment (Stringer et al. 2009; Perrin-Terrin et al. 2010), Krantz and Mehler (2006) concluded that an ECG is necessary before methadone treatment only in patients at risk of arrhythmia, an approach that has been endorsed by Justo et al. (2006) and Peles et al. (2007). Patients at risk of arrhythmia have a history of cardiac illness or other risk factors such as hypokalemia or they use medications that can produce QT elongation such as antipsychotics. Buprenorphine and the L-form of methadone do not cause QT prolongation or Torsade de pointes and should be considered in patients at risk for arrhythmias (Hanon et al. 2010).

In view of different approaches to the cardiac evaluation of patients being started on methadone treatment, an independent panel (Krantz et al. 2009) recently developed safety recommendations for physicians prescribing the drug:

1. Clinicians should inform patients of the risk of arrhythmia when they prescribe methadone (disclosure)
2. Clinicians should ask patients about any history of structural heart disease, arrhythmia, or syncope (clinical history)
3. All patients should receive a pre-treatment ECG to measure the QTc interval and a follow-up ECG within 30 days of starting therapy and then annually. An additional ECG is recommended if the methadone dosage exceeds 100 mg/day or if patients have unexplained syncope or seizures (screening)
4. If the QT interval is greater than 450 ms but less than 500 ms, the potential risks and benefits should be discussed with the patient, who if agreeable to treatment should be monitored more frequently. If the QTc interval exceeds 500 ms, discontinuation or reduction of the methadone dosage should be considered,

contributing factors (e.g., drugs that promote hypokalemia) should be eliminated, and the use of an alternate therapy (such as buprenorphine) discussed with the patient (risk stratification)

5. Clinicians should be aware of interactions between methadone and other drugs that possess QT interval-prolonging properties or slow the elimination of methadone

Recommendation: Methadone is the standard medication for the treatment of opioid dependence (RG1). Its efficacy can be enhanced when combined with contingency management (RG1).

Injectable methadone has occasionally been used in the treatment of opioid dependence (Hartnoll et al. 1980; Strang et al. 2010), but the results are disappointing (Strang et al. 2000, 2010). This form will, therefore, not be discussed further in these practice guidelines.

LAAM

L- α -Acetylmethadol (LAAM) is structurally similar to methadone and is orally active, but LAAM has a substantially longer duration of action than methadone so that it can be administered less frequently, e.g., twice weekly. However, the drug has been withdrawn in the United States and European countries because of the risk of QT prolongation and cardiac arrhythmia (Deamer et al. 2001) and is no longer recommended for the treatment of opioid dependence.

Slow-release oral morphine

Slow-release oral morphine (SROM) has been proposed as an alternate opioid substitution treatment and is available in some European countries (Mitchell et al. 2003, 2004). However, there are few data on its efficacy and safety. An open-label study showed that switching opioid-dependent patients who did not tolerate methadone to slow-release oral morphine was a potentially useful strategy (Kastelic et al. 2008). However, the abuse potential of SROM seems to be significant. In Austria, SROM is dominating the black market and has nearly replaced heroin (Beer et al. 2010). More studies are needed of this formulation.

Heroin-assisted maintenance treatment

The treatment of heroin dependence with heroin is controversial because it raises multiple clinical and ethical questions. The drug is not yet included in

most treatment guidelines (Kleber et al. 2007). The question of whether heroin maintenance is a suitable treatment must be considered in relation to clinical data and other factors such as safety, cost-effectiveness, risk of diversion and social and legal barriers that vary considerably among countries. The prescription of heroin is generally advocated for patients with severe dependence that are resistant to other recommended treatments. To date, heroin maintenance is available for routine use in The Netherlands, Switzerland and Denmark and will soon be available in Germany. High-quality, RCTs of heroin were conducted in Switzerland, Germany, the UK, Spain, The Netherlands, and Canada. All studies showed a significant and clinically relevant positive outcome on the main pre-defined outcomes (Blanken et al. 2010), including reductions in illicit heroin use, improved measures of psychological, physical, and social well-being and reduced criminality. In a recent Cochrane review of 19 studies, Ferri et al. (2006) concluded that the available evidence suggests that there is added value to prescribing heroin alongside a flexible dosage of methadone for long-term, treatment-refractory opioid users. This is based on a decrease in the use of street heroin and other illicit substances, a decrease in the probability of imprisonment, and an increase in treatment retention. However, due to a slightly higher rate of serious adverse events, prescribed heroin should remain a treatment of last resort for people who are currently or have previously failed maintenance treatment. Two long-term, naturalistic studies have shown sustained positive effects for previously treatment-refractory patients who remain in heroin-assisted treatment (Blanken et al. 2010).

The use of heroin as a medication has a number of obvious disadvantages: first, the drug has to be given either intravenously or through inhalation (van den Brink et al. 2003; Blanken et al. 2010). Second, there is a small risk of overdose that, to date, has not led to any fatalities. Third, the short half-life of the drug requires several (usually two to three; Blanken et al. 2010) administrations each day and/or the concomitant use of methadone at night to avoid the appearance of withdrawal symptoms. In addition, the logistics of heroin treatment (including its production, distribution and storage) and the monitoring of patients who self-administer heroin to avoid overdose, asphyxia and other serious adverse outcomes make it suitable for use only in specialized centres where prompt medical intervention is available (Oviedo-Joekes et al. 2009). Hepatic impairment does not seem to have a clinically relevant effect on the pharmacokinetics of heroin and its metabolites, and renal impairment has modest effects (Rook et al. 2006). Recently, orally administered

heroin has been studied as a possible alternative to injectable heroin with some promising initial results, though data on this approach are very limited (Frick et al. 2010). Finally, there are indications that heroin-assisted treatment for treatment-refractory patients is expensive but cost-effective from a societal perspective (e.g., Dijkgraaf et al. 2005).

Recommendation: There is compelling evidence for the efficacy of heroin-assisted treatment in treatment-refractory, opioid-dependent patients (3). Based on data from Switzerland (Uchternhagen 2010) and The Netherlands (Blanken et al. 2010), it appears that heroin-assisted treatment can be implemented routinely in medical settings. Further study of this treatment is needed. Despite ethical concerns among both scientists and the lay public over heroin substitution, such treatment is routine in some countries.

Partial mu agonist therapy: buprenorphine and buprenorphine/naloxone

Buprenorphine is a long-acting opioid that, like methadone, has robust analgesic effects; it has been used for decades in low dosages as an analgesic (Wesson and Smith 2010). It is a mixed opioid agonist-antagonist that produces a less than maximal or partial agonist effect at the mu-opioid receptor and is an antagonist at the kappa-opioid receptor (Gutstein and Akil 2001). There are data showing a ceiling on the respiratory, but not analgesic, effect of buprenorphine (Dahan et al. 2006). It has poor oral bioavailability and is, therefore, used sublingually, where it is absorbed through the oral mucosa (for reviews see Davids and Gastpar 2004; Orman and Keating 2009; Mammen and Bell 2010). Steady-state drug concentrations for a 16-mg dose of buprenorphine are reached after 7 days (Compton et al. 2006). The analgesic dose of buprenorphine ranges from 0.2 to 0.4 g. The plasticity of the brain opioid system after chronic opioid use and the tolerance due to up-regulation of opioid receptors are underscored by the need for doses of buprenorphine as high as 32 mg/day for the treatment of opioid dependence (Kleber et al. 2007). Because of its long duration of action, buprenorphine can be dosed on a less-than-daily basis. One strategy has been to double the daily dosage for use every other day and triple the dosage for use every 3 days (Eisenberg et al. 1997; Amass et al. 1998; Bickel et al. 1999; Petry et al. 1999, 2000).

Two forms of buprenorphine are available: a tablet containing only buprenorphine and one that combines buprenorphine with the opioid antagonist naloxone in a 1:4 ratio. Naloxone has poor oral bioavailability

but good parenteral bioavailability (Preston et al. 1990) and, consequently, when dissolved and injected, the combination buprenorphine-naloxone tablet will precipitate opioid withdrawal. This is thought to reduce the abuse potential of buprenorphine and improve its safety. American Psychiatric Association (APA) guidelines (Kleber et al. 2007) state that the combination tablet significantly reduces the risk that the medication will be diverted for other uses. There are some supporting clinical and laboratory data for these assertions (Amass et al. 2000; Stoller et al. 2001; Alho et al. 2007) although Italian and Malaysian data still indicate a high risk for diversion (Monte et al. 2009; Vicknasingam 2010). The combination of buprenorphine and naloxone may reduce but not eliminate intravenous misuse (Mammen and Bell 2009). Recent findings also show that the introduction of the combination drug in Malaysia did not reduce opioid use or injection-related risk behaviours such as syringe sharing and was associated with increased benzodiazepine use (Bruce et al. 2009).

Buprenorphine effectively suppresses opioid withdrawal. Clinical studies that have compared the detoxification effects of methadone, primarily in moderate dosages (50–60 mg), with those of buprenorphine (12–16 mg) have generally shown the two drugs to have comparable efficacy (Schottenfeld et al. 1997; Kakko et al. 2007; Soyka et al. 2008a). However, other studies have been more mixed, showing a better retention rate or less substance use with buprenorphine than with higher dosages of methadone or vice versa (Strain et al. 1994; Ling et al. 1996; Schottenfeld et al. 1997; Petitjean et al. 2001; Mattick et al. 2003a). A double-blind study comparing the efficacy of a buprenorphine–naloxone combination with methadone showed no differences between the two treatments (Kamien et al. 2008). A multi-centre study of 4 weeks of office-based treatment in opioid-dependent patients demonstrated a robust effect of buprenorphine with or without naloxone in reducing opiate use and drug craving (Fudala et al. 2003).

Extended buprenorphine treatment is more effective than short-term treatment in young opioid users (Woody et al. 2008). However, a recent systematic review suggested that flexible dosing of methadone is superior to buprenorphine with respect to retention but not opioid use (Connock et al. 2007). Although current American Psychiatric Association (APA) guidelines (Kleber et al. 2007) recommend the use of buprenorphine in patients with mild to moderately severe physical dependence, current data do not show that the severity of opioid dependence (as measured by the Addiction Severity Index or other instruments) predicts the outcome of opioid dependence treatment in either buprenorphine-

methadone-treated patients (Mattick et al. 2003b). Some research shows that concurrent psychosocial treatment may improve clinical outcomes in buprenorphine-treated patients (Galanter et al. 2004; Connock et al. 2007). However, a recent meta-analysis showed that contingency management does not add to the efficacy of buprenorphine maintenance treatment (NICE 2010). Possible explanations for the apparent difference in the effect of concurrent contingency management between methadone (where it is effective) and buprenorphine (where it is not effective) are that reinforcing values in the buprenorphine studies were too low and that the contingencies were directed at more than one drug (NICE 2010).

A recent 6-month, randomized, controlled trial compared the effects of four buprenorphine implants (80 mg each) with placebo implants. The active treatment group was significantly more likely to complete the study and had significantly fewer opioid-positive urine tests over the first 16 weeks of the study (Ling et al. 2010). The implant was well tolerated. The clinical value of a buprenorphine implant requires additional study in other samples before its use can be recommended. An important consideration is the relative advantages of treatment with oral and implanted buprenorphine.

Safety

The major advantage of buprenorphine is its relative safety, including what appears to be a smaller risk of fatal overdose than with methadone. Buprenorphine does not easily cause respiratory depression (Davids and Gastpar 2004). Toxicological findings, especially from France, suggest a lower risk of death in buprenorphine-treated patients than in methadone-treated patients (Auriacombe et al. 2001; Pirnay et al. 2004), though longitudinal studies do not support this view (Soyka et al. 2008a). Fatal overdoses associated with buprenorphine are usually due to intoxication with a combination of buprenorphine with other drugs (e.g., benzodiazepines, alcohol). Another advantage of buprenorphine is its relatively mild withdrawal syndrome, which makes its gradual reduction easier to accomplish than for methadone (Gutstein and Akil 2001). Buprenorphine produces the typical adverse effects of opioid analgesics, including mild elevations in liver function tests (Davids and Gastpar 2004; Kleber et al. 2007; Wesson and Smith 2010). A pooled analysis of randomized clinical trials revealed no differences in serious adverse events between methadone and buprenorphine (Connock et al. 2007). Buprenorphine does not cause QT prolongation and may have advantages over methadone in patients with cardiac

risk factors or QT prolongation from methadone (see below). Although methadone may be slightly more cost effective than buprenorphine, both drugs are more cost effective than placebo (Connock et al. 2007).

Recommendation: Buprenorphine and buprenorphine/naloxone are standard medications for the treatment of opioid dependence. (1) Whether the combination of buprenorphine and naloxone has advantages over buprenorphine alone requires empirical validation. There are no indications that adding contingency management to buprenorphine maintenance treatment enhances its effectiveness (1).

Allocation of patients and predictors of outcome

In many cases, the choice of an opioid agonist for substitution therapy is based on the clinician's experience and the patient's preference, rather than being based on evidence of superior efficacy or patient predictors of outcome. Although methadone and buprenorphine have different pharmacological profiles, few longitudinal studies of predictors of outcome or studies aimed at identifying features that help to match patients to one or the other medication have been conducted. A Cochrane review on methadone and buprenorphine (Mattick et al. 2003b) concluded that the effectiveness of high-dose buprenorphine is equal to high-dose methadone in terms of retention but inferior in reducing heroin use. Interestingly, a recent systematic review by Connock et al. (2007) yielded a different result, showing better retention in the methadone studies and no difference in the effects of the two medications on opioid use. The review by Mattick et al. (2003b) showed that flexible-dose studies had a better outcome than fixed-dose studies, and a more rapid induction to buprenorphine yielded a better outcome than more gradual induction. Most studies show a lower retention rate in patients with a higher rate of heroin injection or a greater number of previous treatments (Kerr et al. 2005; Fischer et al. 2008; Soyka et al. 2008a; Havens et al. 2009). Connock et al. (2007) and, more recently, Burns et al. (2009) concluded that the mortality rate may be lower in buprenorphine patients than in methadone patients, but these findings were not replicated in another study (Soyka et al. 2006, 2008b). Although the addition of naloxone may reduce the risk of overdose and the abuse potential of buprenorphine, there are few data to evaluate this question.

Cognitive effects

Abstinent opioid-dependent patients have been shown to have cognitive deficits (Davis et al. 2002; Lee and Pau 2002; Pau et al. 2002; Mintzer et al. 2005; Verdejo et al. 2005; Prosser et al. 2006). Data on cognitive performance of patients taking methadone and buprenorphine are mixed (Specka et al. 2000; Curran et al. 2001; Mintzer and Stitzer 2002; Mintzer et al. 2005; Gruber et al. 2006; Prosser et al. 2006; Mintzer 2007; Messinis et al. 2009). Although some non-randomized or preliminary studies have shown better cognitive functioning in some domains in buprenorphine-maintained patients (Soyka et al. 2001, 2005), other studies, including both a non-randomized study (Loeber et al. 2008) and a randomized one (Soyka et al. 2006, 2008b), failed to replicate these findings. Most patients without other substance use, neurological disorders or head trauma show no or only subtle cognitive impairments when being treated with either methadone or buprenorphine.

These findings have implications for an individual's driving ability, which may be affected not only by cognitive function, but also by comorbid drug use, individual skills and personal driving history. Many maintenance patients have been shown to be fit to drive, at least based on their cognitive function (Mintzer and Stitzer 2002; Mintzer et al. 2005; Mintzer 2007).

Research perspectives

Some specific hypotheses should be addressed in future studies of opioid agonist maintenance treatments. Sex differences and the role of cognitive function and comorbid psychiatric disorders in treatment outcome have been neglected (McCowan et al. 2009). In addition, more research is needed in the area of concurrent psychosocial interventions (Dutra et al. 2010). Kerr et al. (2005) reported a better retention rate in female methadone patients. Schottenfeld et al. (1999) found buprenorphine to be superior to methadone in women. The role of depression, which is very common in opioid-dependent patients, warrants specific attention. Although clinical evidence is limited, both methadone and buprenorphine have been postulated to have antidepressant effects. A possible mechanism for the antidepressant effects of methadone is its serotonin reuptake inhibition and for buprenorphine its kappa receptor antagonism (for the antidepressant effects of opioids see Aldrich and McLaughlin 2009; Berrososo et al. 2009). However, some studies indicate that depressed opioid patients may benefit more from buprenorphine than from methadone (Gerra et al. 2004). In

an open-label study, cognitive improvement was more marked in buprenorphine patients than in those treated with methadone (Pirastu et al. 2006); however, randomized studies do not show better cognitive function in buprenorphine patients (Soyka et al. 2008b).

Abstinence oriented pharmacotherapies

Opioid antagonist therapy: naltrexone

Naltrexone is an opioid antagonist that binds tightly to opioid receptors but has no psychoactive effects. It blocks the euphoric effects of heroin and other opioids, thereby discouraging the use of these drugs and diminishing conditioned craving (Kleber et al. 2007). Naltrexone treatment is an abstinence-oriented approach requiring patient cooperation and compliance; it cannot be given to patients who are being treated with opioids because it will precipitate opioid withdrawal (A). Before initiating treatment with naltrexone, patients must be free from short-acting opioids such as heroin for at least 5 days and from longer-acting opioids such as methadone for a minimum of 7 days; this must be verified by urine toxicology. A test dose of 0.8 mg naloxone intramuscularly can be used to confirm abstinence; since naloxone has a very short duration of action, it will precipitate opioid withdrawal only briefly.

The usual oral dosage of naltrexone is 50 mg once daily. Imaging studies indicate that the mu-opioid receptor is entirely blocked at this dosage (Weerts et al. 2008). Because of its long duration of action, naltrexone can also be administered thrice weekly at a dosage of 100 mg (on Monday and Wednesday) and 150 mg (on Friday; Kleber et al. 2007). The drug has no abuse potential and is approved in the United States and most European countries for the treatment of opioid dependence. A clinically important risk associated with naltrexone treatment is that after chronic use patients are no longer tolerant of opioid effects. This increased sensitivity to opioid effects is probably due to an upregulation of opioid receptors (Zukin et al. 1982; Lesscher et al. 2003). As a consequence, there is an increased risk of fatal overdose if patients relapse to heroin use after naltrexone treatment is discontinued.

Adverse events associated with naltrexone treatment include dysphoria, anxiety and gastrointestinal distress (APA 2007). Liver enzymes may be increased in some patients receiving naltrexone, usually among individuals over 40 years of age who take higher dosages than recommended (Pfohl et al. 1986). Despite a black box warning in the prescribing guidelines for the drug, there is no evidence of significant hepatotoxicity of naltrexone at the recommended dosage

(Yen et al. 2006; Garbutt 2010), even in patients with acute viral hepatitis (Brewer and Wong 2004). A meta-analysis showed no differences in the risk or severity of adverse events between patients treated with naltrexone and those receiving placebo (Adi et al. 2007).

Data on the efficacy of naltrexone for the treatment of opioid dependence are mixed. One placebo-controlled study yielded positive results (Mello et al. 1981), but others failed to show an advantage for naltrexone over placebo and were characterized by a very high rate of patient attrition (National Research Council Committee on Clinical Evaluation of Narcotic Antagonists 1978). A recent meta-analysis (Adi et al. 2007) examining 26 randomized, controlled trials concluded that the methodological quality of most of the studies was poor to moderate. Adi et al. (2007) concluded that oral naltrexone provides limited benefit in helping formerly opioid-dependent patients to remain abstinent.

Based on these data and clinical experiences, oral naltrexone is not widely used for the treatment of opioid dependence and is not considered to be a first-line medication for that indication. Patient subgroups that may benefit from this treatment are difficult to identify. The drug may have its greatest benefit in the treatment of addicted physicians and other white-collar patients or patients on probation who are motivated to recover and are compliant with the medication regimen (Washton et al. 1984; Cornish et al. 1997).

Recommendation: Oral naltrexone is not a first line treatment for opioid dependence (1). However, oral naltrexone might be effective in a small subgroup of highly motivated and well-integrated patients (3). Retention in naltrexone treatment is usually poor.

Depot and implant naltrexone

Recent studies have evaluated the feasibility and efficacy of sustained naltrexone in the form of intramuscular injections (Comer et al. 2006; Sullivan et al. 2006; Degenhardt et al. 2008) or as subcutaneous implants in opioid users (Reece 2007; Hulse et al. 2009, 2010; Stotts et al. 2009; Krupitsky and Blokhina 2010). Although a Cochrane analysis by Lobmeier et al. (2008) concluded that there is insufficient evidence to recommend sustained-release naltrexone for the treatment of opioid dependence, data from an unpublished study conducted in Russia served as the basis for the approval by the US Food and Drug Administration of a one-month naltrexone formulation for the treatment of opioid dependence.

This formulation is the same one that is approved in the United States for the treatment of alcohol dependence.

Naltrexone implants have been studied most often in Australia and Russia (Krupitsky and Blokhina 2010). Studies of a naltrexone implant in opioid-dependent patients in Australia showed a reduction in morbidity and mortality (Ngo et al. 2008; Tait et al. 2008). Despite studies showing that a naltrexone implant is superior to oral naltrexone (Hulse et al. 2009, 2010), with an implant approved for clinical use in Russia, more data are needed to define more clearly its clinical potential and long-term effectiveness. There are also safety concerns, including reports of emergency admissions for severe dehydration and opioid withdrawal and deaths due to overdose (for a review see Stotts et al. 2009).

Recommendation: Although depot naltrexone is now approved and available in the United States for the treatment of opioid dependence, additional studies are needed to define more clearly its clinical efficacy over the long term. Naltrexone implants cannot yet be recommended for clinical use because although there are promising efficacy data for them, safety concerns remain and require further evaluation.

Treatment of withdrawal symptoms

Heroin withdrawal is initially characterized by agitation, anxiety, myalgia, rhinorrhoea, insomnia, sweating and yawning. Other signs and symptoms include abdominal cramps, diarrhoea, mydriasis, gooseflesh, nausea and vomiting, which peak 48–72 h after the last dose and disappear within 7–10 days. The time course of withdrawal varies with the pharmacokinetics of the opioid agonist and the peak intensity of withdrawal is inversely correlated with the duration of action of the agonist. For morphine, withdrawal symptoms appear after 14–20 h and peak after 36–48 h; for heroin, symptoms appear after 8–12 h, peak at 48–72 h and usually end within 5–10 days (Koob and Le Moal 2006). A protracted abstinence syndrome often follows and includes opioid craving. Often, opioid withdrawal occurs in the context of emergency treatment (e.g., after a traumatic injury) or more often, when the patient tires of the addicted lifestyle and is motivated to be drug free.

The overall goal of opioid-withdrawal treatment is to minimize symptoms and enhance a transition to drug-free treatment. Standardized rating scales such as the Short Opiate Withdrawal Scale are not routinely employed to assess withdrawal symptoms but may help to optimize dosing. Contingency management is a psychosocial intervention that is

often used to support opioid detoxification (NICE 2007). There are several pharmacological strategies used to treat opioid withdrawal:

- a. Replacement by and gradual reduction of the dose of methadone
- b. Replacement followed by an abrupt or gradual buprenorphine taper
- c. Abrupt opioid discontinuation and use of clonidine or another alpha-2-adrenoreceptor agonist to alleviate withdrawal symptoms
- d. Precipitation of withdrawal with naltrexone and the use of clonidine and other medications to alleviate the acute withdrawal symptoms
- e. Use of other medications (e.g., benzodiazepines) to reduce withdrawal symptoms

Replacement by and gradual tapering of methadone

Replacement by methadone followed by a gradual methadone taper is a well-established and frequently used strategy to detoxify patients from heroin or other opioids (Kleber et al. 2007; NICE 2007). The initial dosage is based on the patient's opioid use history, severity of dependence, the subjective and objective withdrawal signs present at the time of assessment and the setting in which detoxification is conducted (NICE 2007). After an initial stabilization dosage of 40–60 mg/day, methadone can be reduced gradually by 5–10 mg/day. The speed of reduction depends on the clinical setting, the patient's motivation and the severity of the signs and symptoms of withdrawal. In an inpatient setting, opioid detoxification can usually be completed within seven days. In an outpatient setting, which has a greater risk of premature termination of treatment, a more gradual reduction is recommended over a period of weeks. APA guidelines (Kleber et al. 2007) recommend the use of a higher dosage of methadone for outpatient detoxification to help dependent individuals end their illicit drug use and to reduce high rates of early discontinuation of treatment and relapse. However, there is limited evidence for this recommendation.

Recommendation: Methadone is a standard and safe medication for opioid detoxification (1)

Replacement followed by abrupt or gradual tapering of buprenorphine

Studies of sublingual buprenorphine with or without naloxone show that the drug is more efficacious than clonidine for the treatment of opioid withdrawal (Nigam et al. 1993; Janiri et al. 1994; Fingerhood

et al. 2001; Oreskovich et al. 2005; Ziedonis et al. 2009) (for a review see Orman and Keating 2009; Meader 2010), especially in the reduction of the symptoms (but not the signs) of withdrawal. There are few well-designed studies comparing methadone and buprenorphine in opioid withdrawal (Kleber et al. 2007). A recent meta-analysis has identified three relatively small trials directly comparing methadone and buprenorphine detoxification (Seifert et al. 2002; Petitjean et al. 2002; Umbricht et al. 2002). Overall, buprenorphine and methadone showed equal efficacy and were both more effective than clonidine or lofexidine (see also Meader 2010).

Buprenorphine is a long-acting drug and withdrawal symptoms are typically mild. PET studies using carfentanil show that 50–60% occupancy of the mu-receptor by buprenorphine is required for adequate suppression of withdrawal symptoms (Greenwald et al. 2007). Buprenorphine can be used successfully alone or in combination with naloxone to treat opioid withdrawal (Ling et al. 2005; Ziedonis et al. 2009). The initial dosage of buprenorphine in inpatient detoxification is typically 8 mg/day, which is adequate to suppress withdrawal symptoms. This dosage can be reduced by 2 mg/day.

Initially, outpatients should be stabilized on a dosage of 8–32 mg/day of buprenorphine, which should then be gradually withdrawn. Some guidelines (Kleber et al. 2007) recommend the use of the buprenorphine/naloxone combination formulation for the outpatient treatment of withdrawal, but there are no comparative studies to support this view. The dosage of buprenorphine can usually be reduced over a 10–14-day period. The 1-year outcome of patients treated with buprenorphine for opioid withdrawal is poorer than that of individuals in buprenorphine maintenance therapy (Kakko et al. 2003). Similar results have been published for methadone detoxification compared with maintenance (Sees et al. 2000)

Buprenorphine can be used for detoxification from both short-acting opioids such as heroin and longer-acting drugs such as methadone. Withdrawal from buprenorphine is typically associated with fewer symptoms than withdrawal from methadone, making this approach potentially useful in patients who are intolerant of methadone withdrawal symptoms. However, switching patients to buprenorphine from doses of methadone greater than 60 mg/day can be difficult (Walsh et al. 1995; Levin et al. 1997; Greenwald et al. 2003). In such patients, the dosage of methadone should be reduced to about 40 mg/day before the switch is made to buprenorphine. Patients receiving higher dosages of methadone do not readily tolerate this procedure.

Recommendation: Buprenorphine is a standard and safe medication for opioid detoxification (Kleber et al. 2007; NICE 2007 RG1).

Use of clonidine or other alpha-2 adrenoceptor agonists

Clonidine is a centrally active alpha-2-adrenergic agonist medication that is widely used to treat hypertension. The rationale for its use in the treatment of opioid withdrawal is that it decreases noradrenergic activity, which is elevated during withdrawal from a variety of drugs, including opioids. Although the drug is not approved in any country to treat opioid withdrawal, it has been studied extensively. A recent, updated Cochrane review (Gowing et al. 2009) concluded that clonidine and lofexidine – which is similar pharmacologically to clonidine – are more effective than placebo. However, methadone is better than clonidine at maintaining treatment participation and adverse events are more frequent with clonidine. A recent mixed treatment comparison meta-analysis, which included 20 randomized clinical trials, concluded that methadone and buprenorphine are most effective in opioid detoxification followed by lofexidine and then clonidine (Meader 2010).

Clonidine decreases symptoms such as insomnia, muscle aches, distress and drug craving (Charney et al. 1981; Kleber et al. 1985). It is generally safe for use in opioid withdrawal and has no abuse potential. Adverse effects of the drug include hypotension and sedation. Contraindications for the use of clonidine are acute and chronic cardiac disorders, renal and metabolic diseases and moderate-to-severe hypotension (Jasinski et al. 1985).

Clonidine is usually given for 4–6 days to treat withdrawal from a short-acting opioid such as heroin. Withdrawal from longer-acting opioids such as methadone may require longer treatment with clonidine. The usual dosage of clonidine for the treatment of opioid withdrawal is 0.1 mg three times a day. Higher dosages, such as are used to treat hypertension, are likely to produce sedation. The drug is frequently used in combination with other medications, and careful monitoring and dose titration are necessary since clonidine overdoses can be fatal (Gold et al. 1980; Kleber et al. 1987). Given the potential for the drug to cause hypotension, the drug's dosage should be reduced if the patient's blood pressure falls below 90/60 mmHg (Kleber et al. 2007).

Because of the potential for diversion and abuse of opioid agonists, clonidine has a number of advantages for the outpatient treatment of opioid withdrawal (Washton et al. 1980; Spencer and Gregory

1989; Fingerhood et al. 2001). However, clonidine-induced sedation is more easily detected and managed in an inpatient setting. Clonidine is an alternative to methadone, but the completion rate for outpatients is relatively modest (Kleber et al. 1987). The use of a transdermal clonidine patch (Honey et al. 2009) could improve adherence. In contrast to earlier guidelines in which alpha-2-adrenergic agonists were considered preferable to methadone for brief treatment (Lingford-Hughes et al. 2004), more recent guidelines do not recommend routine use of the drug for opioid detoxification (NICE 2007). Clearly, methadone and buprenorphine are the standard medications for opioid detoxification (Meader 2010).

In recent years, lofexidine has been studied as a possible alternative to clonidine to treat opioid withdrawal (for a review see Gish et al. 2010). Lofexidine is an alpha-2-adrenoreceptor agonist that is structurally related to clonidine but is not active as a hypertensive agent. The dosage of lofexidine for the treatment of opioid withdrawal is 1.6–3.2 mg/day. In a preliminary study, the drug was shown to decrease stress-related opioid craving (Sinha et al. 2007). It also reduced the increased sympathetic activity that occurs in opioid withdrawal (for a review see Gish et al. 2010; Gowing et al. 2009). Not all withdrawal symptoms such as insomnia and myalgia are alleviated by the drug (Gish et al. 2010). Lofexidine is not as well studied as clonidine, so additional research is warranted (Gish et al. 2010; Meader 2010). Although treatment outcomes are similar in patients treated with clonidine or lofexidine (Gowing et al. 2009; Meader 2010), lofexidine appears to have a better safety profile than clonidine. If approved, lofexidine would be the first non-opioid medication approved for the treatment of opioid withdrawal. Lofexidine might be useful in patients with mild or uncertain dependence (NICE 2007).

With respect to special subgroups, central alpha-2-adrenoreceptor agonists have been studied for the treatment of iatrogenic opioid abstinence syndrome in critically ill patients. On the basis of a systematic review, Honey et al. (2009) concluded that these drugs are effective and safe as second-line agents in this population. There seems to be little value in combining clonidine with methadone (Wilson and DiGeorge 1993; Agthe et al. 2009). Alpha-2-receptor function is down-regulated in opioid dependence (Stine et al. 2001, 2002).

Recommendation: Clonidine (3) and lofexidine (3) are less effective than methadone and buprenorphine in reducing the symptoms of opioid withdrawal.

Clinical experience has shown that combining alpha-2-adrenoreceptor agonists with methadone or possibly buprenorphine can be useful and practicable only in cases with marked hypertension or related symptoms.

Rapid detoxification using naltrexone in combination with clonidine

The rationale for combining naltrexone and clonidine is to precipitate withdrawal by naltrexone and reduce the resultant symptoms by pre-treatment with clonidine. Even a single dose of naltrexone can rapidly antagonize the opioid receptor (Krystal et al. 1989). This approach makes particular sense when a patient is scheduled for continued maintenance antagonist treatment. On the first day of treatment, the patient must be monitored closely for 8 h because of the potential for severe naltrexone-induced withdrawal. The potential for hypotension from clonidine necessitates ongoing blood pressure monitoring during the entire detoxification period (Kleber et al. 2007). According to the APA guidelines, the combined use of clonidine and naltrexone is safe and effective (Kleber et al. 2007).

This approach has been extended to include heavy sedation or general anaesthesia. This “ultra-rapid detoxification” has predominantly been studied using open or uncontrolled study designs, but some randomised controlled trials have been performed (Collins et al. 2005; de Jong et al., 2005). Data from Tretter et al. (1998) on 14 patients indicate that most patients treated in this manner suffered from withdrawal symptoms after awakening from anaesthesia; similar results were reported by de Jong (2005). This corresponds to data from an animal model, which indicate that withdrawal symptoms may be prolonged after anaesthesia and naloxone treatment, raising doubts about the utility of this approach (Spanagel et al. 1998). The few randomized controlled trials in this area have not shown opioid antagonist detoxification under anaesthesia to be superior to other treatments (De Jong 2005; Favrat et al. 2006). Taking into account the medical risks of the procedure (particularly those related to general anaesthesia in patients who may be dependent on multiple kinds of drugs) and other safety concerns (Gowing et al. 2010), this method cannot be recommended and should not be used (NICE 2007). (Evidence level E)

Recommendation: There is no convincing evidence for the use of the combination of opioid antagonists plus

clonidine under heavy sedation. Given the lack of evidence for a substantial advantage of this approach, the associated risks and costs do not appear to be justified.

Other medications

Other opioid drugs or formulations are currently being developed for use in opioid-dependent patients. For example, slow-release oral morphine (SRM) was as effective as methadone in the treatment of opioid withdrawal (Madlung-Kratzer et al. 2009) and is available in the United States (though not approved for use in opioid dependence) and some European countries (Austria, Switzerland). The opioid analgesic tramadol has been tested as an alternative for buprenorphine, but only retrospective chart reviews have been published (Threlkeld et al. 2006). Many other medications are used to treat specific symptoms in opioid withdrawal. These include antidepressants, anxiolytics and sedatives, vitamins, non-steroidal anti-inflammatory drugs and antispasmodics. There are few controlled studies on the use of these medications (O'Connor et al. 1998). One small, uncontrolled, open-label study provided some evidence of efficacy for a delta-sleep-inducing peptide in the treatment of opioid withdrawal (Backmund et al. 1998). The drug apparently has not been studied since then. The abuse potential of anxiolytics and sedatives/hypnotics must be kept in mind and patients must be carefully selected and monitored when these medications are prescribed for the treatment of opioid withdrawal.

Pregnancy

There are a number of gender issues in opioid dependence. Women have an earlier age of initiation of substance use and a more rapid progression to drug involvement and dependence than men (Unger et al. 2010). Opioid-dependent women rarely use contraceptives (Kakko et al. 2008), and pregnancy is common. Since the immune and endocrine systems stabilize following maintenance therapy the probability of pregnancies increases (Kreek and Hartman 1982). Opioid-dependent pregnant women frequently smoke cigarettes, have medical problems, including poor nutrition, with vitamin and other deficiencies, hypertension, HIV infection and other sexually transmitted diseases, and many are in treatment for the first time (De Leon and Jainchill 1991). The foetus and neonate are thus susceptible to low birth weight, premature birth, stillbirth, neonatal abstinence syndrome (NAS) and sudden infant death syndrome (Suffert and Brotman 1984). Many

newborn babies are dependent on opioids and display withdrawal signs after birth, though intellectual development is not usually affected (Suffert and Brotman 1984). The primary goal of treatment for the pregnant opioid-using woman is to ensure medical and physiological stabilization and lifestyle changes to facilitate prenatal care. Detoxification should be avoided in the first trimester (Lingford-Hughes et al. 2004). Other authors state that withdrawal from methadone is contraindicated throughout pregnancy (Jones et al. 2000, 2001; Kleber et al. 2007; Winklbaur et al. 2008a,b). RG 4

Methadone maintenance has been shown to improve infant outcomes (Hulse et al. 1997, 1998; Kandall et al. 1999; Linford-Hughes et al. 2004). Carroll et al. (1995) reported that methadone treatment plus enhanced care improved neonatal outcomes, but did not affect substance use. A recent meta-analysis shows that the severity of the neonatal abstinence syndrome does not differ between mothers on high- or low-dose maintenance therapy (Cleary et al. 2010). Contingency management approaches improve treatment adherence (Kleber et al. 2007).

A number of recent observational studies suggest that buprenorphine has some advantages over methadone with respect to the neonatal abstinence syndrome (Johnson et al. 2003; Jones et al. 2008). A small randomized, double-dummy, double-blind, flexible-dose study compared methadone and buprenorphine. It showed a slightly better retention rate in the buprenorphine group but significantly less use of other opioids in the methadone group with little difference in the severity of abstinence symptoms in the newborns (Fischer et al. 2006). Another controlled, randomized study failed to demonstrate differences between these drugs (Jones et al. 2005).

About half of the babies born to women treated with methadone or high-dose buprenorphine require treatment for NAS (Simmat-Durand et al. 2009). Binder and Vavrinka (2008) reported the results of a randomized, prospective study of 147 intravenous heroin-addicted pregnant women in the Czech Republic. The study compared the effects of buprenorphine, methadone and heroin on neonatal outcomes. Interestingly, none of the women delivered before the end of the 34th week of gestation. The lowest birth weight was in the heroin group, while the most severe NAS occurred in the methadone group. The investigators concluded that buprenorphine was the preferred agent for the treatment of pregnant opioid users. A population-based comparison of buprenorphine-exposed pregnancies and a retrospectively analyzed methadone sample also showed same advantages for buprenorphine

with regards to neonatal outcomes and the abstinence syndrome (Kakko et al. 2008). In a randomized, open-label study, Kraft et al. (2008) compared the effects of sublingual buprenorphine with those of an oral neonatal opium solution in 26 infants. Three infants in the buprenorphine group and one infant in the standard care group required additional therapy with phenobarbital. Both treatment duration and hospital stay were shorter in the buprenorphine group (means of 22 and 32 days vs. 27 and 38 days, respectively).

Although treatment studies are difficult to conduct in pregnant women, buprenorphine treatment may result in a less severe NAS, making this an important clinical question that warrants additional research attention. There are also studies of clonidine used as an adjunct to methadone for the NAS (Agthe et al. 2009). Neonates of women treated with slow release morphine may require treatment for NAS more often than women treated with methadone and especially buprenorphine (Ebner et al. 2007).

Recommendation: During pregnancy, detoxification should be avoided, especially in the first trimester. RG 4. Methadone and buprenorphine are effective and safe in the treatment of opioid-dependent pregnant women.

Use of multiple substances by opioid-dependent individuals

Use of multiple substances is very common in opioid-dependent patients. Rates of co-occurring cocaine use vary among countries but are as high as 40% in the United States (Kosten et al. 1986; Kosten et al. 1987; Condelli et al. 1991; Leri et al. 2003; Dobler-Mikola et al. 2005) and 80% in treatment refractory patients in The Netherlands (van den Brink et al. 2003). Higher doses of methadone (Peles et al. 2006) and high-dose buprenorphine (Montoya et al. 2004) in conjunction with contingency management (Gross et al. 2006) have been recommended to treat patients with co-occurring drug dependence. A recent systematic review on 37 studies concluded that higher doses of opioids are preferable to lower ones and methadone to buprenorphine in these patients (Castells et al. 2009).

Alcohol and benzodiazepine use and dependence are also frequent in this population (Stimmel et al. 1983; Anglin et al. 1989; Backmund et al. 2003; Backmund et al. 2005b; Wittchen et al. 2008). Comorbid substance use may reflect an inadequate dosage of methadone and can be treated by increasing the dosage (Stine et al. 1992). Consumption of cocaine, but not of other drugs, was lower in opioid-dependent

patients treated with depot naltrexone compared to placebo (Comer et al. 2006). However, the abuse of other substances may also reflect the lifestyle of the opioid-dependent patient. No randomized studies have been conducted in this area. General treatment recommendations emphasize the gradual withdrawal of other substances during maintenance therapy (Kleber et al. 2007), although this is not effective in many cases. Some clinicians believe that maintenance therapy should be stopped in patients with recurrent co-occurring use of other substances, but others believe that treatment should be continued despite substance use. The use of take-home doses is difficult to implement safely and effectively in patients who are abusing other substances and is illegal in some countries.

Naltrexone, although efficacious in the treatment of alcohol dependence, cannot be combined with opioid agonist treatment in individuals with comorbid alcohol dependence. Although acamprosate is also effective in reducing relapse risk in patients with alcohol dependence (Rosner et al. 2008, 2010; Soyka et al. 2008a) and it has no pharmacological interactions or safety problems when combined with opioid agonist therapy, no data are available on the efficacy of this drug in patients with comorbid alcohol and opioid dependence. There are also no relevant data in opioid dependence of other medications that have shown potential utility in the treatment of alcohol dependence, such as disulfiram, topiramate and baclofen (Soyka and Rösner 2010a,b)

Recommendation: Increasing the dosage of methadone or buprenorphine, particularly in conjunction with contingency management, are generally effective in the treatment of cocaine use by opioid-dependent individuals. RG 4.

Comorbid psychiatric disorders

Patients with opioid dependence frequently have a comorbid psychiatric disorder, and each disorder can complicate the course of the other. Perron et al. (2010) recently argued that practice guidelines usually make no recommendations regarding the treatment of co-occurring psychiatric disorders. Group counselling, contingency management and residential dual diagnosis treatment are frequently used psychosocial interventions in this population and generally show positive effects on substance use (Drake et al. 2008). However, a recent Cochrane review showed no compelling evidence to support any one psychosocial treatment over another in reducing substance use or improving psychiatric

status among people with serious mental illnesses (Cleary et al. 2008).

With respect to medications, antidepressant treatment is usually recommended in patients with comorbid depressive disorder, but the risk of pharmacological interactions with drugs such as St. John's Wort, desipramine, carbamazepine, phenytoin and paroxetine must be considered (Begre et al. 2002; for a review see McCance-Katz et al. 2010). Although patients with schizophrenia have a four-fold risk of substance use disorders, few studies have been conducted in patients with the comorbid conditions (for a review see San et al. 2007; Wobrock and Soyka 2008). Treatment with antipsychotics may be necessary and is safe in most patients, but pharmacological interventions that are specific for substance dependence must be kept in mind (Eap et al. 2002; McKane-Katz et al. 2010). Despite the absence of randomized controlled trials, treatment with second-generation antipsychotics can generally be safely recommended (San et al. 2007; Wobrock and Soyka 2008). There is limited evidence for clozapine to reduce craving in patients with comorbid substance use disorders and schizophrenia (Drake et al. 2000; Brunette et al. 2006; Green et al. 2003, 2008). The best approach to treat this patient population may be to optimize the antipsychotic treatment by using novel antipsychotics, which have a lower risk of extrapyramidal effects and tardive dyskinesia and may reduce the risk of self-medication with drugs of abuse.

Conclusions

This guideline for the treatment of opioid use and dependence is the second such guideline published by the WFSBP and follows guidelines for alcoholism that were published in 2008 (Soyka et al. 2008a). Review of numerous clinical studies, meta-analyses, and treatment guidelines show that there has been significant progress in the pharmacological treatment of opioid use and dependence. Treatment recommendations in this area depend on the available medications and local regulations concerning narcotics, which differ substantially between even neighbouring countries. Not all of the limitations of the existing literature can be addressed in such a guideline.

For the treatment of opioid dependence, which can be viewed as a chronic, relapsing and potentially fatal disease, a number of different agents can be used. First, for detoxification (which without further treatment results in extremely high relapse rates), methadone and buprenorphine can be used with very good efficacy and safety. Clonidine and potentially lofexidine are second-line medications. For

overdose, the opioid antagonist naloxone is available. Detoxification followed by immediate or extended release naltrexone is a potential treatment for a selected group of highly motivated and socially integrated patients. However, only a small minority of opioid-dependent patients will remain abstinent in the long run. For abstinence-oriented treatment, the use of oral naltrexone can be recommended in some cases but the retention rate is extremely low and there is a risk of fatal outcomes following heroin use in patients who have been successfully treated for a time with naltrexone. Long-acting injectable naltrexone is now an approved option in the United States and could improve adherence over oral naltrexone. Agonist maintenance therapy in opioid dependence is by far the best-established and most effective therapy for opioid dependence. Both methadone and buprenorphine or buprenorphine-naloxone have well demonstrated efficacy in opioid dependence treatment. L- α -acetyl-methadol (LAAM) has been withdrawn from the market and the evidence for slow release morphine is very limited, with an apparent substantial risk for diversion. More recently, heroin-assisted treatment has been found to be effective in severely dependent, treatment-resistant opioid-dependent patients and heroin maintenance is already available in several countries. However, due to safety concerns and a high risk of diversion, the use of heroin requires caution. Novel opioid agonists with a better safety profile, longer mechanism of action and lower risk of diversion may be available in the future.

Pharmacological interventions should always be combined with at least moderately intensive psychosocial interventions. Contingency management and some forms of cognitive-behavioural therapy are effective treatments for opioid dependence and co-occurring drug use.

Acknowledgments

We would like to thank Jacquie Klesing, ELS, for editorial assistance with the manuscript and Leah Zindel, R.Ph., M.A.L.S. for her careful editorial review.

Statements of interest

Michael Soyka has received travel grants from Eli Lilly, Bristol-Myers Squibb and AstraZeneca, support for scientific studies from Sanofi-Aventis Essex and speakers' fees from Prempharm and has worked as a consultant for Phoenix. Henry R. Kranzler has been a paid consultant for Alkermes, Glaxo-SmithKline and Gilead. He has received research support from Merck. He also reports associations

with Eli Lilly, Janssen, Schering Plough, Lundbeck, Alkermes, GlaxoSmithKline, Abbott, and Johnson & Johnson, as these companies provide support to the ACNP Alcohol Clinical Trials Initiative (ACTIVE) and Dr. Kranzler receives support from ACTIVE. Wim van den Brink has received travel grants from Eli Lilly, has been a paid consultant of Bristol-Myers Squibb and has been a study advisor for Lundbeck.

John Krystal has received grants or is a consultant for or on the advisory boards of Abbott Laboratories, Aisling Capital LLC, AstraZeneca Pharmaceuticals, Brintnall & Nicolini, Inc., Bristol-Myers Squibb, Easton Associates, Eisai Inc., Eli Lilly and Co., F. Hoffmann-La Roche Ltd, Gilead Sciences Inc., GlaxoSmithKline, Janssen Pharmaceuticals, Lohocla Research Corporation, Lundbeck Research USA, Medivation Inc., Merz Pharmaceuticals, MK Medical Communications, Naurex Inc., Pfizer Pharmaceuticals, SK Holdings Co. Ltd, Takeda Industries, Tetragenex Pharmaceuticals, Teva Pharmaceutical Industries Ltd.

Hans-Jürgen Möller has received grants or is a consultant for and on the speakership bureaus of AstraZeneca, Bristol-Myers Squibb, Eisai, Eli Lilly, GlaxoSmithKline, Janssen Cilag, Lundbeck, Merck, Novartis, Organon, Pfizer, Sanofi-Aventis, Schering-Plough, Schwabe, Sepracor, Servier and Wyeth.

Siegfried Kasper has received grant/research support from Bristol Myers-Squibb, Eli Lilly, GlaxoSmithKline, Lundbeck, Organon, Sepracor and Servier; has served as a consultant or on advisory boards for AstraZeneca, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Janssen, Lundbeck, Merck Sharp and Dome (MSD), Novartis, Organon, Pfizer, Schwabe, Sepracor, and Servier; and has served on speakers' bureaus for Angelini, AstraZeneca, Bristol Myers-Squibb, Eli Lilly, Janssen, Lundbeck, Pfizer, Pierre Fabre, Schwabe, Sepracor, and Servier.

References

Abbott PJ 2009. A review of the community reinforcement approach in the treatment of opioid dependence. *J Psychoactive Drugs* 41:379–385.

Adi Y, Juarez-Garcia A, Wang D, Jowett S, Frew E, Day E, et al. 2007. Oral naltrexone as a treatment for relapse prevention in formerly opioid-dependent drug users: a systematic review and economic evaluation. *Health Technol Assess* 11:iii–iv, 1–85.

Agthe AG, Kim GR, Mathias KB, Hendrix CW, Chavez-Valdez R, Jansson L, et al. 2009. Clonidine as an adjunct therapy to opioids for neonatal abstinence syndrome: a randomized, controlled trial. *Pediatrics* 123:e849–856.

Aldrich JV, McLaughlin JP 2009. Peptide kappa opioid receptor ligands: potential for drug development. *AAPS J* 11:312–322.

Alho H, Sinclair D, Vuori E, Holopainen A. 2007. Abuse liability of buprenorphine-naloxone tablets in untreated IV drug users. *Drug Alcohol Depend* 88:75–78.

Amass L, Bickel WK, Crean JP, Blake J, Higgins ST. 1998. Alternate-day buprenorphine dosing is preferred to daily

dosing by opioid-dependent humans. *Psychopharmacology (Berlin)* 136:217–225.

Amass L, Kamien JB, Reiber C, Branstetter S. 2000. Abuse liability of buprenorphine-naloxone tablets in untreated IV drug users. *Drug Alcohol Depend* 60(Suppl 1):S6.

Amato L, Minozzi S, Davoli M, Vecchi S, Ferri M, Mayet S. 2008a. Psychosocial combined with agonist maintenance treatments versus agonist maintenance treatments alone for treatment of opioid dependence. *Cochrane Database Syst Rev*:CD004147.

Amato L, Minozzi S, Davoli M, Vecchi S, Ferri M, Mayet S. 2008b. Psychosocial and pharmacological treatments versus pharmacological treatments for opioid detoxification. *Cochrane Database Syst Rev*:CD005031. DOI: 005010.001002/14651858. CD14005031.pub14651853.

American Psychiatric Association Practice Guidelines. 2007. Treatment of Patients with Substance Use Disorders, Second edition. *Am J Psychiatry* 164:4(Suppl).

Anglin MD, Almog IJ, Fisher DG, Peters KR. 1989. Alcohol use by heroin addicts: evidence for an inverse relationship. A study of methadone maintenance and drug-free treatment samples. *Am J Drug Alcohol Abuse* 15:191–207.

Arias A, Feinn R, Kranzler HR. 2006. Association of an Asn40Asp (A118G) polymorphism in the mu-opioid receptor gene with substance dependence: a meta-analysis. *Drug Alcohol Depend* 83:262–268.

Auriacombe M, Franques P, Tignol J. 2001. Deaths attributable to methadone vs buprenorphine in France. *J Am Med Assoc* 285:45.

Backmund M, Meyer K, Rothenhaeusler HB, Soyka M. 1998. Opioid detoxification with delta sleep-inducing peptide: results of an open clinical trial. *J Clin Psychopharmacol* 18:257–258.

Backmund M, Schutz CG, Meyer K, Eichenlaub D, Soyka M. 2003. Alcohol consumption in heroin users, methadone-substituted and codeine-substituted patients – frequency and correlates of use. *Eur Addict Res* 9:45–50.

Backmund M, Henkel C, Jordan F, Habsch J, Meyer K, Käb S. 2005a. Das QT-Intervall während der Substitutionsbehandlung Heroinabhängiger [in German]. *Suchtmed* 7:161–164.

Backmund M, Meyer K, Henkel C, Soyka M, Reimer J, Schutz CG. 2005b. Co-consumption of benzodiazepines in heroin users, methadone-substituted and codeine-substituted patients. *J Addict Dis* 24:17–29.

Backmund M, Schütz C, Mayer K, Edlin BR, Reimer J 2009. The risk of emergency treatment due to overdose in injection users. *J Addict Dis* 89:176–182.

Bandelow B, Zohar J, Hollander E, Kasper S, Moller HJ, Allgulander C, et al. 2008. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the pharmacological treatment of anxiety, obsessive-compulsive and post-traumatic stress disorders - first revision. *World J Biol Psychiatry* 9:248–312.

Barnett PG, Rodgers JH, Bloch DA. 2001. A meta-analysis comparing buprenorphine to methadone for treatment of opiate dependence. *Addiction* 96:683–690.

Beer B, Rabl W, Libiseller K, Giacomuzzi S, Riemer Y, Pavlic M. 2010. Impact of slow-release oral morphine on drug abusing habits in Austria (in German). *Neuropsychiatry* 24:108–117.

Begre S, von Bardeleben U, Ladewig D, Jaquet-Rochat S, Cosendai-Savary L, Golay KP, et al. 2002. Paroxetine increases steady-state concentrations of (R)-methadone in CYP2D6 extensive but not poor metabolizers. *J Clin Psychopharmacol* 22:211–215.

Berglund M, Thelander S, Jonsson E. 2003. Treating alcohol and drug abuse. An evidence based review. Weinheim: Wiley-VCH.

Berrosco E, Sanchez-Blazquez P, Garzon J, Mico JA. 2009. Opiates as antidepressants. *Curr pharm Res* 15:1612–1622.

- Bickel WK, Amass L, Crean JP, Badger GJ. 1999. Buprenorphine dosing every 1, 2, or 3 days in opioid-dependent patients. *Psychopharmacology (Berlin)* 146:111–118.
- Binder T, Vavrinkova B. 2008. Prospective randomised comparative study of the effect of buprenorphine, methadone and heroin on the course of pregnancy, birthweight of newborns, early postpartum adaptation and course of the neonatal abstinence syndrome (NAS) in women followed up in the outpatient department. *Neuroendocrinol Lett* 29:80–86.
- Blanken P, Hendriks VM, van Ree JM, van den Brink W. 2009. Outcome of long-term heroin-assisted treatment offered to chronic, treatment-resistant heroin addicts in the Netherlands. *Addiction* 105:300–308.
- Blanken P, van den Brink W, Hendriks VM, Huijsman IA, Klous MG, Rook EJ, et al. 2010. Heroin-assisted treatment in the Netherlands: History, findings, and international context. *Eur Neuropsychopharmacology* 20(Suppl 2):5105–5158.
- Bond C, LaForge KS, Tian M, Melia D, Zhang S, Borg L, et al. 1998. Single-nucleotide polymorphism in the human mu opioid receptor gene alters beta-endorphin binding and activity: possible implications for opiate addiction. *Proc Natl Acad Sci USA* 95:9608–9613.
- Boscarino JA, Rukstalis M, Hoffman SN, Han JJ, Erlich PM, Gerhard GS, Stewart F. 2010. Risk factors for drug dependence among out-patients on opioid therapy in a large US health-care system. *Addiction* 105:1776–1782.
- Boulton DW, Arnaud P, DeVane CL. 2001. Pharmacokinetics and pharmacodynamics of methadone enantiomers after a single oral dose of racemate. *Clin Pharmacol Ther* 70:48–57.
- Brewer C, Wong VS. 2004. naltrexone: report of lack of hepatotoxicity in acute viral hepatitis, with a review of the literature. *Addict Biol* 9:81–87.
- Bruce RD, Govindasamy S, Sylla L, Kamarulzaman A, Altice FL. 2009. Lack of reduction in buprenorphine injection after introduction of co-formulated buprenorphine/naloxone to the Malaysian market. *Am J Drug Alcohol Abuse* 35:68–72.
- Brunette MF, Drake RE, Xie H, McHugo GJ, Green AI. 2006. Clozapine use and relapse of substance use disorder among patients with co-occurring schizophrenia and substance use disorders. *Schizophr Bull* 32:637–643.
- Bunten H, Liang W-J, Pounder D, Senevirantne C, Osselton MD. 2010. CYP2B6 and OPRM1 gene variations predict methadone-related deaths. *Addict Biol* 16:142–144.
- Burns L, Randall D, Hall WD, Law M, Butler T, Bell J, et al. 2009. Opioid agonist pharmacotherapy in New South Wales from 1985 to 2006: patient characteristics and patterns and predictors of treatment retention. *Addiction* 104:1363–1372.
- Caplehorn JR, Dalton MS, Haldar F, Petrenas AM, Nisbet JG. 1996. Methadone maintenance and addicts' risk of fatal heroin overdose. *Subst Use Misuse* 31:177–196.
- Carroll KM, Chang G, Behr H, Clinton B, Kosten TR. 1995. Improving treatment outcome in pregnant, methadone-maintained women. *Am J Addict* 4:56–59.
- Carroll KM, Ball SA, Nich C, O'Connor PG, Eagan DA, Frankforter TL, et al. 2001. Targeting behavioral therapies to enhance naltrexone treatment of opioid dependence: efficacy of contingency management and significant other involvement. *Arch Gen Psychiatry* 58:755–761.
- Castells X, Kosten TR, Capellà D, Vidal X, Colom J, Casas M. 2009. Efficacy of opiate maintenance therapy and adjunctive interventions for opioid dependence with comorbid cocaine use disorders: A systematic review and meta-analysis of controlled clinical trials. *Am J Drug Alcohol Abuse* 35:339–349.
- Charney DS, Sternberg DE, Kleber HD, Heninger GR, Redmond DE Jr. 1981. The clinical use of clonidine in abrupt withdrawal from methadone. Effects on blood pressure and specific signs and symptoms. *Arch Gen Psychiatry* 38:1273–1277.
- Chevillard L, Megarbane B, Faud FJ, Risede P, Declèves X, Mager D, et al. 2010. Mechanisms of respiratory insufficiency induced by methadone overdose in rats. *Addict Biol* 15:62–80.
- Chou R, Fanciullo GJ, Fine PG, Adler JA, Ballantyne JC, Davies P, et al. 2009. Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. *J Pain* 10:113–130.
- Cleary BJ, Donnelly J, Strawbridge J, Gallagher PJ, Fahey T, Clarke M, Murphy DJ. 2010. Methadone dose and neonatal abstinence syndrome – systematic review and meta-analysis. *Addiction* 105:2071–2084.
- Cleary M, Hunt G, Matheson S, Siegfried N, Walter G. 2008. Psychosocial interventions for people with both severe mental illness and substance misuse. *Cochrane Database Syst Rev* 23:CD001088.
- Cook S, Moeschler O, Katarzyna M, Yersin B. 1998. Acute opiate overdose: characteristics of 190 consecutive cases. *Addiction* 93:1559–1565.
- Collins ED, Kleber HD, Whittington RA, Heitler NE. 2005. Anesthesia-assisted vs buprenorphine- or clonidine-assisted heroin detoxification and naltrexone induction: a randomized trial. *J Am Med Assoc* 294:903–913.
- Comer SD, Sullivan MA, Yu E, Rothenberg JL, Kleber HD, Kampman K, et al. 2006. Injectable, sustained-release naltrexone for the treatment of opioid dependence: a randomized, placebo-controlled trial. *Arch Gen Psychiatry* 63:210–218.
- Compton P, Ling W, Moody D, Chiang N. 2006. Pharmacokinetics, bioavailability and opioid effects of liquid versus tablet buprenorphine. *Drug Alcohol Depend* 82:25–31.
- Condelli WS, Fairbank JA, Dennis ML, Rachal JV. 1991. Cocaine use by clients in methadone programs: significance, scope, and behavioral interventions. *J Subst Abuse Treat* 8:203–212.
- Connock M, Juarez-Garcia A, Jowett S, Frew E, Liu Z, Taylor RJ, et al. 2007. Methadone and buprenorphine for the management of opioid dependence: a systematic review and economic evaluation. *Health Technol Assess* 11:iii–iv, 1–171.
- Corkery JM, Schifano F, Ghodse AH, Oyefeso A. 2004. The effects of methadone and its role in fatalities. *Hum Psychopharmacol* 19:565–576.
- Cornish JW, Metzger D, Woody GE, Wilson D, McLellan AT, Vandergrift B, et al. 1997. Naltrexone pharmacotherapy for opioid dependent federal probationers. *J Subst Abuse Treat* 14:529–534.
- Crettol S, Deglon JJ, Besson J, Croquette-Krokar M, Gothuey I, Hammig R, et al. 2005. Methadone enantiomer plasma levels, CYP2B6, CYP2C19, and CYP2C9 genotypes, and response to treatment. *Clin Pharmacol Ther* 78:593–604.
- Crettol S, Deglon JJ, Besson J, Croquette-Krokar M, Hammig R, Gothuey I, et al. 2006. ABCB1 and cytochrome P450 genotypes and phenotypes: influence on methadone plasma levels and response to treatment. *Clin Pharmacol Ther* 80:668–681.
- Crettol S, Besson J, Croquette-Krokar M, Hämmig R, Gothuey I, Monnat M, et al. 2008. Association of dopamine and opioid receptor genetic polymorphisms with response to methadone maintenance treatment. *Prog Neuropsychopharmacol Biol Psychiatry* 32:1722–1727.
- Curran HV, Kleckham J, Bearn J, Strang J, Wanigaratne S. 2001. Effects of methadone on cognition, mood and craving in detoxifying opiate addicts: a dose-response study. *Psychopharmacology (Berlin)* 154:153–160.
- Dahan A. 2006. Opioid-induced respiratory effects: new data on buprenorphine.
- Dahan A, Yassen A, Romberg R, Sarton E, Teppema L, Olofsen E, et al. 2006. Buprenorphine induces ceiling in respiratory depression but not in analgesia. *Br J Anaesth* 96:627–632.
- Dahan A, Aarts L, Smith TW. 2010. Incidence, reversal, and prevention of opioid-induced respiratory depression. *Anesthesiology* 112:226–238.

- Darke S, Hall W. 2003. Heroin overdose: Research and evidence-based intervention. *J Urban Health* 80:189–200.
- Darke S, Ross J. 2002. Suicide among heroin users: rates, risk factors and methods. *Addiction* 97:1383–1394.
- Darke S, Sims J, McDonald S, Wickes W. 2000. Cognitive impairment among methadone maintenance patients. *Addiction* 95:687–695.
- Darke S, Degenhardt L, Mattick R. 2007. Mortality amongst illicit drug users. *Epidemiology, causes and intervention*. Cambridge: Cambridge University Press.
- Davids E, Gastpar M. 2004. Buprenorphine in the treatment of opioid dependence. *Eur Neuropsychopharmacol* 14:209–216.
- Davis PE, Liddiard H, McMillan TM. 2002. Neuropsychological deficits and opiate abuse. *Drug Alcohol Depend* 67:105–108.
- Day E, Ison J, Strang J. 2005. Inpatient versus other settings for detoxification for opioid dependence. *Cochrane Database Syst Rev*:CD004580.
- De Jong CJ. 2005. General anaesthesia is patient-friendly in opioid antagonist detoxification treatment. *Addiction* 100:1742–1744.
- de Vos JW, Ufkes JG, Kaplan CD, Tursch M, Krause JK, van Wilgenburg H, et al. 1998. L-Methadone and D,L-methadone in methadone maintenance treatment: a comparison of therapeutic effectiveness and plasma concentrations. *Eur Addict Res* 4:134–141.
- Deamer RL, Wilson DR, Clark DS, Prichard JG. 2001. Torsades de pointes associated with high dose levomethadyl acetate (ORLAAM). *J Addict Dis* 20:7–14.
- Degenhardt L, Gibson A, Mattick RP, Hall W. 2008. Depot naltrexone use for opioid dependence in Australia: large-scale use of an unregistered medication in the absence of data on safety and efficacy. *Drug Alcohol Rev* 27:1–3.
- De Leon G, Jainchill N. 1991. Residential therapeutic communities for female substance abusers. *Bull NY Acad Med* 67:277–290.
- Dobler-Mikola A, Hättenschwiler J, Meili D, Beck T, Böni E, Modestin J. 2005. Patterns of heroin, cocaine, and alcohol abuse during long-term methadone maintenance treatment. *J Subst Abuse Treat* 29:259–265.
- Donny EC, Brasser SM, Bigelow GE, Stitzer ML, Walsh SL. 2005. Methadone doses of 100 mg or greater are more effective than lower doses at suppressing heroin self-administration in opioid-dependent volunteers. *Addiction* 100:1496–1509.
- Drake RE, Xie H, McHugo GJ, Green AI. 2000. The effects of clozapine on alcohol and drug use disorders among patients with schizophrenia. *Schizophr Bull* 26:441–449.
- Drake RE, O Neal EL, Wallach MA. 2008. A systematic review of psychosocial research on psychosocial interventions for people with co-occurring severe mental and substance use disorders. *J Subst Abuse Treat* 34:123–138.
- Dutra L, Stathopoulou G, Basden SL, Leyro TM, Powers MB, Otto MW. 2008. A meta-analytic review of psychosocial interventions for substance use disorders. *Am J Psychiatry* 165:179–187.
- Eap CB, Buclin T, Baumann P. 2002. Interindividual variability of the clinical pharmacokinetics of methadone: implications for the treatment of opioid dependence. *Clin Pharmacokinet* 41:1153–1193.
- EBDD (Europäische Beobachtungsstelle für Drogen und Drogensucht). 2009. Jahresbericht 2009: Stand der Drogenproblematik in Europa [in German]. Luxemburg: Amt für amtliche Veröffentlichungen der Europäischen Union.
- Ebner N, Rohrmeister K, Winklbaur B, Bauert A, Jagsch R, Pternell A, et al. 2007. Management of neonatal abstinence syndrome in neonates born to opioid maintained women. *Drug Alcohol Depend* 87:131–138.
- Ehret GB, Voide C, Gex-Fabry M, Chabert J, Shah D, Broers B, et al. 2006. Drug-induced long QT syndrome in injection drug users receiving methadone: high frequency in hospitalized patients and risk factors. *Arch Intern Med* 166:1280–1287.
- Ehret GN, Desmeules JA, Broers B. 2007. Methadone-associated long QT syndrome: improving pharmacotherapy for dependence on illegal opioids and lessons learned for pharmacology. *Expert Opin Ther Targets* 6:289–303.
- Eissenberg T, Johnson RE, Bigelow GE, Walsh SL, Liebson IA, Strain EC, et al. 1997. Controlled opioid withdrawal evaluation during 72 h dose omission in buprenorphine-maintained patients. *Drug Alcohol Depend* 45:81–91.
- Elsner H. 2005. Kammertachykardien (“Torsade de Pointes”) und weitere Herzrhythmusstörungen unter Methadonsubstitution: Risikominderung durch Medikamentenumstellung [in German]. *Suchtdem* 7:257–263.
- Faggiano F, Vigna-Taglianti F, Versino E, Lemma P. 2003. Methadone maintenance at different dosages for opioid dependence. *Cochrane Database Syst Rev* CD002208.
- Farre M, Mas A, Torrens M, Moreno V, Cami J. 2002. Retention rate and illicit opioid use during methadone maintenance interventions: a meta-analysis. *Drug Alcohol Depend* 65:283–290.
- Fareed A, Casarella J, Roberts M, Sleboda M, Amar R, Vayalapalli S, Drexler K. 2009. High dose versus moderate dose methadone maintenance: is there a better outcome? *J Addict Dis* 28:399–405.
- Fareed A, Casarella J, Amar R, Vayalapalli S, Drexler K. 2010. Methadone maintenance dosing guideline for opioid dependence, a literature review. *J Addict Dis* 29:1–14.
- Farrell M, Neeleman J, Gossop M, Griffiths P, Buning E, Finch E, et al. 1996. The legislation, organisation and delivery of methadone in 12 EU member states. Brussels: European Commission.
- Favrat B, Zimmermann G, Zullino D, Krenz S, Dorogy F, Muller J, et al. 2006. Opioid antagonist detoxification under anaesthesia versus traditional clonidine detoxification combined with an additional week of psychosocial support: a randomised clinical trial. *Drug Alcohol Depend* 81:109–116.
- Ferri M, Davoli M, Perucci CA. 2010. Heroin maintenance for chronic heroin-dependent individuals: *Cochrane Database Syst Rev* CD00333410.
- Fingerhood MI, Thompson MR, Jasinski DR. 2001. A comparison of clonidine and buprenorphine in the outpatient treatment of opiate withdrawal. *Subst Abuse* 22:193–199.
- Fischer B, Cruz MF, Patra J, Rehm J. 2008. Predictors of methadone maintenance treatment utilization in a multisite cohort of illicit opioid users (OPICAN). *J Subst Abuse Treat* 34:340–346.
- Fischer G, Ortner R, Rohrmeister K, Jagsch R, Baewert A, Langer M, Aschauer H. 2006. Methadone versus buprenorphine in pregnant addicts: a double-blind, double-dummy comparison study. *Addiction* 101:275–281.
- Frick U, Rehm J, Zullino D, Vignati M, Wiesbeck G, Ammann J, Uchtenhagen A. 2010. Long-term follow-up of orally administered diacetylmorphine substitution treatment. *Eur Addict Res* 16:131–138.
- Foster DJ, Somogyi AA, Dyer KR, White JM, Bochner F. 2000. Steady-state pharmacokinetics of (R)- and (S)-methadone in methadone maintenance patients. *Br J Clin Pharmacol* 50:427–440.
- Foster DJ, Somogyi AA, White JM, Bochner F. 2004. Population pharmacokinetics of (R)-, (S)- and rac-methadone in methadone maintenance patients. *Br J Clin Pharmacol* 57:742–755.
- Fudala PJ, Bridge TP, Herbert S, Williford WO, Chiang CN, Jones K, et al. 2003. Office-based treatment of opiate addiction with a sublingual-tablet formulation of buprenorphine and naloxone. *New Engl J Med* 349:949–958.
- Galanter M, Dermatis H, Glickman L, Maslansky R, Sellers MB, Neumann E, et al. 2004. Network therapy: decreased secondary opioid use during buprenorphine maintenance. *J Subst Abuse Treat* 26:313–318.

- Garbutt JC. 2010. Efficacy and tolerability of naltrexone in the management of alcohol dependence. *Curr Pharm Des* 16: 2091–2097.
- Gerra G, Borella F, Zaimovic A, Moi G, Bussandri M, Bubici C, et al. 2004. Buprenorphine versus methadone for opioid dependence: predictor variables for treatment outcome. *Drug Alcohol Depend* 75:37–45.
- Gil M, Sala M, Anguera I, Chapinal O, Cervantes M, Guma JR, et al. 2003. QT prolongation and Torsades de Pointes in patients infected with human immunodeficiency virus and treated with methadone. *Am J Cardiol* 92:995–997.
- Gish EC, Miller JL, Honey BL, Johnson PN. 2010. Lofexidine, an α_2 -receptor agonist for opioid detoxification. *Ann Pharmacother* 44:343–351.
- Glatt SJ, Bousman C, Wang RS, Murthy KK, Rana BK, Lasky-Su JA, et al. 2007. Evaluation of OPRM1 variants in heroin dependence by family-based association testing and meta-analysis. *Drug Alcohol Depend* 90:159–165.
- Gold MS, Pottash AC, Sweeney DR, Kleber HD. 1980. Opiate withdrawal using clonidine. A safe, effective, and rapid nonopiate treatment. *J Am Med Assoc* 243:343–346.
- Goldstein A, Herrera J. 1995. Heroin addicts and methadone treatment in Albuquerque: a 22-year follow-up. *Drug Alcohol Depend* 40:139–150.
- Gourevitch MN, Friedland GH. 2000. Interactions between methadone and medications used to treat HIV infection: a review. *Mt Sinai J Med* 67:429–436.
- Gowing L, Ali R, White J. 2006. Buprenorphine for the management of opioid withdrawal. *Cochrane Database Syst Rev*:CD002025.
- Gowing L, Farrell M, Ali R, White JM. 2009. Alpha2-adrenergic agonists for the management of opioid withdrawal. *Cochrane Database Syst Rev*:CD002024.
- Gowing L, Ali R, White JM. 2010. Opioid antagonists under heavy sedation or anaesthesia for opioid withdrawal. *Cochrane Database Syst Rev*:CD002022.
- Grabowski J, O'Brien CP, Greenstein R, Ternes J, Long M, Steinberg-Donato S. 1979. Effects of contingent payment on compliance with a naltrexone regimen. *Am J Drug Alcohol Abuse* 6:355–365.
- Green AI, Burgess ES, Dawson R, Zimmet SV, Strous RD. 2003. Alcohol and cannabis use in schizophrenia: effects of clozapine vs. risperidone. *Schizophr Res* 60:81–85.
- Green AI, Noordsy DL, Brunette MF, O'Keefe C. 2008. Substance abuse and schizophrenia: pharmacotherapeutic intervention. *J Subst Abuse Treat* 34:61–71.
- Greenwald M, Johanson CE, Bueller J, Chang Y, Moody DE, Kilbourn M, et al. 2007. Buprenorphine duration of action: mu-opioid receptor availability and pharmacokinetic and behavioral indices. *Biol Psychiatry* 61:101–110.
- Greenwald MK, Schuh KJ, Stine SM. 2003. Transferring methadone-maintained outpatients to the buprenorphine sublingual tablet: a preliminary study. *Am J Addict* 12:365–374.
- Gross A, Marsch LA, Badger GJ, Bickel WK. 2006. A comparison between low-magnitude voucher and buprenorphine medication contingencies in promoting abstinence from opioids and cocaine. *Exp Clin Psychopharmacol* 14:148–156.
- Gruber SA, Tzilos GK, Silveri MM, Pollack M, Renshaw PF, Kaufman MJ, et al. 2006. Methadone maintenance improves cognitive performance after two months of treatment. *Exp Clin Psychopharmacol* 14:157–164.
- Gruber VA, McCance-Katz EF. 2010. Methadone, buprenorphine, and street drug interactions with antiretroviral medications. *Curr HIV/AIDS Rep* 7:152–160.
- Grunze H, Vieta E, Goodwin GM, Bowden C, Licht RW, Moller HJ, et al. 2009. The World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the biological treatment of bipolar disorders: update 2009 on the treatment of acute mania. *World J Biol Psychiatry* 10:85–116.
- Gutstein HB, Akil H. 2001. Opioid analgesics. in: Goodman and Gilman's. *The Pharmacological Basis of Therapeutics*, 10th ed. Hardman JG, Limbirt LE, Gilman AG, editors. New York: McGraw-Hill. p. 569–620.
- Haile CN, Kosten TA, Kosten TR. 2008. Pharmacogenetic treatments for drug addiction: alcohol and opiates. *Am J Drug Alcohol Abuse* 34:355–381.
- Hanon S, Seewald RM, Yang F, Schweitzer P, Rosman J. 2010. Ventricular arrhythmias in patients treated with methadone for opioid dependence. *J Interv Card Electrophysiol* 28:19–22.
- Haasen C, Verthein U, Degkwitz P, Berger J, Krausz M, Naber D. 2007. Heroin-assisted treatment for opioid dependence: randomised controlled trial. *Br J Psychiatry* 191:55–62.
- Hartnoll RL, Mitcheson MC, Battersby A, Brown G, Ellis M, Fleming P, Hedley N. 1980. Evaluation of heroin maintenance in controlled trial. *Arch Gen Psychiatry* 37:877–884.
- Havens JR, Latkin CA, Pu M, Cornelius LJ, Bishai D, Huettner S, et al. 2009. Predictors of opiate agonist treatment retention among injection drug users referred from a needle exchange program. *J Subst Abuse Treat* 36:306–312.
- Honey BL, Benefield RJ, Miller JL, Johnson PN. 2009. Alpha2-receptor agonists for treatment and prevention of iatrogenic opioid abstinence syndrome in critically ill patients. *Ann Pharmacother* 43:1506–1511.
- Hser YI, Hoffman V, Grella CE, Anglin MD. 2001. A 33-year follow-up of narcotics addicts. *Arch Gen Psychiatry* 58:503–508.
- Hulse GK, Milne E, English DR, Holman CD. 1997. The relationship between maternal use of heroin and methadone and infant birth weight. *Addiction* 92:1571–1579.
- Hulse GK, Milne E, English DR, Holman CD. 1998. Assessing the relationship between maternal opiate use and neonatal mortality. *Addiction* 93:1033–1042.
- Hulse GK, English DR, Milne E, Holman CD. 1999. The quantification of mortality resulting from the regular use of illicit opiates. *Addiction* 94:221–229.
- Hulse GK, Morris N, Arnold-Reed D, Tait RJ. 2009. Improving clinical outcomes in treating heroin dependence: Randomized, controlled trial of oral or implant naltrexone. *Arch Gen Psychiatry* 66:1108–1115.
- Hulse GK, Ngo HT, Tait RJ. 2010. Risk factors for craving and relapse in heroin users treated with oral or implant naltrexone. *Biol Psychiatry* 68:296–302.
- Iguchi MY, Lamb RJ, Belding MA, Platt JJ, Husband SD, Morral AR. 1996. Contingent reinforcement of group participation versus abstinence in a methadone maintenance program. *Exp Clin Psychopharmacol* 4:1–7.
- Ikeda K, Ide S, Han W, Hayashida M, Uhl GR, Sora I. 2005. How individual sensitivity to opiates can be predicted by gene analyses. *Trends Pharmacol Sci* 26:311–317.
- Janiri L, Mannelli P, Persico AM, Serretti A, Tempesta E. 1994. Opiate detoxification of methadone maintenance patients using lefetamine, clonidine and buprenorphine. *Drug Alcohol Depend* 36:139–145.
- Janetto PJ, Bratanow NC. 2009. Utilization of pharmacogenomics and therapeutic drug monitoring for opioid pain management. *Pharmacogenomics* 10:1157–1167.
- Jasinski DR, Johnson RE, Kocher TR. 1985. Clonidine in morphine withdrawal. Differential effects on signs and symptoms. *Arch Gen Psychiatry* 42:1063–1066.
- Johnson RE, Jones HE, Fischer G. 2003. Use of buprenorphine in pregnancy: patient management and effects on the neonate. *Drug Alcohol Depend* 70:S87–101.
- Jones HE, Haug NA, Stitzer ML, Sviki DS. 2000. Improving treatment outcomes for pregnant drug-dependent women using low-magnitude voucher incentives. *Addict Behav* 25:263–267.

- Jones HE, Haug N, Silverman K, Stitzer M, Svikis D. 2001. The effectiveness of incentives in enhancing treatment attendance and drug abstinence in methadone-maintained pregnant women. *Drug Alcohol Depend* 61:297–306.
- Jones HE, Johnson RE, Jasinski DR, O'Grady KE, Chisholm CA, Choo RE, et al. 2005. Buprenorphine versus methadone in the treatment of pregnant opioid-dependent patients: effects on the neonatal abstinence syndrome. *Drug Alcohol Depend* 79: 1–10.
- Jones HE, Martin PR, Heil SH, Kaltenbach K, Selby P, Coyle MG, et al. 2008. Treatment of opioid-dependent pregnant women: clinical and research issues. *J Subst Abuse Treat* 35:245–259.
- Judson BA, Horns WH, Goldstein A. 1976. Side effects of levomethadone and racemic methadone in a maintenance program. *Clin Pharmacol Ther* 20:445–449.
- Justo D. 2006. Methadone-induced long QT syndrome vs methadone-induced torsades de pointes. *Arch Intern Med* 166:2288; author reply 2289–2290.
- Kakko J, Svanborg KD, Kreek MJ, Heilig M. 2003. 1-year retention and social function after buprenorphine-assisted relapse prevention treatment for heroin dependence in Sweden: a randomized, placebo-controlled trial. *Lancet* 361:662–668.
- Kakko J, Gronbladh L, Svanborg KD, von Wachenfeldt J, Ruck C, Rawlings B, et al. 2007. A stepped care strategy using buprenorphine and methadone versus conventional methadone maintenance in heroin dependence: a randomized controlled trial. *Am J Psychiatry* 164:797–803.
- Kakko J, Heilig M, Sarman I. 2008. Buprenorphine and methadone treatment of opiate dependence during pregnancy: comparison of fetal growth and neonatal outcomes in two consecutive case series. *Drug Alcohol Depend* 96:69–78.
- Kamien JB, Branstetter SA, Amass L. 2008. Buprenorphine-naloxone versus methadone maintenance therapy: a randomized double-blind trial with opioid-dependent patients. *Heroin Addict Relat Clin Probl* 10:5–18.
- Kandall SR, Doberczak TM, Jantunen M, Stein J. 1999. The methadone-maintained pregnancy. *Clin Perinatol* 26:173–183.
- Kastelic A, Dubajic G, Strbad E. 2008. Slow-release oral morphine for maintenance treatment of opioid addicts intolerant to methadone or with inadequate withdrawal suppression. *Addiction* 103:1837–1846.
- Kerr T, Marsh D, Li K, Montaner J, Wood E. 2005. Factors associated with methadone maintenance therapy use among a cohort of polysubstance using injection drug users in Vancouver. *Drug Alcohol Depend* 80:329–335.
- Khantzian EJ, Halliday KS, MacAuliffe WE. 1990. *Addiction and the vulnerable self: Modified dynamic group therapy for substance abusers*. New York: Guilford.
- Kharasch ED, Hoffer C, Whittington D, Sheffels P. 2004. Role of hepatic and intestinal cytochrome P450 3A and 2B6 in the metabolism, disposition, and miotic effects of methadone. *Clin Pharmacol Ther* 76:250–269.
- Kimber J, Copeland L, Hickman M, Macleod J, McKenzie J, De Angelis D, Robertson JR. 2010. Survival and cessation in injecting drug users: prospective observational study of outcomes and effect of opiate substitution. *Br Med J* 341:c3374. doi: 10.1136/bmj.c3172.
- Kleber HD, Riordan CE, Rounsaville B, Kosten T, Charney D, Gaspari J, et al. 1985. Clonidine in outpatient detoxification from methadone maintenance. *Arch Gen Psychiatry* 42: 391–394.
- Kleber HD, Topazian M, Gaspari J, Riordan CE, Kosten T. 1987. Clonidine and naltrexone in the outpatient treatment of heroin withdrawal. *Am J Drug Alcohol Abuse* 13:1–17.
- Kleber HD, Weiss RD, Anton RF Jr, George TP, Greenfield SF, Kosten TR, et al. 2007. *Treatment of patients with substance use disorders*, second edition. *Am J Psychiatry* 164:5–123.
- Koob GF, Le Moal M. 2006. *Neurobiology of addiction*. Amsterdam: Academic Press.
- Kosten TR, Gawin FH, Rounsaville BJ, Kleber HD. 1986. Cocaine abuse among opioid addicts: demographic and diagnostic factors in treatment. *Am J Drug Alcohol Abuse* 12:1–16.
- Kosten TR, Rounsaville BJ, Kleber HD. 1987. A 2.5-year follow-up of cocaine use among treated opioid addicts. Have our treatments helped? *Arch Gen Psychiatry* 44:281–284.
- Kosten TR, Gawin FH, Morgan C, Nelson JC, Jatlow P. 1990a. Desipramine and its 2-hydroxy metabolite in patients taking or not taking methadone. *Am J Psychiatry* 147:1379–1380.
- Kosten TR, Gawin FH, Morgan C, Nelson JC, Jatlow P. 1990b. Evidence for altered desipramine disposition in methadone-maintained patients treated for cocaine abuse. *Am J Drug Alcohol Abuse* 16:329–336.
- Kraft WK, Gibson E, Dysart K, Damle VS, Larusso JL, Greenspan JS, et al. 2008. Sublingual buprenorphine for treatment of neonatal abstinence syndrome: a randomized trial. *Pediatrics* 122:e601–607.
- Krantz MJ, Mehler PS. 2006. QTc prolongation: methadone's efficacy-safety paradox. *Lancet* 368:556–557.
- Krantz MJ, Lewkowiec L, Hays H, Woodroffe MA, Robertson AD, Mehler PS. 2002. Torsade de pointes associated with very-high-dose methadone. *Ann Intern Med* 137:501–504.
- Krantz MJ, Kutinsky IB, Robertson AD, Mehler PS. 2003. Dose-related effects of methadone on QT prolongation in a series of patients with torsade de pointes. *Pharmacotherapy* 23: 802–805.
- Krantz MJ, Rowan SB, Schmittner J, Bucher Bartelson B. 2007. Physician awareness of the cardiac effects of methadone: results of a national survey. *J Addict Dis* 26:79–85.
- Krantz MJ, Martin J, Stimmel B, Mehla D, Haigney MC. 2009. QTc interval screening in methadone treatment. *Ann Intern Med* 150: 387–395.
- Kreek MJ, Hartman N. 1982. Chronic use of opioids and antipsychotic drugs. side effects, effects on endogenous opioids, and toxicity. *Ann NY Acad Sci* 398:151–172.
- Kreek MJ, Hachey DL, Klein PD. 1979. Stereoselective disposition of methadone in man. *Life Sci* 24:925–932.
- Kristensen K, Blemmer T, Angelo HR, Christrup LL, Drenck NE, Rasmussen SN, et al. 1996. Stereoselective pharmacokinetics of methadone in chronic pain patients. *Ther Drug Monit* 18: 221–227.
- Krupitsky EM, Blokhina EA. 2010. Long-acting depot formulations of naltrexone for heroin dependence: a review. *Curr Opin Psychiatry* (in press).
- Krystal JH, Walker MW, Heninger GR. 1989. Intermittent naloxone attenuates the development of physical dependence on methadone in rhesus monkeys. *Eur J Pharmacol* 160:331–338.
- Langendam MW, van Brussel GH, Coutinho RA, van Ameijden EJ. 2001. The impact of harm-reduction-based methadone treatment on mortality among heroin users. *Am J Publ Health* 91:774–780.
- Lee TM, Pau CW. 2002. Impulse control differences between abstinent heroin users and matched controls. *Brain Inj* 16: 885–889.
- Leri F, Bruneau J, Stewart J. 2003. Understanding polydrug use: review of heroin and cocaine co-use. *Addiction* 98:7–22.
- Levin FR, Fischman MW, Connerney I, Foltin RW. 1997. A protocol to switch high-dose, methadone-maintained subjects to buprenorphine. *Am J Addict* 6:105–116.
- Ling W, Charuvastra C, Kaim SC, Klett CJ. 1976. Methadyl acetate and methadone as maintenance treatments for heroin addicts. A veterans administration cooperative study. *Arch Gen Psychiatry* 33:709–720.
- Ling W, Wesson DR, Charuvastra C, Klett CJ. 1996. A controlled trial comparing buprenorphine and methadone maintenance in opioid dependence. *Arch Gen Psychiatry* 53:401–407.

- Ling W, Amass L, Shoptaw S, Anton JJ, Hillhouse M, Babcock D, 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 Trial Network. *Addiction* 100:1090–1100.
- Ling W, Casadonte P, Bigelow G, Kampman KM, Patkar A, Bailey GL, et al. 2010. Buprenorphine implants for treatment of opioid dependence: a randomized controlled trial. *J Am Med Assoc* 304:1578–1583.
- Lingford-Hughes AR, Welch S, Nutt DJ 2004. Evidence-based guidelines for the pharmacological management of substance misuse, addiction and comorbidity: recommendations from the British Association for Pharmacology. *J Psychopharmacol* 18: 293–335.
- Lobmaier P, Kornor H, Kunoe N, Bjorndal A. 2008. Sustained-release naltrexone for opioid dependence. *Cochrane Database Syst Rev*:CD006140.
- Loeber S, Kniest A, Diehl A, Mann K, Croissant B. 2008. Neuropsychological functioning of opiate-dependent patients: a nonrandomized comparison of patients preferring either buprenorphine or methadone maintenance treatment. *Am J Drug Alcohol Abuse* 34:584–593.
- Lotsch J, Geisslinger G. 2005. Are mu-opioid receptor polymorphisms important for clinical opioid therapy? *Trends Mol Med* 11:82–89.
- Madlung-Kratzer E, Spitzer B, Brosch R, Dunkel D, Haring C. 2009. A double-blind, randomized, parallel group study to compare the efficacy, safety and tolerability of slow-release oral morphine versus methadone in opioid-dependent inpatients willing to undergo detoxification. *Addiction* 104: 1549–1557.
- Mammen K, Bell J. 2009. The clinical efficacy and abuse potential of combination buprenorphine-naloxone in the treatment of opioid dependence. *Expert Opin Pharmacother* 10:2537–2544.
- Manchikanti L, Fellows B, Ailani H, Pampati V. 2010. Therapeutic use, abuse, and nonmedical use of opioids: a ten-year perspective. *Pain Phys* 13:401–435.
- Marsden J, Eastwood B, Bradbury C, Dale-Perera A, Farrell M, Hammond P, et al. 2009. Effectiveness of community treatments for heroin and crack cocaine addiction in England: a prospective, in-treatment cohort study. *Lancet* 374:1262–1270.
- Maremmani I, Canoniero S, Pacini M. 2000a. Methadone dose and retention in treatment of heroin addicts with bipolar I disorder comorbidity: preliminary results. *Heroin Addict Relat Clin Prob* 2:29–46.
- Maremmani I, Zolesi O, Aglietti M, Marini G, Tagliamonte A, Shinderman M, et al. 2000b. Methadone dose and retention during treatment of heroin addicts with Axis I psychiatric comorbidity. *J Addict Dis* 19:29–41.
- Maremmani I, Pacini M, Cesaroni C, Lovrecic M, Perugi G, Tagliamonte A. 2005. QTc interval prolongation in patients on long-term methadone maintenance therapy. *Eur Addict Res* 11:44–49.
- Martell BA, Arnsten JH, Krantz MJ, Gourevitch MN. 2005. Impact of methadone treatment on cardiac repolarization and conduction in opioid users. *Am J Cardiol* 95:915–918.
- Mattick RP, Ali R, White JM, O'Brien S, Wolk S, Danz C. 2003a. Buprenorphine versus methadone maintenance therapy: a randomized double-blind trial with 405 opioid-dependent patients. *Addiction* 98:441–452.
- Mattick RP, Kimber J, Breen C, Davoli M. 2003b. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. *Cochrane Database Syst Rev*:CD002207.
- Mattick RP, Breen C, Kimber J, Davoli M. 2009. Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence. *Cochrane Database Syst Rev*:CD 002209.
- Maxwell JC, Pullum TW, Tannert K. 2005. Deaths of clients in methadone treatment in Texas: 1994–2002. *Drug Alcohol Depend* 78:73–81.
- Maxwell S, Shinderman M, Miner A, Bennet A. 2002. Correlation between Hepatitis C serostatus and methadone dose requirement in 1,163 methadone-maintained patients. *Heroin Addict Relat Clin Prob* 4:5–10.
- McCance-Katz EF, Sullivan LE. 2010. Drug interactions of clinical importance among the opioids, methadone and buprenorphine, and other frequently prescribed medications: A review. *Am J Addict* 19:4–16.
- McCowan C, Kidd B, Fahey T. 2009. Factors associated with mortality in Scottish patients receiving methadone in primary care: retrospective cohort study. *Br Med J* 338:b2225.
- McLellan AT, Arndt IO, Metzger DS, Woody GE, O'Brien CP. 1993. The effects of psychosocial services in substance abuse treatment. *J Am Med Assoc* 269:1953–1959.
- Meador N. 2010. A comparison of methadone, buprenorphine and alpha (2) adrenergic agonists for opioid detoxification: a mixed treatment comparison meta-analysis. *Drug Alcohol Depend* 108:110–114.
- Megarbane B, Hreiche R, Pirnay S, Marie N, Baud FJ, 2006. Does high-dose buprenorphine cause respiratory depression?: possible mechanisms and therapeutic consequences. *Toxicol Rev* 25:79–85.
- Megarbane B, Buisien A, Jacobs F, Resiere D, Chevillard L, Vicaut E, Baud FJ. 2010. Prospective comparative assessment of buprenorphine overdose with heroin and methadone: clinical characteristics and response to antidotal treatment. *J Subst Abuse Treat* 38:403–407.
- Meili D, Broers B, Bruggmann, Fink A, Hämmig R. 2008. Medical Recommendations for maintenance therapy in opioid dependence (Swiss Society of Addiction Medicine, in German). *Suchtmittel* 10:29–53.
- Mello NK, Mendelson JH, Kuehnle JC, Sellers MS. 1981. Operant analysis of human heroin self-administration and the effects of naltrexone. *J Pharmacol Exp Ther* 216:45–54.
- Messinis L, Lyros E, Andrian V, Katsakiori P, Panagis G, Georgiou V, et al. 2009. Neuropsychological functioning in buprenorphine maintained patients versus abstinent heroin abusers on naltrexone hydrochloride therapy. *Hum Psychopharmacol* 24:524–531.
- Mintzer MZ. 2007. Effects of opioid pharmacotherapy on psychomotor and cognitive performance: A review of human laboratory studies of methadone and buprenorphine. *Heroin Addict Relat Clin Prob* 9:5–24.
- Mintzer MZ, Stitzer ML. 2002. Cognitive impairment in methadone maintenance patients. *Drug Alcohol Depend* 67:41–51.
- Mintzer MZ, Copersino ML, Stitzer ML. 2005. Opioid abuse and cognitive performance. *Drug Alcohol Depend* 78:225–230.
- Mitchell TB, White JM, Somogyi AA, Bochner F. 2003. Comparative pharmacodynamics and pharmacokinetics of methadone and slow-release oral morphine for maintenance treatment of opioid dependence. *Drug Alcohol Depend* 72:85–94.
- Mitchell TB, White JM, Somogyi AA, Bochner F. 2004. Slow-release oral morphine versus methadone: a crossover comparison of patient outcomes and acceptability as maintenance pharmacotherapies for opioid dependence. *Addiction* 99:940–945.
- Monte AA, Mandell T, Wilford BB, Tennyson J, Boyer EW. 2009. Diversion of buprenorphine/naloxone coformulated tablets in a region with high prescribing prevalence. *J Addict Dis* 28: 226–231.
- Montoya ID, Gorelick DA, Preston KL, Schroeder JR, Umbricht A, Cheskin LJ, et al. 2004. Randomized trial of buprenorphine for treatment of concurrent opiate and cocaine dependence. *Clin Pharmacol Ther* 75:34–48.

- Nakamura K, Hachey DL, Kreek MJ, Irving CS, Klein PD. 1982. Quantitation of methadone enantiomers in humans using stable isotope-labeled [2H3]-, [2H5]-, and [2H8]Methadone. *J Pharm Sci* 71:40–43.
- National Institute for Health and Clinical Excellence. 2007a. Drug misuse, psychosocial interventions. NICE Clinical Guideline 51, London.
- National Institute for Health and Clinical Excellence. 2007b. Drug misuse, Opioid detoxification. NICE Clinical Guideline 52, London.
- National Research Council Committee on Clinical Evaluation of Narcotic Antagonists. 1978. Clinical evaluation of naltrexone treatment of opiate-dependent individuals. Report of the National Research Council Committee on Clinical Evaluation of Narcotic Antagonists. *Arch Gen Psychiatry* 35:335–340.
- Neuman MG, Monteiro M, Rehm J. 2006. Drug interactions between psychoactive substances and antiretroviral therapy in individuals infected with human immunodeficiency and hepatitis viruses. *Subst Use Misuse* 41:1395–1463.
- Ngo HT, Tait RJ, Hulse GK. 2008. Comparing drug-related hospital morbidity following heroin dependence treatment with methadone maintenance or naltrexone implantation. *Arch Gen Psychiatry* 65:457–465.
- Nicholis L, Bragaw L, Ruetsch C. 2010. Opioid dependence treatment and guidelines. *J Manag Care Pharm* 16:S14–21.
- Nielsen S, Lintzeris N. 2008. The Use of sublingual buprenorphine-naloxone for reversing heroin overdose: a high-risk strategy that should not be recommended. *Addiction* 103: 2065–2066.
- Nigam AK, Ray R, Tripathi BM. 1993. Buprenorphine in opiate withdrawal: a comparison with clonidine. *J Subst Abuse Treat* 10:391–394.
- O'Connor PG, Oliveto AH, Shi JM, Triffleman EG, Carroll KM, Kosten TR, et al. 1998. A randomized trial of buprenorphine maintenance for heroin dependence in a primary care clinic for substance users versus a methadone clinic. *Am J Med* 105:100–105.
- Okruhlica L, Klempova D. 2000. Hepatitis C infected patients and higher doses of methadone. *Heroin Addict Relat Clin Prob* 2:57–58.
- Oreskovich MR, Saxon AJ, Ellis ML, Malte CA, Reoux JP, Knox PC. 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* 77:71–79.
- Orman JS, Keating GM. 2009. Buprenorphine/naloxone: a review of its use in the treatment of opioid dependence. *Drugs* 69:577–607.
- Oviedo-Joekes E, Brissette S, Marsh DC, Lauzon P, Guh D, Anis A, et al. 2009. Diacetylmorphine versus methadone for the treatment of opioid addiction. *New Engl J Med* 361:777–786.
- Pau CW, Lee TM, Chan SF. 2002. The impact of heroin on frontal executive functions. *Arch Clin Neuropsychol* 17:663–670.
- Peles E, Adelson M. 2006. Gender differences and pregnant women in a methadone maintenance treatment (MMT) clinic. *J Addict Dis* 25:39–45.
- Peles E, Bodner G, Kreek MJ, Rados V, Adelson M. 2007. Corrected-QT intervals as related to methadone dose and serum level in methadone maintenance treatment (MMT) patients: a cross-sectional study. *Addiction* 102:289–300.
- Perrin-Terrin A, Pathak A, Lapeyre-Mestre M. 2010. QT interval prolongation: prevalence, risk factors and pharmacovigilance data among methadone-treated patients in France. *Fundam Clin Pharmacol* (in press).
- Perron BE, Bunger A, Bender K, Vaughn MG, Howard MO. 2010. Treatment guidelines for substance use disorders and serious mental illnesses: do they address co-occurring disorders? *Subst Use Misuse* 45:1262–1278.
- Petitjean S, Stohler R, Deglon JJ, Livoti S, Waldvogel D, Uehlinger C, et al. 2001. Double-blind randomized trial of buprenorphine and methadone in opiate dependence. *Drug Alcohol Depend* 62:97–104.
- Petry NM, Bickel WK, Badger GJ. 1999. A comparison of four buprenorphine dosing regimens in the treatment of opioid dependence. *Clin Pharmacol Ther* 66:306–314.
- Petry NM, Bickel WK, Badger GJ. 2000. A comparison of four buprenorphine dosing regimens using open-dosing procedures: is twice-weekly dosing possible? *Addiction* 95: 1069–1077.
- Pfohl DN, Allen JI, Atkinson RL, Knopman DS, Malcolm RJ, Mitchell JE, et al. 1986. Naltrexone hydrochloride (Trexan): a review of serum transaminase elevations at high dosage. *NIDA Res Monogr* 67:66–72.
- Pirastu R, Fais R, Messina M, Bini V, Spiga S, Falconieri D, et al. 2006. Impaired decision-making in opiate-dependent subjects: effect of pharmacological therapies. *Drug Alcohol Depend* 83:163–168.
- Pirnay S, Borron SW, Giudicelli CP, Tourneau J, Baud FJ, Ricordel I. 2004. A critical review of the causes of death among post-mortem toxicological investigations: analysis of 34 buprenorphine-associated and 35 methadone-associated deaths. *Addiction* 99:978–988.
- Prendergast ML, Podus D, Chang E. 2000. Program factors and treatment outcomes in drug dependence treatment: an examination using meta-analysis. *Subst Use Misuse* 35:1931–1965.
- Prendergast ML, Urada D, Podus D. 2001. Meta-analysis of HIV risk-reduction interventions within drug abuse treatment programs. *J Consult Clin Psychol* 69:389–405.
- Preston KL, Bigelow GE, Liebson IA. 1990. Effects of sublingually given naloxone in opioid-dependent human volunteers. *Drug Alcohol Depend* 25:27–34.
- Preston KL, Silverman K, Umbricht A, DeJesus A, Montoya ID, Schuster CR. 1999. Improvement in naltrexone treatment compliance with contingency management. *Drug Alcohol Depend* 54:127–135.
- Prosser J, Cohen LJ, Steinfeld M, Eisenberg D, London ED, Galynker II. 2006. Neuropsychological functioning in opiate-dependent subjects receiving and following methadone maintenance treatment. *Drug Alcohol Depend* 84:240–247.
- Reece AS. 2007. Psychosocial and treatment correlates of opiate free success in a clinical review of a naltrexone implant program. *Subst Abuse Treat Prev Policy* 2:35.
- Rook EJ, Huitema AD, van den Brink W, van Ree JM, Beijnen JH. 2006. Pharmacokinetics and pharmacokinetic variability of heroin and its metabolites: review of the literature. *Curr Clin Pharmacol* 1:109–118.
- Rosner S, Leucht S, Leher P, Soyka M. 2008. Acamprosate supports abstinence, naltrexone prevents excessive drinking: evidence from a meta-analysis with unreported outcomes. *J Psychopharmacol* 22:11–23.
- Rösner S, Hackl-Herrwerth A, Leucht S, Leher P, Vecchi S, Soyka M. 2010. Acamprosate for alcohol dependence. *Cochrane Database Syst Rev* 8: CD004332.
- SAMHSA (Substance Abuse and Mental Health Services Administration). 2001. National Household Survey on Drug Abuse (NHSDA) [<http://www.samhsa.gov>].
- Salamina G, Diedicue R, Vigna-Taglianti F, Jarre P, Schifano P, Bargagli AM, et al. 2010. Effectiveness of therapies for heroin addiction in retaining patients in treatment: results from the VEdE-TTE study. *Subst Use Misuse* 45:2072–2092.
- San L, Arranz B, Martinez-Raga J. 2007. Antipsychotic drug treatment of schizophrenic patients with substance abuse disorders. *Eur Addict Res* 13:230–243.
- Scherbaum N, Finkbeiner T, Leifert K, Gastpar M. 1996. The efficacy of L-methadone and racemic methadone in substitu-

- tion treatment for opiate addicts – a double-blind comparison. *Pharmacopsychiatry* 29:212–215.
- Schottenfeld RS, Pakes JR, Oliveto A, Ziedonis D, Kosten TR. 1997. Buprenorphine vs methadone maintenance treatment for concurrent opioid dependence and cocaine abuse. *Arch Gen Psychiatry* 54:713–720.
- Sees KL, Delucchi KL, Masson C, Rosen A, Clark HW, Robillard HM, et al. 2000. Methadone maintenance vs 180-day psychosocially enriched detoxification for treatment of opioid dependence: a randomized controlled trial. *J Am Med Assoc* 283: 1303–1310.
- Seifert J, Metzner C, Paetzold W, Borutzky M, Passie T, Rollnik J, et al. 2002. Detoxification of opiate addicts with multiple drug abuse: a comparison of buprenorphine vs. methadone. *Pharmacopsychiatry* 35:159–164.
- Shekelle PG, Woolf SH, Eccles M, Grimshaw J. 1999. Clinical guidelines: developing guidelines. *Br Med J* 318:593–596.
- Silverman K, Higgins ST, Brooner RK, Montoya ID, Cone EJ, Schuster CR, et al. 1996. Sustained cocaine abstinence in methadone maintenance patients through voucher-based reinforcement therapy. *Arch Gen Psychiatry* 53:409–415.
- Silverman K, Wong CJ, Umbricht-Schneiter A, Montoya ID, Schuster CR, Preston KL. 1998. Broad beneficial effects of cocaine abstinence reinforcement among methadone patients. *J Consult Clin Psychol* 66:811–824.
- Simmat-Durand L, Lejeune C, Gourarier L. 2009. Pregnancy under high-dose buprenorphine. *Eur J Obstet Gynecol Reprod Biol* 142:119–123.
- Sinha R, Kimmerling A, Doebrick C, Kosten TR. 2007. Effects of lofexidine on stress-induced and cue-induced opioid craving and opioid abstinence rates: preliminary findings. *Psychopharmacology (Berlin)* 190:569–574.
- Somogyi AA, Barratt DT, Collier JK. 2007. Pharmacogenetics of opioids. *Clin Pharmacol Ther* 81:429–444.
- Soyka M. 2008a. Safety issues in methadone maintenance, part 1: Legal basis, mortality, and clinical results (in German). *Suchtmed* 10:7–27.
- Soyka M. 2008b. Safety issues in methadone maintenance therapy, part 2: Clinical and pharmacological aspects. (in German). *Suchtmed* 10:119–144.
- Soyka M, Rösner S. 2010a. Emerging drugs to treat alcoholism. *Expert Opin Emerg Drugs* 15:695–711.
- Soyka M, Rösner S 2010b. Nalmefene for treatment of alcohol dependence. *Expert Opin Investig Drugs* 19:1451–1459.
- Soyka M, Zingg C. 2009. Feasibility and safety of transfer from racemic methadone to (R)-methadone in primary care: clinical results from an open study. *World J Biol Psychiatry* 10:217–224.
- Soyka M, Horak M, Dittert S, Kagerer S. 2001. Less driving impairment on buprenorphine than methadone in drug-dependent patients? *J Neuropsychiatry Clin Neurosci* 13: 527–528.
- Soyka M, Hock B, Kagerer S, Lehnert R, Limmer C, Kuefner H. 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* 25:490–493.
- Soyka M, Apelt SM, Lieb M, Wittchen HU. 2006. One-year mortality rates of patients receiving methadone and buprenorphine maintenance therapy: a nationally representative cohort study in 2694 patients. *J Clin Psychopharmacol* 26:657–660.
- Soyka M, Kranzler HR, Berglund M, Gorelick D, Hesselbrock V, Johnson BA, et al. 2008a. World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Substance Use and Related Disorders, Part 1: Alcoholism. *World J Biol Psychiatry* 9:6–23.
- Soyka M, Zingg C, Koller G, Kuefner H. 2008b. Retention rate and substance use in methadone and buprenorphine maintenance therapy and predictors of outcome: results from a randomized study. *Int J Neuropsychopharmacol* 11:641–653.
- Spanagel R, Kirschke C, Tretter F, Holsboer F. 1998. Forced opiate withdrawal under anaesthesia augments and prolongs the occurrence of withdrawal signs in rats. *Drug Alcohol Depend* 52:251–256.
- Specka M, Finkbeiner T, Lodemann E, Leifert K, Kluwig J, Gastpar M. 2000. Cognitive-motor performance of methadone-maintained patients. *Eur Addict Res* 6:8–19.
- Spencer L, Gregory M. 1989. Clonidine transdermal patches for use in outpatient opiate withdrawal. *J Subst Abuse Treat* 6: 113–117.
- Spiller H, Lorenz DJ, Bailey EJ, Dart RC. 2009. Epidemiological trends in abuse and misuse of prescription opioids. *J Addict Dis* 28:130–136.
- Simmel B, Cohen M, Sturiano V, Hanbury R, Korts D, Jackson G. 1983. Is treatment for alcoholism effective in persons on methadone maintenance? *Am J Psychiatry* 140:862–866.
- Stine SM, Freeman MS, Burns B, Charney DS, Kosten TR. 1992. The effect of methadone dose on cocaine abuse in methadone program. *Am J Addict* 1:294–303.
- Stine SM, Grillon CG, Morgan CA 3rd, Kosten TR, Charney DS, Krystal JH. 2001. Methadone patients exhibit increased startle and cortisol response after intravenous yohimbine. *Psychopharmacology (Berlin)* 154:274–281.
- Stine SM, Southwick SM, Petrakis IL, Kosten TR, Charney DS, Krystal JH. 2002. Yohimbine-induced withdrawal and anxiety symptoms in opioid-dependent patients. *Biol Psychiatry* 15:642–651.
- Stitzer M, Bigelow G. 1978. Contingency management in a methadone maintenance program: availability of reinforcers. *Int J Addict* 13:737–746.
- Stitzer ML, Bickel WK, Bigelow GE, Liebson IA. 1986. Effect of methadone dose contingencies on urinalysis test results of polydrug-abusing methadone-maintenance patients. *Drug Alcohol Depend* 18:341–348.
- Stitzer ML, Iguchi MY, Felch LJ. 1992. Contingent take-home incentive: effects on drug use of methadone maintenance patients. *J Consult Clin Psychol* 60:927–934.
- Stoller KB, Bigelow GE, Walsh SL, Strain EC. 2001. Effects of buprenorphine/naloxone in opioid-dependent humans. *Psychopharmacology (Berlin)* 154:230–242.
- Stotts AL, Dodrill CL, Kosten TR. 2009. Opioid dependence treatment: options in pharmacotherapy. *Expert Opin Pharmacother* 10:1727–1740.
- Strain EC, Stitzer ML, Liebson IA, Bigelow GE. 1993a. Dose-response effects of methadone in the treatment of opioid dependence. *Ann Intern Med* 119:23–27.
- Strain EC, Stitzer ML, Liebson IA, Bigelow GE. 1993b. Methadone dose and treatment outcome. *Drug Alcohol Depend* 33:105–117.
- Strain EC, Stitzer ML, Liebson IA, Bigelow GE. 1994. Comparison of buprenorphine and methadone in the treatment of opioid dependence. *Am J Psychiatry* 151:1025–1030.
- Strain EC, Bigelow GE, Liebson IA, Stitzer ML. 1999. Moderate- vs high-dose methadone in the treatment of opioid dependence: a randomized trial. *J Am Med Assoc* 281:1000–1005.
- Strassels SA. 2009. Economic burden of prescription opioid misuse and abuse. *J Manag Care Pharm* 15:556–562.
- Stringer J, Welsh C, Tommasello A. 2009. methadone-associated Q-Z interval prolongation and torsade de pointes. *Am J Health Syst Pharm* 66:825–833.
- Strang J, Mardsen J, Cummins M, Farrell M, Finch E, Gossop M, et al. 2000. Randomized trial of supervised inject-

- able versus oral methadone maintenance: report of feasibility and 6-month outcome. *Addiction* 95:1631–1645.
- Strang J, Metrablan N, Lintzeris N, Potts L, Carnwath T, Mayet S, et al. 2010. Supervised injectable heroin or injectable methadone versus optimised oral methadone as treatment for chronic heroin addicts in England after persistent failure in orthodox treatment (RIOTT): a randomized trial. *Lancet* 375:1885–1895.
- Suffet F, Brotman R. 1984. A comprehensive care program for pregnant addicts: obstetrical, neonatal, and child development outcomes. *Int J Addict* 19:199–219.
- Sullivan MA, Vosburg SK, Comer SD. 2006. Depot naltrexone: antagonism of the reinforcing, subjective, and physiological effects of heroin. *Psychopharmacology* (Berlin) 189:37–46.
- Tait RJ, Ngo HT, Hulse GK. 2008. Mortality in heroin users 3 years after naltrexone implant or methadone maintenance treatment. *J Subst Abuse Treat* 35:116–124.
- Termorshuizen F, Krol A, Prins M, van Ameijden EJ. 2005. Long-term outcome of chronic drug use: the Amsterdam Cohort Study among Drug Users. *Am J Epidemiol* 161:271–279.
- Threlkeld M, Parran TV, Adelman CA, Grey SF, Yu J. 2006. Tramadol versus buprenorphine for the management of acute heroin withdrawal: a retrospective matched cohort controlled study. *Am J Addict* 15:186–191.
- Tretter F, Burkhardt D, Bussello-Spieth B, Reiss J, Walcher S, Buchele W. 1998. Clinical experience with antagonist-induced opiate withdrawal under anaesthesia. *Addiction* 93:269–275.
- Uchtenhagen A. 2010. Heroin-Assisted treatment in Switzerland: a case study in policy change. *Addiction* 105:29–37.
- Unger A, Jung E, Winklbaur B, Fischer G. 2010. Gender issues in the pharmacotherapy of opioid-addicted women: buprenorphine. *J Addict Dis* 29:217–230.
- United Nations Office on Drugs and Crime. 2006. 2006 World Drug Report. Vienna: UNODC.
- Umbricht A, Hoover DR, Tucker MJ, Leslie JM, Chaisson Re, Preston KL. 2003. Opioid detoxification with buprenorphine, clonidine, or methadone in hospitalized heroin-dependent patients with HIV infection. *Drug Alcohol Depend* 69:263–272.
- Valotassiou V, Wozniak G, Sifakis N, Demakopoulos N, Georgoulas P. 2008. Radiopharmaceuticals in neurological and psychiatric disorders. *Curr Clin Pharmacol* 3:99–107.
- van den Brink W, Haasen C. 2006. Evidence-based treatment of opioid-dependent patients. *Can J Psychiatry* 51:635–646.
- van den Brink W, van Ree JM. 2003. pharmacological treatments for heroin and cocaine addiction. *Eur Neuropsychopharmacol* 13:476–487.
- van Dorp EL, Yassen A, Dahan A. 2007. Naloxone treatment in opioid addiction: th3 risks and benefits. *Expert Opin Drug Saf* 6:125–132.
- Verdejo A, Toribio I, Orozco C, Puente KL, Perez-Garcia M. 2005. Neuropsychological functioning in methadone maintenance patients versus abstinent heroin abusers. *Drug Alcohol Depend* 78:283–288.
- Verthein U, Nonorden-Kleij K, Degwitz P, Dilg C, Köhler WK, Passie T, et al. 2008. Long-term effects of heroin-assisted treatment in Germany. *Addiction* 103:960–966.
- Walsh SL, June HL, Schuh KJ, Preston KI, Bigelow GE, Stitzer ML. 1995. Effects of buprenorphine and methadone in methadone-maintained subjects. *Psychopharmacology* (Berlin) 119:268–276.
- Washton AM, Resnick RB, Rawson RA. 1980. Clonidine for outpatient opiate detoxification. *Lancet* i:1078–1079.
- Washton AM, Gold MS, Pottash AC. 1984. Successful use of naltrexone in addicted physicians and business executives. *Adv Alcohol Subst Abuse* 4:89–96.
- Wee S, Koob GF. 2010. The role of the dynorphin-kappa opioid system in the reinforcing effects of drugs of abuse. *Psychopharmacology* (Berlin) 210:121–135.
- Welsh C. 2008. The use of buprenorphine to reverse opioid overdose deserves further evaluation. *Addiction* 103:2066–2067.
- Wesson DR, Smith DE. 2010. Buprenorphine in the treatment of opiate dependence. *J Psychoactive Drugs* 42:161–175.
- West SL, O’Neal KK, Graham CW. 2000. A meta-analysis comparing the effectiveness of buprenorphine and methadone. *J Subst Abuse* 12:405–414.
- Wilson RS, Di George WS. 1993. Methadone combined with clonidine versus clonidine alone in opiate detoxification. *J Subst Abuse Treat* 10:529–535.
- Winklbaur B, Kopf N, Ebner N, Jung E, Thau K, Fischer G. 2008a. Treating pregnant women dependent on opioids is not the same as treating pregnancy and opioid dependence: a knowledge synthesis for better treatment for women and neonates. *Addiction* 103:1429–1440.
- Winklbaur B, Jung E, Fischer G. 2008b. Opioid dependence and pregnancy. *Curr Opin Psychiatry* 21:255–259.
- Wittchen HU, Apelt SM, Soyka M, Gastpar M, Backmund M, Golz J, et al. 2008. Feasibility and outcome of substitution treatment of heroin-dependent patients in specialized substitution centers and primary care facilities in Germany: a naturalistic study in 2694 patients. *Drug Alcohol Depend* 95:245–257.
- Wobrock T, Soyka M. 2008. Pharmacotherapy of schizophrenia with comorbid substance use disorder – reviewing the evidence and clinical recommendations. *Prog Neuropsychopharmacol Biol Psychiatry* 32:1375–1385.
- Woody GE, Luborsky L, McLellan AT, O’Brien CP, Beck AT, Blaine J, et al. 1983. Psychotherapy for opiate addicts. Does it help? *Arch Gen Psychiatry* 40:639–645.
- Woody GE, McLellan AT, O’Brien CP. 1984. Treatment of behavioral and psychiatric problems associated with opiate dependence. *NIDA Res Monogr* 46:23–35.
- Woody GE, McLellan AT, Luborsky L, O’Brien CP. 1987. Twelve-month follow-up of psychotherapy for opiate dependence. *Am J Psychiatry* 144:590–596.
- Woody GE, McLellan AT, Luborsky L, O’Brien CP. 1995. Psychotherapy in community methadone programs: a validation study. *Am J Psychiatry* 152:1302–1308.
- Woody GE, Poole SA, Subramaniam G, Dugosh K, Bogenschutz M, Abbott P, et al. 2008. Extended vs short-term buprenorphine-naloxone for treatment of opioid-addicted youth: a randomized trial. *J Am Med Assoc* 300:2003–2011.
- World Health Organization. 2004. The World Health Report 2004. Geneva: WHO.
- Yen MH, Ko HC, Tang FI, Lu RB, Hong JS. 2006. Study of hepatotoxicity of naltrexone in the treatment of alcoholism. *Alcohol* 38:117–120.
- Yuferov V, Levran O, Proudnikov D, Nielsen DA, Kreek MJ. 2010. Search for genetic markers and functional variants involved in the development of opiate and cocaine addiction and treatment. *Ann NY Acad Sci* 1187:184–207.
- Ziedonis DM, Amass L, Steinberg M, Woody G, Krejci J, Annon JJ, et al. 2009. Predictors of outcome for short-term medically supervised opioid withdrawal during a randomized, multicenter trial of buprenorphine-naloxone and clonidine in the NIDA clinical trials network drug and alcohol dependence. *Drug Alcohol Depend* 99:28–36.
- Zukin RS, Sugarman JR, Fitz-Syage ML, Gardner EL, Zukin SR, Gintzler AR. 1982. Naltrexone-induced opiate receptor supersensitivity. *Brain Res* 245:285–292.