European Monitoring Centre
for Drugs and Drug Addiction

ISBN 92-9168-274-8

LITERATURE REVIEW

TREATMENT OF PROBLEM COCAINE USE
A REVIEW OF THE LITERATURE

EMCDDA literature reviews

Treatment of problem cocaine use: a review of the literature

Acknowledgements

This literature review is based on a consultant report by Christian Haasen and Katja Thane, Institut für Interdisziplinäre Sucht- und Drogenforschung (ISD), Hamburg, at the Zentrum für Interdisziplinäre Suchtforschung (ZIS) of the University of Hamburg (Service Contract CT.06.RES.144.1.0**).**

EMCDDA project managers: Dagmar Hedrich and Alessandro Pirona. Other contributors to this project included Prepress Projects, Rosemary de Sousa and Peter Thomas.

Cataloguing data

European Monitoring Centre for Drugs and Drug Addiction, 2007

EMCDDA Literature reviews — Treatment of problem cocaine use: a review of the literature

Lisbon: European Monitoring Centre for Drugs and Drug Addiction

2007 — 50 pp. — 21 x 29.7 cm

Language: EN

Catalogue Number: TD-XB-06-001-EN-N

ISBN: 92-9168-274-8

ISSN: 1725-0579

European Monitoring Centre for Drugs and Drug Addiction

Rua da Cruz de Santa Apolónia 23-25, PT-1149-045 Lisbon, Portugal

Tel: (+351) 21 811 3000 ● Fax: (+351) 21 813 1711

info@emcdda.europa.eu ● http://www.emcdda.europa.eu

List of abbreviations

ADHD	attention deficit hyperactivity disorder
BBD	blood-borne disease
CA	Cocaine Anonymous
CBT	cognitive–behavioural therapy
CEDRO	Centrum voor Drugsonderzoek (Netherlands)
CM	contingency management
CNS	central nervous system
CRA	community reinforcement approach
CRH	corticotrophin-releasing hormone
DA	dopamine
DSM-IV	Diagnostic and Statistical Manual of Mental Disorder (4th edition)
EMCDDA	European Monitoring Centre for Drugs and Drug Addiction
FOS	Forschungsverbund stationäre Suchttherapie (Switzerland)
GABA	gamma-aminobutyric acid
GP	general practitioner
GVG	gamma-vinyl-GABA
HIV	human immunodeficiency virus
IDU	injecting drug user
IFT	Institut für Therapieforschung (Munich, Germany)
ISD	Instituut voor Sociaal Drugonderzoek (Belgium)
MAO	monoamine oxidase
MI	motivational interviewing
MMT	methadone maintenance treatment
NADA	National Acupuncture Detoxification Association
NcA	nucleus accumbens
NHS	National Health Service (UK)
NIDA	National Institute on Drugs and Drug Abuse (USA)
NSAID	non-steroidal anti-inflammatory drug
NTA	National Treatment Agency (UK)
NTORS	National Treatment Outcome Research Study (UK)
RCT	randomised controlled trial
Reitox	European Information Network on Drugs and Drug Addiction
SROM	slow-release oral morphine
SSRI	selective serotonin reuptake inhibitor
TC	therapeutic community
TCA	2,4,6-trichloranisol
Trimbos	Netherlands Institute Of Mental Health And Addiction
WHO	World Health Organization

Table Of Contents

Foreword

Treatment systems in Europe are increasingly confronted with cocaine use-related problems. After opioids and cannabis, cocaine has become the third most commonly reported reason for entering drug treatment and accounted for about 8 % of all treatment demands across the EU in 2004. This overall figure reflects a wide variation between countries; however, the proportion of new clients demanding treatment for cocaine use is estimated to have grown from 10 % to 20 % during the period 1999–2004 (EMCDDA, 2006). Cocaine use has also become more common among drug users in contact with outreach workers or low-threshold agencies, and new findings with respect to treatment need to be evaluated in order to adapt addiction services to the new demands.

The aim of this report is to provide an up-to-date summary of research regarding treatment approaches to cocaine dependency, and their effectiveness[1].

New treatment concepts need to be evidence based, calling for a research perspective in the evaluation of treatments for cocaine dependence. Nonetheless, innovations in treatment also result from individual experiments by clinicians, so that a clinical perspective needs to be added in order to obtain a complete overview of developments in the treatment of cocaine dependence.

In this direction, conferences were organized across Europe to gather further knowledge on cocaine treatment by bringing together European researchers and clinicians. For example, a conference on clinical research on cocaine took place in April 2006 in Paris organised by the Mission Interministérielle de Lutte contre la Drogue et la Toxicomanie. In June 2006, the Federazione Italiana Comunità Terapeutiche (FICT) organised in Rome the Congress 'Cocaina: la FICT tra prassi e innovazione: Esperienze a confronto nel contesto italiano' with the aim of sharing experiences and disseminating best practices in relation to cocaine treatment. A similar conference was held in Madrid on the 17th of May 2007.

In conclusion, the present report aims to portray the state-of-the-art in health responses to cocaine use, with a special emphasis on mental health problems related to cocaine use. However, there is no doubt that current research efforts will in the near future bring about innovations of great importance in this field. We hope that this report will support the dynamic research process that is under way and at the same time support adjustments in policy regarding addiction services to improve their response to cocaine users.

(1) This report reviews the current literature on cocaine treatment, based on a search of the databases Medline, PubMed and PsychInfo for the years 2002–07, using the following keywords: cocaine, treatment, dependence. In addition, the reference lists of all publications identified through the search were evaluated and reports from European research centres, including Trimbos and Cedro in the Netherlands, ISD in Belgium, IFT in Germany and the NTA in the UK, were also considered. Please note that the present review does not cover medical complications of cocaine consumption. A review of the literature on this topic can be found in the EMCDDA's Selected Issue 2007 on cocaine.

1 History and epidemiological characteristics of cocaine use

Cocaine is a natural alkaloid isolated from the leaves of the *Erythroxylum coca* shrub, native to the South American mountain chains, which demonstrates marked psychostimulant effects.

Traditionally, and this is still the case in Latin America, the drug was consumed by chewing coca leaves, which, owing to the relatively slow absorption rate, results in low blood concentrations of the alkaloid. The experienced acute effects of cocaine are increased euphoria, well-being andself-confidence, reduced social inhibitions and facilitated interpersonal communication (Hall et al., 1990; Gold and Miller, 1997; Marcos et al., 1998). Furthermore, cocaine also reduces fatigue, increases vigilance, motor and sexual activity, and facilitates most cognitive functions (Hall et al., 1990; Gold and Miller, 1997; Marcos et al., 1998). Its marked gratifying properties significantly contribute to the initiation and maintenance of the addictive process (Gardner, 1992; Chen, 1993; Di Chiara, 1995; Koob and Le Moal, 1997), and preclinical studies suggest that cocaine has an elevated potential for addiction, given that the degree of gratification it provides is significantly greater than that of other psychoactive substances (Gold and Miller, 1997).

It is the pharmacological action of cocaine in blocking catecholamine reuptake in the brain that is believed to induce cocaine misuse and even dependence. However, these risks did not become known until long after cocaine was chemically isolated and used in the cocaine hydrochloride form. Cocaine hydrochloride was first isolated from coca leaves in 1860, and became widely available around 1880, even being found as an additive in beverages, creams and toothpaste. Its misuse potential led to its use being made illegal in many countries around 1920.

The illicit use of cocaine continued, but was not as widespread as the use of other illicit substances. However, it became a popular drug in the USA in the late 1960s and early 1970s, particularly among middle-class or well-to-do users. With the introduction in the early to mid-1980s of the smokeable form of cocaine, crack cocaine, cocaine also became popular among the inner-city poor, and consumption rates within this demographic segment increased substantially. The availability of this South American drug was increased by the geographical proximity to the USA and well-established Caribbean and Central American trafficking routes. The spread of cocaine to other industrialised nations, mainly in Europe, accelerated when a US crackdown (the Reagan–Bush ‘war on drugs’) forced suppliers of cocaine to search for new markets. New trafficking routes to Europe emerged, including an air bridge via the Netherlands Antilles to the Netherlands and sea–land routes via West Africa and the Iberian peninsula. A subsequent increase in lifetime prevalence of cocaine use in Europe was seen during the 1990s, although prevalence rates in Europe did not reach the same levels as in the USA.

In the 2004 United States National Survey on Drug Use and Health, 14.2 % of adults (defined as 12 years or older) reported lifetime experience with cocaine, and 2.4 % reported recent use; among younger adults, the average figure for last year use was 5.1 % ([2]). In the EU, 3 % of the population between 15 and 64 years of age (about 10 million people) have tried cocaine at least once in their lives, and 1 in 100 European adults have used cocaine in the last 12 months. Cocaine use is more concentrated among younger age groups, and last year experience among 15- to 34-year olds is above 2 % in Denmark, Ireland, Italy and the Netherlands and reaches 4% in Spain and the United Kingdom (EMCDDA, 2006).

Among the general population, cocaine use seems to be occasional, occurring mainly at weekends and in the recreational settings of bars and discos, where it can reach high levels. Research studies conducted among young people in dance and music settings in different countries reveals prevalence estimates for cocaine use that are much higher than those found in general populations, with lifetime prevalence ranging from 10 % to 75 % (EMCDDA, 2006, selected issues).

Cocaine can be self-administered through various routes: orally or sublingually via direct application to the gums, nasally via snorting, by inhalation in vapour form, by smoking (crack cocaine, coca paste or cocarettes) or by injection. From a European perspective, cocaine hydrochloride (powder cocaine)

([2]) Source: SAMHSA, Office of Applied Studies, 2004 National Survey on Drug Use and Health (http://oas.samhsa.gov/nsduh.htm#nsduhinfo). The comparatively higher lifetime figures in the United States may be in part related to earlier spread of cocaine use in that country.

is the main form of cocaine on the market and is generally either snorted or injected. Coca paste, a precursor in the chemical process of producing cocaine hydrochloride, and one of the most widely misused substances in South America, is generally not found in Europe. Crack cocaine has emerged in several European countries, but for unknown reasons remains confined to specific geographical areas, mainly bigger European cities. Crack cocaine is mainly smoked, although injection has also been reported where the street market availability of crack cocaine is greater than that of cocaine hydrochloride. Freebase cocaine, a smokeable form of cocaine extracted from a mix of an alkaline solution of cocaine hydrochloride with a solvent such as ether or acetone, is still used in a few areas of Europe, but overall has been replaced by crack cocaine because of the flammability risk of smoking freebase, a risk not associated with crack cocaine. Smoking cocarettes (tobacco cigarettes to which cocaine hydrochloride is added) seems to be a very rare form of cocaine use and is favoured mainly by cocaine users who generally snort cocaine but who have developed nasal complications (Haasen et al., 2003a).

The different routes of administration are associated with differences in bioavailability. The fastest onset of action is found with smoked cocaine, followed closely by injected cocaine, whereas snorting and oral use have a slower onset of action. The onset of action corresponds to different levels of intensity with regard to the effect of cocaine on the brain, which results in differences in the risk of dependence. Smoking crack cocaine therefore bears the highest risk of dependence; snorting cocaine hydrochloride a lower risk. Cocaine or crack injecting has a high dependence potential and is furthermore associated with the risk of transmissible infections such as hepatitis and HIV.

Patterns of cocaine use also vary between different social groups of users in European cities. A multicentre study on patterns of cocaine use in nine European cities found that socially integrated cocaine users mainly snorted (95 %) the substance, whereas only a small fraction had smoked or injected it, but combined use of cannabis and alcohol was very common (Haasen et al., 2004a). In the cities for which data were available, injection was frequent among users in addiction treatment settings or in socially marginalised groups. Crack use was usual in Hamburg, London and Paris, and to a lesser extent in Barcelona and Dublin. Although crack use among the European general population seems to be low, it is an increasing concern among marginalised groups and opioid users in some European cities.

Overall, most cocaine treatment demands in Europe are not related to crack cocaine: around 80 % of new outpatient cocaine clients are reported to be using cocaine hydrochloride (cocaine powder) and less than 20 % use crack cocaine. However, crack cocaine users may pose particular challenges for treatment services as they tend to have a more marginalised social profile than users of cocaine powder.

2 Current issues in the treatment of problem cocaine use

To date, little consensus exists on what constitutes effective treatment for cocaine dependence. Treatment issues are complicated by the polydrug use of powder cocaine in combination with crack cocaine and other substances, especially opiates, which often mask which treatment has been beneficial in addressing cocaine use. In addition, the orientation of treatment services around opiate dependence problems, alongside the lack of established cocaine treatment programmes, has resulted in primary cocaine users being reluctant to present themselves for treatment (Bottomley et al., 1997). Some research (e.g. San Molina and Arranz Diez, 2001) suggests that the combination of pharmacological and psychotherapeutic interventions is most effective, whereas predominantly pharmacological treatment has not been found to be helpful (see section 3). In addition, attrition and relapse rates of primary cocaine users are generally high (e.g. Weaver 2007; Higgins et al., 1993). More recently, a British Audit Commission report has highlighted the failure of treatment services to address adequately the needs of stimulant users, and in particular the treatment needs of women and black and ethnic minorities (Audit Commission, 2002)[3]. The question whether cocaine-targeted or non-drug-specific interventions hold the most promise is also not yet answered.

2.1 Research and evaluation

Most research concerning treatment for cocaine problems has been carried out in the USA. Because of the different history of cocaine and crack use in the USA and the specific sociocultural background and treatment context, these findings cannot directly be transferred to the situation in Europe. Treatment options for cocaine users in European countries seem to be rather limited and exist in only a few countries, and the treatment needs of crack cocaine users are frequently unmet.

Systematic research or even evaluations of cocaine treatment provision in Europe hardly exist. A good overview on the 'state of the art for evidence based treatments and other interventions', mainly referring to the Netherlands, is given by Rigter et al. (2004). Another study with a focus on Germany has been produced by Kraus et al. (2004). Both publications also evaluate the international literature on cocaine use and treatment. The effectiveness of the treatment of crack cocaine users was reviewed by Thom (2001), but, overall, little research evidence is available assessing the treatment of crack cocaine, even in those countries with relatively high local prevalence levels of crack cocaine use, such as Germany, Spain, France and the United Kingdom. However, a different approach is required to engage crack users in treatment because of the highly erratic patterns of use that are associated with the drug. While some new treatment approaches are proving to be promising, counselling and psychological therapy remain important where no obvious pharmacological replacement therapy is available (Haasen et al. 2003b).

2.2 Polydrug use and heterogeneity of client profiles

As multiple substance or polydrug use is the dominant pattern of use among cocaine users, this should also be reflected in treatment. Many treatment models in Europe still focus on the heroin user, whereas models in the USA target mainly a single substance. Rounsaville et al. (2003) reviewed clinical trials on single-drug versus multiple-drug focus in research and concluded by recommending that researchers consider moving away from a single-drug focus.

The increase in treatment demand for cocaine dependence reflects changes in consumption patterns and in consumers' profiles. For example, the recreational or weekend cocaine user is very different from a typical heroin addict, for whom most of the treatment models have been developed. Consequently, guidances for professionals working with cocaine and crack users have been issued in various European countries, such as the one presented by the National Treatment Agency and the Royal College of General Practitioners in the United Kingdom (Witton and Ashton, 2002; Ford, 2004). This guidance covers a variety of treatment options and their role in cocaine treatment. In Germany, practical experiences in the work with crack users were addressed at a conference in 2001 (Dworsky, 2001), which was followed by the publication of guidance in 2002 (Dworsky, 2002). Specific directions

([3]) Audit Commission (2002). Changing Habits. The commissioning and management of community drug treatment services for adults. London, Audit Commission.

for psychiatrists and other medical staff were published in 2004 (Thomasius et al., 2004), which presented some general directions regarding standards, work with special subgroups and treatment options.

Data from the United Kingdom suggest that the average time in treatment for cocaine or crack dependence is 5–7 years, and that benefits for clients accumulate after a series of treatments (NHS, 2005). According to a study carried out in the primary care sector, two issues are important to optimise treatment outcomes: the adjustment of treatment to individual needs of the user and application of the least restrictive and repressive treatment (Ford, 2004).

A Swedish meta-analysis examined factors that were related to improved treatment outcomes (Berglund, 2005). One important beneficial factor appeared to be a strong treatment relationship between the recipient and therapist. Another beneficial factor was the additive effect of combining different kinds of treatment, although this additive effect was not applicable to all types of treatment. Berglund proposed three areas for further research into optimising treatment: the effectiveness of short-term treatment compared with long-term treatment; the concurrent use of psychosocial and pharmacological treatment; and, finally, interactions between the first and second session of intervention.

The heterogeneity of the cocaine-using population, the considerable variations in patterns of cocaine use and the high incidence of concurrent polydrug use create a need for a diverse range of culturally appropriate services and treatment responses. For example, recreational cocaine users who are not highly involved in a drug culture are unlikely to make demands on service providers (Green et al., 1994). Conversely, polydrug cocaine users (including methadone-maintained cocaine users) may already be in contact with existing opiate-based services but may not report their cocaine use, or their cocaine use may not be adequately addressed. Those who use powder cocaine as their main drug are more marginal to the established drug culture and are less likely to have knowledge of drug services and less willing to identify with the 'junkie' lifestyle (Green et al., 1994). In the USA it has been suggested that there is a 2- to 4-year time lag between initiation into cocaine use and presentation to services depending on the type of user (Kleber, 1988). Consequently, services need to be accessible and attractive to the target group in order to ensure early intervention.

2.3 Treatment entry

As entry into treatment is a milestone for both the user and the services providing treatment, it merits special attention. On entry into treatment a careful assessment should be made to identify needs and, in some cases, to create a care plan tailored to the needs of the client (Ford, 2004).

Cocaine users entering treatment are predominantly introduced by self-referral or family referral. Similarly, crack cocaine users entering treatment in Europe tend to be self-referrals or referrals by family members or friends (Vanderplasschen et al., 2002; Act-info-FOS, 2004), while in the USA a study found that crack cocaine users referred to treatment by the court accounted for almost half of all those entering treatment (Siegal et al., 2002). Nonetheless, even in the case of family and friend referrals, pressure from the legal system can directly or indirectly contribute to seeking treatment. In Ireland for example, users frequently attend services at the request of the courts, or because of pending criminal charges (Haasen et al., 2003b). The earlier mentioned US study among crack cocaine users found that younger users, users with more severe legal problems and users with prior treatment experience were more likely to enter treatment than other users (Siegal et al., 2002). In Canada, almost two-thirds of cocaine treatment entrants had legal problems, and half of those were introduced to treatment via a court referral (Rush and Wild, 2003). Another study looked at differences between cocaine users in Brazil entering treatment for the first time or re-entering treatment (Ferri et al., 2002). The results showed that those entering treatment for the first time had a tendency towards use of higher dosages, were more likely to be problematic drinkers and had increased awareness of their problem. Re-entering users, on the other hand, were more often involved in acquisitive crimes, had received social support in entering treatment and suffered from more severe dependence. It can therefore be useful to distinguish between first treatment cases and clients re-entering treatment when assessing treatment options.

2.4 Quality assurance

In Europe, the definition of standards for treatment provision and the implementation of quality assurance mechanisms with regard to training of staff, as well as monitoring and evaluation, are

increasingly recognised as key to better treatment outcomes (Solberg, 2003). Several European countries have focused their attention on the quality aspects of treatment.

The NTA and Healthcare Commission in the United Kingdom have developed a system to measure the quality of treatment and to facilitate improvements based on the results of the assessment. 'Drug treatment should encourage improvement in substance misuse, health and social functioning, and reductions in crime and public health risks' and evaluation should be based on measured performance, e.g. retention rates (NHS, 2005). They also emphasise the importance of focusing on local needs and partnerships to establish high-quality treatment and to define quality requirements for drug treatment. Wanigaratne et al. (2005) listed speed of treatment entry and treatment duration as further factors that can contribute to a higher effectiveness of treatment. Clients with complex needs benefited more if the available spectrum of treatment responses was broader. Treatment quality was also determined by factors associated with the therapist, such as empathy, collaborative relationship, motivational dialogue and willingness to be supervised.

In a Dutch concept-mapping exercise, involving 90 representatives of three groups of stakeholders, the quality framework for addiction treatment was examined (Nabitz et al., 2005). 'Best practice' and 'performance' emerged as the main dimensions along with three main conceptual clusters: client orientation, treatment practice and attitude of staff. The quality factors that best stood up to scrutiny included the evidence base of the treatment approach, respectful interaction with the patient and the immediacy of access to treatment. Furthermore, a Belgian study evaluated coordination and continuity of care and identified the need for improvements in this field: there was a lack of communication between services; client registration was not harmonised; and a care plan existed only for 10 % of clients (Vanderplasschen et al., 2002). Finally, in a review of ethical aspects in the treatment and care of addicts by Guggenbühl et al. (2000), the authors concluded that a commitment to continuity of support is crucial, regardless of the treatment type offered.

Adequate staff training is (or should be) an integral part of good-quality treatment and may need to be adjusted to new circumstances or events. Owing to the increase in crack cocaine use in Germany and a parallel increase in the incidence of aggression and violence towards staff at drug help facilities (Klee, 2001), experts predict an increasing demand for continuous staff education. In Frankfurt, for example, many collaborators in low-threshold services have already been sent to anti-violence and de-escalation trainings (Stöver, 2001). In addition, staff may need special training not only in the pharmacology of cocaine, but also to further develop skills in, for example, relapse management and dealing with psychiatric comorbidity (Wallace, 1992), working with family members (Higgins et al., 1994) and social networks (McAuliffe et al., 1991). Another important issue for staff is the need to provide informality and confidentiality wherever possible (NTA, 2002a).

The effectiveness of treatment also increases when treatment is able to perform well against quality indicators. With regard to the client–therapist relationship, it is important to establish a good relationship from the beginning and to show empathy – this is thought to increase the number of clients who stay longer in treatment and demonstrate better outcomes (NTA, 2002b). A study on the use of the community reinforcement approach among female cocaine users found higher abstinence rates, longer abstinence and greater retention among those patients whose therapist's empathy was rated higher (Pantalon et al., 2004). These findings stress the importance of monitoring both mechanistic (big picture goals, functional analyses of behaviour, non-drug-related activities, skills training and homework) and interpersonal (empathy, response to resistance, and therapeutic alliance) processes during treatment.

Furthermore, treatment quality, as well as the closely connected factor of effectiveness of treatment, also needs to be examined. The NTA identified two main success factors associated with more effective treatment:

- improving the clients' journey through treatment;
- improving local drug treatment systems.

Success in these areas implies focusing on the user's needs – not only drug needs but wider needs such as housing, education and employment – and can be improved by short waiting times for treatment and good care planning (NHS, 2005).

One way of measuring the effectiveness of treatment is via long-term follow-up. Thus, several longitudinal studies showed the positive effects of treatment on long-term abstinence, with different observed outcomes depending on treatment conditions and methodological conditions of the studies. For example, 95 % of 131 crack cocaine users who attended a treatment unit in Sao Paulo, Brazil,

were followed up after 2 and 5 years (Ribeiro et al., 2007). A notable finding was the very high mortality rate of 17.6 % at 5 years, with most deaths attributable to homicide or AIDS. Among the remainder, there was a progressive trend towards abstinence over the follow-up period, and there was evidence that once abstinence had been achieved it was maintained.

An evaluation of community treatment outcomes in 708 cocaine-dependent users in the USA obtained largely positive results: large decreases in cocaine use were sustained over a 5-year period (Simpson et al., 2002). The findings also showed that the severity of drug and psychosocial problems at admission was predictive of long-term outcomes, while outcomes improved in direct relation to level of treatment exposure. Prospective studies of cocaine treatment outcome have also been conducted in the United Kingdom. Thus, the NTORS (Gossop et al., 2002) investigated outcomes among stimulant users over a 5-year period and found significant reductions in crack use by those using at intake, although over 20 % of patients not using at intake had started using crack cocaine at follow-up (Gossop et al., 2002).

Similarly, a British national postal survey of treatment services reported that cessation of opiate use may be associated with an increased likelihood of initiating crack cocaine use (Seivewright et al., 2000). However, the same survey also reported important improvements among a smaller follow-up sample of cocaine misusers, providing further evidence that ‘treatment works’.

Interesting results were also found in a 1-year follow-up study on the role of social support following short-term inpatient treatment (Broome et al., 2002). The results showed that social support networks following treatment were more important than variables investigated before or during treatment in predicting treatment outcome. This indicates that drug use is not only influenced by the pharmacological properties of the substance but is at least as much affected by the social context of the user. Thus, higher rates of relapse were observed among those with no positive support for abstinence at home and/or those who were living with a drug or alcohol user. In summary, support from family and peers appears to play a substantial role in lowering the risk of cocaine relapse, even after short-term treatments.

3 Pharmacological treatment

Distinct pharmacological therapies have been developed mainly on the basis of the modification of cerebral dopaminergic transmission (see section 3.1). In general, pharmacotherapies follow two principal strategies. The administration of dopamine receptor antagonists aims to counteract cocaine's gratifying effects, while the opposite effect is sought with agents that facilitate dopaminergic transmission. These facilitatory agents are generally used to prevent dopaminergic depletion observed during cocaine withdrawal or to reduce cravings during abstinence (see reviews by Gorelick, 1995; McCance, 1997; Gorelick et al., 2004). Other pharmacological agents, acting on serotonergic or noradrenergic transmission, have also been tested for their potential therapeutic benefits regarding cocaine dependence. To date, however, the most innovative treatment being tested is the cocaine vaccine, the aim of which is to block the desired effects of cocaine, and thus reduce its abuse potential, by producing cocaine antibodies (see also section 3.3). Finally, a special case in the treatment of cocaine dependence arises in patients who are also dependent on opioids. Opioid maintenance treatment is the most commonly used pharmacological treatment for opioid dependence, which in the case of additional cocaine use must be optimised (see also section 3.4).

Different stages in the addiction process have been identified and are commonly labelled initiation, continuation, withdrawal and relapse. These stages are characterised by the actions of specific neurotransmitters on different brain structures and neural circuits. In the first stage (initiation of use), dopamine (DA) is thought to play an important role in the acute reinforcing effects of the drug, with the ventral tegmental area (VTA) and the nucleus accumbens (NcA) as the primary areas of interest. In the second stage (continued drug use), several neurotransmitters are involved, including DA in the NcA, corticotrophin-releasing hormone (CRH) in the amygdala and glutamate in the frontal–cingulate circuit. In the third stage (withdrawal), glutamate and noradrenaline in the locus coeruleus seem to be crucial. Finally, in the fourth stage (relapse after sustained abstinence), the orbitofrontal cortex, the anterior cingulate gyrus and the amygdala are important brain regions in the addictive process, with noradrenaline and CRH involved in the brain stress system (stress-induced relapse) and gamma-aminobutyric acid (GABA) and glutamate involved in the compulsive and habit system (cue-induced relapse). This short description of the neurobiology of addiction clearly reveals that there are many different ways to intervene in the addictive process of cocaine self-administration. For example, the rewarding process can be blocked, illicit drugs can be replaced by other less harmful or less addictive compounds, hyperactivity in the stress axis can be prevented and the balance between the different neural systems can be restored. In the following review of currently available pharmacological treatments for cocaine dependence, many of these neurotransmitter systems and neural circuits are targeted to either reduce cocaine use or prevent relapse during sustained abstinence.

3.1 Substances for relapse prevention

The pharmacological treatment approaches reported below all aim at relapse prevention. Unlike opiate withdrawal, acute cocaine withdrawal is less dramatic and usually does not necessitate medication. In the last two decades, a great number of compounds belonging to different pharmacological classes have been tested for their effectiveness in the prevention of relapse and the promotion of stable abstinence in cocaine addicts. These drug classes include (see also the following reviews on pharmacological approaches to cocaine dependence: van den Brink and van Ree, 2003; Sofuoglu and Kosten, 2005; Wiesbeck and Dursteler-Macfarland, 2006):

- dopamine receptor agonists (e.g. bromocriptine, pergolide, DAS431, d-amphetamine);
- dopamine partial receptor agonists (e.g. terguride, BP897);
- dopamine reuptake inhibitors (e.g. amantadine, mazindol, methylphenidate, GBR12909 (vanoxerine), various tricyclic antidepressants and SSRIs);
- dopamine metabolism inhibitors (e.g. selegiline, disulfiram);
- dopamine antagonists (e.g. haloperidol, flufenazine, flupenthixol, ritanserine, risperidone, ecopipam);
- GABAergic compounds (e.g. baclofen, gabapentin, tiagabine, lamotrigine, valproate, carbamazepine, topiramate);

- β-adrenergic antagonists (e.g. propanolol, labetalol);
- opioids (e.g. naltrexone, buprenorphine, cyclazone);
- cortisol synthesis inhibitors and glucocorticoid receptor antagonists (e.g. ketoconazole, metyrapone, dexamethasone);
- calcium channel blockers (e.g. nimodipine, isradipine);
- various antidepressants (e.g. desipramine, imipramine, fluoxetine, venlavaxine, bupropion, gepirone, selegiline).

In a systematic review on medications used in the prevention of cocaine relapse, Silva de Lima et al. (2001) were able to detect more than 1 000 citations (1966–2000), from which they identified 49 different efficacy studies of acceptable methodological quality: 20 on antidepressants (14 on desipramine), five on carbamazepine, 13 on dopamine agonists and 11 on miscellaneous interventions (e.g. phenytoin, nimodipine, lithium carbonate, naltrexone). Dropout rates ranged from 0 % to 84 %, but in general the proportion of patients remaining in treatment was similar between those taking active medication or placebo. The same was true for cocaine-positive urine samples: again no significant differences were found in a statistical meta-analysis regardless of the type of medication or dosage. Furthermore, no significant differences between medications and placebo were generally observed in terms of specific side-effects. More recent reviews have revealed that disulfiram appears to have the most consistent effect in preventing relapse, whereas most other medications show very inconsistent results or still need further evaluation in larger controlled trials (Vocci and Elkashef, 2005; Vocci and Ling, 2005; Sofuoglu and Kosten, 2006). Nonetheless, a detailed description of each drug class is necessary in order to understand its mechanisms and its potential therapeutic benefits.

3.1.1 Dopamine receptor antagonists

To date, no conclusive findings on the efficacy of dopaminergic receptor antagonists in the treatment of cocaine dependency have been reported. However, some clinical studies have indicated that dopaminergic receptor antagonists, primarily acting on D2 dopamine receptors, such as classical neuroleptics, can partially block the subjective effects of cocaine in humans and thereby potentially reduce its consumption (Berger et al., 1989; Sherer et al., 1989; Khalsa et al., 1994). Nevertheless, this therapeutic approach suffers from two main problems. Firstly, chronic administration of such agents induces anhedonia and undesirable extrapyramidal motor effects, resulting in elevated treatment dropout rates (Kosten and Kleber, 1988; Decker and Ries, 1993). Secondly, repeated treatment with DA antagonists can lead to an increase in dopaminergic postsynaptic receptor sensitivity, which, indirectly, can increase the subjective effects of cocaine and thereby its abuse liability (Goldfrank and Hoffman, 1991; Kosten and McCance, 1997).

Regarding specific typical antipsychotic drugs, clinical trials have been conducted mainly on dually diagnosed (substance use disorder and psychotic disorder) patients, with only a few substances showing an effect on cocaine-dependent subjects without a second diagnosis. For example, flupenthixol treatment resulted in a reduction in cocaine use, especially in cocaine users with additional alcohol abuse (Soyka and De-Vry, 2000). In contrast to classical neuroleptics, new atypical antipsychotics used in the pharmacotherapy of cocaine dependence have the advantage of presenting a low profile of undesirable effects. However, results from studies employing atypical antipsychotic drugs in cocaine-dependent patients have not yet shown conclusive results (Meil and Schechter, 1997; Farren et al., 2000; Grabowski et al., 2000). Nonetheless, the atypical antipsychotic drug with the most reported benefit for cocaine dependence was found to be quetiapine, which appeared to have a particularly positive effect on substance-induced anxiety disorder (Sattar et al., 2004). Another atypical antipsychotic drug, risperidone, was tested under the hypothesis that it could reduce cue-elicited cocaine craving among cocaine-dependent individuals. However, the results did not support this hypothesis and, although a reduction in craving over time was observed, there were no significant differences among users treated with risperidone compared with those taking a placebo (Smelson et al., 2004).

Newer atypical antipsychotic substances such as ziprasidone and ondansetron are only at a preclinical experimentation stage but appear to be promising pharmacological agents in treating cocaine dependence (Davidson et al., 2004; Cleveland et al., 2005). For example, ondansetron (0.2 mg/kg) injected 3.5 h after cocaine self-administration in rats reduced cocaine intake the

following day while having no effect on water intake (Davidson et al., 2004). Promising therapeutic potential is also attributed to the D1 antagonist adrogolide. Preclinical trials revealed that adrogolide attenuated the ability of cocaine to induce cocaine-seeking behaviour and did not itself induce cocaine-seeking behaviour in a rodent model of cocaine craving and relapse. Furthermore, clinical trials have shown that intravenous injections of adrogolide in cocaine-dependent users reduced cocaine craving and other cocaine-induced subjective effects (Giardina and Williams, 2001). Finally, preclinical trials with a selective D3 antagonist revealed an inhibition of cocaine-seeking and cocaine-enhanced brain reward in rats (Vorel et al., 2002). In another study, however, the D3 antagonist nafadotride appeared to increase cocaine self-administration in rats (Caine et al., 1997). The unclear role of D3 dopamine receptors is potentiated by the finding that D3 agonists have been shown to reduce cocaine self-administration in rats (Caine et al., 1997; Le Foll et al., 2000). Future research is required to elucidate the role of D3 in drug abuse to clearly determine the therapeutic potential of D3 blockading agents in cocaine dependence.

3.1.2 Dopamine agonists

Cocaine acutely enhances dopamine transmission and chronically decreases dopamine concentrations in the brain. Therefore, during the initial period of abstinence after cocaine use, subjects may experience symptoms such as depression, fatigue, irritability, anorexia and sleep disturbances. One treatment strategy to counteract these effects has been to administer dopamine agonists, such as amantadine, bromocriptine and pergolide. In a randomised placebo-controlled trial, subjects receiving amantadine used significantly less cocaine during the trial than those taking a placebo (Kampman et al., 2000). In a screening trial, amantadine-treated cocaine-dependent patients were retained significantly longer than placebo and were more likely to be cocaine abstinent (Shoptaw et al., 2002). However, a large number of studies have reported negative results. Thus, in a pilot trial with cocaine-dependent subjects, amantadine did not modify the choice to self-administer cocaine (Collins et al., 2003), while a clinical trial testing methadone tapering plus amantadine to detoxify heroin-dependent cocaine users showed no efficacy with respect to retention in treatment or reduction in use or cocaine craving (Perez de los Cobos et al., 2001). Furthermore, mazindol, a dopamine and noradrenaline reuptake inhibitor used for the treatment of obesity, was also tested in cocaine-dependent subjects. The results showed either no difference compared with placebo (Stine et al., 1995) or a statistically non-significant treatment effect (Margolin et al., 1995). The efficacy of bromocriptine in the treatment of cocaine dependence was tested in an open-label study (Montoya et al., 2002) and in a double-blind placebo-controlled study (Handelsman et al., 1997). These and previous studies did not find any evidence to support the clinical use of bromocriptine in the treatment of cocaine dependence. The dopamine agonist pergolide was studied in a preliminary placebo-controlled trial, but was not associated with any significant reduction in cocaine use compared with placebo (Levin et al., 1999). In a double-blind, multiple-dose comparison, pergolide also did not show any positive effect in the treatment of cocaine dependence (Malcolm et al., 2001). In another placebo-controlled study, pergolide was ineffective in reducing craving or cocaine use (Focchi et al., 2005). Finally, a Cochrane review analysed 17 studies on the use of dopamine agonists, including a total of 1 224 patients, and came to the conclusion that current evidence does not support the clinical use of dopamine agonists in the treatment of cocaine dependence (Soares et al., 2003).

3.1.3 MAO inhibitors

Therapeutic approaches that involve dopaminergic transmission-facilitating agents for the treatment of cocaine dependence include a great variety of drugs with distinct molecular mechanisms, such as DA precursors and releasers or monoamine oxidase (MAO) inhibitors, and selective serotonin reuptake inhibitors (SSRIs). The results of a variety of clinical investigations show that these agents are mildly effective in reducing craving and, to some extent, in reducing the signs and symptoms of cocaine dependence (for a review see Crosby et al., 1991; Gorelick, 1995; McCance, 1997; Bartzokis et al., 1999; Kampman et al., 2000). For example, the MAO-B inhibitor selegiline was tested as a transdermal patch in cocaine-dependent subjects and it was found that selegiline reduces the physiological and subjective effects of cocaine (Houtsmuller et al., 2004). However, in preclinical trials, MAO-A inhibitors did not reduce cocaine self-administration in rats (e.g. Pepper et al., 2001).

3.1.4 Antidepressants

Various antidepressants have also been tested with respect to their effect on cocaine use in cocaine-dependent subjects. Since the 1980s, desipramine has been investigated for its effects on the noradrenergic system, initially with promising results (Gawin et al., 1989), which have not been corroborated in subsequent clinical trials (Arndt et al., 1992; Kosten et al., 1992). Nonetheless, some more recent studies have indicated a possible therapeutic role of desipramine in cocaine dependence. Thus, a double-blind, placebo-controlled study showed that desipramine-treated subjects were retained in treatment significantly longer than those receiving placebo (Campbell et al., 2003), while another placebo-controlled double-blind study showed desipramine and contingency management (CM) to have independent and additive effects in reducing cocaine use in buprenorphine-maintained patients (Kosten et al., 2003). SSRIs have also been tried in cocaine-dependent users, but without conclusive results (Covi et al., 1995; Petrakis et al., 1998). A Cochrane review on the efficacy of antidepressants for cocaine dependence concluded that there was no current evidence supporting the clinical use of antidepressants in the treatment of cocaine dependence (Lima et al., 2003). Thus, of the 18 studies included, desipramine performed better than placebo, but results reached only non-significant trends. Imipramine performed better than placebo in only one single trial, while only one single trial showed that fluoxetine patients were less likely to drop out. A more recent review also found no evidence to justify the use of antidepressants in patients with substance use disorders without comorbid depression (Torrens et al., 2005). Recent trials with modern antidepressants have also shown that paroxetine, pentoxifylline, riluzole, pramipexole and venlafaxine (Ciraulo et al., 2005a; Streeter et al., 2005), fluoxetine (Harris et al., 2004) and nefazodone (Passos et al., 2005) have no effect on cocaine use, while only one trial found that venlafaxine resulted in a small but significant reduction in cocaine use (Foltin et al., 2003). The only substance which has shown promising results in the reduction of cocaine use is reboxetine (Szerman et al., 2005), which, however, requires further corroborative studies.

3.1.5 Stimulants

With a perspective similar to that of methadone maintenance treatment in the case of opiate addiction, diverse psychostimulating substances have been proposed as substitution therapies. The use of methylphenidate or phenmetrazine as a substitution agent has, however, led to unsatisfactory results. Although both substances, at the outset, appeared to decrease craving, they did not reduce cocaine use (Grabowski, 1994), and in the long term they appeared to increase both cocaine consumption and craving (Gawin et al., 1985; Tennant et al., 1993). These undesired effects are believed to be caused by the marked drug abuse liability of these medications (Litten and Allen, 1997). However, methylphenidate appears to be effective in decreasing cocaine use amongst patients with co-occurring attention deficit disorder (Khantzian et al., 1984; Biederman et al., 1999; Castaneda et al., 2000), suggesting a self-medicating use of cocaine.

Dexamphetamine (dextroamphetamine), a stereoisomer of amphetamine with greater stimulant properties than amphetamine, has also been investigated as a potential therapeutic agent in cocaine dependence. An initial randomised placebo-controlled study showed dexamphetamine to be effective in reducing cocaine use (Grabowski et al., 2001), while a small randomised study comparing dexamphetamine with placebo showed equal retention rates in both groups, but better outcome (fewer cocaine-positive urine samples) in the group receiving dexamphetamine. However, the group differences did not reach statistical significance (Shearer et al., 2003). A descriptive study of the case notes of cocaine-dependent patients consulting a psychiatrist found that dexamphetamine treatment helped to reduce cocaine use and to retain patients in treatment (Moselhy and El-Sheikh, 2004). Reports on the dexamphetamine treatment of cocaine dependence are, however, still inconclusive and need to be replicated in larger controlled trials.

Finally, the use of stimulants with minor addictive potential, such as pemoline and diethylpropion, has had relatively little success. Thus, in a clinical trial, diethylpropion treatment was associated with a significant number of side-effects, without any obvious therapeutic efficacy, so that it was not considered a candidate for future medication development (Alim et al., 1995). An open-label trial with pemoline also found no therapeutic benefit in the treatment of cocaine abuse in methadone-maintained patients (Margolin et al., 1996).

In summary, clinical trials and therapeutic approaches using only dopaminergic transmission-facilitating agents for the treatment of cocaine dependence have been demonstrated to be only mildly effective in reducing cocaine use and associated symptoms, such as craving (for further information

consult reviews by Crosby et al., 1991; Gorelick, 1995; McCance, 1997; Bartzokis et al., 1999; Kampman et al., 2000; Grabowski et al., 2004a).

3.1.6 Opiate antagonists

It is thought that the endogenous opioid system is also involved in the cocaine reinforcement process. Furthermore, the administration of naloxone has been found to reduce the reinforcing effects of cocaine in self-stimulating behaviour in rats (Bain and Kornetsky, 1987). Naltrexone has also been shown to reduce the reinforcing effects of low doses of cocaine (De Vry et al., 1989). However, the results are inconclusive, and it is therefore doubtful whether it is useful to pursue this line of research (McCance, 1997). Nonetheless, preliminary studies have shown that naltrexone may be effective in reducing both cocaine and alcohol use in subjects using both substances (Oslin et al., 1999), while another study has shown that naltrexone in combination with coping skills training can reduce cocaine use in dependent patients (Schmitz et al., 2001).

3.1.7 GABAergic agonists and glutamatergic antagonists

It has also been suggested that GABAergic agonists, and especially glutamatergic antagonists, could be useful agents in the treatment of cocaine addiction. A recent laboratory study evaluating how maintenance on baclofen influenced smoked cocaine's reinforcing and subjective effects, as well as mood and cocaine craving prior to and after the initiation of cocaine use, showed baclofen to decrease self-administration of low doses of cocaine in non-opioid-dependent patients seeking treatment for cocaine dependence, whereas no effect was observed in opioid-dependent cocaine users (Haney et al., 2006). Gabapentin treatment for cocaine dependence has recently been tested in a randomised placebo-controlled study in 129 cocaine-dependent individuals (Bisaga et al., 2006). The gabapentin group received 3 200 mg per day over 12 weeks and the outcome showed trends favouring only the gabapentin group, although on most measures there were no differences between the gabapentin-treated and placebo groups. Previously, two pilot studies with a lower dose of gabapentin also failed to show an effect that could be clinically useful (Hart et al., 2004; Haney et al., 2005). Despite the lack of evidence of an effect of gabapentin, the authors concluded that further studies were required in order to fully evaluate the potential of gabapentin as a relapse preventative agent for cocaine treatment.

Antiepileptic drugs, such as valproate and carbamazepine, have also failed to deliver promising results in the management of cocaine dependence. Small initial studies found that carbamazepine had no effect (Cornish et al., 1995; Kranzler et al., 1995; Montoya et al., 1995), while a more recent study showed that carbamazepine was effective only in cocaine-using individuals with a comorbid affective disorder (Brady et al., 2002). Similarly, a Cochrane review concluded that there was no existing evidence supporting the clinical use of carbamazepine in the treatment of cocaine dependence, and larger randomised studies, which would be needed, should take into account the fact that such time-consuming efforts should be reserved for medications for which more relevant and promising evidence is available (Lima et al., 2002). Nonetheless, a more recent study did show that depression and irritability were reduced in antidepressant-treated compared with placebo-treated crack cocaine-dependent patients, but no group difference in sustained abstinence or negative urine samples was observed (Campbell et al., 2003). With respect to valproate, an open pilot project with divalproex (a combination of sodium valproate and valproic acid) showed a retention rate of 79 % at week 4 and 50 % at week 8 (Myrick et al., 2001), while a recent randomised controlled trial (RCT) found no support for the effectiveness of valproate in the treatment of cocaine dependence (Reid et al., 2005a).

Topiramate is another antiepileptic drug being considered for the treatment of cocaine dependence (Johnson, 2005; Cubells, 2006). A pilot double-blind placebo-controlled trial found that subjects in the topiramate group were more likely to be abstinent from cocaine than those in the placebo group (Kampman et al., 2004).

Other GABAergic agents that have been tested for their effect in reducing cocaine use in cocaine-dependent subjects are tiagabine and vigabatrin. In a randomised pilot study, tiagabine was found to moderately improve cocaine-free urine samples in cocaine-dependent methadone-treated patients (Gonzalez et al., 2003). In a comparative study, tiagabine, in contrast to sertraline and donepezil, was found to be associated with lower cocaine use in cocaine-dependent subjects (Winhusen et al., 2005), while an experimental study showed that tiagabine treatment attenuated some of the

subjective effects of cocaine (Sofuoglu et al., 2005). Two small preclinical studies have found vigabatrin (gamma-vinyl GABA (GVG)) to be a promising substance for the treatment of cocaine dependence by inhibiting cocaine-induced increases in dopamine levels (Schiffer et al., 2003).

Modafinil is also a substance being tested for its effect in reducing cocaine use in cocaine-dependent subjects and is involved in the glutamate reward circuit. A wakefulness-promoting drug approved for the treatment of narcolepsy, modafinil is a substance that increases brain glutamate, and its stimulant-like action is thought to reduce cocaine withdrawal symptoms, such as hypersomnia, anergia, depressed mood, hyperphagia, psychomotor retardation and poor concentration (Dackis and O'Brien, 2003). In a pilot study, modafinil treatment blunted cocaine euphoria without intensifying cocaine craving (Dackis et al., 2003). A recent double-blind, placebo-controlled trial provided preliminary evidence that modafinil improves clinical outcome when combined with psychosocial treatment (Dackis et al., 2005).

3.1.8 Disulfiram

Disulfiram, commonly known as Antabuse and used in the treatment of alcoholism, has also been tested for an effect in cocaine dependence. Thus, it has been observed that the quantity and frequency of cocaine use were reduced in disulfiram-treated subjects to a significantly greater extent than in those treated with placebo (George et al., 2000; Petrakis et al., 2000). As disulfiram deters concomitant alcohol consumption, it is thought that the drug also affects the desire to use cocaine (McCance, 1997; for a review see Rawson et al., 2002). These beneficial effects of disulfiram on cocaine and alcohol use have been shown to be sustained during a 12-week follow-up (Petrakis et al., 2000). Furthermore, a large randomised, placebo-controlled study confirmed the effectiveness of disulfiram treatment in reducing cocaine use, and appeared to exert a direct effect on cocaine use rather than through reducing concurrent alcohol use (Carroll et al., 2004). However, men treated with disulfiram tended to have better outcomes than men not treated with disulfiram, whereas women had an intermediate outcome regardless of whether or not they had received disulfiram (Nich et al., 2004). The authors suggested that disulfiram treatment be combined with psychosocial interventions, e.g. cognitive–behavioural therapy (CBT), in order to enhance treatment adherence and effectiveness (Gossop and Carroll, 2006).

3.1.9 Other pharmacological agents

A medication screening trial evaluated reserpine, gabapentin and lamotrigine, and found that the best results, in terms of reduction in cocaine use, were achieved in the reserpine group, suggesting that this drug merits further investigation (Berger et al., 2005). Another antihypertensive medication, the calcium channel blocker isradipine, was tested with respect to its treatment potential, but, although preclinical studies suggested that isradipine may antagonise the abuse liability of cocaine, the drug did not affect cocaine-induced euphoric mood in cocaine-using volunteers (Roache et al., 2005). Kappa opioid agonists are still in the phase of being tested in animal studies, but have been shown to induce a decrease in cocaine self-administration in rhesus monkeys (Mello and Negus, 2000; Preston et al., 2004; Stevenson et al., 2004). However, L-tryptophan, a serotonergic precursor, showed no effect on cocaine use in a controlled clinical trial in cocaine-dependent subjects (Jones et al., 2004). Another substance being studied for its effect on cocaine use is the steroid hormone progesterone, with initial trials showing that acute progesterone treatment may attenuate some of the subjective effects of cocaine as well as cocaine-induced diastolic blood pressure increases. These findings suggest that progesterone might have potential therapeutic benefits in cocaine dependence (Sofuoglu et al., 2002, 2004).

The list of drugs tested for the treatment of cocaine dependence would be longer if it were to include further substances tested without any positive results, such as the non-steroidal anti-inflammatory drug (NSAID) celecoxib, which showed no evidence of effectiveness (Reid et al., 2005b).

3.1.10 Clinical practice

Considering the lack of real substantial efficacy of any of the above-mentioned drugs, prescribing practices have developed that are not necessarily evidence based but reflect clinical experience. Seivewright et al. (2000) reviewed a substantial range of pharmacological treatments employed by treatment services in the United Kingdom. The two most frequently used antidepressants were

fluoxetine and desipramine, used by 21 and 10 services respectively, for which there is some supporting evidence (Levin and Lehman, 1991; Batki et al., 1993; Covi et al., 1995; Warner et al., 1997), but also negative reports (e.g. Grabowski et al., 1995). Amitriptyline, a tricyclic antidepressant, was prescribed by four services to approximately 21 clients, although a report by Keaney et al. (2002) reported complications with the use of tricyclic antidepressants when detoxifying polydrug patients. Despite the controversy associated with prescribing benzodiazepines to illicit drug users, many services appear to prescribe them for their sedative effects in withdrawal states (Darke et al., 1994), while a minority of services prescribe antipsychotics to address cocaine-induced psychosis.

3.2 Other pharmacological measures

Cocaine or amphetamine maintenance programmes as prophylaxis of illegal substance consumption have been tried in psychostimulant addiction programmes (Bagasra et al., 1992), with the goal of reducing withdrawal symptomatology and relapse prevention (Siegel et al., 1986; Llosa, 1991, 1994), but with little success (Fleming and Roberts, 1994). In the United Kingdom, cocaine was prescribed for cocaine dependence to a limited extent until 1968, with physicians prescribing injectable cocaine to approximately 1 000 clients. However, with the introduction of regional drug clinics in 1968, this practice was immediately stopped (Strang and Edwards, 1989). A few trials have been carried out with cocaine substitution (prescribing cocaine for the dependent subject), but there have been no RCTs yet (Haasen, 2003; Stohler, 2004).

3.3 Immunisation and vaccination

Immunisation and vaccination are two strategies with a long tradition and very little empirical proof of effectiveness (Kantak, 2003). In (passive) immunisation, catalytic antibodies are injected that bind cocaine and subsequently hydrolyse cocaine into the inactive products ecognine methyl ester and benzoic acid.

A cocaine vaccine has also been proposed; this would attempt to block the effects of cocaine using cocaine antibodies (Bagasra et al., 1992; Garcia Sevilla, 1997; Navarro and Rodriguez De Fonseca, 2000). This unique approach to the pharmacotherapy of cocaine addiction was initiated by immunisation experiments that demonstrated specific cocaine antibody production in animals (Carrera et al., 1995, 2000; Fox, Kantak et al., 1996; Fox, 1997). Cocaine-specific antibodies can sequester cocaine molecules in the bloodstream, thereby allowing naturally occurring enzymes (cholinesterases) to convert cocaine into inactive metabolites, which are then excreted. As the antibodies cannot cross the blood–brain barrier, the vaccine is not expected to have any direct psychoactive effect. As the antibodies prevent cocaine from having an effect, the reinforcing effect of continued cocaine use will be dampened. Furthermore, the vaccine persists for months, so there is no need for daily administration of medication.

A randomised, double-blind, placebo-controlled clinical trial involving 34 former cocaine users was carried out to assess the safety and immunogenicity of the therapeutic cocaine vaccine TA-CD (Kosten et al., 2002). The results of this trial showed that the vaccine induced cocaine antibodies in a time- and dose-dependent manner and that it was well tolerated with no serious adverse events during 12 months of follow-up. This trial was then followed up by an open-label, 14-week, dose escalation study evaluating the safety, immunogenicity and clinical efficacy of the cocaine vaccine (Martell et al., 2005). Ten cocaine-dependent subjects received a total dose of 400 µg of vaccine in four injections over the course of 8 weeks and eight cocaine-dependent subjects received a total dose of 2 000 µg of vaccine in five injections over the course of 12 weeks. The results showed a high completion rate, no serious adverse events, good tolerance and a significantly higher likelihood of cocaine-free urine in the high-dose group at 6 months. The results are most encouraging when compared with other pharmacological strategies, but will have to be replicated in further studies.

Despite the promising results, some ethical questions have arisen with respect to the vaccine (Ashcroft and Franey, 2004; Katsnelson, 2004): Can an addict truly consent to treatment? Should governments compel high-risk individuals to be vaccinated, in order, for example, to reduce criminality associated with cocaine dependence? If so, who would decide who is at risk? These questions have been discussed in several advisory panels both in the USA as well as in the United Kingdom, where the British biotech company Xenova, which holds the licence for the vaccine, is located. Furthermore, one of the major drawbacks of the vaccine is that a crucial factor in its effectiveness is the subject's continued motivation to take booster vaccinations (Kantak, 2003), and this necessary motivation is by itself one of the most effective elements of any cocaine treatment.

Separate from efforts to develop a strategy of treating cocaine dependence by immunisation or vaccination, efforts are also being made to develop immunotherapy for cocaine overdose. By using protein-based technology, anti-cocaine monoclonal antibodies have been developed that bind cocaine in the bloodstream, thereby inactivating its toxic effects (Carrera et al., 2005). The antibody GC92H2 has been tested in mice and was found to significantly block cocaine toxicity and therefore prevent death even after cocaine injection. Further studies are likely to determine whether this treatment will be possible and effective in humans.

3.4 Optimising opioid treatment in the presence of additional cocaine use

As many dependent cocaine users are also heroin or other opiates users, they are often receiving methadone maintenance treatment (MMT) or some other agonist maintenance treatment for the treatment of heroin misuse. In the USA, for example, approximately 50 % of all methadone treatment applicants also use cocaine (Katz et al., 2002). In Europe, numbers vary greatly and are generally correlated with the overall number of cocaine users in each country. Usually, MMT is accompanied by some psychosocial intervention or drug counselling, but this occasionally focuses only on cocaine use. As cocaine use is widespread among patients in MMT and often interferes with this therapy, many experts and projects in this field have demanded the development of specific strategies to deal with cocaine and crack co-abuse. To date, cognitive behavioural based approaches combined with contingency management (CM) seem to have the most beneficial results for cocaine-abusing clients in MMT (e.g. Silverman et al., 1998; Rowan-Szal et al., 2005), although CM is rarely practised in Europe (see also section 4.2).

Following enactment of a law in California requiring all MMT patients to undergo drug counselling, the cocaine-using population within the MMT programme showed significant reductions in cocaine use after counselling compared with before the implementation of the new law (Kletter, 2003). The study also found similar reductions in heroin use. Crack users receiving MMT who do not reduce their cocaine use exhibit poorer compliance and poorer psychological health and increased acquisitive crime rates (Mitcheson et al., 2007), and also experience negative sequelae (Bovasso and Cacciola, 2003). An Australian study also found that the outcome of opioid substitution therapy was poorer if cocaine use was continued, but was significantly improved when cocaine use decreased (Williamson et al., 2006a). This emphasises the importance of concentrating on cocaine co-use during MMT.

Agonist maintenance treatment is considered the first-line treatment for opioid dependence (van den Brink and van Ree, 2003). If additional cocaine use hampers the outcome of maintenance treatment, a first measure would be to optimise this treatment. Thus, an important factor determining treatment outcome is the dose of opioid agonist administered. A Cochrane review has found that the dose administered to MMT patients should ideally be in the order of 60–100 mg/day; when the agonist dose is too low, the risk of concurrent use of other drugs, such as cocaine, increases (Faggiano et al., 2003). A second step would be to consider switching the agonist agent – several reviews have shown similar efficacy for methadone and buprenorphine (van den Brink and van Ree, 2003), whereas the efficacy of other agonists, such as codeine and slow-release oral morphine (SROM), remains to be proved in the future. However, a recent study has shown that methadone may be superior to buprenorphine for maintenance treatment patients with co-occurring cocaine and opioid dependence, being associated with longer periods of sustained abstinence and a greater proportion of drug-free tests (Schottenfeld et al., 2005).

One important line of treatment of opioid dependence that is of particular interest in the case of those opioid-dependent subjects who are also using cocaine is the medical prescription of heroin to chronic, treatment-refractory heroin-dependent patients, an intervention that has been and will be tested in a variety of countries in Europe and North America (Fischer et al., 2002). Opioid-dependent patients who also use cocaine suffer from a more severe substance use disorder than non-cocaine-using opioid-dependent patients (Disney et al., 2005). Two reports about the Swiss experience concluded that supervised medical prescription of heroin is associated with good retention (70 % over 12 months) and results in reduced opiates and cocaine use in heroin-assisted clients (Rehm et al., 2001; Güttinger and Rehm, 2005). However, as first reported in Farrell and Hall (1998), limitations in the original methodological design of the Swiss study raises questions on causality and thereby on interpretation of any consequently observed positive results as observed in the two mentioned studies above.

In a recent report on two randomised controlled trials that were conducted in the Netherlands, combined treatment with methadone plus injectable or inhalable heroin was compared with treatment

with methadone alone while keeping the psychosocial treatment offer constant. The results of these trials were similar to those of the Swiss trials, but for the first time the observed improvements could be attributed to the medical prescription of heroin (van den Brink et al., 2003). Moreover, from a societal perspective, the co-prescription of heroin in this specific population was found to be cost-effective compared with treatment with methadone alone (Dijkgraaf et al., 2005). Recently, similar results were reported from a small controlled trial from Spain and from a large RCT from Germany (manuscripts under review). In a recent Cochrane review, the authors stated that, based on the currently available results (not including the Spanish and the German data), no definitive conclusions about the overall effectiveness of heroin prescription was possible because of the non-comparability of the experimental studies (Ferri et al., 2005). However, reports of the German and Spanish data confirm the initial Swiss and Dutch results, showing a significant advantage of heroin/diamorphine over methadone treatment. Therefore, cocaine-using chronic opioid-dependent patients may be one of the target groups for heroin-assisted treatment.

A number of studies have found that a longer period in treatment also resulted in reduced cocaine use among patients in MMT (Dobler-Mikola et al., 2005; Williamson et al., 2006b), although some did continue their cocaine use. In a Swiss study, 63 % of MMT patients used cocaine at treatment entry, and 37 % did so after 2 years (Dobler-Mikola et al., 2005). Magura et al. (2002) found no difference in reduction in cocaine use in MMT patients receiving either enhanced, intensive CBT or standard treatment. This lack of effect of treatment intensity has also been found in other clinical trials, but findings from the USA on this topic are inconsistent (Magura et al., 2002). Similar findings were obtained by Rawson et al. (2002), who compared two psychosocial approaches for the treatment of cocaine dependence: contingency management (CM) and CBT. Patients were randomly assigned to CM, to CBT, to combined CM and CBT or to treatment as usual (MMT only). The study findings provided solid evidence of the efficacy of CM and CBT, without evidence of an additive effect for the two treatments in the CM plus CBT group. Furthermore, a couple of studies have examined the combination of psychosocial interventions with other pharmacological agents in methadone-maintained patients. Thus, one randomised double-blind study using desipramine with and without CM in cocaine-dependent methadone-maintained patients found that the combination of desipramine and CM had independent and additive effects in reducing cocaine use (Kosten et al., 2003). In another controlled study using bupropion with and without CM in cocaine-dependent methadone-maintained patients, the combination of bupropion and CM significantly improved outcome (Poling et al., 2006).

Other pharmacological agents have shown different results. In a trial comparing sustained-release d-amphetamine with risperidone as an adjunct to MMT, risperidone showed no effect while sustained-release d-amphetamine was found to be promising in the treatment of cocaine-dependent methadone-maintained patients (Grabowski et al., 2004b). In a trial studying methadone tapering plus amantadine to detoxify heroin-dependent cocaine users, amantadine did not show any efficacy with respect to retention in treatment or reduction in use or craving (Perez de los Cobos et al., 2001). A cost-effectiveness study on the adjunctive use of disulfiram in MMT found it to slightly increase the cost of MMT, but with an increase in effectiveness sufficient to warrant its use in cocaine-dependent methadone-maintained patients (Jofre-Bonet et al., 2004).

In the United Kingdom, one-third of methadone patients are using crack at the time of entering treatment, a problem that may become worse even while treatment successfully reduces heroin use (NTA, 2002b). A United Kingdom study found a clear reduction in opiate use after motivational interviewing (MI) and pointed out the need to take into account additional non-prescribed drug use in general rather than specific crack use during MMT. It also demonstrated that it is feasible to integrate MI sessions into routine MMT practice (Mitcheson et al., 2007).

3.5 Treatment of cocaine use in subjects with other psychiatric disorders

The treatment of cocaine use in subjects with a comorbid psychiatric disorder has also been studied, particularly in four categories of patients: those with attention deficit hyperactivity disorder (ADHD); those with a depressive disorder; those with a bipolar disorder; and those with a schizophrenic or schizoaffective disorder. The main treatment strategy, similar to the treatment of cocaine-using opioid-dependent patients, is to optimise the treatment of the comorbid psychiatric disorder. Pharmacological strategies therefore involve those drugs generally used in the treatment of the psychiatric disorder, sometimes in combination with one of the drugs described in section 3.1.

The comorbidity of ADHD and cocaine dependence has not yet been sufficiently examined, but several studies point to the fact that the risk of developing cocaine dependence is higher in patients with a medical history of ADHD during childhood (Clure et al., 1999; Ros Soler et al., 2004; Rounsaville et al., 1991). Carroll et al. (1993) pointed out that a previous ADHD diagnosis is associated with earlier initiation of cocaine use and more frequent and severe cocaine use. The frequency of a previous ADHD diagnosis among cocaine-dependent subjects has been reported to be between 17 % and 40 % (Carroll et al., 1993; Castaneda et al., 1999). In the past ADHD was frequently not treated pharmacologically, with the result that many cocaine-dependent patients with a previous ADHD diagnosis profit from treatment with methylphenidate. Methylphenidate has been shown in several studies not only to lead to remission of ADHD symptoms, but also to attenuate cocaine use (Castaneda et al., 1999, 2000; Somoza et al., 2004), so that cocaine use has been understood to possibly be a self-medication of ADHD symptoms (Khantzian, 1985). However, there are also studies showing that methylphenidate is not effective in reducing ADHD symptoms or cocaine use (e.g. Levin et al., 2006) or reduces only ADHD symptoms but not cocaine use (Schubiner et al., 2002). Furthermore, there is concern about the abuse potential of methylphenidate, with some people expressing strong reservations about prescribing methylphenidate to ADHD patients who abuse psychoactive substances. Nonetheless, the evidence does not suggest that methylphenidate treatment in cocaine-abusing ADHD patients leads to increased abuse of either cocaine or methylphenidate (Collins et al., 2006).

Recently, a new drug has been introduced for the treatment of ADHD – atomoxetine – which has similar efficacy to methylphenidate (Kratochvil et al., 2002). However, unlike methylphenidate, atomoxetine has been shown to have no craving-inducing properties in light drug users (Heil et al., 2002), so that it could be considered the first-line treatment for ADHD in patients with additional substance use disorders (Wilens et al., 2003). Clinical experience has shown promising results in the treatment of ADHD and cocaine dependence (Haasen et al., 2005). However, there are as yet no controlled trials comparing the efficacy of atomoxetine and methylphenidate in cocaine-abusing ADHD patients.

As is the case with all other classes of substance use disorders, cocaine dependence has been shown to be strongly associated with depression. However, there are great diagnostic difficulties in assessing a depressive disorder in cocaine-dependent subjects, as it is difficult to distinguish between the depressive symptoms caused in the initial phase of abstinence after cocaine use and an enduring depressive syndrome associated with an independent depressive disorder. Nonetheless, both depressive syndromes – that is, the ‘substance-induced’ and the independent syndrome – may require treatment with an antidepressant. A meta-analytical review of antidepressant efficacy for combined cocaine dependence and depression evaluated 11 RCTs: negative studies used SSRI treatment, while positive studies used agents such as desipramine or buproprion (Rounsaville, 2004). A more recent placebo-controlled study found desipramine to be effective in improving mood, which in turn was associated with reduced cocaine abuse without a clear direct effect of medication on cocaine outcome (McDowell et al., 2005). Another recent placebo-controlled study found that nefazodone treatment reduces cocaine craving, suggesting that this more modern antidepressant, which is also associated with fewer side-effects than desipramine, could be a promising drug for the treatment of cocaine-abusing depressive patients (Ciraulo et al., 2005b).

Several studies have demonstrated an increased rate of comorbid substance use disorders in patients with bipolar disorder, with rates lying between 44 % and 61 % (Brown et al., 2001; Cassidy et al., 2001). Two substances have been explicitly tested for the treatment of cocaine-dependent subjects with a comorbid bipolar disorder – quetiapine and lamotrigine. The use of quetiapine was associated with substantial improvement in psychiatric symptoms and cocaine cravings, although cocaine use was not significantly decreased (Brown et al., 2002). Similarly, lamotrigine was associated with a statistically significant improvement in mood and drug cravings but not drug use (Brown et al., 2003a). Both substances warrant further research in larger samples.

Treatment of cocaine dependence in patients with a comorbid schizophrenic or schizoaffective disorder has been examined in several studies. One of the main questions of interest was whether atypical antipsychotics have an advantage over typical antipsychotics in cocaine-abusing schizophrenic patients. An open-label pilot study compared risperidone with typical antipsychotics in a sample of cocaine-dependent schizophrenic patients, and found risperidone to be associated with lower cue-elicited craving and fewer substance abuse relapses (Smelson et al., 2002). A recent trial evaluating cocaine and amphetamine use in patients either continued or discontinued on a typical antipsychotic (and in part switched to an atypical antipsychotic) found a significant benefit in the

discontinuation group with respect to drug use (Brown et al., 2003b). The patients in the discontinued group who needed antipsychotic treatment were switched to quetiapine. Another case report, in which quetiapine was combined with gabapentin in the treatment of a cocaine-abusing patient with a schizoaffective disorder, showed a dramatic improvement with respect to psychiatric symptoms as well as reduction of cocaine cravings (Wayne and Madigan, 2004). A more recent trial comparing olanzapine with haloperidol found no significant difference in drug screens or psychiatric symptoms, while craving for cocaine was significantly lower in the haloperidol group than in the olanzapine group (Sayers et al., 2005). A third atypical antipsychotic, aripiprazole, was tested in a pilot study in cocaine-dependent schizophrenic patients, and showed possible effects in lowering both desire for and the use of cocaine (Beresford et al., 2005). In a review on the pharmacological treatment of patients with schizophrenia and substance use disorders, typical antipsychotics are described to be less effective than atypical antipsychotics (Tsuang et al., 2005), thereby contradicting the findings of Sayers et al. (2005). In summary, therefore, more rigorously controlled clinical trials are needed to determine the efficacy of atypical antipsychotics in the treatment of cocaine-dependent schizophrenic patients.

4 Psychosocial treatment

Owing to the limited therapeutic benefits of pharmacological treatment for cocaine dependence, more emphasis has been put on psychosocial interventions to intervene in the addictive behaviour of cocaine-dependent persons. The roots of psychological treatments are embedded in behavioural and cognitive theories, including social learning theory (for an overview see Curran and Drummond, 2005). On the one hand, behavioural theories define substance misuse as a set of learned or conditioned behaviours, which can be modified with specific therapies such as cue exposure treatment. On the other hand, cognitive theories are characterised by the existence of thoughts and beliefs (cognitions) that shape our behaviours and emotions, so that cognitive-related treatment consists in changing dysfunctional beliefs and maladaptive thoughts. Other models focus more on motivation and work with the client's ambivalence about changing behaviour. Many treatments, however, combine elements of behavioural, cognitive and motivational approaches.

The only RCT in the field of addiction in which the effects of psychosocial interventions have been systematically investigated can be found in relation to cocaine dependence. Thus, a multicentre investigation examined the efficacy of four different psychosocial interventions for cocaine-dependent patients (Crits-Christoph et al., 1999). The four types of interventions investigated in the study were cognitive psychotherapy, psychodynamic psychotherapy, individual counselling and group counselling, with the primary outcome being assessed on the basis of the Addiction Severity Index–Drug Use Composite score and the number of days of cocaine use in the past month. The results showed that all psychosocial interventions had significantly reduced cocaine dependence, with both psychotherapies showing greater effectiveness for retention rates, while both counselling methods appeared to be more effective in terms of abstinence rates.

Furthermore, evidence shows that even brief interventions have a positive influence on drug-using behaviour (Prinzleve et al., 2003; Mitcheson et al., 2007), although the best results are achieved by longer-term treatment (Thomasius et al., 2004). Unfortunately, as mentioned in Witton and Ashton (2002), comparative studies of psychotherapeutic approaches are lacking, while existing efficacy studies have mainly consisted in assessing the outcomes of single psychosocial approaches. Finally, an overview of the effectiveness of most psychosocial therapies in relation to specific substances has recently been published (Wanigaratne et al., 2005). The following sections in the present review describe various types of psychosocial treatments that are currently employed to treat substance dependence, including cocaine dependence.

4.1 Cognitive–behavioural therapy (CBT) and other behavioural approaches

CBT is based upon social learning principles. It focuses on the identification of cognitive and environmental factors controlling problem behaviour. The aim of this approach is that people learn alternative behaviours instead of behaviours related to cocaine use and learn to practise self-control strategies. CBT is a widely adopted approach to the treatment of cocaine dependence, particularly in the USA, and an extensive manual on CBT for cocaine treatment has been published, which offers guidelines for practitioners working with cocaine users (Carroll, 1998). Although CBT is usually associated with low retention rates, its main benefit appears to be moderation of consumption, and there are some suggestions that CBT works especially well with cocaine users presenting elevated intellectual capacity and users with comorbid depression or heavier addiction (Rigter et al., 2004). Furthermore, among the heaviest users, CBT seems to produce better results than psychotherapy and clinical care (NTA, 2002b). The extent to which participants complete homework assignments also appears to influence treatment outcome. Thus, during CBT and in the follow-up phase 1 year later, cocaine-dependent participants with a strong rate of completed homework showed significantly lower cocaine use (Carroll et al., 2005).

These results suggest that willingness to complete extra session assignments is an important mediator of treatment response. However, cognitive-impaired users appear not to benefit fully from CBT as their dropout rate appears to be much higher than that of non-impaired users. Several studies have shown that retention and abstinence rates are much lower within the former group, with treatment 'completers' performing better on cognitive tests than dropouts (Aharonovich et al., 2003, 2006). These results suggest that the cognitive abilities of the patient should be taken into consideration when choosing treatment settings, especially as empirical studies have shown that chronic cocaine use can have detrimental effects on cognitive functioning (e.g. Strickland et al.,

1998). Finally, another study has shown that cocaine-dependent users presenting comorbid alcohol problems during behavioural treatment have lower cocaine abstinence rates than users who abstained from alcohol use at treatment entry (Mengis et al., 2002).

In Europe, CBT or similar behavioural approaches are widely offered within general treatment facilities, but special units or facilities for cocaine users are limited. In Denmark, however, in an attempt to integrate and develop the experiences from other countries within a Danish treatment environment, the Copenhagen Municipality has allocated budget resources to a high-quality development programme, in which a relevant cocaine-related treatment concept will be tried out and which will include cognitive treatment with some degree of behavioural therapy elements (Danish national report, 2006).

Furthermore, in November 2005 in Ireland, a number of pilot projects were conducted to examine methods of managing cocaine users. One of the goals of the projects was to train professional counsellors working with cocaine users to deliver more intensive, psychotherapeutic basis CBT-type interventions, with the aim of enabling practitioners to deliver appropriate interventions to cocaine/stimulant users. The syllabus provided at these training sessions introduced students to cognitive and behavioural learning theories of addiction and the research supporting this treatment approach. Specific skills were practised to enable practitioners to deliver competent, effective CBT interventions, brief interventions and motivational Interviewing. These included behavioural analysis of drug and alcohol use, coping skills, goal setting, planning and monitoring. This intensive training was completed over four intensive 2-day sessions. A total of 104 people, a mix of health service and community-based professionals and volunteers, participated and evaluated the training as highly helpful as it increased their skills and knowledge about working with cocaine users. The treatment intervention aspect of the project was piloted in four areas of Dublin. Each intervention focused on a different aspect of cocaine use (intravenous cocaine users, problematic intranasal cocaine users, female problematic cocaine users or polydrug cocaine users). The treatment intervention consisted of individual drug counselling, brief interventions, motivational interviewing and CBT. The evaluation of these interventions is currently being evaluated (NACD, 2007).

In Portugal, pilot projects are under way to test two different treatment approaches to cocaine dependency, one strictly pharmacological and the other (mainly as a complement and frequently accompanied by the use of medication) through psychosociological support (Portuguese national report, 2006). Furthermore, in Germany, CBT or CBT-orientated treatment is offered for cocaine users in a small number of services, with specialised outpatient services being located in cities with a high prevalence of cocaine and crack abuse. Thus, Kokon ([4]), an independent drug service in Berlin, offers clients a first assessment phase of 4–6 months, and focuses on the clients' preferred drug of consumption (cocaine or opiates). Thereafter, the treatment is continued as an integral programme for all kinds of drug users. Kokon is working with a cognitive–behavioural approach on the basis of an interactive personality model (Kokon, 1999; Tossmann et al., 2000; Stöver, 2001). The Seehaus-Projekt, a special cocaine consulting and therapy service in Hamburg, follows a similar approach. The therapeutic programme, lasting up to 18 months, comprises an initial phase, during which the individual's situation and treatment goals are clarified, followed by 8 months of CBT-type treatment. The remainder of the programme consists of a non-substance-specific phase of further consolidation (N. Essberger and A. Hansen, unpublished).

A specialised outpatient service at the Hamburg University Department of Psychiatry comprises two parts and also has a sequential structure: an initial so-called 'cocaine counselling hour' for diagnostic and treatment planning and, if indicated, brief cognitive–behavioural training in coping skills. This two-step approach was chosen to evaluate and detect conditions that frequently lead to treatment cessation, in particular psychiatric comorbidity and abuse of multiple substances. If psychotherapy is indicated, a brief cognitive–behavioural intervention is offered. This approach seems to be most appropriate for the main target group of the service, which are users with average consumption and for whom reduced or more controlled use is an acceptable aim. The first results are promising, but based only on a very small sample size (Prinzleve et al., 2003). A similar approach is followed by a treatment agency in the Swiss city of Winterthur (Schuetz, 2006).

([4]) www.kokon.de.

In recent years, some inpatient institutions, particularly those located near cities with a relatively high prevalence of cocaine use, have started to offer inpatient treatment for cocaine-related problems. Most of these treatments have adapted CBT approaches for the individual treatment of cocaine and crack users. However, inpatient units targeting exclusively users of cocaine as the primary drug seem to be scarce, and studies concerning the effects of cocaine-specific treatment in residential treatment settings are lacking.

Another form of behavioural intervention is the community reinforcement approach (CRA), which is a multifaceted behavioural treatment incorporating a range of interventions, including family counselling, stress management, social skills training and job counselling (Peele and DeGrandpre, 1998). Reinforcers are used to reduce cocaine use and should, theoretically, be available in the community and incompatible with cocaine use. CRA is often but not always combined with CM (e.g. Higgins et al., 2003). Relatively positive results for this kind of treatment have been reported from the USA, in terms of both retention and abstinence rates. Higgins et al. (2003) found an increased retention rate for the combined therapy compared with voucher-only therapy ([5]). Roozen et al. (2004) reviewed 11 studies on the effectiveness of CRA and found that the combination with CM was more effective than CRA alone. A comparison of CRA with and without incentives found strong evidence that treatment with incentives is more effective with regard to abstinence in cocaine users. In the Netherlands, an experiment with CRA for cocaine users (with or without heroin addiction and in or out of methadone maintenance treatment) is in its last phase. It tests the applicability and effectiveness of the CRA combined with voucher incentives in the Dutch situation (Dutch national report, 2006).

4.2 Rewards/punishment-based therapies

CM treatment – also known as voucher-based therapy – is also based on behavioural principles. It makes use of 'reinforcers', usually vouchers for goods or services. Typically the value of the reinforcers increased during treatment on the basis of negative urinalysis. Cocaine abstinence is usually tested via urine a few times a week and rewards are given for negative tests. A number of studies have reported good results for CM. For example, Petry et al. (2005) found that retention rate and abstinence duration were increased in patients treated with CM plus reinforcers compared with patients undergoing CM alone. However, it also has to be noted that the effects of CM tend to dissipate after its discontinuation (e.g. Rawson et al., 2002; Roozen et al., 2004). When compared with CBT, the results of CM tend to be better during the treatment period, whereas CBT shows better outcomes during follow-up (e.g. Rawson et al., 2006). Furthermore, some studies have found that voucher reinforcement provides no additional benefit in the outpatient treatment setting (Katz et al., 2002). Some authors have suggested that reinforcers ought to be suitably aspirational to be attractive to the user and, predictably, settings offering vouchers of higher value have been found to result in greater levels of abstinence (Petry et al., 2004). Of course, this does, however, mean that the costs of this kind of treatment are relatively high. Finally, it has been found that treatment results are best when rewards (and, by association, punishment) are handed out immediately after urine test results (NTA, 2002b).

Studies have also been conducted on the effectiveness of incentive-based brief interventions. In one study Katz et al. (2002) found that the majority of MMT patients refrained from cocaine use for 2 days when offered a voucher for abstinence. What might be more important for treatment strategies is that these patients subsequently exhibit higher rates of immediate cocaine abstinence. Although the study found relatively high rates of relapse despite the continued availability of substantial monetary reinforcers, the authors considered the initial abstinence to be a positive start.

Furthermore, research on CM as short-term intervention for cocaine users in MMT found significant improvement among those receiving CM compared with a control group who received only verbal encouragement to abstain (Sigmon et al., 2004). It made no difference whether the reward was given for a negative urinalysis on a quantitative or qualitative basis, although the sample size in all three groups was too small to draw any conclusions. In the quantitative method, a negative urinalysis is defined as a 50 % or greater reduction in urine benzoylecgonine concentration over 2 days (Preston et al., 1997). In contrast, in the qualitative urinalysis testing approach, the urine benzoylecgonine

([5]) Voucher programmes provide motivational points for patients whose urine specimens test negative for cocaine: high-scoring patients receive vouchers that can be redeemed for rewards (such as clothing, rent payments, YMCA passes).

concentration must be below 300 ng/ml for the sample to be considered negative, so that participants may need to abstain from cocaine use for 2–5 days to produce a negative urine specimen. Thus, quantitative testing is considered to be more sensitive and allows the differentiation between 'new' cocaine use and carry-over from previous uses. As a direct consequence, this increased sensitivity reduces the delay between initiation of cocaine abstinence and reinforcement provision, which results in a more accurate implementation of the reinforcement contingencies (i.e. fewer instances of non-reinforced abstinence) and possibly in increased treatment efficacy (Preston et al., 2001).

In line with Preston et al. (2001), Katz et al. (2002) found that quantitative procedures produced better outcomes, which confirms that these are more accurate and relevant to brief periods of abstinence. Another variation of CM has been reported in which gradual cocaine abstinence is rewarded by handing out vouchers for decreased cocaine use (as determined by urine analysis) during the first weeks of treatment, as opposed to demanding total abstinence. This stepwise approach to CM resulted in better outcomes than standard CM (Preston et al., 2001). Finally, one modified form of this approach consists in using prizes as reinforcers, with clients being rewarded with opportunities to enter a draw to win different prizes of varying financial value. This has also been tested, with similar results to standard CM (Petry et al. 2005). As the prize system is more cost-effective, it is considered likely to become the method of choice (Petry and Martin 2002). Looking at the comparison between non-contingent and contingent vouchers, no causal relationship was found between non-contingent voucher receipt and increased drug use (Schroeder et al., 2003).

Furthermore, CM programmes have shown specific value in the treatment of cocaine users with antisocial personality disorder (Messina et al. 2003). However, because of the short-lived effects of CM, combinations with other forms of treatment are often applied. The combination of CM with CRA is quite common, and an increased retention rate is one of the most reliable effects of combined CRA and voucher intervention (Higgins et al., 2003). When combined with behavioural day treatment, positive treatment outcome is twice as likely as with day treatment alone (Schumacher et al., 2003).

Comparisons of CM and CBT have found solid evidence of efficacy for both types of treatment. Although CM appears to result in significantly better outcome during treatment, CBT shows better outcome in the long term, although both approaches combined showed no additive effect (Rawson et al., 2002, 2006). Another study even found that CBT had brief detrimental effects on the outcome of CM when both were combined (Epstein et al., 2003). A further treatment combination was investigated in homeless cocaine users (Milby et al., 2003, 2004, 2005). Thus, during behavioural day treatment, housing could be offered as a reward for abstinence. The group that was offered housing exhibited a better outcome, with more abstinent users, increased duration of abstinence and fewer patients relapsing compared with the group that received day treatment only (Milby et al., 2004). Another approach was used by a study that provided access to a 'therapeutic workplace' when urinalysis was found to be negative (Silverman et al. 2002). This approach was found to be particularly appealing to poor and long-term unemployed patients.

Reinforcers are used to reward not only negative urinalyses but can also the performance of tasks related to individual treatment, e.g. attending medical appointments or treatment sessions or achieving legal and money management tasks. This approach has been shown to result in better retention in MMT and a higher abstinence rate (Villano et al., 2002).

In summary, the CM method has shown substantial efficacy in the treatment of cocaine dependence, but it remains to be seen whether CM can be adapted and implemented in a community-based setting (Petry and Simcic, 2002). Furthermore, this largely US approach has been very little implemented in Europe, and no data on voucher reinforcement from European countries are yet available.

4.3 Motivational interviewing

Motivational interviewing (MI) is an interventional approach with cognitive–behavioural basis used as a short-term intervention. It aims to support clients during the change process. It is a client-centred directive method for enhancing motivation to change problem behaviour, in this case problematic cocaine use, by exploring and resolving ambivalence. The concept of MI, established by Miller and Rollnick (1991), centres on the intrinsic ambivalence of the problematic user. The main purpose of MI is the examination and resolution of ambivalence, and the counsellor is intentionally directive in pursuing this goal. The guiding principle is to actively support the client's decision to bring about the change. The four main principles of MI are:

- express empathy;
- develop discrepancy;
- roll with resistance;
- support self-efficacy.

Furthermore, MI is characterised by a number of distinct working methods such as asking questions, summing up the important arguments of the client and reflective listening (Körkel and Veltrup, 2003). Research has shown that motivational enhancement is more beneficial for clients with lower initial motivation to change than for those with higher motivation (Rohsenow et al., 2004). MI in the form of brief intervention (one session of MI) has also been shown to have positive outcomes with regard to abstinence (Bernstein et al., 2005).

MI appears to be used in a number of European countries and in different treatment settings. In Germany, MI as part of an individual case management approach (Schmid and Vogt 2001), as well as integrated in other types of individual intensive treatment, is found to be effective for different types of cocaine users (Stöver, 2001). In the United Kingdom, Thom (2001) highlighted the common pairing of alcohol and cocaine and the potential of MI to indirectly address cocaine use through alcohol problems. Several Spanish literature reviews have found that optimal treatment involves a combination of psychotherapy – using relapse prevention techniques and MI – and pharmacological treatment with anxiolytics (Garcia et al. 2001; San Molina and Arranz Diez, 2001; Sole Puig, 2001).

4.4 Relapse prevention

As mentioned earlier, psychosocial interventions, which are based on social learning theories, are used to provide users with the coping skills and protective techniques they need to cope with relapse triggers. These can include lifestyle and cognitive strategies. Among cognitive–behavioural strategies, a United Kingdom review identified the following as vital for a minimum satisfactory result (Wanigaratne et al., 2005):

- identifying high-risk situations and triggers for craving;
- developing strategies to limit exposure to high-risk situations;
- developing skills to manage cravings and other painful emotions without using substances;
- learning to cope with lapses;
- learning how to recognise, challenge and manage unhelpful or dysfunctional thoughts about substance use;
- developing an emergency plan for coping with high-risk situations when other skills are not working;
- generating pleasurable sober activities and relationships, building a life worth living and attaining a lifestyle balance.

In addition, the following approaches have been found to increase success rates of abstinence: thinking about positive and negative consequences; alternative behaviours; relaxation; meditation; seeking social support; offer refusal; spiritual methods; problem-solving; working towards goals, clean recreation; not carrying much money; keeping busy; thinking about consequences (Rohsenow et al., 2005). The same authors also suggested concentrating on enhancing the cognitive and lifestyle skills that have proven efficient for the user. Interestingly, another study by the same authors found that the use of coping skill training in group therapy was more beneficial to women than to men in terms of reducing cocaine and alcohol use (Rohsenow et al., 2004). The authors suggested that group settings allow less attention on individual specific issues, which appear to be crucial for developing cognitive coping skills, and that women may be more likely to open up in a group setting than men, who often reported fearing to disclose illegal activities in a group.

In Spain the most frequently used psychotherapeutic treatment approach is the relapse prevention model proposed by Marlatt and Gordon, which consists in cognitive restructuring, and the learning of confrontation and problem resolution skills (Marlatt and Gordon, 1985). Prochaska y Di Clemente's change process model is also frequently used, which involves matching treatment strategies with the patient's stage of readiness for change (Pedrero Pérez and Puerta Garcia, 2001). Finally, according

to Wanigaratne and colleagues, relapse prevention is among the most common approaches used in the treatment of cocaine users in the United Kingdom (Wanigaratne et al. 2005).

4.5 Family therapy

The term family therapy is used to describe a variety of family interventions, all sharing the common characteristic of involving the user's family or closer social network in treatment. Family therapy works towards altering family structures using a non-blaming, non-judgemental approach with a strong emphasis on behaviourism (Wanigaratne et al., 2005). The integration of the family into the treatment process can be of considerable importance, particularly in the case of adolescent cocaine users (Thomasius et al., 2004). No recent research on family therapy has been conducted, but two earlier randomised clinical trials found that treatment involving family therapy was associated with a better outcome than standard treatment (McLellan et al., 1993; Fals-Stewart et al., 1996).

4.6 Counselling

Wanigaratne et al. (2005) defined counselling as a humanistic, client-centred, non-directive approach to the problems presented by the individual. Structured drug counselling can have positive results for most cocaine users and can be offered as individual or group counselling, each with different base guidelines. Counselling typically comprises a well-structured psychosocial procedure, and is usually based on a procedural manual that includes, for example, an individual care plan. Weiss et al. (2003) used a 'cocaine craving questionnaire' to predict cocaine use in the week following psychosocial treatment. They reported that the relationship between craving and subsequent cocaine use varied by treatment condition. Thus, the authors compared CBT plus group counselling, psychodynamic therapy plus group counselling and group counselling alone, and found a combination of individual and group drug counselling to be the most successful treatment method. However, although such combination treatments seemed to be the most successful in reducing cocaine craving, it remained unclear exactly which aspects of individual and group counselling were the most beneficial. Finally, Kletter (2003) also found that cocaine use in users was reduced during court-enforced counselling.

4.7 Other approaches

The Minnesota method (12-step), which originated in the USA, is an approach based on the self-help philosophy of Narcotics Anonymous and Alcoholics Anonymous. According to Wanigaratne et al. (2005), the 12-step approach regards 'addiction as a relapsing illness with complete abstinence as the only treatment goal. As part of the process towards recovery, individuals must acknowledge to themselves (and other people) the harm that substance use has caused to themselves and others and where possible make amends'. There is, however, hardly any evidence-based research on the effectiveness of this approach. However, Weiss et al. (2005) found active 12-step group participation by cocaine-dependent patients to be more efficient than meeting attendance alone, which was reflected by a decrease in cocaine use among the active participants. The authors also found an increase in effectiveness for treatments that combine individual drug counselling and active 12-step participation. Furthermore, Crits-Christoph et al. (1999) found that clients receiving 12-step individual counselling in addition to group drug counselling were more likely to achieve and maintain abstinence than those receiving other studied interventions (cognitive therapy plus group drug counselling or group drug counselling alone). The same authors also found engagement in the 12-step activities to be a partial statistical mediator of drug use outcomes (Crits-Christoph et al., 2003). The Minnesota method has also achieved a long tradition in European countries, and research carried out in Italy found good results of this method when combined with a psychodynamic intervention (Conte et al., 2006). McKay et al. (2004) examined a telephone-based continuing care programme for cocaine and alcohol dependence. With respect to abstinence-related outcomes, the study found no differences between those groups that received either relapse prevention or 12-step group counselling and the control groups.

A recent innovative strategy examined the effect of providing mobile phones to homeless crack cocaine-addicted users (Freedman et al., 2006). Users were asked to record current states of cocaine craving and use episodes, and also received computer-automated telephone interviews. Participants indicated that the survey made them more aware of phenomena leading to cravings and use, and it was suggested that such mobile phone reporting approaches could be considered a potentially useful intervention.

Other types of interventions that have been tested with cocaine users include special group interventions, such as 'anger management' groups (Reilly and Shopshire, 2000), and, according to several German studies, an extended version of the individual case management approach has shown promising effects (Schmid and Vogt, 2001; Wendt, 2001). 'Cue exposure' therapy, based on learning theory principles, has also been proposed for the treatment of cocaine dependence. This particular approach typically involves repeated exposure to stimuli previously associated with drug use and aims at 'deconditioning' the user's responses (Hamilton et al., 1998; Modesto-Lowe and Kranzler, 1999). Nonetheless, the cue exposure approach has, to date, shown little efficacy, and some authors have even suggested abandoning this approach or combining it with some other intervention such as coping response training (Conklin and Tiffany, 2002).

Acupuncture therapy is also believed to decrease craving for cocaine and is gaining in popularity across Europe (Haasen et al., 2003b). Studies evaluating the efficacy of acupuncture have, however, shown conflicting results. One study found that cocaine-dependent, methadone-maintained patients were significantly more likely to provide cocaine-negative urine samples than were control groups (e.g. those receiving random needle insertion or only relaxation therapy) (Avants et al., 2000), whereas others did not find any effectiveness. Recent reviews have confirmed that the existing evidence fails to document the benefit of acupuncture in treating cocaine addiction as the sole treatment (Kim et al., 2005; Gates et al., 2006). However, one study showed possible benefits of acupuncture when used as an adjunctive treatment (Kim et al., 2005) . A recent Cochrane review came to the conclusion that the evidence of a benefit of acupuncture is inconclusive and lacks quality but nonetheless warrants further randomised trials (Gates et al., 2006). Finally, even if results are not conclusive, it has been suggested that acupuncture may still be a useful tool to retain users in treatment (NTA, 2002b).

Finally, a total of 123 experts, including members of the CocinEU team ([6]) as well as well-known clinicians in Europe, were surveyed to report activities that could be relevant for this review. The results of the survey showed that the majority of European clinicians is currently treating cocaine-dependent patients with pharmacological or established psychosocial treatment options. Only two innovative treatment strategies were identified that were not based on published research on the treatment of cocaine dependence. One is a psychosocial intervention, the other a pharmacological option, both originating from the psychiatric hospital Vall d'Hebron in Barcelona, Spain (director: Professor Miguel Casas). The psychosocial intervention consisted in the addition of psychoeducation to standard pharmacological treatment. The pharmacological option involved an RCT of the use of a methylxanthine (caffeine) in the treatment of cocaine dependence.

Psychoeducation as a tool in the treatment of mental health disorders has been more widely used in the last 10 years, particularly for the treatment of schizophrenia. The positive outcome in the treatment of schizophrenia has led to a spread to treatment of other mental health disorders, including substance use disorders. However, little research has been published in this area. The use of psychoeducation in the treatment of cocaine dependence is in some ways similar to the use of other interventions offering advice and information (see section 5). It differs, however, in having a more structured approach in the group setting and in its aim of empowering individuals to cope with their cocaine problem.

The use of caffeine for cocaine dependence can be considered as a treatment option similar to other options using stimulants as substitution agents (see section 3.1). The effect of caffeine to some extent imitates the effect of cocaine, so that the desire to use cocaine is diminished. To avoid the usual rapid development of tolerance, the anticholinergic agent biperidene is added. A randomised double-blind trial is under way (M. Casas, personal communication), comparing placebo with caffeine only and with a combination of caffeine and biperidene. The RCT has been accepted by the responsible ethics committee on the basis of findings in animal studies and considering the relatively low efficacy of pharmacological treatment of cocaine dependence so far. The results are expected during 2007.

([6]) http://www.zis-hamburg.de/forschung_kokain_eu.de.html#centers.

5 Harm reduction

It is recommended that general advice and information for drug users should be made available to anyone who seeks it on an 'open access' basis, i.e. in places such as public libraries, hospitals, government information offices, via telephone helplines and/or on the Internet. Information should include advice on the drug and its potential effects, and on harm reduction and treatment possibilities, and should also discuss the drug in terms of its potential consequences on other aspects of the user's life such as housing, health, education and employment. With regard to assessment upon treatment entry, it is important for cocaine users that the first contact is made without delay and the client is helped to maintain further treatment sessions (NTA, 2002b). This kind of help is often part of general treatment or intervention practice, and is usually not focused purely on cocaine users, often forming part of a general harm reduction programme. For example, in Spain the general programme of intervention includes advice for medical professionals on how to treat cocaine users (Ramon and Torrecilla, 1999). Telephone helplines, as well as helplines on the internet, are other possible methods of providing information. They are provided in most countries, and offer the benefit of being confidential and accessible at any time.

There are different harm reduction measures aimed at reducing the relative risks associated with drug misuse and in turn promoting better health and social life conditions for cocaine users. Cocaine use has been associated with high levels of injecting and sexual risk behaviour (Weiss, 1989). Low-threshold (low barrier-to-entry) measures such as quiet rooms, measures to control use (Prinzleve et al., 2002) and measures to ensure quality of the substance (Decorte, 2001) may be implemented, as well as syringe exchanges for injecting users and counselling on health problems of any kind but in particular blood-borne diseases (BBDs). It has been suggested that harm reduction strategies be tailored to the needs of cocaine users, which may differ from other drug users' experiences. It has been suggested that harm reduction should be available before, during and after structured treatment (NHS, 2005).

Research has highlighted the difficulties that mainstream services experience in engaging with chaotic and erratic users, characteristics associated with sporadic binge patterns of cocaine use, and the need to offer flexible and immediate walk-in services rather than scheduled appointments, which clients fail to make use of (Haasen et al., 2003b). To counteract the stimulant qualities of cocaine, drug services have been advised to offer a calming, tranquil environment, with rooms in which to relax, and which serve as a forum for making contact (Stöver, 2002). In order to build overlap with the hours during which use typically takes place, opening hours might need to be more flexible (evenings and weekends) than has traditionally been the case.

One of the most in-depth sources of evidence comes from Seivewright et al. (2000), who conducted a postal survey of all known drug misuse treatment services in the UK. Fifty per cent of services responded (n = 318), 53 % of which reported cocaine users presenting for treatment in the previous 6 months. In general, the survey revealed that the services adopted a broad-based approach, not specific to cocaine problems, with a very practical approach to addressing general living problems and harm reduction techniques, which staff rated as more effective than short-term measures.

Most harm reduction measures do not focus specifically on cocaine users but instead target all users of illicit drugs, based on an understanding that many drug-related problems – criminal contacts, imprisonment and criminal records, marginalisation, financial and housing problems, stigmatisation, etc. – are linked to the illegal status of substances and only to a lesser degree to the properties of the substances themselves.

There is some evidence that harm reduction measures may decrease mental health problems as these are connected with the intensity of use (Haasen et al., 2005). Special treatment for crack cocaine users is offered in some of the cities where crack cocaine prevalence is highest, such as London, Frankfurt, Vienna and Barcelona (EMCDDA, 2005).

In the German addiction services system, particularly in Frankfurt and Hamburg, the effectiveness of programmes for the emerging group of crack users has been intensively discussed. The city of Frankfurt, in particular, has responded to increased prevalence by intensifying its efforts to access this target group. In 1995, the Crack-Street-Projekt was initiated, an inter-institutional project involving different drug help services located in the city centre. The main institutions working together in this project are the local 'AIDS-Hilfe', running a consulting and care centre with an integrated consumption room, a local healthcare institution and a street work project, Walkman, which focuses on homeless

crack users in the main station area (Crack-Street-Projekt, 1998; Roth, 1999). In Hamburg the streetwork project Laufwerk already existed before the increase in problems with crack users in the area around Hamburg's main station (Grosche and Voges, 2000). While this project officially focuses mainly on transient and homeless drug users, it also reaches crack cocaine users..

Other harm reduction projects have also had to modify their work as a result of the increasing number of cocaine and crack users. Discussion has centred on the problems of low-threshold and walk-in services when confronted with large numbers of (sometimes aggressive) crack users. Accordingly, some experts have demanded more specific harm reduction offers for cocaine and crack users and more intensive networking among existing facilities. Because of the stimulant qualities of crack, it has been proposed that services should offer a calming, stress-free environment (Stöver, 2002). Various other measures have been suggested, ranging from the development of more specific information and harm reduction materials to the extension of supervised consumption rooms (Stöver, 2001; Dworsky, 2002; Haasen et al., 2004, 2005). In addition to existing harm reduction leaflets targeted at crack users, suggestions have been made on peer involvement in practical work and prevention campaigns as well as on the development of self-control strategies for cocaine and crack users (Stöver, 2001).

Another helpful measure seems to be the establishment of so-called chill-out rooms or daytime rest rooms (*Tagesruheräume*) for cocaine and crack users. In Frankfurt, there are special rest rooms with 10 day-sleeping beds and 23 emergency beds for people primarily using crack (Vogt et al., 2000; Stöver, 2001). Recently, rest rooms for crack users were introduced in Hamburg as well, which are integrated within a low-threshold drug help centre. This centre includes counselling, medical and psychiatric help, a consumption room and a shelter.

Finally, experts offer little consensus on the usefulness of consumption rooms for crack and/or freebase users, or of 'smoke sites' (*Rauchplätze*) within existing consumption rooms for opiate users. Some believe that special consumption rooms for crack and/or freebase users are not useful or practical because of the often highly kinetic or agitated state of crack users (Stöver, 2001). On the other hand, there are consumption rooms with special sites for cocaine and crack users, thus succeeding in gaining access to this poorly reached group without major problems being reported (Poschadel et al., 2002;,Verthein et al., 2001; Zurhold et al., 2001; Vogt and Zeissler, 2005).

6 Inpatient treatment

Inpatient treatment is characterised by staying overnight in a treatment facility, and can roughly be divided into emergency and short-term interventions, for example in general hospital psychiatric units or in drug detoxification units that are not specifically designed for cocaine users but offer general emergency healthcare assistance, and into longer-term treatment such as residential rehabilitation. However, short-term interventions and detoxification treatments do not necessarily lead to longer-term treatment and are generally not suited to cocaine users, as indicated by the following study. Day et al. (2005) surveyed 91 British inpatient detoxification units and found that, during 2003/2004, approximately 6 829 admissions were to specialised units (services treating solely with substance misuse in either stand-alone facilities or wards within psychiatric or general medical facilities) and about 2 077 admissions were to non-specialised units (psychiatric or acute medical wards that are theoretically available for drug users, but in practice are occupied by general or medical psychiatric patients), while only one-fifth of admissions (1 805) were to residential rehabilitation settings. The last facilities are usually characterised by the provision of medically assisted detoxification as a prelude to longer residential treatment. Furthermore, the study showed that the average length of stay ranged from 4 to 77 days, with specialised units reporting longer durations of treatment. However, the same survey found that only 17 of the specialised units and 16 of the non-specialised services required patients to have an aftercare plan in place prior to admission, while only one-third of the admissions were discharged to residential or day care rehabilitation services. Finally, the study showed that services tended to be mainly dedicated to the treatment of opioid misuse and presented a clear lack of provision for poly-substance and stimulant (cocaine/crack and amphetamine) misusers.

In Germany, immediate access to detoxification and treatment without a waiting period also targets crack users. The roots of this initiative, Therapie sofort (Therapy now), can be traced back to a national model project from the early 1990s, set up in response to an increasing number of drug-related deaths.

Generally, during inpatient treatment, a range of diverse measures aimed at improving aspects of the user's life other than substance use-specific problems are offered. Treatment approaches in residential settings are not uniform and can include coping skills training as well as behavioural interventions, while some programmes have a religious or other ideological foundation. As there is a clear relationship between time spent on a programme and the probability of relapse for a number of (inpatient) treatments (Fernandez-Hermida et al., 2002), focus on how to keep people motivated for treatment has been prioritised. Residential rehabilitation seems to be especially successful for users with considerable problems in the emotional or psychiatric area and those with low levels of social support (e.g. homeless or long-term unemployed users) (NTA, 2002b). However, a recent study found that some groups of cocaine users, for example with a stable social background, do better in outpatient than in inpatient treatment (Ford, 2004).

Cost-effectiveness must also be considered when setting up treatment programmes. Group counselling has been shown to be as effective as individual counselling except for the treatment of problematic users and has the benefit of being much cheaper for the community. Furthermore, a study by Simpson et al. (1999) examined the relationship between the length of stay and the severity of psychosocial problems in cocaine-dependent users, and their results confirmed that the patients with the most severe problems were more likely to be found in long-term residential programmes. In addition, they analysed the outcomes reported by those treated for 90 days or longer and found that better outcomes for patients with medium- to high-level problems are associated with longer treatment stays. However, duration of treatment alone has been found not to be an indicator of better outcome of a study on different treatment approaches; however, this research did not specifically focus on cocaine but included other drug use treatment as well (Zhang et al., 2003).

One form of residential rehabilitation is the 'therapeutic community' (TC), which is usually a relatively long-term intervention. Originally orientated towards opiate users, interventions also exist for multiple substance users. Key elements of the TC approach are the orientation towards building long-term relationships between the agency and patients and the employment of former users as therapeutic agents (Thomasius et al., 2004). The concept of TCs originated in the USA and spread to European countries. A study by Fernandez-Hermida et al. (2002) measured outcomes of a TC for drug users (not cocaine specific) in Spain and found low retention rates (less than 50 %), which can be considered as typical for drug-free programmes. However, outcomes among treatment completers –

a self-selected group – were found to be very positive, as dropouts showed significantly higher rates of relapse and, moreover, relapses were more severe and lasted longer.

7 Aftercare

Aftercare consists in supporting clients after they leave structured treatment. It can include drug-related interventions, such as MMT for stabilised opiate users (NHS, 2005), harm reduction and also non-drug-related help with, for example, housing or education. Aftercare programmes can include support groups, individual sessions or self-help groups. It has been suggested that support should be made available both immediately after structured treatment as well as later, depending on the needs of the client.

In the USA, self-help groups are often based on Cocaine Anonymous, a variant of Alcoholics Anonymous. These groups mainly work with the 12-steps programme, based on more or less religious or spiritual ideas, and aim at mutual support. In Europe, Cocaine Anonymous groups exist in the United Kingdom (17 cities), the Netherlands (2), Spain (2), France, Sweden, Germany, Greece, and Belgium (Cocaine Anonymous, 2006). Other forms of self-help groups working with similar principles also exist in most countries.

Some studies have found reduced drug use among those attending self-help groups, while others have not found any difference (Broome et al., 2002). An explanation for different study outcomes has been suggested to lie in the spiritual beliefs or ideology underpinning the setting. Hence, for some participants this aspect might engender stronger social support (Broome et al., 2002).

8 Conclusion

In summary, the treatment of cocaine dependence frequently still includes the use of antidepressants, especially SSRIs, despite the low evidence level for their efficacy. More promising results are expected from topiramate and other antiepileptic drugs, and much hope is being placed in the development of the cocaine vaccine. Because of the lack of effective pharmacological treatment, European clinicians working with cocaine-dependent clients rely mostly on psychosocial interventions to reduce cocaine-related problems. These interventions involve mainly drug counselling such as Motivational Interviewing and case management, as well as CBT, but promising results have been reported from the USA using an incentive-based approach, namely Contigency Management. Furthermore, outpatient treatment, in contrast to residential rehabilitation, appears to be better suited to the treatment of most cases of cocaine dependence. Nonetheless, the efficacy of cocaine treatment is still considered to be much lower than the efficacy of treatment options for opioid dependence.

Concerning the research situation in general, it has to be pointed out that a huge body of evidence comes from international studies, most of them originating in the USA. These international studies have uncovered many issues related to cocaine use, its consequences and the treatment of cocaine problems, and not all of these findings are limited to the USA. Nevertheless, there is an urgent need for research concerning problematic cocaine use in relation to the European treatment context.

Furthermore, as clearly reflected by cocaine use patterns, polydrug use has become the rule with important gaps in our knowledge about treatment and harm reduction responses to multiple drug use being brought to light. Research dealing with this topic is therefore urgently required.

There is also a need for studies investigating the reasons for the differences in the prevalence of crack cocaine use between European countries and within individual European countries. The evidence so far shows that the use of crack cocaine has to be considered on a local level, taking into account the social environment (e.g. poverty, marginalization) and cultural diversity as well as locally predominant consumption patterns.

Both issues, multiple substance use and the differences in crack cocaine use, have an important influence on the choice of treatment, including harm reduction measures for problems in connection with cocaine use. There is evidence that multiple substance use in general has a negative impact on treatment outcomes, and often masks what might be an effective treatment for cocaine problems. Some evidence suggests that there are differences in the treatment outcome between crack cocaine users and cocaine powder users, which in turn might be related to different patterns of multiple substance use. Harm reduction measures developed for problems related to the use of opiates have to be further developed and matched to the specific harm problems of cocaine use.

The social context plays an important role in psychosocial interventions, and approaches used in the USA have only limited transferability to the European context. However, in the case of pharmacological treatments, including the cocaine vaccine, results can be more easily transferred, as the neurobiological basis for these interventions is not as strongly affected by cultural differences. As highlighted by this review, there is an urgent need to carry out large trials on psychosocial interventions among cocaine-dependent populations treated in Europe.

Bibliography

Act-info-FOS (2004), *Der Forschungsverbund stationäre Suchttherapie act-info-FOS im Jahr 2003*. Tätigkeitsbericht und Zusammenfassung, Zurich, ISF.

Aharonovich E, Nunes E and Hasin D. (2003), 'Cognitive impairment, retention and abstinence among cocaine abusers in cognitive-behavioral treatment,' *Drug and Alcohol Dependence* 71, pp. 207–11.

Aharonovich E, Hasin DS, Brooks AC et al. (2006), 'Cognitive deficits predict low treatment retention in cocaine dependent patients,' *Drug and Alcohol Dependence* 81, pp. 313–22.

Alim TN, Rosse RB, Vocci Jr FJ et al. (1995), 'Diethylpropion pharmacotherapeutic adjuvant therapy for inpatient treatment of cocaine dependence: a test of the cocaine-agonist hypothesis,' *Clinical Neuropharmacology* 18, pp. 183–95.

Arndt IO, Dorozynsky L, Woody GE et al. (1992), 'Desipramine treatment of cocaine dependence in methadone-maintained patients,' *Archives of General Psychiatry* 49, pp. 888–93.

Ashcroft RE and Franey C. (2004), 'Further ethical and social issues in using a cocaine vaccine: response to Hall and Carter,' *Journal of Medical Ethics* 30, pp. 341–3.

Avants SK, Margolin A, Holford TR and Kosten TR (2000), 'A randomized controlled trial of auricular acupuncture for cocaine dependence,' *Archives of Internal Medicine* 160, pp. 2305–12.

Bagasra O, Forman LJ, Howeedy A and Whittle P (1992), 'A potential vaccine for cocaine abuse prophylaxis,' *Immunopharmacology* 23, pp. 173–9.

Bain GT and Kornetsky C (1987), 'Naloxone attenuation of the effect of cocaine on rewarding brain stimulation,' *Life Sciences* 40, pp. 1119–25.

Bartzokis G, Beckson M, Newton T et al. (1999), 'Selegiline effects on cocaine-induced changes in medial temporal lobe metabolism and subjective ratings of euphoria,' *Neuropsychopharmacology* 20, pp. 582–90.

Batki SL, Manfredi LB, Jacob 3rd P and Jones RT (1993), 'Fluoxetine for cocaine dependence in methadone maintenance: quantitative plasma and urine cocaine/benzoylecgonine concentrations,' *Journal of Clinical Psychopharmacology* 13, pp. 243–50.

Beresford TP, Clapp L, Martin B et al. (2005), 'Aripiprazole in schizophrenia with cocaine dependence: a pilot study,' *Journal of Clinical Psychopharmacology* 25, pp. 363–6.

Berger P, Gawin F and Kosten TR (1989), 'Treatment of cocaine abuse with mazindol,' *Lancet* 1(8632), p. 283.

Berger SP, Winhusen TM, Somoza EC et al. (2005), 'A medication screening trial evaluation of reserpine, gabapentin and lamotrigine pharmacotherapy of cocaine dependence,' *Addiction* 100 (Suppl. 1). pp. 58–67.

Berglund M (2005), 'A better widget? Three lessons for improving addiction treatment from a meta-analytical study,' *Addiction* 100, pp. 742–50.

Bernstein J, Bernstein E, Tassiopoulos K et al. (2005), 'Brief motivational intervention at a clinic visit reduces cocaine and heroin use,' *Drug and Alcohol Dependence* 77, pp. 49–59.

Biederman J, Mick E, Prince J et al. (1999), 'Systematic chart review of the pharmacologic treatment of comorbid attention deficit hyperactivity disorder in youth with bipolar disorder,' *Journal of Child and Adolescent Psychopharmacology* 9, pp. 247–56.

Bisaga A, Aharonovich E, Garawi F et al. (2006), 'A randomised placebo-controlled trial of gabapentin for cocaine dependence,' *Drug and Alcohol Dependence* 81, pp. 267–74.

Blanken P, Hendricks V, Pozzi G et al. (1994), '*European Addiction Severity Index, EuropASI. A guide to training and administering EuropASI interviews'*, European Cooperation in the Field of Scientific and Technical Research, Brussels.

Bottomley T, Carnwath T, Jeacock J et al. (1997), 'Crack cocaine – tailoring services to user need,' *Addiction Research* 5, pp. 223–34.

Bovasso G and Cacciola J (2003), 'The long-term outcomes of drug use by methadone maintenance patients.' *Journal of Behavioral Health Services and Research* 30, pp. 290–303.

Brady KT, Sonne SC, Malcolm RJ, et al. (2002), 'Carbamazepine in the treatment of cocaine dependence: subtyping by affective disorder,' *Experimental and Clinical Psychopharmacology* 10, pp. 276–85.

van den Brink W and van Ree JM (2003), 'Pharmacological treatments for heroin and cocaine addiction,' *European Neuropsychopharmacology* 13, pp. 476–87.

van den Brink W, Hendriks VM, Blanken P et al. (2003), 'Medical prescription of heroin to treatment resistant heroin addicts: two randomised controlled trials,' *British Medical Journal* 327, pp. 310.

Broome KM, Simpson DD and Joe GW (2002), 'The role of social support following short-term inpatient treatment,' *American Journal of Addiction* 11, pp. 57–65.

Brown E, Nejtek V, Perantie D and Bobadilla B (2001), 'Quetiapine in patients with bipolar disorder and cocaine dependence,' *Proceedings of the Fourth International Conference on Bipolar Disorder*, Pittsburgh, PA.

Brown, ES, Nejtek VA, Perantie DC, Bobadilla L. (2002), 'Quetiapine in bipolar disorder and cocaine dependence,' *Bipolar Disorder* 4, pp. 406–11.

Brown ES, Nejtek VA, Perantie DC et al. (2003a). 'Lamotrigine in patients with bipolar disorder and cocaine dependence,' *Journal of Clinical Psychiatry* 64, pp. 197–201.

Brown ES, Nejtek VA, Perantie DC et al. (2003b). 'Cocaine and amphetamine use in patients with psychiatric illness: a randomised trial of typical antipsychotic continuation or discontinuation,' *Journal of Clinical Psychopharmacology* 23, pp. 384–8.

Caine SB, Koob GF, Parsons LH et al. (1997), 'D3 receptor test in vitro predicts decreased cocaine self-administration in rats,' *Neuroreport* 8, pp. 2373–7.

Campbell J, Nickel EJ, Penick EC et al. (2003), 'Comparison of desipramine or carbamazepine to placebo for crack cocaine-dependent patients,' *American Journal of Addiction* 12, pp.: 122–36.

Carrera MR, Ashley JA, Parsons LH et al. (1995), 'Suppression of psychoactive effects of cocaine by active immunisation,' *Nature* 378, pp. 727–30.

Carrera MR, Ashley JA, Zhou B et al. (2000), 'Cocaine vaccines: antibody protection against relapse in a rat model,' *Proceedings of the National Academy of Sciences of the USA* 97, pp. 6202–6.

Carrera MR, Trigo JM, Wirsching P (2005), 'Evaluation of the anticocaine monoclonal antibody GNC92H2 as an immunotherapy for cocaine overdose,' *Pharmacology Biochemistry and Behavior* 81, pp. 709–14.

Carroll KM (1998), *Therapy Manuals for Drug Addiction. A Cognitive-Behavioral Approach: Treating Cocaine Addiction*, US Department of Health and Human Services, National Institutes of Health, National Institute on Drug Abuse, Bethesda, MD.

Carroll KM and Rounsaville BJ (1993), 'History and significance of childhood attention deficit disorder in treatment-seeking cocaine abusers,' *Comprehensive Psychiatry* 34(2), pp. 75 –82.

Carroll K, Rounsaville B and Bryant K (1993), 'Alcoholism in treatment-seeking cocaine abusers: clinical and prognostic significance,' *Journal of Studies on Alcohol* 54, pp. 199–208.

Carroll KM, Fenton LR, Ball SA et al. (2004), 'Efficacy of disulfiram and cognitive behavior therapy in cocaine-dependent outpatients: a randomised placebo-controlled trial,' *Archives of General Psychiatry* 61, pp. 264–72.

Carroll, KM, Nich C and Ball SA (2005), 'Practice makes progress? Homework assignments and outcome in treatment of cocaine dependence,' *Journal of Consulting and Clinical Psychology* 7, pp. 749–55.

Cassidy F, Ahearn EP and Carroll BJ (2001), 'Substance abuse in bipolar disorder,' *Bipolar Disorder* 3, pp. 181–8.

Castaneda R, Sussman N, Levy R and Trujillo M (1999), 'A treatment algorithm for attention deficit hyperactivity disorder in cocaine-dependent adults: a one-year private practice study with long-acting stimulants, fluoxetine, and bupropion,' *Substance Abuse* 20, pp. 59–71.

Castaneda R, Levy R, Hardy M and Trujillo M (2000), 'Long-acting stimulants for the treatment of attention-deficit disorder in cocaine-dependent adults,' *Psychiatric Services* 51, pp. 169–71.

Chen J (1993), 'Dopaminergic mechanisms and brain reward,' *Seminars in Neurosciences* 5, pp. 315–320.

Ciraulo DA, Sarid-Segal O, Knapp CM et al. (2005a), 'Efficacy screening trials of paroxetine, pentoxifylline, riluzole, pramipexole and venlafaxine in cocaine dependence,' *Addiction* 100 (Suppl. 1), pp. 12–22.

Ciraulo DA, Knapp C, Rotrosen J et al. (2005b), 'Nefazodone treatment of cocaine dependence with comorbid depressive symptoms,' *Addiction* 100 (Suppl. 1). pp. 23–31.

Cleveland NJ, Dewitt CD and Heard K (2005), 'Ziprasidone pretreatment attenuates the lethal effects of cocaine in a mouse model,' *Academic Emergency Medicine* 12, pp. 385–8.

Clure C, Brady KT, Saladin E et al. (1999), 'Attention-deficit/hyperactivity disorder and substance use: symptom pattern and drug choice', American Journal of Drug Alcohol Abuse 25 (3), pp. 441–448.

Cocaine Anonymous (2006), *The twelve steps of Cocaine Anonymous 2006*.

Cohen P (2003), *Harm refusal. Making peace with cocaine, and advancing from harm reduction to harm refusal*. Democracia, derechos Humanos, Guerras y Cultivos de Uso Ilícito, Columbia.

Collins ED, Vosburg SK, Hart CL et al. (2003), 'Amantadine does not modulate reinforcing, subjective, or cardiovascular effects of cocaine in humans,' *Pharmacology Biochemistry and Behavior* 76, pp. 401–7.

Collins SL, Levin FR, Foltin RW et al. (2006), 'Response to cocaine, alone and in combination with methylphenidate, in cocaine abusers with ADHD,' *Drug and Alcohol Dependence* 82, pp. 158–67.

Conklin CA and Tiffany ST (2002), 'Applying extinction research and theory to cue-exposure addiction treatments,' *Addiction* 97, pp. 155–67.

Conte G, Angelicola Nizza L, Di Paolo M et al. (2006), 'Rehabilitative-psychotherapeutic group treatment for cocaine-addicted patients, in combination with other psychiatric therapies: securing a best-compliance to the therapy,' *European Psychiatry* 21(Suppl.), p. 129.

Cornish J, Manny I, Fudala P et al. (1995), 'Carbamazepine treatment for cocaine dependence,' *Drug and Alcohol Dependence* 38, pp. 221–27.

Covi L, Hess JM, Kreiter NA and Haertzen CA (1995), 'Effects of combined fluoxetine and counseling in the outpatient treatment of cocaine abusers,' *American Journal of Drug and Alcohol Abuse* 21, pp. 327–44.

Crack-Street-Projekt (1998), *Erfahrungsbericht über aufsuchende Sozialarbeit in Frankfurt/M.* September 1997–Dezember 1998, Frankfurt.

Crits-Christoph P, Siqueland L, Blaine J et al. (1999), 'Psychosocial treatments for cocaine dependence: National Institute on Drug Abuse Collaborative Cocaine Treatment Study,' *Archives of General Psychiatry* 56, pp. 493–502.

Crits-Christoph P, Gibbons MB, Barber JP et al. (2003), 'Mediators of outcome of psychosocial treatments for cocaine dependence,' *Journal of Consulting and Clinical Psychology* 71, pp. 918–25.

Crosby RD, Halikas JA and Carlson G (1991), 'Pharmacotherapeutic interventions for cocaine abuse: present practices and future directions,' *Journal of Addictive Disease* 10, pp. 13–30.

Cubells JF (2006), 'Topiramate for cocaine dependence,' *Current Psychiatry Reports* 8, pp. 130–1.

Curran V and Drummond C (2005), 'Psychological treatments of substance misuse and dependence,' Foresight Brain Science, Addiction and Drugs Project (www.Foresight.gov.uk).

Dackis C and O'Brien C (2003), 'Glutamatergic agents for cocaine dependence,' *Annals of the New York Academy of Science* 1003, pp. 328–45.

Dackis C, Lynch KG, Yu E et al. (2003), 'Modafinil and cocaine: a double-blind, placebo-controlled drug interaction study,' *Drug and Alcohol Dependence* 70, pp. 29–37.

Dackis CA, Kampman KM, Lynch KG et al. (2005), 'A double-blind, placebo-controlled trial of modafinil for cocaine dependence,' *Neuropsychopharmacology* 30, pp. 205–11.

Darke S, Swift W and Hall W (1994), 'Prevalence, severity and correlates of psychological morbidity among methadone maintenance clients,' *Addiction* 89, pp. 211–7.

Davidson C, Lazarus C, Lee TH and Ellinwood EH (2004), 'Ondansetron, given during the acute cocaine withdrawal, attenuates oral cocaine self-administration,' *European Journal of Pharmacology* 503, pp. 99–102.

Day E, Ison J, Keaney F et al. (2005), *A national survey of inpatient drug services in England,* National Treatment Agency for Substance Misuse Online Report RB15.

De Vry J, Donselaar I and Van Ree JM (1989), 'Food deprivation and acquisition of intravenous cocaine self-administration in rats: effect of naltrexone and haloperidol,' *Journal of Pharmacology and Experimental Therapeutics* 251, pp. 735–40.

Decker KP and Ries RK (1993), 'Differential diagnosis and psychopharmacology of dual disorders,' *Psychiatric Clinics of North America* 16, pp. 703–18.

Decorte T (2001), 'Quality control by cocaine users: underdeveloped Harm reduction strategies,' *European Addiction Research* 7, pp. 161–175.

Di Chiara G (1995), 'The role of dopamine in drug abuse viewed from the perspective of its role in motivation', *Drug and Alcohol Dependence* 38, pp. 95–137.

Dijkgraaf MG, van der Zanden BP, de Borgie CA et al. (2005), 'Cost utility analysis of co-prescribed heroin compared with methadone maintenance treatment in heroin addicts in two randomised trials,' *British Medical Journal* 330, pp. 1297.

Disney ER, Kidorf M, King VL et al. (2005), 'Prevalence and correlates of cocaine physical dependence subtypes using the DSM-IV in outpatients receiving opioid agonist medication,' *Drug and Alcohol Dependence* 79, pp. 23–32.

Dobler-Mikola A, Hattenschwiler J, Meili D et al. (2005), 'Patterns of heroin, cocaine, and alcohol abuse during long-term methadone maintenance treatment,' *Journal of Substance Abuse Treatment* 29, pp. 259–65.

Dworsky N (2001), *Praktischer Umgang der Drogenhilfe mit Crack-Konsumenten/innen. Crack! Stein(e) des Anstoßes. Realität, Konflikte, Angebote*, Dokumentation der Fachtagung, GAL-Bürgerschaftsfraktion, Hamburg.

Dworsky N (2002), 'Zum praktischen Umgang der Drogenhilfe mit Crack-Konsumenten,' *Suchttherapie* 3, pp. 24–25.

EMCDDA (2002), *Classifications of drug treatment and social reintegration and their availability in EU Member States plus Norway*, European Monitoring Centre for Drugs and Drug Addiction, Lisbon.

EMCDDA (2005), *Annual Report 2005*, *the state of the drugs problem in Europe*, European Monitoring Centre for Drugs and Drug Addiction, Lisbon.

EMCDDA (2006), *Annual Report 2006, the state of the drugs problem in Europe*, European Monitoring Centre for Drugs and Drug Addiction, Lisbon.

Epstein DH, Hawkins WE, Covi L et al. (2003), 'Cognitive-behavioral therapy plus contingency management for cocaine use: findings during treatment and across 12-month follow-up,' *Psychology of Addictive Behaviours* 17, pp. 73–82.

Faggiano F, Vigna-Taglianti F, Versino E and Lemma P (2003), 'Methadone maintenance at different dosages for opioid dependence (Cochrane Review),' *Cochrane Database System Review* 3, CD002208.

Fals-Stewart W, Birchler GR and O'Farrell TJ (1996), 'Behavioral couples therapy for male substance-abusing patients: effects on relationship adjustment and drug-using behavior,' *Journal of Consulting and Clinical Psychology* 64, pp. 959–72.

Farrell M and Hall W (1998), 'The Swiss heroin trials: testing alternative approaches,' *British Medical Journal* 316, pp. 639.

Farren CK, Hameedi FA, Rosen MA et al. (2000), 'Significant interaction between clozapine and cocaine in cocaine addicts,' *Drug and Alcohol Dependence* 59, pp. 153–63.

Fernandez-Hermida JR, Secades-Villa R, Fernandez-Ludena JJ and Marina-Gonzalez PA (2002), 'Effectiveness of a therapeutic community treatment in Spain: a long-term follow-up study,' *European Addiction Research* 8, pp. 22–9.

Ferri CP, Gossop M, Rabe-Hesketh S and Laranjeira RR (2002), 'Differences in factors associated with first treatment entry and treatment re-entry among cocaine users,' *Addiction* 97, pp. 825–32.

Ferri M, Davoli M and Perucci CA (2005), 'Heroin maintenance for chronic heroin dependents,' *Cochrane Database System Review* 2, CD003410.

Fischer B, Rehm J, Kirst M et al. (2002), 'Heroin-assisted treatment as a response to the public health problem of opiate dependence,' *European Journal of Public Health* 12, pp. 228–34.

Fleming PM and Roberts D (1994) 'Is prescription of amphetamine justified as a harm reduction measure?,' *Journal of the Royal Society of Health* 114, pp. 127–31.

Focchi GR, Leite MC, Andrade AG and Scivoletto S (2005), 'Use of dopamine agonist pergolide in outpatient treatment of cocaine dependence,' *Substance Use and Misuse* 40, pp. 1169–77.

Foltin RW, Ward AS, Collins ED et al. (2003), 'The effects of venlafaxine on the subjective, reinforcing, and cardiovascular effects of cocaine in opioid-dependent and non-opioid-dependent humans.' *Experimental and Clinical Psychopharmacology* 11, pp. 123–30.

Ford C (2004), *Guidance for working with cocaine and crack users in primary care*, Royal College of General Practitioners, London.

Fox BS (1997), 'Development of a therapeutic vaccine for the treatment of cocaine addiction,' *Drug and Alcohol Dependence* 48, pp. 153–8.

Fox BS, Kantak KM, Edwards MA et al. (1996), 'Efficacy of a therapeutic cocaine vaccine in rodent models,' *Nature Medicine* 2, pp. 1129–32.

Freedman MJ, Lester KM, McNamara C et al. (2006), 'Cell phones for ecological momentary assessment with cocaine-addicted homeless patients in treatment,' *Journal of Substnce Abuse Treatment* 30, pp. 105–11.

Garcia I, González A and Epifanio MM (2001), 'Tratamiento farmacologico de la dependencia a la cocaina. [Pharmacological treatment of cocaine addiction],' *Archivos de Psiquiatria* 64, pp. 333–50.

Garcia Sevilla, JA (1997), 'Vacunas contra la cocaina: ¿La penultima frivolidad?,' *Quark* 6, pp. 28–37.

Gardner EL (1992), 'Brain reward mechanisms,' in: Lowinson JH, Ruiz P, Millman RB, Langrod JG (eds), *Substance abuse: a comprehensive textbook*, Williams and Wilkins, Baltimore.

Gates S, Smith LA and Foxcroft DR (2006), 'Auricular acupuncture for cocaine dependence,' *Cochrane Database System Review* 1, CD005192.

Gawin F, Riordan C and Kleber H (1985), 'Methylphenidate treatment of cocaine abusers without attention deficit disorder: a negative report,' *American Journal of Drug and Alcohol Abuse* 11, pp. 193–7.

Gawin FH, Allen D and Humblestone B (1989), 'Outpatient treatment of "crack" cocaine smoking with flupenthixol decanoate. A preliminary report,' *Archives of General Psychiatry* 46, pp. 322–5.

George TP, Chawarski MC, Pakes J et al. (2000), 'Disulfiram versus placebo for cocaine dependence in buprenorphine-maintained subjects: a preliminary trial,' *Biological Psychiatry* 47, pp. 1080–6.

Giardina WJ and Williams M (2001), 'Adrogolide HCl (ABT-431; DAS-431), a prodrug of the dopamine D1 receptor agonist, A-86929: preclinical pharmacology and clinical data,' *CNS Drug Reviews* 7, pp. 305–16.

Gold MS, Miller NS (1997), 'Cocaine (and crack): neurobiology,' in: Lowinson JH, Ruiz P (eds), *Substance abuse. A comprehensive textbook*, third edition, New York: The American Psychiatric Press.

Goldfrank LR and Hoffman RS (1991), 'The cardiovascular effects of cocaine,' *Annals of Emergency Medicine* 20, pp. 165–75.

Gonzalez G, Sevarino K, Sofuoglu M et al. (2003), 'Tiagabine increases cocaine-free urines in cocaine-dependent methadone-treated patients: results of a randomised pilot study,' *Addiction* 98, pp. 1625–32.

Gorelick DA (1995), 'Pharmacological therapies of cocaine addiction,' in: Miller N, Gold MS (eds), *Pharmacological therapies for drug and alcohol addictions*, New York, Marcel Dekker.

Gorelick DA, Gardner EL and Xi ZX (2004), 'Agents in development for the management of cocaine abuse,' *Drugs* 64, pp. 1547–73.

Gossop, M and Carroll KM (2006), 'Disulfiram, cocaine, and alcohol: two outcomes for the price of one?' *Alcohol and Alcoholism* 41, pp. 119–20.

Gossop M, Marsden J, Stewart D and Kidd T (2002), 'Changes in use of crack cocaine after drug misuse treatment: 4–5 year follow-up results from the National Treatment Outcome Research Study (NTORS),' *Drug and Alcohol Dependence* 66, pp. 21–8.

Grabowski BS (1994), 'Pharmacy-based automated medication records: methods, application, and a survey of use,' *Topics in Hospital Pharmacy Management* 14, pp. 58–72.

Grabowski J, Rhoades H, Elk R et al. (1995), 'Fluoxetine is ineffective for treatment of cocaine dependence or concurrent opiate and cocaine dependence: two placebo-controlled double-blind trials,' *Journal of Clinical Psychopharmacology* 15, pp. 163–74.

Grabowski J, Rhoades H, Silverman P et al. (2000), 'Risperidone for the treatment of cocaine dependence: randomised, double- blind trial,' *Journal of Clinical Psychopharmacology* 20, pp. 305–10.

Grabowski J, Rhoades H, Schmitz J et al. (2001), 'Dextroamphetamine for cocaine-dependence treatment: a double-blind randomised clinical trial,' *Journal of Clinical Psychopharmacology* 21, pp. 522–6.

Grabowski J, Shearer J, Merril J and Negus SS (2004a), 'Agonist-like, replacement pharmacotherapy for stimulant abuse and dependence', *Addictive Behaviours* 29, pp. 1439–64.

Grabowski J, Rhoades H, Stotts A et al. (2004b), 'Agonist-like or antagonist-like treatment for cocaine dependence with methadone for heroin dependence: two double-blind randomised clinical trials,' *Neuropsychopharmacology* 29, pp. 969–81.

Green A, Pickering H, Fosster R et al. (1994), 'Who uses cocaine? Social Profiles of cocaine users,' *Addiction Research* 2, pp. 141–154.

Grosche V and Voges M (2000), 'Projekt Laufwerk. Aufsuchende Sozialarbeit in offenen Drogenszenen Hamburgs,' *Streetcorner* 13, pp. 48–61.

Guggenbuhl L, Uchtenhagen A and Fabian C (2000), *Adequacy in drug abuse treatment and care in Europe (ADAT). Part I: Ethical Aspects in the treatment and care of drug addicts*, Addiction Research Institute, Zurich.

Güttinger F and Rehm J (2005), 'Konsummuster bei verschiedenen Gruppen von Kokaingebrauchern in Zürich: Implikationen für das Drogenhilfesystem,' *Sucht* 51, pp. 225–32.

Haasen C (2003), 'Substitutionsmöglichkeiten der Kokainabhängigkeit,' in: Krausz M, Haasen C, Naber D (eds), *Pharmakotherapie der Sucht*, Karger, Freiburg.

Haasen C and Prinzleve M (2003), 'Support needs for cocaine and crack users in Europe,' http://www.zis-hamburg.de/D2_Research_situation_final.pdf#search=%22cocineu%2.

Haasen C, Prinzleve M, Reimer J and Krausz M (2003a), 'Smoking cocarettes: a less harmful alternative of cocaine use?' *European Addiction Research* 9, pp. 188–9.

Haasen C, Prinzleve M, Zurhold H et al. (2003b). *Support needs for cocaine and crack users in Europe*, Zentrum für Interdisziplinäre Suchtforschung, Hamburg.

Haasen C, Prinzleve M, Zurhold H et al. (2004a), 'Cocaine use in Europe – a multi-centre study. Methodology and prevalence estimates,' *European Addiction Research* 10, pp. 139–46.

Haasen C, Zurhold H and Prinzleve M (2004b), 'Safer Use: Kokain und Crack,' in: Stoever H, Prinzleve M (eds), *Kokain und Crack. Pharmakodynamiken, Verbreitung und Hilfeangebote*, Lambertus, Freiburg im Breisgau.

Haasen C, Zurhold H and Prinzleve M (2005a), 'Safer Use: Kokain und Crack,' in: Heudtlass J-H, Stoever H (eds), *Risiko mindern beim Drogengebrauch. Gesundheitsförderung – Verbrauchertipps – Beratungswissen – Praxishilfen*, Fachhochschulverlag, Frankfurt am Main.

Haasen C, Prinzleve M, Gossop M et al. (2005b), 'Relationship between cocaine use and mental health problems in a sample of European cocaine powder or crack users,' *World Psychiatry* 4, pp. 173–6.

Hall WC, Talbert RL, Ereshefsky L (1990), 'Cocaine abuse and its treatment', *Pharmacotherapy* 10, pp. 47–65.

Hamilton M, Voris J, Sebastian P and Singha A (1998), 'Money as a tool to extinguish conditioned responses to cocaine in addicts,' *Journal of Clinical Psychology* 54, pp. 211–18.

Handelsman L, Rosenblum A, Palij M et al. (1997), 'Bromocriptine for cocaine dependence. A controlled clinical trial,' *American Journal of Addiction* 6, pp. 54–64.

Haney M, Hart C, Collins ED and Foltin RW (2005), 'Smoked cocaine discrimination in humans: effects of gabapentin,' *Drug and Alcohol Dependence* 80, pp. 53–61.

Haney M, Hart CL and Foltin RW (2006), 'Effects of baclofen on cocaine self-administration: opioid- and nonopioid-dependent volunteers,' *Neuropsychopharmacology* 31, pp. 1814-21.

Harris DS, Batki SL and Berger SP(2004), 'Fluoxetine attenuates adrenocortical but not subjective responses to cocaine cues,' *American Journal of Drug and Alcohol Abuse* 30, pp. 765–82.

Hart CL, AS Ward, Collins ED et al. (2004), 'Gabapentin maintenance decreases smoked cocaine-related subjective effects, but not self-administration by humans,' *Drug and Alcohol Dependence* 73, pp. 279–287.

Heil SH, Holmes HW, Bickel WK et al. (2002), 'Comparison of the subjective, physiological, and psychomotor effects of atomoxetine and methylphenidate in light drug users,' *Drug and Alcohol Dependence* 67, pp. 149–56.

Higgins S, Budney A, Bickel W and Badger G (1994), 'Participation of significant others in outpatient behavioural treatment predicts greater cocaine abstinence,' *American Journal of Drug and Alcohol Abuse* 20, pp. 47–56.

Higgins ST, Sigmon SC, Wong CJ et al. (2003), 'Community reinforcement therapy for cocaine-dependent outpatients,' *Archives of General Psychiatry* 60, pp. 1043–52.

Higgins ST, Budney AJ, Bickel WK et al. (1993), 'Achieving cocaine abstinence with a behavioural approach,' *American journal of Psychiatry* 150, pp. 763-69.

Houtsmuller EJ, Notes LD, Newton T et al. (2004), 'Transdermal selegiline and intravenous cocaine: safety and interactions,' *Psychopharmacology (Berlin)* 172, pp. 31–40.

Jofre-Bonet M, Sindelar JL, Petrakis IL et al. (2004), 'Cost effectiveness of disulfiram: treating cocaine use in methadone-maintained patients,' *Journal of Substance Abuse Treatment* 26, pp. 225–32.

Johnson BA (2005), 'Recent advances in the development of treatments for alcohol and cocaine dependence: focus on topiramate and other modulators of GABA or glutamate function,' *CNS Drugs* 19, pp. 873–96.

Jones HE, Johnson RE, Bigelow GE et al. (2004), 'Safety and efficacy of L-tryptophan and behavioral incentives for treatment of cocaine dependence: a randomised clinical trial,' *American Journal of Addiction* 13, pp. 421–37.

Kampman KM, Rukstalis M, Pettinati H et al. (2000a), 'The combination of phentermine and fenfluramine reduced cocaine withdrawal symptoms in an open trial,' *Journal of Substnce Abuse Treatment* 19, pp. 77–9.

Kampman KM, Volpicelli JR, Alterman AI et al. (2000b), 'Amantadine in the treatment of cocaine-dependent patients with severe withdrawal symptoms,' *American Journal of Psychiatry* 157, pp. 2052–4.

Kampman K, Pettinati H, Lynch KG et al. (2004), 'A pilot trial of topiramate for the treatment of cocaine dependence,' *Drug and Alcohol Dependence* 75, pp. 233–40.

Kantak KM (2003), 'Vaccines against drugs of abuse: a viable treatment option?' *Drugs* 63, pp. 341–52.

Katsnelson A (2004), 'Ethical quagmire awaits vaccine for cocaine addiction,' *Nature Medicine* 10, p. 1007.

Katz EC, Chutuape MA, Jones HE and Stitzer ML (2002a), 'Voucher reinforcement for heroin and cocaine abstinence in an outpatient drug-free program,' *Experimental and Clinical Psychopharmacology* 10, pp. 136–43.

Katz EC, Robles-Sotelo E, Correia CJ et al. (2002b), 'The brief abstinence test: effects of continued incentive availability on cocaine abstinence,' *Experimental and Clinical Psychopharmacology* 10, pp. 10–7.

Keaney F, Crimlisk H and Bearn J (2002), 'Lofexadine, desipramine and opioid withdrawal,' *International Journal of Psychiatry in Clinical Practice* 6, pp. 179–81.

Khalsa ME, Kowalewski M-R, Lunn R et al. (1994), 'AIDS-related knowledge, beliefs and risk behaviors in a sample of crack addicts,' *Journal of Drug Issues* 24, pp. 537–53.

Khantzian EJ (1985) 'The self-medication hypothesis of addictive disorders: focus on heroin and cocaine dependence,' *American Journal of Psychiatry* 142, pp. 1259–64.

Khantzian EJ, Gawin F, Kleber HD and Riordan CE (1984), 'Methylphenidate (Ritalin) treatment of cocaine dependence – a preliminary report,' *Journal of Substance Abuse Treatment* 1, pp. 107–12.

Kim YH, E Schiff, Waalen J and Hovell M (2005), 'Efficacy of acupuncture for treating cocaine addiction: a review paper,' *Journal of Addictive Diseases* 24, pp. 115–32.

Kleber H (1988), 'Epidemic cocaine abuse: America's present, Britain's future?' *British Journal of Addiction* 83, pp. 1359–1371.

Klee J (2001), 'Praktische Erfahrungen einer Drogenhilfeeinrichtung mit Crack.' *Crack! Stein(e) des Anstoßes. Realität, Konflikte, Angebote. Dokumentation der Fachtagung*, GAL-Bürgerschaftsfraktion, Hamburg.

Kletter E (2003), 'Counseling as an intervention for the cocaine-abusing methadone maintenance patient,' *Journal of Psychoactive Drugs* 35, pp. 271–7.

KOKON (1999), *Jahresbericht 1999*, Berlin.

Koob GF and Le Moal M (1997) 'Drug abuse: hedonic homeostatic dysregulation', *Science* 278, pp. 52–58.

Korkel J and Veltrup C (2003), 'Motivational Interviewing: Eine Übersicht,' *Suchttherapie* 4, pp. 115–24.

Kosten TR and Kleber HD (1988), 'Buprenorphine detoxification from opioid dependence: a pilot study,' *Life Sciences* 42, pp. 635–41.

Kosten TR and McCance E (1997), 'A review of pharmacological treatments for substance abuse,' *Revista de Toxicomanias* 11, pp. 5–9.

Kosten TA, Kosten TR, Gawin F et al. (1992), 'An open trial of sertraline for cocaine abuse,' *American Journal on Addictions* 1, pp. 349–53.

Kosten TR, Rosen M, Bond J et al. (2002), 'Human therapeutic cocaine vaccine: safety and immunogenicity,' *Vaccine* 20, pp. 1196–204.

Kosten T, Oliveto A, Feingold A et al. (2003), 'Desipramine and contingency management for cocaine and opiate dependence in buprenorphine maintained patients,' *Drug and Alcohol Dependence* 70(3): 315–25.

Kranzler HR, Bauer LO, Hersh D and Klinghoffer V (1995), 'Carbamazepine treatment of cocaine dependence: a placebo-controlled trial,' *Drug and Alcohol Dependence* 38, pp. 203–11.

Kratochvil CJ, Heiligenstein JH, Dittmann R et al. (2002), 'Atomoxetine and methylphenidate treatment in children with ADHD: a prospective, randomised, open-label trial,' *Journal of the American Academy of Child and Adolescent Psychiatry* 41, pp. 776–84.

Kraus L, Semmler C, Kunz-Ebrecht S et al. (2004), *Kokainkonsum und kokainbezogene Störungen: Epidemiologie, Therapie und Prävention*, Institut für Therapieforschung, München.

Le Foll B, Schwartz JC and Sokoloff P (2000), 'Dopamine D3 receptor agents as potential new medications for drug addiction,' *European Psychiatry* 15, pp. 140–6.

Levin FR and Lehman AF (1991), 'Meta-analysis of desipramine as an adjunct in the treatment of cocaine addiction,' *Journal of Clinical Psychopharmacology* 11, pp. 374–8.

Levin FR, McDowell D, Evans SM et al. (1999), 'Pergolide mesylate for cocaine abuse: a controlled preliminary trial,' *American Journal of Addiction* 8, pp. 120–7.

Levin FR, Evans SM, Brooks DJ et al. (2006), 'Treatment of methadone-maintained patients with adult ADHD: double-blind comparison of methylphenidate, bupropion and placebo,' *Drug and Alcohol Dependence* 81, pp. 137–48.

Lima AR, MS Lima, Soares BG and Farrell M (2002), 'Carbamazepine for cocaine dependence,' *Cochrane Database System Review* 2, CD002023.

Lima MS, Reisser AA, Soares BG and Farrell M (2003), 'Antidepressants for cocaine dependence,' *Cochrane Database System Review* 2, CD002950.

Litten R-Z and Allen J-P (1997), 'Medicational aids to treat alcohol problems,' in: Johnson BA, Roache JD (eds) *Drug addiction and its treatment: nexus of neuroscience and behavior*, Lippincott Williams & Wilkins, Philadelphia.

Llosa T (1991), *Coca: uses and abuses*, DESA, Lima.

Llosa T (1994), 'The standard low dose of oral cocaine: Used for treatment of cocaine dependence,' *Substance Abuse* 15, pp. 215–20.

McAuliffe W, Albert J, Cordill-London G and Garraghty T (1991), 'Contributions to a social conditioning model of cocaine recovery,' *International Journal of Addictions* 25: 1141–77.

McCance EF (1997), 'Overview of potential treatment medications for cocaine dependence,' *NIDA Research Monograph* 175, pp. 36–72.

McDowell D, Nunes EV, Seracini AM et al. (2005), 'Desipramine treatment of cocaine-dependent patients with depression: a placebo-controlled trial,' *Drug and Alcohol Dependence* 80, pp. 209–21.

McKay JR, Lynch KG, Shepard DS et al. (2004), 'The effectiveness of telephone-based continuing care in the clinical management of alcohol and cocaine use disorders: 12-month outcomes,' *Journal of Consulting and Clinical Psychology* 72, pp. 967–79.

McLellan AT, Kushner H, Metzger D, et al. (1992), 'The fifth edition of the Addiction Severity Index,' *Journal of Substance Abuse Treatment* 9, pp. 199–213.

McLellan AT, Arndt IO, Metzger DS et al. (1993), 'The effects of psychosocial services in substance abuse treatment,' *Journal of the American Medical Association* 269(15): 1953–9.

Magura S, Rosenblum A, Fong C et al. (2002), 'Treating cocaine-using methadone patients: predictors of outcomes in a psychosocial clinical trial,' *Substance Use and Misuse* 37, pp. 1927–55.

Malcolm R, Herron J, Sutherland SE and Brady KT (2001), 'Adverse outcomes in a controlled trial of pergolide for cocaine dependence,' *Journal of Addictive Diseases* 20, pp. 81–92.

Marcos MP, García ME and de Alba Romero C (1998), 'Cocaína: actuar es posible,' *Formación Médica Continuada en Atención Primaria* 5, pp. 582–9.

Margolin A, Avants SK and Kosten TR (1995), 'Mazindol for relapse prevention to cocaine abuse in methadone-maintained patients,' *American Journal of Drug and Alcohol Abuse* 21, pp. 469–81.

Margolin A, Avants SK and Kosten TR (1996), 'Pemoline for the treatment of cocaine dependence in methadone-maintained patients,' *Journal of Psychoactive Drugs* 28, pp. 301–4.

Marlatt GA and Gordon JR (eds). (1985), *Relapse prevention: maintenance strategies in the treatment of addictive behaviors*, Guilford Press, New York.

Martell BA, Mitchell E, Poling J et al. (2005), 'Vaccine pharmacotherapy for the treatment of cocaine dependence,' *Biological Psychiatry* 58, pp. 158–64.

Meil WM and Schechter MD (1997), 'Olanzapine attenuates the reinforcing effects of cocaine,' *European Journal of Pharmacology* 340, pp. 17–26.

Mello NK and Negus SS (2000), 'Interactions between kappa opioid agonists and cocaine. Preclinical studies,' *Annals of the New York Academy of Sciences* 909, pp. 104–32.

Mengis MM, Maude-Griffin PM, Delucchi K and Hall SM (2002), 'Alcohol use affects the outcome of treatment for cocaine abuse,' *American Journal of Addiction* 11, pp. 219–27.

Messina N, Farabee D and Rawson R (2003), 'Treatment responsivity of cocaine-dependent patients with antisocial personality disorder to cognitive-behavioral and contingency management interventions,' *Journal of Consulting and Clinical Psychology* 71, pp. 320–9.

Milby JB, Schumacher JE, Wallace D et al. (2003), 'Day treatment with contingency management for cocaine abuse in homeless persons: 12-month follow-up,' *Journal of Consulting and Clinical Psychology* 71, pp. 619–21.

Milby JB, Schumacher JE, Vuchinich RE et al. (2004), 'Transitions during effective treatment for cocaine-abusing homeless persons: establishing abstinence, lapse, and relapse, and reestablishing abstinence,' *Psychology of Addictive Behaviors* 18, pp. 250–6.

Milby JB, Schumacher JE, Wallace D et al. (2005), 'To house or not to house: the effects of providing housing to homeless substance abusers in treatment,' *American Journal of Public Health* 95, pp. 1259–65.

Miller WR and Rollnick S (1991), *Motivational interviewing: preparing people to change addictive behavior*, Guilford Press, New York.

Mitcheson L, McCambridge J and Byrne S (2007), 'Pilot cluster randomised trial of adjunctive motivational interviewing to reduce crack cocaine use in clients on methadone maintenance,' *European Addiction Research*, in press.

Modesto-Lowe V and Kranzler H (1999), 'Using cue reactivity to evaluate medications for treatment of cocaine dependence: a critical review,' *Addiction* 94, pp. 1639–51.

Montoya ID, Levin FR, Fudala PJ and Gorelick DA (1995), 'Double-blind comparison of carbamazepine and placebo for treatment of cocaine dependence,' *Drug and Alcohol Dependence* 38, pp. 213–9.

Montoya ID, Preston KL, Rothman R and Gorelick DA (2002), 'Open-label pilot study of bupropion plus bromocriptine for treatment of cocaine dependence,' *American Journal of Drug and Alcohol Abuse* 28, pp. 189–96.

Moselhy FH and El-Sheikh H (2004), 'Outpatient treatment of cocaine dependence with dexamphetamine,' *Addictive Disorders and their Treatment* 3, pp. 133–7.

Myrick H, Henderson S, Brady KT et al. (2001), 'Divalproex loading in the treatment of cocaine dependence,' *Journal of Psychoactive Drugs* 33, pp. 283–7.

Nabitz U, Van den Brink W and Walburg J (2005), 'A quality framework for addiction treatment programmes: Results of a concept mapping strategy,' *Sucht* 51, pp. 138–50.

Navarro M and Rodriguez De Fonseca F (2000), 'New strategies in cocaine treatment,' *Proyecto Hombre* 34, pp. 5–9.

NHS (2005), *Consultation report. Models of care for the treatment of adult drug misusers. Update 2005*, National Treatment Agency for Substance Misuse, London.

Nich C, McCance-Katz EF, Petrakis IL et al. (2004), 'Sex differences in cocaine-dependent individuals' response to disulfiram treatment,' *Addictive Behaviors* 29, pp. 1123–8.

NTA (2002a), 'Commissioning cocaine/crack treatment, Research into practice: 1b commissioners' briefing,' *Drug and Alcohol Findings*. London.

NTA (2002b), 'Treating cocaine/crack dependence. Research into practice: 1a drug services briefing,' *Drug and Alcohol Findings*. London.

Oslin DW, Pettinati HM, Volpicelli JR et al. (1999), 'The effects of naltrexone on alcohol and cocaine use in dually addicted patients,' *Journal of Substnce Abuse Treatment* 16, pp. 163–7.

Pantalon MV, Chawarski MC, Falcioni J et al. (2004), 'Linking process and outcome in the community reinforcement approach for treating cocaine dependence: a preliminary report,' *American Journal of Drug and Alcohol Abuse* 30, pp. 353–67.

Passos SR, Camacho LA, Lopes CS and dos Santos MA (2005), 'Nefazodone in out-patient treatment of inhaled cocaine dependence: a randomised double-blind placebo-controlled trial,' *Addiction* 100, pp. 489–94.

Pedrero Pérez EJ and Puerta Garcia C (2001), 'Atención usuarios de cocaína desde un centro de atención a drogodependencias (CAD-4),' *Trastornos adictivos* 3, pp. 11–20.

Peele S and DeGrandpre R (1998), 'Cocaine and the concept of addiction: environmental factors in drug compulsions,' *Addiction Research* 6, pp. 235–63.

Pepper J, Baumann MH, Ayestas M and Rothman R (2001), 'Inhibition of MAO-A fails to alter cocaine-induced increases in extracellular dopamine and norepinephrine in rat nucleus accumbens,' *Brain Research. Molecular Brain Research* 87, pp. 184–9.

Perez de los Cobos J, Duro P, Trujols J et al. (2001), 'Methadone tapering plus amantadine to detoxify heroin-dependent inpatients with or without an active cocaine use disorder: two randomised controlled trials,' *Drug and Alcohol Dependence* 63, pp. 187–95.

Petrakis I, Carroll KM, Nich C et al. (1998), 'Fluoxetine treatment of depressive disorders in methadone-maintained opioid addicts,' *Drug and Alcohol Dependence* 50, pp. 221–6.

Petrakis I, Carroll KM, Nich C et al. (2000), 'Disulfiram treatment for cocaine dependence in methadone-maintained opioid addicts,' *Addiction* 95, pp. 219–28.

Petry NM and Martin B (2002), 'Low-cost contingency management for treating cocaine- and opioid-abusing methadone patients,' *Journal of Consulting and Clinical Psychology* 70, pp. 398–405.

Petry NM and Simcic F Jr (2002), 'Recent advances in the dissemination of contingency management techniques: clinical and research perspectives,' *Journal of Substance Abuse Treatment* 23, pp. 81–6.

Petry NM, Tedford J, Austin M et al. (2004), 'Prize reinforcement contingency management for treating cocaine users: how low can we go, and with whom?' *Addiction* 99, pp. 349–60.

Petry NM, Alessi SM, Marx J et al. (2005), 'Vouchers versus prizes: contingency management treatment of substance abusers in community settings,' *Journal of Consulting and Clinical Psychology* 73, pp. 1005–14.

Poling J, Oliveto A, Petry N et al. (2006), 'Six-month trial of bupropion with contingency management for cocaine dependence in a methadone-maintained population,' *Archives of General Psychiatry* 63, pp. 219–28.

Poschadel S, Höger R, Schnitzler J and Schreckenberg D (2002), *Evaluation der Arbeit der Drogenkonsumräume in der Bundesrepublik Deutschland. Endbericht im Auftrag des Bundesministeriums für Gesundheit*, ZEUS, Bochum.

Preston KL, Silverman K, Schuster CR, Cone EJ (1997), 'Comparison of self-reported drug use with quantitative and qualitative urinalysis for assessment of drug use in treatment studies,' *NIDA Research Monograph* 167, pp. 130–45.

Preston KL, Umbricht A, Wong CJ and Epstein DH (2001), 'Shaping cocaine abstinence by successive approximation,' *Journal of Consulting and Clinical Psychology* 69, pp. 643–54.

Preston KL, Umbricht A, Schroeder JR et al. (2004), 'Cyclazocine: comparison to hydromorphone and interaction with cocaine,' *Behavioural Pharmacology* 15, pp. 91–102.

Prinzleve M, Verthein U and Degkwitz P (2002), 'Ambulante Suchtakupunktur als Begleittherapie in der Substitutionsbehandlung,' *Suchttherapie* 3, pp. 197–204.

Prinzleve M, Haasen C, Brückner E and Krausz M (2003), 'Darstellung und erste Ergebnisse einer ambulanden Kurzintervention für Kokainkonsumenten,' *Sucht* 49, pp. 49–53.

Ramon F and Torrecilla JM (1999), *Primeros auxilios. El drogodependiente en urgencias*, Agencia antidroga de la Comunidad de Madrid, Madrid.

Rawson RA, Huber A, McCann M et al. (2002), 'A comparison of contingency management and cognitive-behavioral approaches during methadone maintenance treatment for cocaine dependence,' *Archives of General Psychiatry* 59, pp. 817–24.

Rawson RA, McCann MJ, Flammino F et al. (2006), 'A comparison of contingency management and cognitive-behavioral approaches for stimulant-dependent individuals,' *Addiction* 101, pp. 267–74.

Rehm J, Gschwend P, Steffen T et al. (2001), 'Feasibility, safety, and efficacy of injectable heroin prescription for refractory opioid addicts: a follow-up study,' *Lancet* 358, pp. 1417–23.

Reid MS, Casadonte P, Baker S et al. (2005a), 'A placebo-controlled screening trial of olanzapine, valproate, and coenzyme Q10/L-carnitine for the treatment of cocaine dependence,' *Addiction* 100 (Suppl. 1), pp. 43–57.

Reid MS, Angrist B, Baker S et al. (2005b), 'A placebo-controlled screening trial of celecoxib for the treatment of cocaine dependence,' *Addiction* 100 (Suppl. 1), pp. 32–42.

Reilly PM and Shopshire MS (2000), 'Anger management group treatment for cocaine dependence: preliminary outcomes,' *American Journal of Drug and Alcohol Abuse* 26, pp. 161–77.

Ribeiro M, Dunn J, Sesso R et al (2007), 'Crack cocaine: a five-year follow-up study of treated patients,' *European Addiction Research* 13, pp. 11–19.

Rigter H, van Gageldonk A, Ketelaars T and van Laar M (2004), *Treatment of Problematic Use of Drugs*, Trimbos Institute, Utrecht (Netherlands).

Roache JD, Johnson BA, Ait-Daoud N et al. (2005), 'Effects of repeated-dose isradipine on the abuse liability of cocaine,' *Experimental and Clinical Psychopharmacology* 13, pp. 319–26.

Rohsenow DJ, Monti PM, Martin RA et al. (2004), 'Motivational enhancement and coping skills training for cocaine abusers: effects on substance use outcomes,' *Addiction* 99, pp. 862–74.

Rohsenow DJ, Martin RA and Monti PM (2005), 'Urge-specific and lifestyle coping strategies of cocaine abusers: relationships to treatment outcomes,' *Drug and Alcohol Dependence* 78, pp. 211–19.

Rollnick S and Miller WR (1995), 'What is motivational interviewing?' *Behavioural and Cognitive Psychotherapy* 23, pp. 325–34.

Roozen HG, Boulogne JJ, van Tulder MW et al. (2004), 'A systematic review of the effectiveness of the community reinforcement approach in alcohol, cocaine and opioid addiction,' *Drug and Alcohol Dependence* 74, pp. 1–13.

Rós Soler AI, Valoria A, Iriarte A (2004), 'Consumo de cocaína – trastorno por déficit de atención con hiperactividad: variación sociodemográfica según subtipos', *Conductas adictivas* 4 (2), pp. 91–97.

Roth, M. (1999), *Das Frankfurter Crack-Street-Projekt. Ein neuer Weg der Drogenhilfe, untersucht am Beispiel des Crack-Street-Projektes*, Fachhochschule Frankfurt am Main, Frankfurt.

Rounsaville BJ (2004), 'Treatment of cocaine dependence and depression,' *Biological Psychiatry* 56, pp. 803–9.

Rounsaville BJ, Anton SF, Carroll K et al. (1991), 'Psychiatric diagnoses of treatment-seeking cocaine abusers,' *Archives of General Psychiatry* 48, pp. 43–51.

Rounsaville BJ, Petry N and Carroll KM (2003), 'Single versus multiple drug focus in substance abuse clinical trials,' *Drug and Alcohol Dependence* 70, pp. 117–25.

Rush BR and Wild TC (2003), 'Substance abuse treatment and pressures from the criminal justice system: data from a provincial client monitoring system,' *Addiction* 98, pp. 1119–28.

San Molina L and Arranz Diez B (2001), 'Aproximacion terapeutica de la dependencia de cocaina,' *Adicciones* 13, pp. 191–208.

Sattar SP, Bhatia SC and Petty F (2004), 'Potential benefits of quetiapine in the treatment of substance dependence disorders,' *Journal of Psychiatry and Neuroscience* 29, pp. 452–47.

Sayers SL, Campbell EC, Kondrich J et al. (2005), 'Cocaine abuse in schizophrenic patients treated with olanzapine versus haloperidol,' *Journal of Nervous and Mental Disease* 193, pp. 379–86.

Schiffer WK, Marsteller D and Dewey SL (2003), 'Sub-chronic low dose gamma-vinyl GABA (vigabatrin) inhibits cocaine-induced increases in nucleus accumbens dopamine,' *Psychopharmacology (Berlin)* 168, pp. 339–43.

Schmid M and Vogt I (2001), 'Case Management und Motivierende Beratung,' *Suchttherapie* 2, pp. 73–9.

Schmitz JM, Stotts AL, Rhoades HM and Grabowski J (2001), 'Naltrexone and relapse prevention treatment for cocaine-dependent patients,' *Addictive Behaviors* 26, pp. 167–80.

Schottenfeld RS, Chawarski MC, Pakes JR et al. (2005), 'Methadone versus buprenorphine with contingency management or performance feedback for cocaine and opioid dependence,' *American Journal of Psychiatry* 162, pp. 340–9.

Schroeder JR, Gupman AE, Epstein DH et al. (2003), 'Do noncontingent vouchers increase drug use?' *Experimental and Clinical Psychopharmacology* 11, pp. 195–201.

Schubiner H, Saules KK, Arfken CL et al. (2002) 'Double-blind placebo-controlled trial of methylphenidate in the treatment of adult ADHD patients with comorbid cocaine dependence,' *Experimental and Clinical Psychopharmacology* 10, pp. 286–94.

Schuetz, C. (2006), *Ambulante Behandlung von Kokainabhängigen. Kokainsprechstunde*, Integrierte Psychiatrie Winterthur, Winterthur.

Schumacher JE, Milby JB, Wallace D et al. (2003), 'Diagnostic compared with abstinence outcomes of day treatment and contingency management among cocaine-dependent homeless persons,' *Experimental and Clinical Psychopharmacology* 11, pp. 146–57.

Shearer J, Wodak A, van Beek I et al. (2003), 'Pilot randomised double blind placebo-controlled study of dexamphetamine for cocaine dependence,' *Addiction* 98, pp. 1137–41.

Sherer MA, Kumor KM and Jaffe JH (1989), 'Effects of intravenous cocaine are partially attenuated by haloperidol,' *Psychiatry Research* 27, pp. 117–25.

Shoptaw S, Kintaudi PC, Charuvastra C and Ling W (2002), 'A screening trial of amantadine as a medication for cocaine dependence,' *Drug and Alcohol Dependence* 66, pp. 217–24.

Siegal HA, Falck RS, Wang J and Carlson RG (2002), 'Predictors of drug abuse treatment entry among crack-cocaine smokers,' *Drug and Alcohol Dependence* 68, pp. 159–66.

Siegel RK, Elsohly MA, Plowman T et al. (1986), 'Cocaine in herbal tea,' *Journal of the American Medical Association* 255, pp. 40.

Sievewright N, Donmall M, Douglas J et al. (2000), 'Cocaine misuse treatment in England,' *International Journal of Drug Policy* 11, pp. 203–215.

Sigmon SC, Correia CJ and Stitzer ML (2004), 'Cocaine abstinence during methadone maintenance: effects of repeated brief exposure to voucher-based reinforcement,' *Experimental and Clinical Psychopharmacology* 12, pp. 269–75.

Silva de Lima M, Reisser AA, Soares BG and Farrell M (2001), 'Antidepressants for cocaine dependence,' *Cochrane Database System Review* 4, CD002950.

Silverman K, Bigelow GE and Stitzer ML (1998), 'Treatment of Cocaine Abuse in Methadone Maintenance Patients,' in: Higgins ST, Katz JL (eds), *Cocaine Abuse: Behavior, Pharmacology, and Clinical Applications*, Academic Press, San Diego.

Silverman K, Svikis D, Wong CJ et al. (2002), 'A reinforcement-based therapeutic workplace for the treatment of drug abuse: three-year abstinence outcomes,' *Experimental and Clinical Psychopharmacology* 10, pp. 228–40.

Simpson DD, Joe GW, Fletcher BW et al. (1999), 'A national evaluation of treatment outcomes for cocaine dependence,' *Archives of General Psychiatry* 56, pp. 507–14.

Simpson DD, Joe GW and Broome KM (2002), 'A national 5-year follow-up of treatment outcomes for cocaine dependence,' *Archives of General Psychiatry* 59, pp. 538–44.

Smelson DA, Losonczy MF, Davis CW et al. (2002), 'Risperidone decreases craving and relapses in individuals with schizophrenia and cocaine dependence,' *Canadian Journal of Psychiatry* 47, pp. 671–5.

Smelson DA, Williams J, Ziedonis D et al. (2004), 'A double-blind placebo-controlled pilot study of risperidone for decreasing cue-elicited craving in recently withdrawn cocaine dependent patients,' *Journal of Substance Abuse Treatment* 27, pp. 45–9.

Soares BG, MS Lima, Reisser AA and Farrell M (2003), 'Dopamine agonists for cocaine dependence,' *Cochrane Database System Review* 2, CD003352.

Sofuoglu M and Kosten TR (2005), 'Novel approaches to the treatment of cocaine addiction,' *CNS Drugs* 19, pp. 13–25.

Sofuoglu M and Kosten TR (2006), 'Emerging pharmacological strategies in the fight against cocaine addiction,' *Expert Opinion on Emergent Drugs* 11, pp. 91–8.

Sofuoglu M, Babb DA and Hatsukami DK (2002), 'Effects of progesterone treatment on smoked cocaine response in women,' *Pharmacology, Biochemistry, and Behavior* 72, pp. 431–5.

Sofuoglu M, Mitchell E and Kosten TR (2004), 'Effects of progesterone treatment on cocaine responses in male and female cocaine users,' *Pharmacology, Biochemistry, and Behavior* 78, pp. 699–705.

Sofuoglu M, Poling J, Mitchell E and Kosten TR (2005), 'Tiagabine affects the subjective responses to cocaine in humans,' *Pharmacology, Biochemistry, and Behavior* 82, pp. 569–73.

Solberg U (2003), *Standards and quality assurance in treatment related to illegal drugs and social reintegration in EU Member States and Norway*, EMCDDA, Lisbon.

Sole Puig J (2001), 'Tratamiento del consumo de cocaina. Integrando psicoterapia y farmacoterapia,' *Adicciones* 13, pp. 209–25.

Somoza EC, Winhusen TM, Bridge TP et al. (2004), 'An open-label pilot study of methylphenidate in the treatment of cocaine dependent patients with adult attention deficit/hyperactivity disorder,' *Journal of Addictive Diseases* 23, pp.77–92.

Soyka M and De-Vry J (2000), 'Flupenthixol as a potential pharmacotreatment of alcohol and cocaine abuse/dependence,' *European Journal of Neuropsychopharmacology* 10, pp. 325–32.

Stevenson GW, Wentland MP, Bidlack JM et al. (2004), 'Effects of the mixed-action kappa/mu opioid agonist 8-carboxamidocyclazocine on cocaine- and food-maintained responding in rhesus monkeys,' *European Journal of Pharmacology* 506, pp. 133–41.

Stine SM, Krystal JH, Kosten TR and Charney DS (1995), 'Mazindol treatment for cocaine dependence,' *Drug and Alcohol Dependence* 39, pp. 245–52.

Stohler R (2004), Behandlung von Kokainabhängigen mit Kokain – bisherige Erfahrungen (www.infoset.ch/de/dokumente/2004_08_Kokainsubstitution.pdf).

Stöver H (2001), *Bestandsaufnahme „Crack-Konsum" in Deutschland: Verbreitung, Konsummuster, Risiken und Hilfeangebote*, BISDRO, Bremen.

Stöver H (2002), 'Crack cocaine in Germany – current state of affairs,' *Journal of Drug Issues* 32, pp. 413–22.

Strang J and Edwards G (1989), 'Cocaine and crack,' *British Medical Journal* 299, pp. 337–8.

Streeter CC, Hennen J, Ke Y et al. (2005), 'Prefrontal GABA levels in cocaine-dependent subjects increase with pramipexole and venlafaxine treatment,' *Psychopharmacology (Berlin)* 182, pp. 516–26.

Strickland TL, Miller BL, Kowell A, Stein R (1998), 'Neurobiology of cocaine-induced organic brain impairment: contributions from functional neuroimaging,' *Neuropsychology Review* 8, pp. 1–9.

Szerman N, Peris L, Mesias B et al. (2005), 'Reboxetine for the treatment of patients with Cocaine Dependence Disorder,' *Human Psychopharmacology* 20, pp. 189–92.

Tennant F, Tarver A, Sagherian A and Loveland D-B (1993), 'A placebo-controlled elimination study to identify potential treatment agents for cocaine detoxification,' *American Journal of Addiction* 2, pp. 299–308.

Thom B (2001), *Treatment of crack cocaine. Review of the literature of effectiveness*, Middlesex University, London.

Thomasius R, Gouzoulis-Mayfrank E, Kraus C et al. (2004), 'AWMF-Behandlungsleitline: Psychische und Verhaltensstörungen durch Kokain, Amphetamine, Ecstasy und Halluzinogene,' *Fortschritte der Neurologie-Psychiatrie* 72, pp. 679–95.

Torrens, M., F. Fonseca, G. Mateu and M. Farre (2005), 'Efficacy of antidepressants in substance use disorders with and without comorbid depression. A systematic review and meta-analysis,' *Drug and Alcohol Dependence* 78, pp. 1–22.

Tossmann P, Götz W and Tensil M (2000), *Soziodemographische und soziale Charakteristika von Kokainkonsumenten. Eine Auswertung klientenbezogener Daten der ambulanen Therapieeinrichtung ‚KOKON' aus den Jahren 1995–1999*, Berlin.

Tsuang J, Fong TW and Pi E (2005), 'Pharmacological treatment of patients with schizophrenia and substance abuse disorders,' *Addictive Disorders and their Treatment* 4, pp. 127–37.

Vanderplasschen W, De Bourdeaudhuij I and Van Oost P (2002), 'Co-ordination and continuity of care in substance abuse treatment. An evaluation study in Belgium,' *European Addiction Research* 8, pp. 10–21.

Verthein U, Haasen C, Prinzleve M et al. (2001), 'Cocaine use and the utilisation of drug help services by consumers of the open drug scene in Hamburg,' *European Addiction Research* 7, pp. 176–83.

Villano C, Rosenblum A, Magura S and Fong C (2002), 'Improving treatment engagement and outcomes for cocaine-using methadone patients,' *American Journal of Drug and Alcohol Abuse* 28, pp. 213–30.

Vocci FJ and Elkashef A (2005), 'Pharmacotherapy and other treatments for cocaine abuse and dependence,' *Current Opinion in Psychiatry* 18, pp. 265–70.

Vocci F and Ling W (2005), 'Medications development: successes and challenges,' *Pharmacology and Therapy* 108, pp. 94–108.

Vogt I, Schmid M and Roth M (2000), 'Crack-Konsum in der Drogenszene in Frankfurt am Main: Ergebnisse empirischer Studien,' *Wiener Zeitschrift für Suchtforschung* 23, pp. 5–13.

Vogt I and Zeissler E (2005), *Abschlussbericht der Evaluation des Projektes Rauchraum im Drogennotdienst Frankfurt des Vereins Jugendberatung und Jugendhilfe e.V.*, ISFF, Frankfurt.

Vorel SR, Ashby CR Jr, Paul M et al. (2002), 'Dopamine D3 receptor antagonism inhibits cocaine-seeking and cocaine-enhanced brain reward in rats,' *Journal of Neuroscience* 22, pp. 9595–603.

Wallace B (1992), 'Treating cocaine dependence: the critical role of relapse prevention,' *Journal of Psychoactive Drugs* 24, pp. 213–22.

Wanigaratne S, Davis P, Pryce K and Brotchie J (2005), *The effectiveness of psychological therapies on drug misusing clients*, National Treatment Agency for Substance Misuse, London.

Warner EA, Kosten TR and O'Connor PG (1997), 'Pharmacotherapy for opioid and cocaine abuse,' *Medical Clinics of North America* 81, pp. 909–25.

Wayne D and Madigan T (2004), 'Quetiapine and gabapentin dramatically improve treatment-resistant schizoaffective disorder in a patient with a long history of cocaine abuse,' *Addictive Disorders and their Treatment* 3, pp. 83–6.

Weiss RD, Griffin ML, Gallop RJ et al. (2005), 'The effect of 12-step self-help group attendance and participation on drug use outcomes among cocaine-dependent patients,' *Drug and Alcohol Dependence* 77, pp. 177–84.

Weiss RD, Griffin ML, Mazurick C et al. (2003), 'The relationship between cocaine craving, psychosocial treatment, and subsequent cocaine use,' *American Journal of Psychiatry* 160, pp. 1320–5.

Weiss S (1989), 'Links between cocaine and retroviral infection,' *Journal of the American Medical Association* 261, pp. 607–68.

Wendt WR (2001), 'Case Management: Prozess-Steuerung und Koordination in der Arbeit mit Abhängigen,' *Suchttherapie* 2, pp. 61–4.

Wiesbeck GA and Dursteler-Macfarland K (2006), 'Neue Entwicklungen in der Pharmakotherapie der Kokainabhängigkeit' [New developments in the pharmacotherapy of cocaine dependence] *Nervenarzt* 77(9), pp. 1066–70.

Wilens TE, Prince JB, Spencer T et al. (2003), 'An open trial of bupropion for the treatment of adults with attention-deficit/hyperactivity disorder and bipolar disorder,' *Biological Psychiatry* 54, pp. 9–16.

Williamson A, Darke S, Ross J and Teesson M (2006a). 'The association between cocaine use and short-term outcomes for the treatment of heroin dependence: findings from the Australian Treatment Outcome Study (ATOS),' *Drug and Alcohol Review* 25, pp. 141–18.

Williamson A, Darke S, Ross J and Teesson M (2006b). 'The effect of persistence of cocaine use on 12-month outcomes for the treatment of heroin dependence,' *Drug and Alcohol Dependence* 81, pp. 293–300.

Winhusen TM, Somoza EC, Harrer JM et al. (2005), 'A placebo-controlled screening trial of tiagabine, sertraline and donepezil as cocaine dependence treatments,' *Addiction* 100 (Suppl. 1), pp. 68–77.

Witton J and Ashton M (2002), *Treating cocaie /crack dependence*, NTA, London.

Zhang Z, Friedmann PD and Gerstein DR (2003), 'Does retention matter? Treatment duration and improvement in drug use,' *Addiction* 98, pp. 673–84.

Zurhold H, Kreutzfeld N, Degkwitz P and Verthein U (2001), *Drogenkonsumräume. Gesundheitsförderung und Minderung öffentlicher Belastungen in europäischen Großstädten*, Lambertus, Freiburg i. Br.

(end of document)