Literature review on the

Treatment of Psychotropic Substance Use Disorder

Submitted to

Beat Drug Fund Association

Submitted by

Prof. Wai Kwong Tang, MD, Department of Psychiatry, Shatin Hospital

Huajun Liang, MPhil, Department of Psychiatry, the Chinese University of Hong Kong

Prof. Kwing Chin Kenneth Lee, BSc (Pharmacy), MPhil, PhD, School of Pharmacy, the Chinese University of Hong Kong

Dr. Alan Tang, MRCPsy, Department of Psychiatry, Shatin Hospital

Prof. Wai Kei Christopher Lam, PhD, Department of Chemcial Pathology, the Chinese University of Hong Kong

Dr. Ho Ming Michael Chan, FHKAM (Pathology), Department of Chemcial Pathology, Prince of Wales Hospital

Dr. Ming Lam, FHKAM (Psychiatry), Department of Psychiatry, Castle Peak Hospital

Contents

Executive summary

Psychotropic substance abuse and dependence is a serious problem around the world and in Hong Kong. During the last three decades, treatments for dependence on cocaine, amphetamine, cannabis and other psychotropic substances have been developing rapidly. This review provides an overview of the current status of treatments for psychotropic substances.

The review explores the following treatment aspects: psychosocial treatments, pharmacotherapies, biological therapies, traditional medicine, integrated treatment models and the framework of addiction treatment.

The data are from published articles and books and the majority are from research performed in North America and European. Psychosocial treatments play the primary role in treating psychotropic substance use disorders and evidence-based psychosocial treatments have been established. Pharmacotherapies and immunological therapies are promising treatment candidates, but so far no medication or vaccine has been proven to be effective in treating psychotropic substance use disorders. Several integrated treatment models based on psychosocial treatments have been developed and more comprehensive models that emphasize multidisciplinary cooperation are under exploration. Along with recognition of the chronic nature of addiction disorder, the framework of treatments in this field is now facing a transformation from a traditional acute care model to a continuing care model. High dropout and relapse rates and a low abstinence rate are common despite the treatment methods.

The treatment of psychotropic substance use disorders is still a tough problem. Future studies or practice may put effort into developing optimistic treatment methods and models, and fostering a more sustainable care system. The provision of local evidence-based treatment approaches is also an urgent task for local authorities.

行政撮要

精神活性物質濫用在香港和全世界範圍都是一個很嚴重的問題。近三十年，在這一領域的研究進展迅速。本綜述旨在對精神活性物質濫用治療的研究現狀做一個概述。

本文將從心理社會治療、藥物治療、生物治療、中醫治療、綜合治療模型以及精神衛生服務模式幾個角度來闡述精神活性物質濫用治療現狀這一主題。本文資料來源於出版的學術論文和論著。

資料主要來源於歐美的研究結果。心理社會治療是最主要的治療方法並已建立循證學依據。藥物和免疫治療雖然有治療前景但目前沒有一種藥物或者疫苗獲得食品藥品監督管理局的批准用於治療精神活性物質濫用。將幾種循證學支援的治療方法進行綜合的治療模式已經建立而更綜合的，建立在多學科合作基礎上的治療模式正在探索當中。隨著成癮性疾病的慢性特徵得到認識，藥物成癮障礙的治療面臨著由傳統的急性治療模式到持續性治療模式的轉變。高脫失率和復發率是各種治療方法共同的問題。

精神活性物質濫用的治療仍然是一個困難的課題。未來的研究和實踐將朝著開發出更有效的治療方法，以及培育可持續性的治療與服務模式努力。將已有的具有循證學支援的治療方法本土化也是當前政府的一個緊要任務。

Introduction

Psychotropic substance abuse and dependence is a serious problem around the world, and is more prominent in Hong Kong than other substance use disorders, such as opioid addiction (Narcotics Division 2009). Evidence for the treatment of substance use disorders (SUDs) is focused on opioid and alcohol addiction, but research into treatments for dependence on cocaine, amphetamine and cannabis has been increasing rapidly during the past three decades. However, the majority of studies have been conducted in North America and European, thus the research findings need to be replicated in different cultures in future. This review describes recent advances in psychosocial treatments, pharmacotherapies, biological therapies, traditional medicine, integrated treatment models and the framework of addiction treatment. The literature reviewed here is limited to three categories of substances: stimulants, hallucinogens and cannabis, as almost all research efforts are concentrated in these three areas, especially stimulant use disorders. The present review focuses on treatments for the general population, and treatments for specific populations such as women, adolescents and the elderly are not included.

Evidence-Based Psychosocial Therapy

Psychosocial treatments aim to counter compulsive substance use by bringing about changes in patients' behaviours, thought processes, affect regulation and social functioning. Although theories and techniques vary across different treatment approaches, they all address one or more common tasks: motivating patients to stop or reduce substance use, teaching coping skills, changing reinforcement contingencies, fostering the management of painful affects and enhancing social support and interpersonal functioning (Kleber *et al.* 2007). The evidenced-based psychosocial therapies that are reviewed below include cognitive-behaviour therapy, contingency management therapy, community reinforcement therapy, motivational therapy, 12-step self-help groups and several treatment models.

Cognitive-Behaviour Therapy (CBT)

Introduction of CBT

The theory underpinning behavioural therapy is based on classical and operant conditioning, and cognitive therapy regards problematic information processing as leading to psychological distress. CBT synthesizes these two therapeutic approaches and is based on social learning theory. The understanding of CBT for substance use disorder is that an individual first uses a substance by observing other people using it, and subsequently, the pleasurable effects lead to repeated use via operant conditioning and the development of craving. Classical conditioning may contribute to cue-stimuli, whereby certain people, locations, times, situations and moods can trigger craving for

the substance. From the point of view of CBT, learning processes play an important role in drug dependence and recovery, which in turn can lead to the revision of patients' drug use behaviour (Barry & Petry 2009).

CBT is a short-term, highly structured, goal-oriented and individualized treatment method. The two main components of CBT are functional analysis and skills training. Functional analysis is about identifying the patient's thoughts, feelings and circumstances before and after drug use, which helps the patient and therapist to assess the determinants, or high-risk situations that are likely to lead to drug use, and thus provide insights into some of the reasons the individual may be using drugs. Skills training is a highly individualized training programme to help abusers cope with a wide range of interpersonal and intrapersonal problems, such as the skill to refuse drugs and cope with craving. CBT addresses five critical tasks: 1. Foster the motivation for abstinence; 2. Teach coping skills; 3. Change reinforcement contingencies; 4. Foster the management of painful affects; and 5. Improve interpersonal functioning and enhance social support. The therapy may be offered in 12 to 16 sessions, usually over 12 weeks. Because abusers encounter the triggers for craving and high-risk situations related to drug use in their daily lives, it is recommended that CBT should be delivered in an outpatient setting so that abusers can learn to identify those triggers and practice how to cope with them (Carroll 1998).

Relapse prevention (RP) is a specific CBT intervention in which CBT techniques are used for coping with relapse. The RP model regards relapse as part of the recovery process and as an opportunity for learning (Barry & Petry 2009). The CBT-RP model aims at initiating and maintaining abstinence. The core component of RP is the assessment of high-risk situations for relapse. The assessment should encompass interpersonal motivation and commitment, relapse history and susceptibility. Other strategies include coping skills training, increasing self-efficacy and coping with relapse. A more global RP intervention involves lifestyle revision and learning skills such as relaxation and mindfulness to further decrease the desire for drugs and to improve insight and self-control (Alan Marlatt & Bowen 2009) .

Evidence for the Efficacy of CBT

1.2.1 CBT

In randomized control trials (RCT), CBT has been shown to reduce cocaine/amphetamine use when measured by urinalysis (Carroll *et al.* 2004) and self-reported cocaine use (Rawson *et al.* 2002, Rawson *et al.* 2006), albeit some reports have found CBT to be no more effective than a control condition (Carroll *et al.* 1994, Epstein *et al.* 2003, Budney *et al.* 2006). However, almost all of the above studies showed a post-treatment effect of CBT in reducing cocaine/amphetamine use even one year after treatment. The skills learned in a CBT programme need time to be integrated into daily life, which may explain the delayed effect of CBT (Epstein *et al.*

2003). The efficacy of CBT, both during treatment and post-treatment, was confirmed in two systematic reviews (Dutra *et al.* 2008) (Lee & Rawson 2008, Magill & Ray 2009), but not in another review (Knapp *et al.* 2007) and a NIDA (National Institute on Drug Abuse) study (Crits-Christoph *et al.* 1999). When compared with other psychotherapies, CBT was more likely to achieve abstinence in cocaine dependent people during a 12-week treatment and at 14-week follow-up than therapy based on the 12-step model (Maude-Griffin *et al.* 1998). However, when compared with contingency management (CM), 16 sessions of CBT was less potent during treatment, but equivalent to CM at 26 and 52 weeks post-treatment (Rawson *et al.* 2002, Shoptaw *et al.* 2005, Budney *et al.* 2006, Rawson *et al.* 2006). In some studies, participants' characteristics were associated with treatment outcomes; those with high abstract reasoning, history of depression (Maude-Griffin *et al.* 1998), severe cocaine abuse (Carroll *et al.* 1994), and those who were female and with cannabis as the primary abused drug (Magill & Ray 2009) were more likely to benefit from CBT. The RP model has been found to be as effective as any other treatment for SUDs and more effective than no treatment (Carroll *et al.* 1996, Dutra *et al.* 2008).

1.2.2 Computer-based training in CBT

Although CBT has been substantially supported though clinical trials, it is rarely adopted in clinical practice. The barriers preventing its application include high caseload and limitation of resources (work spaces, trained clinicians and workforce), complexity and cost of training, supervision and certification in a CBT programme (Carroll *et al.* 2008). Therefore, computer-based training in CBT (CB-CBT) for substance use disorders has been developed. In clinical studies, six bi-weekly sessions of CB-CBT reduced substance use compared with general drug counselling in a heterogeneous sample (Carroll *et al.* 2008), and the effect remained for at least 6 months after treatment (Carroll *et al.* 2009). Moreover, at 12-month follow-up, CB-CBT was as effective as therapist-assisted CBT in reducing cannabis use, though it had less potent short-term beneficial effects than therapist-assisted CBT in patients with comorbid depression and alcohol/cannabis misuse (Kay-Lambkin *et al.* 2009, Kay-Lambkin *et al.* 2011).

1.2.3 Brief CBT

Several studies have tested the efficacy of brief CBT for treating cocaine, amphetamine or cannabis abuse. In an opiate treatment group, both two and four sessions of CBT plus a self-help booklet increased the likelihood of abstinence and reduced self-reported amphetamine use at 6-month follow-up, compared with a self–help booklet alone (Baker *et al.* 2005). Another clinical trial with cannabis abuse/dependence users compared either six sessions or one session of CBT (6CBT or 1CBT) plus a self–help booklet with a control condition that only included baseline assessment. Both CBT groups increased the likelihood of being abstinent at 24-week follow up compared with the control condition. The 6CBT group reduced self-reported cannabis use significantly more than the control condition, whereas the

1CBT group did not. The 6CBT group decreased the Severity of Dependence Score (SDS) and drug-related problems notably more than 1CBT. Compared with the control condition, 1CBT decreased SDS and drug-related problems. Based on this study, more intensive CBT is suggested in future studies, especially for heavy users (Copeland *et al.* 2001). In one non-RCT clinical trial with amphetamine dependent patients, four sessions of CBT improved anxiety, depressive and somatic symptoms and social dysfunction at the end of the 4-week intervention, assessed by the General Health Questionnaire-28 (GHQ-28) (Feeney *et al.* 2006). In summary, brief CBT for treating substance abuse/dependence may not provide stable and lasting improvements (Carroll 1998).

Summary of CBT

CBT has proven efficacy for treating substance abuse/dependence, with robust evidence from empirical studies in a wide range of SUDs including cocaine, amphetamine and cannabis. During the treatment itself, CBT may not produce a rapid reduction in drug use, although it may improve psychosocial functioning; its efficacy in reducing drug use may occur after treatment and can remain for up to one year after treatment. The dosage and duration of CBT sessions and the level of therapists' experience may influence the treatment results, but this finding remains inconsistent among studies. However, although CBT is better than no treatment for substance use disorders, it has not been proven to be superior to any other psychological treatments.

Contingency Management (CM) and Community Reinforcement Approach (CRA)

Introduction of CM and CRA

CM and CRA are forms of behavioural therapy and are based on learning and conditioning theory, especially operant conditioning. These treatments are intended to reorganize the abuser's environment to systematically increase the rate of reinforcement obtained from drug-use cessation, while reducing or eliminating the rate of reinforcement obtained through drug use and associated activities. That is, they work by changing reinforcement contingencies (Higgins & Rogers 2009). CM is usually based on providing patients with vouchers that can be used in exchange for goods or services, although this has recently been extended to prize-based (Petry *et al.* 2005) and employment-based rewards (Petry *et al.* 2005, DeFulio *et al.* 2009). In a typical voucher-based CM system, patients receive $2.5 for the first negative urine sample and $1.25 per negative sample thereafter. When they achieve three consecutive negative samples, patients get a $10 bonus. A positive sample or failure to submit a sample resets the vouchers. Over a 12-week treatment period, patients can earn a maximum of $997.5 (Higgins & Rogers 2009).

CRA uses different kinds of reinforcements from CM. Whereas CM uses artificial sources of reinforcement, CRA applies naturalistic resources such as employment, a stable family life, participation in social groups that reinforce abstinence and so on. CRA usually contains complex components and overlaps with CBT, possibly including skills training, couple therapy, employment or education counselling, HIV/AIDS education and also integrated therapies for alcohol abuse. It is logical that these two treatments can be combined to help drug users initially reduce their drug use for contrived rewards and then progress to more sustained natural alternative reinforcement. The original CM is used in methadone clinics to keep patients in treatment, and the reinforcement contingencies include take-home medication. The voucher system was developed in the 1990s for the treatment of cocaine dependence and to improve treatment retention, but has since been extended to other substances and goals, such as maintaining abstinence, facilitating treatment attendance and medication compliance (Higgins & Rogers 2009). Different types of vouchers have also been introduced, such as prize draws, cash and jobs.

Evidence for the Efficacy of CM

During the treatment period, CM can rapidly reduce cocaine (Rawson *et al.* 2002, Epstein *et al.* 2003, Rawson *et al.* 2006), amphetamine (Higgins 2006, Roll *et al.* 2006) or cannabis use (Budney *et al.* 2000, Sigmon & Higgins 2006). Its

therapeutic effects in SUDs have been confirmed by several meta-analysis reviews (Denis *et al.* 2006, Knapp *et al.* 2007, Dutra *et al.* 2008, Lee & Rawson 2008). A meta-analysis of 10 studies concluded that when CM was targeted at maintaining abstinence or medication compliance, it had a moderate effect (effect size = 0.32), but when targeted at facilitating treatment entry, the effect size was as small as 0.15 (Lussier *et al.* 2006). However, the long-term effect of CM in maintaining abstinence is in debate (McKay *et al.* 2010). Recently, a long-term clinical trial demonstrated that CM produced cocaine-free urine samples 6 months after providing the incentive to stop (McKay *et al.* 2010). Extending the treatment period to 36 weeks compared with 12 weeks significantly increased the duration of abstinence and this effect lasted for 1 year (Carpenedo *et al.* 2010).

There is robust evidence for the efficacy of CM in treating SUDs, but the greatest disadvantage is the high cost of treatment. The mean value of vouchers earned per patient during a 12-week treatment period is about $600 (Higgins *et al.* 2000, Petry *et al.* 2005). Prize-based CM was developed mainly for this reason (Petry & Martin 2002). In this treatment programme, for example, patients might receive one prize draw for one negative sample, with an additional one for each consecutive negative specimen up to a maximum of five. The number of draws is set back to one following a positive specimen or failure to submit a sample. In a total of 500 draws, more than half of them will yield no prize, 30% will yield a prize with a value of $1, 7% will yield a prize of $20 and only one draw will yield a prize of $100 (Petry *et al.* 2005). Prize-based CM is effective in prolonging cocaine abstinence and improving retention compared with standard treatment (CBT or 12-step) (Petry *et al.* 2005), even in severe cocaine users (Petry *et al.* 2005). Prize-based CM has also been shown to be as effective as voucher-based CM for treating cocaine dependence (Petry *et al.* 2005, Petry *et al.* 2007), but is more cost-effective (Olmstead & Petry 2009). The mean value of the prizes earned by participants was $117-203 in the two prize-based CM studies described above (Petry *et al.* 2005, Petry *et al.* 2005). Another variation in the format of CM is money-based CM. Money-based CM is attractive because it reduces costs by cutting the programme's operating expense (Vandrey *et al.* 2007). Money also provides a stronger reinforcement than food (Stoops *et al.* 2010). A small-sample clinical trial reported a trend for cash-based CM to produce a greater abstinence rate compared with the same value of goods-based CM (Vandrey *et al.* 2007). Giving cash directly to patients did not increase the use of drugs in this and another study (Festinger *et al.* 2008). Long-term treatment with voucher-, prize- or cash-based CM is difficult due to the high cost, and for most SUD patients, long-term care is important to prevent relapse. Employment-based CM is a more recently emergent model. Patients in this model are employed and paid, although the payment is not fixed and increases or decreases depending on the results of regular urinalysis (DeFulio *et al.* 2009). Compared with an employment-only format (payment is fixed and independent of urinalysis), employment-based CM produces significantly more negative urine samples in a 1-year treatment model (DeFulio *et al.* 2009). However, in another small-sample trial, the superiority of employment-based CM over

employment-only CM had disappeared 6 months after treatment discontinuation (Silverman *et al.* 2007). More research is needed, and employment-based CM could be incorporated into community treatment programmes for the long-term care of patients (DeFulio *et al.* 2009).

The value of vouchers in a CM program has been reported to influence treatment results. Greater monetary value is associated with greater effect sizes (Lussier *et al.* 2006) and this superiority can last up to 18 months when combined with CRA (Higgins 2006). In a recent 24-week treatment study, higher monetary value vouchers showed a clear trend to be more effective in retaining patients in treatment and maintaining abstinence than lower monetary value voucher at 6-month follow-up (Garcia-Rodriguez *et al.* 2009). In a cash-based model, higher doses also resulted in a better retention rate (Festinger *et al.* 2008). Nevertheless, cost is one of the biggest obstacles for the generalization of CM. Cost-effectiveness studies have compared CM with other therapy or evaluated the cost of adding CM to another study. One study compared higher value ($240) prize-based and lower value ($80) prize-based CM, combined with standard treatment in a cocaine community-based treatment centre. The cost per unit of incremental weeks of consecutive abstinence was measured, and higher-value prizes were found to be more cost-effective. The inclusion of lower-value prizes did not enhance the treatment outcome (Sindelar *et al.* 2007). However, whether society is willing to pay extra for the additional efficacy remains unknown.

For poly-drug abusers, CM could be designed as a dual therapy for abstinence from both drugs. For example, opiate-cocaine users might receive one prize draw for a cocaine-free sample and four prize draws for an opiate- and cocaine-free sample. This design could help to reduce the use of both drugs better than focusing on only one of them when offering prize draws. However, this conclusion is supported by only a few studies (Preston *et al.* 2008). Other factors, such as ethnicity (Barry *et al.* 2009) and income over the past year (Rash *et al.* 2009) were not related to treatment outcomes. Delivering the voucher immediately after verifying abstinence (during same clinic visit) rather than later resulted in significantly larger effect sizes (Lussier *et al.* 2006).

Evidence for the Efficacy of CRA Combined with CM

CRA studies were originally and most extensively focused on treating severe alcohol dependency; when extended to cocaine or opiate use disorders, CRA has generally been combined with CM. In early studies, CRA with 12- or 24-week CM was reported to be much better than standard drug counselling in achieving 8 or more weeks of cocaine abstinence and promoting retention (Higgins *et al.* 1991, Higgins *et al.* 1993). CRA+CM for 24 weeks significantly improved retention and provided more drug-free samples, compared with CBT alone during treatment and at 6-month follow-up (Secades-Villa *et al.* 2008, Garcia-Rodriguez *et al.* 2009), and the

effectiveness extend to 12 months in cocaine-dependent patients (Secades-Villa *et al.* 2011). An earlier study comparing CRA with CRA+CM showed 24-week CRA + 12-week CM produced more negative urine samples than CRA alone during the treatment period, but no difference remained after completion of CM. However, psychosocial functioning was still better in the voucher group than the non-voucher group 6 months after treatment entry in cocaine-dependent patients (Higgins *et al.* 2003). This result has been replicated in a more recently study (Garcia-Fernandez *et al.* 2011).

Summary

Without doubt, CM treatment alone or CM combined with CRA show a significant treatment effect across a range of substances. The biggest drawback of these treatment methods is the duration of their effect. However, a number of studies have shown that the effects can be retained after discontinuation of the reinforcement contingency. CM can facilitate treatment entry, retention and abstinence. Future studies should work towards developing a more cost-effective model, revising the format for different subgroups of patients and adapting it to community treatment programmes to provide a long-term treatment approach for patients with SUDs (Petry 2010).

Motivational Interviewing (MI)

Introduction of MI

Motivational interviewing is a brief intervention using clinically focused, directive methods to enhance intrinsic motivation and elicit change by exploring and resolving ambivalence (Miller & Rollnick 2002). MI has four principles: expressing empathy, developing discrepancy, rolling with resistance and supporting self-efficacy (Glynn & Moyers 2009), and uses techniques such as open-ended questioning, reflective listening, selectively reinforcing participants' change-related statements, and skills to handle resistance (Carroll *et al.* 2006). In the MI model, "denial" is considered to be normal and the task of the counsellor is to build up a strong client-counsellor relationship, help the client to explore their ambivalence and encouraging them towards behavioural change. The format of MI usually varies from 15 minutes to multiple sessions depending on the treatment condition (Carroll *et al.* 2006, D'Amico *et al.* 2008, Walker *et al.* 2011). During the MI session, special attention must be paid to the client's language, in which self-motivating statements of change, or "change talk", are thought to predict further changes of behaviour up to one year after the intervention, whereas "counterchange talk" refers to the resistance to change and predicts negative outcomes. Counsellors are suggested to empathically guide the client in expressing a style of "change talk" (Glynn & Moyers 2009).

Evidence for the Efficacy of MI

MI has been evaluated in various treatment settings, such as community-based outpatient programmes for SUDs, primary clinics and schools, and as a single intervention or as a component of an integrated programme. Most evidence comes from alcoholism studies (Glynn & Moyers 2009).

Studies based in community-based outpatient settings have evaluated the effect of MI on facilitating engagement and retention in a treatment programme and reducing drug use in the short and long term. A number of early studies provided strong support for MI in SUD treatment (Dunn *et al.* 2001, Burke *et al.* 2003, Hettema *et al.* 2005). In one study, a 2-hour MI was compared with a 2-hour standard intake assessment (information collection, clinic orientation), both followed by 28-day weekly group treatment and with follow-up assessment after 84 days. MI had a significantly better retention rate than standard intake assessment at 28 days but only a trend at 84 days. No effect on reducing drug use was found in the MI group (Carroll *et al.* 2006). However, in other studies, there was no difference between the MI + standard group and the standard group on any outcome measure of drug use (Donovan *et al.* 2001, Miller *et al.* 2003). The mechanism of effect in MI is not clear. Possible

reasons for the negative result may be that the effect of MI was diluted by the subsequent extensive treatment (Carroll *et al.* 2006), or that MI may not work equally well for all types of patients (Martino *et al.* 2006). Several studies have shown that two sessions of MI can reduce cannabis use in outpatient treatment settings (Martin & Copeland 2008), though it was less potent than more extensive treatment (The Marijuana Treatment Project Research Group 2004).

In school settings, MI is used as a single intervention for reducing drug use in high-risk subjects or mild-moderate users. A single session (60 minutes) of MI was reported to significantly reduce self-reported alcohol, cigarette and cannabis use 3 months after intervention compared with usual educational intervention in a multi-site study (McCambridge & Strang 2004). However, the group difference had disappeared 12 months after intervention, although cannabis use in the MI group remained less than at baseline (McCambridge & Strang 2005). In another study, two-session MI was compared with educational feedback (EF) and no-treatment. At the 3-month assessment, those in the MI and EF groups used less cannabis than the no-treatment group and MI was better than EF. Both MI and EF maintained their effect at 12 months, with no difference between them (Walker *et al.* 2011).

Health care settings such as hospitals or emergency departments can also provide MI treatment if abusers come to seek medical treatment. Short-MI, usually less than one hour, has been proved effective in reducing alcohol consumption or related harmful behaviours (Monti *et al.* 2005) (Knight *et al.* 2005). An evaluation of an even shorter MI (15 minutes) was performed in a community-based primary clinic. Participants accepted either MI or usual care. At 3-month assessment, the MI group had less cannabis use, fewer friends who used cannabis and lower intention to use cannabis in the next 6 months than those who received usual care (D'Amico *et al.* 2008).

Summary

MI as a brief intervention can be used both as a one-off intervention and as a prelude to an extensive treatment programme. When combined with other treatments, MI may help to improve initial treatment retention but might not affect drug use outcome directly. Single-session MI can be applied in schools or medical care settings to encourage drug users to change their drug use behaviour. However, most evidence has come from youth studies with mild drug use.

12-step facilities and self-help groups (SHG)

Introduction of 12-step and SHG

The most widely available self-help groups are those based on the 12-step

programme originally developed in the alcohol abuse field and known as AA (Alcoholics Anonymous). The 12-step approach has been adapted to other areas, including CA (Cocaine Anonymous), NA (Narcotics Anonymous) and, more recently, CMA (Crystal Meth Anonymous), and many fields other than SUDs. The 12-step approach focuses on abstinence but views it as a lifelong process. Recognizing and relying on a "higher power" is a central component, and other key points are self-acceptance, personal inventory and making changes (Kleber *et al.* 2007). The group can prevent members from relapsing via role modelling, social support, organizing social events and helping members to cope with high-risk situations. Apart from simple attendance, some behaviours are regarded as active participation, such as speaking at meetings, working on one or more of the 12 steps, having a sponsor, or performing duties such as making coffee at meetings (McKay *et al.* 1998). The advantage of such self-groups is their ready availability, effectiveness and no or low cost (Donovan & Wells 2007). However, enrolment in 12-step self-help groups is low and the dropout rate is high in patients discharged from either outpatient or inpatient treatment programmes or in patients never seeking treatment (Kelly & Moos 2003). Based on their success in the alcohol treatment field, 12-step affiliated treatments have been increasingly studied in the treatment of drug use disorder.

Evidence for the Efficacy of 12-step and SHG

Strong evidence has demonstrated the effectiveness of 12-step affiliated treatment for maintaining abstinence. However, most of the evidence comes from alcohol treatment studies. Some support from other SUD studies has emerged in the past decade and the number of studies is increasing. Attending an SHG during (Fiorentine & Hillhouse 2000) (McKay *et al.* 1998, Laudet *et al.* 2007) or after (Fiorentine 1999, Humphreys & Moos 2007, Timko & DeBenedetti 2007, Grella *et al.* 2010, Bonn-Miller *et al.* 2011) treatment has been found to be effective in increasing and maintaining abstinence rates, and reduces the cost of continuing care (Humphreys & Moos 2007). Attending an SHG during treatment facilitated attendance in the post-treatment period (Laudet *et al.* 2007). Further studies proved that only those with frequent and active participation achieved good outcomes. Those attending 12-step group meetings, either weekly or more frequently post-treatment, had less stress (Laudet & White 2008) (Humphreys & Moos 2001) and lower drug use for up to 2 years than those attending group meetings less than once a week or never attending (Laudet *et al.* 2007). Active participation by cocaine-dependent patients is more important than meeting attendance in reducing cocaine use (Weiss *et al.* 2005, Majer *et al.* 2011).

As 12-step SHGs are a cost-effective treatment for long-term remission from substance abuse, more studies have focused on how to encourage the utilization of SHGs. Studies found that those receiving 12-step oriented treatment are more likely to attend a SHG during or after treatment (McKay *et al.* 1998, Humphreys *et al.* 1999). Outpatient treatment programmes with 12-step self-meetings held on site have a higher percentage of patients involved in self-help groups (Laudet *et al.* 2007).

Intensive referral increases post-treatment SHG attendance and is associated with higher abstinence rates (Timko & DeBenedetti 2007). The religious aspect of SHGs has been viewed as an obstacle to participation, although in one study, individuals who engaged in fewer religious activities still benefited (Winzelberg & Humphreys 1999).

Summary

12-step self-help groups are a cost-effective approach for SUD treatment. They can enhance or maintain treatment outcome both during and after a standard treatment. Their role in the long-term care of SUDs patients has been confirmed. However, they are underutilized and studies are now focusing on how to make full use of them.

Treatment Combination and Treatment Model

Treatment Combination

The single psychological treatment approaches mentioned above are all evidence-based and effective, but may work on different time frames. For example, CM is effective soon after treatment begins but may not last in the long term. In contrast, CBT is effective in initiating abstinence and preventing relapse, but its effect has a late onset. In clinical practice, these treatment approaches are usually combined to provide better benefits for patients.

CM can be an important component in a treatment program. It can speed up and enhance the effect onset, and encourages patients to stay in treatment longer so that they have a chance to benefit from other treatment methods. As mentioned above, CM combined with CRA has been proven to be better than CRA alone, and CM combined with CBT (Rawson *et al.* 2002, Budney *et al.* 2006, Rawson *et al.* 2006) (Shoptaw *et al.* 2005) or with RP are better than CBT or RP alone (McKay *et al.* 2010). Although CBT combined with CM did not show a greater effect than CM alone during treatment period, the benefits tend to emerge gradually after treatment and last up to one year. In a multi-site study, CM combined with treatment as usual significantly improved 3-month retention in both settings, and the duration of continuous abstinence also improved in the incentive condition (Stitzer *et al.* 2010). MI is a brief intervention when performed before initiating a formal treatment, and can enhance engagement and retention (McKee *et al.* 2007). A 12-step self-group, as mentioned above, is strongly recommended to combine with or follow a standard treatment to maintain abstinence over a longer period. Drug abuse treatment, psychiatric comorbidity screening and treatment, the need for education and work skills, house and so on, are all urgent problems that challenge therapists. Collaboration between services and professionals from different disciplines is needed to overcome these challenges.

Intensive Outpatient Treatment Model: The Matrix Model

The Matrix Model is an outpatient community reinforcement approach established in the 1980s, targeting cocaine abuse. Counselling was administered by professional therapists with a master degree in counselling. Relapse prevention is the core component of the model. The model includes a 16-week treatment phase and an aftercare phase of up to a year. The first 4 weeks is the early recovery period. There are three sessions of individual therapy, distributed into the three phrases. The therapist will discuss treatment goals and progress with clients in these individual sessions and this is critical for building up a relationship between client and therapist. Family members can also attend these individual sessions. In the first 4 weeks, there are eight sessions of recovery skills training in which clients learn how to stop drug use. During weeks 5-16, relapse prevention group sessions are held twice a week,

together with weekly family group education. In the last 4 weeks of the 16-week treatment period, a weekly social support group session is added after the family group and this continues for up to one year. During the whole year, weekly 12-step meetings are held on site. Clients in any stage are encouraged to attend these meetings. Drug and alcohol tests are held once a week. This model integrates relapse prevention, family and group therapies, drug education, drug abuse monitoring and onsite 12-step meetings (Obert *et al.* 2000).

In one control study, the Matrix Model was compared with other community resources; at 6-month and 12-month assessment, both treatment conditions had reduced methamphetamine significantly, with no difference found between conditions. However, a positive association between negative urine samples and the amount of treatment received was found in the Matrix Model (Rawson *et al.* 1995). In a follow-up study, 114 of the total 500 methamphetamine (MA) dependent patients attended assessments made 2-5 years after their outpatient treatment; of these, 17.5% reported MA use in the past month, which was significantly reduced from 86% at baseline, one month prior to treatment (Rawson *et al.* 2002). In a later study conducted on methamphetamine abused patients, the Matrix Model was compared with treatment as usual. The Matrix Model retained clients longer in treatment, and provided more negative samples and longer periods of abstinence. However, the superiority of the Matrix Model disappeared at 6/12-month follow-up (Rawson *et al.* 2004). Though the Matrix Model failed to show better long-lasting effects than other treatments in the follow-up assessments, it may have short-term benefits (Rawson *et al.* 2004).

Residential Treatment Model

The most popular residential treatment takes place in therapeutic communities (TCs). Treatment lasts a relatively a long time, from 6 to 12 months, especially for those with more severe problems, such as a longer history of drug abuse or co-occurring mental disorders, and for offenders and the homeless. TCs develop a culture in which patients learn to change themselves and others through a self-help process, developing vocational, social and living skills and promoting pro-social values within a no-drug environment, using social networks to sustain recovery. In later practices, the TC model has been modified to be more flexible, less intense and more individualized, and renamed as modified therapeutic communities (MTC) (Sacks *et al.* 2008). A meta-analysis reviewed three studies comparing MTC and standard treatment in abusers with homelessness (De Leon *et al.* 2000) or offending behaviour (Sacks *et al.* 2004, Sullivan *et al.* 2007), and with MTC added to an outpatient treatment for co-occurring mental disorders (Sacks *et al.* 2008). MTC was superior to standard treatment on drug use, mental health, crime, HIV-risk behaviour, employment and housing outcome measurements.

Long-term Recovery Model: The Recovery Management Model (RM)

Most of the treatments mentioned above are based on an “acute care model” (AC) in which intervention usually lasts no more than 1 year. The individual, family

and community tend to regard discharge as meaning "cure has occurred" and long-term abstinence is viewed as personally self-sustainable without ongoing professional assistance (White & McLellan 2008). However, addiction is now recognized as a chronic disease; the pattern of drug use is long-term across all kinds of drugs (Hser & Anglin 2011) and the relapse rate is high (Hser *et al.* 2006, Dennis *et al.* 2007). Based on this background, long-term recovery care models have emerged but are still being developed (Hser & Anglin 2011).

The Recovery Management Model (RM)

Recovery management is about organizing treatment and recovery support to enhance early pre-recovery engagement, recovery initiation, long-term recovery maintenance, and to improve quality of life. Compared with AC, RM makes changes to several components involved in a treatment programme. First, RM makes an effort to increase access to treatment. In contrast to AC, in which patients usually enter treatment by referral, RM aims to reach patients in the early and middle stages of the development of their drug problem. RM has developed methods and skills to attract and actively contact patients. Second, once in contact, RM tries to keep them in the care system and performs continual, comprehensive, asset-based, family inclusive assessments to screen for possible problems that might need intervention. Third, the RM model has a more complex service team composition than the AC model, including physicians, psychiatrists, psychologists and social workers, and also recovered peers, alumni associations, volunteer programmes and formal indigenous healers. Fourth, RM prefers to offer teaching and support services rather than just treatment. Professional treatment is focused on client-directed treatment plans. Fifth, RM extends the treatment dose and treatment menu to clinical and non-clinical recovery support. Sixth, RM provides services or care in a community-based or natural environment. Seventh, RMC has a strong link with other community recovery programmes, such as self-help groups. Eighth, RM is more flexible and comprehensive, all clients are admitted and long-lasting post-treatment monitoring is included (White & Kelly 2011). Although RM is still developing, some evidence has been provided.

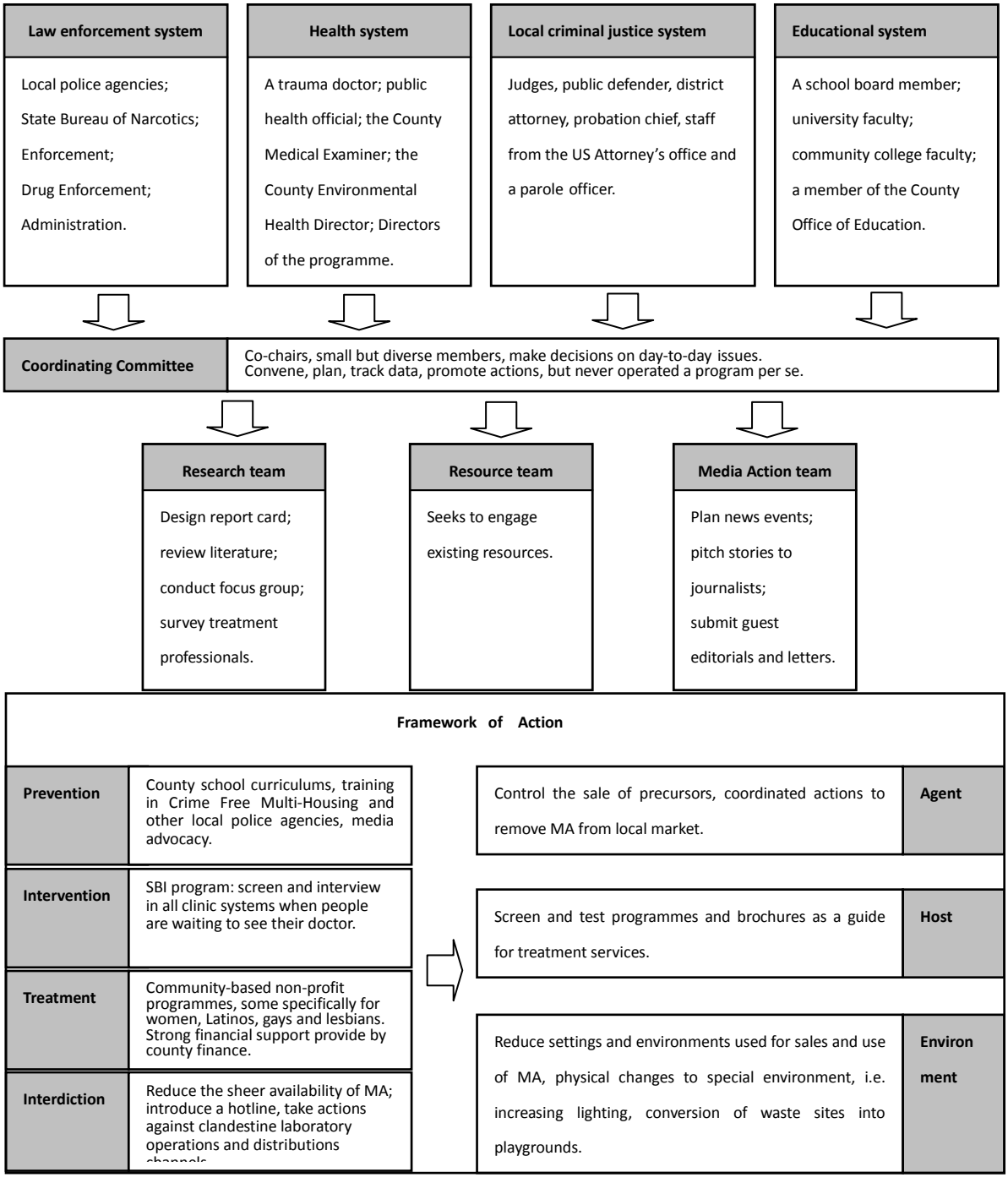
A programme named Recovery Management Checkup was proposed recently, based on the philosophy of RM. Patients in this programme are followed for 2-3 years, and are interviewed every 3 months. Participants meeting the criteria for treatment are immediately transferred to a link manager, and undergo a motivational interview. The manager in charge arranges scheduling and transportation to treatment. Compared with a control condition, patients in an RM checkup group had better drug use outcomes and were less likely to be in need of treatment in five or more quarters and in the final quarter (Dennis *et al.* 2003). In a later study, patients in an adapted RM model significantly had more days of abstinence during the 2-year follow up, though the effect was only two extra days of abstinence per month (Scott & Dennis 2009). Another model that was adapted from RM, named telephone monitoring and

counselling (TMC), provided services by telephone. In an 18-month study, TMC produced less frequent drinking than treatment-as-usual at 12-month, 15-month and 18-month assessments. TMC was better than TM (monitoring only, no counselling) at 6-month assessment (McKay *et al.* 2011).

A Collaborative Model: The Methamphetamine Strategy Force Model

This model was introduced in 1996, in San Diego County, USA, and was advocated by the San Diego County Alcohol and Drug Services to tackle the methamphetamine problem. To promote better collaboration between different disciplines, the MA Strategy Force created a leadership committee with members selected from public or private agencies at local, state and federal level. Four consecutive meetings are held over three months to exchange perspectives on local MA problems. The Strategy Force model integrates four areas: prevention, intervention, treatment and interdiction strategies. Efforts are concentrated on three areas: controlling the development and circulation of MA, enhancing screening and facilitating treatment engagement; renovating drug-plagued housing areas or rural manufacturing sites by increasing lighting and turning waste sites into playgrounds; and increasing law enforcement. Figure 1 shows the organization of the Strategy Force. Under the umbrella of the MA Strategy Force, several projects or campaigns have been introduced, such as Drug Endangered Children (DEC), which require cooperation between the local police department and the Health and Human Services Agency to provide early intervention for children involved in drug crime. The MA Strategy Force can be seen as an example of how coordinated collective action can be used to shape community norms through community organizing, policy development, law enforcement and strong media coverage (Goldberg 2007).

Figure 1 Construction and framework of the programme



Summary

Treatment combination and treatment models can further enhance retention and outcome. Psychotherapies vary in quality and quantity among different treatment programmes and settings. Staying longer in treatment and early abstinence are important predictors of abstinence at follow-up (Higgins *et al.* 2000). Long-term outcome studies have reported increased abstinence times; better health, personal and social resources and higher self-efficacy are important for maintaining recovery (Hser & Anglin 2011). Recently, continuing care has been recognized as critical for the long-term recovery of addicted patients.

Summary of Psychosocial Therapy

Psychosocial therapy has been proven to be effective in addiction treatment and is especially important for substances other than opiates, alcohol and nicotine. CBT, CM, MET, CRA and 12-step self-help groups are all evidence-based treatment methods. The 12-step self-help group is particularly important in providing long-term care for addiction patients. Treatment models of varied intensity are also effective and better than single treatment methods, especially for severe abusers. Besides the traditional acute care model, continuing care models are increasingly studied for the chronic characteristic of addiction disorder. The main challenge now facing psychosocial therapy is poor treatment retention and the difficulty of initiating and maintaining abstinence. The mean dropout rate among therapies is 35.4%, and patients treated for cocaine use have a higher dropout rate than for cannabis and poly-drug use. About 31% of patients achieve post-treatment and/or clinically significant abstinence (Dutra *et al.* 2008). One long-term outcome evaluation study showed that treatment outcomes are generally stable in the 5 years after discharge from long-term residential, short-term residential and outpatient treatment settings. However, readmission is common, with 25-35% patients readmitted into an addiction treatment programme within one year and 50% within 2-5 years (Simpson *et al.* 1999, Simpson *et al.* 2002), with drug use slowly increasing 1 year after discharge from treatment. In general, longer treatment duration (more than 6 months) (Hubbard *et al.* 2003), more active participation, and stronger personal and social resources are associated with better outcomes (Hser & Anglin 2011). Future work should concentrate* on facilitating long-term recovery from addiction.

Pharmacological Treatment Methods

Neurotransmittors such as dopamine (DA), opioid peptides, serotonin (5-HT), gamma-aminobutyric acid (GABA) and endocannabinoids are involved in the acute reinforcement of drugs. Increased activation in the brain's stress system, corticotropin-releasing factor (CRF) and norepinephrine (NE), together with dysregulation of the neuropeptide Y brain anti-stress system, also contribute to the development of drug dependence (Caldeiro *et al.* 2009). A chronic increase in DA induced by drugs can impair the glutamine system, which together with the DA system plays an important role in drug-seeking behaviours during the abstinence stage (Kalivas *et al.* 2005, Kalivas 2007, Kalivas & Volkow 2011). Based on these theories, dozens of agents have been tested in preclinical or clinical experiments in the search for an ideal pharmacological treatment that can achieve and maintain abstinence.

The pharmacological treatments recommended in the APA (American Psychiatric Association) guidelines include 1) medications to treat intoxication and withdrawal states, 2) medications to decrease the reinforcing effects of abused substances, 3) agonist maintenance therapies, 4) antagonist therapies, 5) abstinence promoting and relapse prevention therapies, and 6) medications to treat comorbid psychiatric conditions (Kleber *et al.* 2007). This charter will focus on the treatments targeted at decreasing craving or achieving and maintaining abstinence.

Agonist maintenance therapies are also called replacement therapies, as they usually act in the same way as the abused drug but have a slow onset and extended pharmacological effect. Even so, any medication that is used as a replacement for an abused drug has a high risk of dependence itself. Antagonist therapy, however, is designed to block the effect of the abused drug to eliminate or decrease its reinforcing effects. An antagonist binds to a specific receptor to prevent binding between the abused drug and the receptor. In this way, the activation of an abused drug is blocked. There are other medications that do not act directly on the receptor to directly mediate the activation effect of the abused drug, but indirectly modify the effect of the abused drug via other receptor systems. Medications targeted at removing the symptoms of withdrawal come under relapse management, such as using antidepressants to treat depressive symptoms during the withdrawal stage. Although no single medication has so far been recommended to treat substance abuse or dependence, many therapies have shown the potential to decrease craving (Caldeiro *et al.* 2009).

Pharmacological Treatment for Cocaine Use Disorder

Introduction to the Biological Mechanism of Cocaine Addiction

Acute use of cocaine inhibits the reuptake of DA, 5-HT and NE, leading to increased levels of monoamine neurotransmitters in the brain. Activation of the mesocorticolimbic DA system plays a key role in the euphoric effect of drugs and this effect is mainly mediated by the D_2 receptor (Haile *et al.* 2009). Despite the established DA theory of drugs' euphoric effect, growing evidence shows that NE is also important in the amphetamine-induce euphoric effect (Rothman *et al.* 2001). Chronic use of cocaine depletes DA and other neurotransmitters, such as 5-HT and NE, and also induces hypersensitivity in the DA receptor; these effects are the basis for the development of dependence and withdrawal symptoms (Herin *et al.* 2010).

Antagonist-like Therapies

1.2.1 DA receptor antagonists

Cocaine increases brain DA levels by reuptake inhibition, and activates the reward system via the D_2 receptor, which is crucial for the "high" effect of cocaine. Therefore, blocking the DA receptor may block the "high" effect of cocaine and thus reduce cocaine use. Several antipsychotics that act mainly by blocking the D_2 receptor have been suggested as plausible candidates for treating cocaine addiction. Risperidone has shown no effect in reducing cocaine use and craving in controlled clinical trials (Grabowski *et al.* 2000, Grabowski *et al.* 2004, Smelson *et al.* 2004, Akerele & Levin 2007, Loebl *et al.* 2008). Olanzapine was also ineffective in two controlled clinical trials (Kampman *et al.* 2003, Reid *et al.* 2005, Hamilton *et al.* 2009), though preclinical studies and case reports have shown some effect. In 2010, a systematic review found no evidence to support the efficacy of olanzapine, risperidone and haloperidol in treating cocaine dependence (Amato *et al.* 2007). It is suggested that these antipsychotics worsen the DA depletion in chronic cocaine abusers. Apart from the effects on the D_2 receptor, risperidone also blocks the 5-HT_2 receptor, which may lead to the worsening of depressive symptoms in cocaine abusers (Loebl *et al.* 2008). Neuroleptics have lower D_2 receptor binding; quetiapine has shown promising effects in reducing cocaine or amphetamine craving in several open-label trials (Hanley & Kenna 2008) and one randomized blind clinical trial (Nejtek *et al.* 2008) in patients with comorbid bipolar disorder or schizophrenia. One open-label trial with non-psychotic men reported that quetiapine consistently decreased cocaine craving (Kennedy *et al.* 2008). However, so far there is no evidence from RCTs to prove their efficacy. Unlike dopamine antagonists, aripiprazole is a partial agonist of the D_2 receptor; it acts as an agonist when the extracellular dopamine level is low and acts as an antagonist when the extracellular dopamine level is high. However, in several human laboratory studies, repeated aripiprazole increased cocaine and amphetamine use (Tiihonen *et al.* 2007, Haney *et al.* 2011). Because aripiprazole decreases the "high" effect of acute cocaine use, it may cause compensatory use of cocaine. Although inefficacious for treating cocaine dependent patients, aripiprazole may be useful in relapse prevention because of its effect on blocking the euphoria of cocaine (Haney *et al.* 2011). Two clinical trials of aripiprazole in preventing cocaine

relapse are ongoing.

GABAergic agents

Gamma-aminobutyric acid (GABA) is an important inhibitory neurotransmitter in the central nervous system. GABAergic interneurons inhibit the release of DA in the ventral tegmental area (VTA) and nucleus accumbens (NA) (Kalivas 1993). Activate GABAergic transmission may dampen the increase in extracellular DA levels in the NA caused by cocaine, and thus can theoretically reduce the reinforcement effect of cocaine (Koob & Nestler 1997). Two meta-analysis studies evaluated RCTs of anticonvulsants for treating cocaine addiction, including carbamazepine, gabapentin, lamotrigine, phenytoin, tiagabine, topiramate and valproate, and found no evidence to support their effectiveness. However, the power of this review was limited by the large discrepancies between studies (Minozzi *et al.* 2008, Alvarez *et al.* 2010). Baclofen is a $GABA_B$ agonist. In one RCT study, baclofen significantly reduced cocaine use in a subgroup of heavy users (Shoptaw *et al.* 2003). However, in a more recent RCT study that focused on heavy cocaine users, baclofen failed to show any efficacy (Kahn *et al.* 2009). Further studies could try a higher dose or explore its efficacy in relapse prevention (Kahn *et al.* 2009). Though only one published RCT study has demonstrated its effectiveness in facilitating abstinence in cocaine addicts (Kampman *et al.* 2004), topiramate is strongly anticipated as a medication for cocaine addiction based on its effect on modulating DA neurotransmission via both GABAergic and glutamatergic pathways (Kampman 2010). Vigabatrin is an irreversible inhibitor of GABA transaminase that can elevate brain GABA concentrations. It has been shown to reduce cocaine use and promote abstinence and retention rates in one RCT study (Brodie *et al.* 2009). Several registered clinical trials on topiramate and vigabatrin are in progress.

Opioid receptor antagonist

Chronic cocaine use increases μ-opioid receptor binding in the limbic area, which is associated with cocaine craving (Gorelick *et al.* 2005). Only one controlled study has assessed the efficacy of naltrexone (50mg/d) combined with relapse prevention therapy (RP) for cocaine dependence, and reported that RP-naltrexone could reduce cocaine use compared with RP-placebo (Schmitz *et al.* 2001). Most studies on cocaine-alcohol dual dependence have focused on cocaethylene, a synthesized long-acting metabolite of naltrexone. However, the effects on cocaine-alcohol dual dependence were negative at 50 mg/d (Schmitz *et al.* 2004), and contradictive at 100mg/d (Pettinati *et al.* 2008) (Schmitz *et al.* 2009) and 150 mg/d (Pettinati *et al.* 2008, Schmitz *et al.* 2009). A larger-sample RCT of naltrexone for treating cocaine dependence is ongoing [ClinicalTrials.gov identifier: NCT00218023].

Agonist-like Therapies

DA agonist therapies

Chronic cocaine use causes dopamine depletion, up-regulation of postsynaptic receptors and decreasing cocaine stimulation, all of which may contribute to "craving" during withdrawal. DA agonists can readjust the super-sensitivity of DA receptors and alleviate dopamine depletion in chronic cocaine users, and thus are suggested for use in the withdrawal stage to maintain cocaine abstinence, in the same way as methadone is used in opioid dependent patients (McCance 1997, Soares *et al.* 2003). Several types of DA agonists (Amantadine, bromocriptine and pergolide) have been tested in clinical studies in the past two decades, but none of these agents has proven to be effective in reducing cocaine use and preventing relapse (Malcolm *et al.* 2000, Soares *et al.* 2003, Focchi *et al.* 2005, Soares *et al.* 2010). L-dopa is a precursor of levodopa and can replenish dopamine depletion in cocaine addicts. In a clinical trial, L-dopa was administered in combination with carbidopa, a peripheral decarboxylase inhibitor that can decrease potential side effects while increasing brain dopamine levels. L-dopa/carbidopa alone have no effect on reducing cocaine use (Mooney *et al.* 2007), but have some benefit when combined with a robust behavioural therapy (Schmitz *et al.* 2008). Thus, agonists with a narrow action are suggested to be best reserved for special circumstances or therapeutic approaches (Herin *et al.* 2010).

Metabolism inhibitor

Disulfiram is a general enzyme inhibitor. Its inhibition of dopamine-beta-hydroxylase leads to increased DA levels and decreases NE levels in the reward circuit, which is thought to be related to the decreased "high" effect of cocaine, and thus reduces craving [Schroeder 2011, Gaval-Cruz 2009, Becker 2007]. In clinical trials, disulfiram reduced cocaine use in primary cocaine-dependent abusers (Carroll *et al.* 2004), alcohol-cocaine dependent abusers (Carroll *et al.* 1998, Carroll *et al.* 2000) and dual cocaine/opioid dependent abusers (George *et al.* 2000, Petrakis *et al.* 2000), although other clinical trials have reported conflicting results (Pettinati *et al.* 2008, Oliveto *et al.* 2009). In a recent meta-analysis (Pier Paolo Pani *et al.* 2010), it was concluded that the evidence level for the effectiveness of disulfiram in treating cocaine dependence was low. By blocking the metabolism of cocaine, disulfiram can increase tissue DA and blood cocaine levels, and hence it has the potential to increase the adverse responses of cocaine, such as paranoia and increased blood pressure (Gaval-Cruz & Weinshenker 2009). Though disulfiram was reported to be generally safe in the abovementioned clinical studies, cardiovascular vulnerability and other possible comorbidity should be considered in clinical practice (Pier Paolo Pani *et al.* 2010, Roache *et al.* 2011). So far, the mechanism for how disulfiram could reduce cocaine dependence is not yet clear and pharmacogenetic factors may also influence its effect (Gaval-Cruz & Weinshenker 2009, Haile *et al.* 2009).

Another metabolism inhibitor that has been studied is selegiline, an irreversible selective inhibitor of monoamine oxidase type B (MAO-B). Inhibition of

MAO-B increases concentrations of DA and other neurotransmitters. Chronic use of Selegiline and cocaine could reduce the "high effect" of an acute dosage of cocaine (Bartzokis *et al.* 1999, Houtsmuller *et al.* 2004), and thus may help to reduce drug-seeking behaviours. However, clinical studies have reported contradictive results (Elkashef *et al.* 2006). A recent study of the effect of selegilines on cigarette cessation reported negative results, and nicotine dependence is also related to the DA system [Killen 2011]. Selegiline is safe when used in cocaine dependent subjects (Bartzokis *et al.* 1999, Houtsmuller *et al.* 2004, Harris *et al.* 2009) and may facilitate relapse prevention (Schiffer *et al.* 2003).

Stimulant replacement treatment

Amphetamine-like stimulants

The classical definition of stimulants is based on the behavioural affects that increase the level of activity in the central nervous system, causing effects such as alertness and arousal (Moeller *et al.* 2008). Stimulants do not bind to a single receptor but are more likely to inhibit reuptake or increase the release of monoamines (Moeller *et al.* 2008). As the DA, NE and 5-HT systems are all involved in the acute and chronic effects of cocaine, and agents that selectively affect the dopaminergic system have received less promising results in clinical trials, it has been suggested that medications that broadly affect the DA, NE and 5-HT systems are potent enough to act as substitutes for cocaine, and thus eliminate cocaine use in addicts (Grabowski *et al.* 1997, Herin *et al.* 2010). Although highly addictive substances themselves, oral and sustained release formulations and careful titration may help to reduce the liability of abuse of these replacement drugs. Several amphetamine-like stimulants have been studied as replacements for cocaine.

Methylphenidate (MPH) oral preparation (Ritalin) has been used in treating attention-deficit hyperactivity disorder (ADHD), postural orthostatic tachycardia syndrome and narcolepsy. It was the first stimulant-like agent to be studied as a substitute for cocaine (Grabowski *et al.* 1997). MPH is a monoamine transporter inhibitor whose structure and effects are similar to cocaine and amphetamine; it can increase the levels of dopamine and norepinephrine in the brain with the greatest selectivity on DA transporters. However, its reinforcing effect is less potent and lasts longer than cocaine (Volkow & Swanson 2003). MPH was found to be safe and acceptable in cocaine dependent patients but had no effect in reducing cocaine use in cocaine (Grabowski *et al.* 1997, Roache *et al.* 2000) or dual addicts (Levin *et al.* 2006). However, MPH reduced cocaine use in patients whose comorbid ADHD symptoms responded to MPH (Levin *et al.* 2007). Stronger reinforcers, such as dextroamphetamine, have been recommended (Grabowski *et al.* 1997).

Dextroamphetamine works as a substrate of monoamine transporters to increase extracellular DA, NE and 5-HT levels and can be regarded as a monoamine

releaser (Kuczenski *et al.* 1995). Two studies found that dextroamphetamine at a higher dose (30-60 mg/day) was effective in reducing use and craving in cocaine addicts (Grabowski *et al.* 2001) and methadone maintenance in dual cocaine-opiate dependent addicts (Grabowski *et al.* 2004) without causing severe side effects. A study that used dextroamphetamine-IR (immediate release) showed no improvement compared with placebo (Shearer *et al.* 2003). Dextroamphetamine-SR (sustained release) is better than dextroamphetamine-IR, and higher dosage (30-60 mg/day) is better than lower dosage (15-30 mg/day) (Grabowski *et al.* 2001). These studies, together with studies in amphetamine (mentioned below) or methamphetamine patients, demonstrate the efficacy of dextroamphetamine in treating stimulant dependence, though its efficacy in cocaine addiction needs evidence from more potent clinical trials. Lisdexamfetamine (LDX) is a new amphetamine formulation that consists of dextroamphetamine covalently bonded to the amino acid lysine. After oral intake, LDX is converted to the active drug dextroamphetamine by gastrointestinal enzymatic systems. This new design has several advantages: delaying the onset of effect, prolonging efficacy, reducing the risk of intake by other routes (intravenous or intranasal) and the risk of overdose. A phase II clinical trial of LDX combined with CBT in treating cocaine dependence is in progress (Herin *et al.* 2010).

Methamphetamine is a potent DA/5-HT/NE releaser, and its oral preparation has been proven by the FDA for shortening treatment of refractory ADHD (Desoxyn®). A recent study by Mooney provided robust evidence that methamphetamine SR could dramatically reduce cocaine use with acceptable retention rates and tolerance, whereas IR had no benefit compared with placebo (Mooney *et al.* 2009). A recent meta-analysis indicated that stimulant replacement treatments have promising efficacy in improving sustained cocaine abstinence, but cannot fully support it (Castells *et al.* 2010). Bupropion is a dopamine and norepinephrine reuptake inhibitor and has been proven as a treatment for nicotine dependence. It is not a clear stimulant because studies have not consistently reported its stimulant properties in humans (Castells *et al.* 2007). However, due to its augmented effect on central DA levels, it is considered a plausible candidate for cocaine treatment. Bupropion was reported to reduce cocaine use in addicts with comorbid depression (Margolin *et al.* 1995) or when combined with contingency management (Poling *et al.* 2006).

Although studies have demonstrated the potential clinical application of the above stimulant agents in treating cocaine addiction (Karila *et al.* 2008, Moeller *et al.* 2008, Castells *et al.* 2010, Herin *et al.* 2010), several disadvantages limit their clinical application. The first is the risk of cardiovascular toxicity and psychiatric symptoms. Although stimulant agents were reported as safe and acceptable (Castells *et al.* 2010, Herin *et al.* 2010) and did not cause serious adverse events in any of the abovementioned studies, it should be noted that all of the participants in these studies were screened for cardiovascular disease or had relatively good health (Moeller *et al.* 2008). Another disadvantage is the significant potential for abuse. Preclinical studies

have shown that dextroamphetamine, methylphenidate and high dose bupropion have self-administration effects (Castells *et al.* 2010). Misuse of dextroamphetamine, methylphenidate, bupropion and modafinil has also been observed (Williams *et al.* 2004, Castells *et al.* 2010, Johnston *et al.* 2010), though none of the participants in controlled clinical trials developed abuse of treatment medication (Moeller *et al.* 2008).

New replacement agents

A recent study proposed a dual DA-5-HT deficit model of stimulant withdrawal. Chronic cocaine use causes both DA and 5-HT depletion in the central nervous system. A deficit in synaptic DA underlies ahedonia and psychomotor retardation, whereas depletion of synaptic 5-HT leads to depressed mood, obsessive thoughts and lack of impulse control; both of these systems contribute to withdrawal symptoms, craving and relapse. Instead of focusing on DA replenishment, this model addressed the important role of 5-HT in suppressing the DA-induced reinforcing effect (Rothman & Baumann 2006, Rothman *et al.* 2008). A combination of the DA releaser phentermine and the 5-HT releaser fenfluramine reduced cocaine use in both animal (Glatz *et al.* 2002) and clinical studies (Kampman *et al.* 2000). A new 5-HT/DA releaser, PAL 287, is a more potent 5-HT releaser than a DA-releasing agent. Substantial preclinical studies have shown its effects in reducing or even eliminating cocaine use with minimal abuse potential (Rothman *et al.* 2008). Evidence from clinical trials of this agent is not yet available.

Glutamatergic Agents

Glutamatergic dysregulation is thought to be the final common pathway to drug-seeking behaviour, particularly in the prefrontal cortex (PFC)–NA circuit. This glutamatergic dysregulation may lead to a large release of extracellular glutamate in projections from the PFC to the NA, reduced cysteine/glutamate exchange that primarily controls the extracellular glutamate level, down-regulation of metabotropic glutamate receptors (mGLUR2/3) and up-regulation of postsynaptic AMPA receptors (Kalivas *et al.* 2003). Several compounds targeting these pivotal steps have shown promising results in the treatment of cocaine addiction. N-Acetylcysteine (NAC) can enhance cysteine/glutamate exchange by activating mGLUR2/3, and has been found to reduce the desire for cocaine use in a small-scale, double-blind, placebo-controlled clinical trial (LaRowe *et al.* 2007). Modafinil is a novel, non-amphetamine stimulant with minor abuse potential and can increase extracellular glutamate. Its mechanism is quite complex as it acts on several systems, including the hypocretin/orexin system and the glutamine/GABA system, and also has some dopaminergic effects and alpha-adrenergic effects (Anderson *et al.* 2011). Modafinil reduced cocaine use in two double-blind, placebo-controlled trials (Dackis *et al.* 2005, Hart *et al.* 2007). However, in another larger clinical trial, it only effectively reduced cocaine use in a subgroup of addicts without alcohol dependence (Anderson *et al.* 2009). Because modafinil can also block dopamine and norepinephrine transporters, the mechanisms of its anti-

relapse effect are still not clear (Kalivas & Volkow 2011). Modafinil has been seen as one of the most promising candidates for treating cocaine addiction (Kampman 2010) and several RCT studies are in progress. Other compounds that act on glutamatergic receptors, including mGLUR2/3, AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) and NMDA (N-methyl-D-aspartic acid), and that aim to normalize glutamatergic function, are still undergoing preclinical trials (Blum *et al.* 2009).

Anti-withdrawal Symptoms - Antidepressants and Adrenoceptor Antagonists

Acute intake of cocaine also increases serotonin and norepinephrine levels by blocking their presynaptic reuptake. Chronic use of cocaine leads to down-regulation of these monoamine systems, which is linked to depressive mood and dysphoria during withdrawal. Antidepressants that act as a monoamine system enhancer may alleviate these symptoms and thus play a role in reducing craving and preventing relapse (Kampman *et al.* 2001). Several antidepressants have been evaluated in cocaine addicts.

Desipramine is a tricyclic antidepressant that inhibits the reuptake of noradrenalin and has been most frequently studied. However, most studies have failed to support its effectiveness (Lima *et al.* 2003, Torrens *et al.* 2005). Meta-analysis studies reviewing desipramine, fluoxetine and imipramine, ritanserine and gepirone do not support the use of antidepressants for treating cocaine addiction (Batki 2002, Lima *et al.* 2003, Torrens *et al.* 2005). Much less literature is available on the effect of antidepressants in addicts with comorbid major depression. A meta-analysis based on five RCTs showed that neither selective serotonin reuptake inhibitors (SSRIs) nor other antidepressants had an effect on alleviating depression in cocaine addicts (Batki 2002). However, in a small-scale open trial, reboxetine, a selective NE reuptake inhibitor, significantly improved depressive symptoms and mood improvement associated with less cocaine consumption, yet only showed a trend towards reducing cocaine use and craving (Szerman *et al.* 2005). This may also illustrate the difficulty of treating depressive patients with concomitant cocaine addiction, and therapy should be effective for both mood and drug problems. Although antidepressants are commonly prescribed for substance abusers, more studies are needed to confirm their usefulness (Batki 2002).

The adrenergic system may be involved in mediating the physiological response to cocaine, including increases in heart rate, blood pressure and arousal. Increased adrenergic activity (Harris & Aston-Jones 1993) and arousal are frequently reported in early cocaine abstinence (Childress *et al.* 1992), thus adrenoceptor antagonists may play a role in treating addiction based on their effect in relieving abstinence symptoms. Propranolol is a beta-blocker that has been used in clinical practice to treat anxiety symptoms in alcohol and benzodiazepine withdrawal. One earlier RCT study found that propranolol increased treatment retention and promoted abstinence in a subgroup of patients with more severe withdrawal symptoms

(Kampman *et al.* 2001). Another RCT reported that propranolol consistently promoted retention and abstinence in patients who highly adhered to treatment medication (Kampman *et al.* 2006). Propranolol may help to prolong abstinence when treating those with severe cocaine withdrawal symptoms (Kampman *et al.* 2001). The basis of propranolol in treating cocaine addiction also involves other mechanisms, and several ongoing studies are exploring its effect in disrupting drug-cue memory.

Summary

Although no single medication has sufficient evidence for treating cocaine addiction, several promising medications, including dexamphetamine, modafinil, topiramate and disulfiram, are being investigated in numerous clinical trials (Kampman 2010). Dozens of new compounds that target the receptors or proteins involved in modulating addiction have also been developed and are undergoing testing (Kampman 2010, Kalivas & Volkow 2011), and some have generated promising clinical results (Plebani *et al.* 2011). Studies of novel approaches other than medication, such as deep brain stimulation, are also in progress (Luigjes *et al.* 2011).

Pharmacological Treatment for Amphetamine and Methamphetamine Use Disorder

Amphetamine and methamphetamine are another type of stimulant. Unlike cocaine, they have a relatively weak effect on monoamine reuptake inhibition, but act as substrates for monoamine transporters and promote monoamine release. Like all stimulants, the behavioural and psychological effects of amphetamines are mediated mainly by the monoamine system and the central DA system plays a predominant role in these processes, although other neurotransmitters, including serotonin, norepinephrine, opioid peptides and GABA are all involved (Rush *et al.* 2009). Pharmacological treatment stratagems for amphetamine dependence are similar to those for cocaine dependence and can be divided into three groups: agonists, antagonists and relapse prevention (Rush *et al.* 2009).

Antagonist-like Therapies

Medications that directly or indirectly influence dopamine function have the potential to eliminate the euphoric effect of amphetamines. Several types of such agents have been tested in clinical trials, including atypical antipsychotics, GABA agonists, opioid antagonists and calcium channel blockers.

Atypical antipsychotics

Atypical antipsychotics act as both D2-receptor and 5-HT-receptor antagonists and have been proposed for amphetamine dependence treatment. There is a lack of

published large-scale RCTs in this area. A small-scale (n=11) open-label study reported that risperidone decreased methamphetamine use (Meredith *et al.* 2007). The results from another open-label study that tested long-acting injectable risperidone have not yet been published [ClinicalTrials.gov identifier: NCT00284206]. Both risperidone and quetiapine reduced cocaine/methamphetamine craving in a controlled, blind design clinical trial in patients with both bipolar disorder and stimulant dependence. However, the placebo arm was absent in this study (Nejtek *et al.* 2008). Aripiprazole acts as a partial agonist at D2 and partial antagonist at 5-HT1A and 5-HT2A. In one RCT that compared aripiprazole, methylphenidate and placebo, the aripiprazole group unexpectedly provided more positive urine samples than the placebo group (Tiihonen *et al.* 2007).

GABA agonists

Increased GABA activity may decrease the dopamine transmission caused by stimulants, which is the rationale for using GABA agonists to treat stimulant dependence. The GABAergic system may also be involved in "relief" craving, the desire to reduce tension or anxiety (Addolorato *et al.* 2005). Baclofen, a selective GABAB agonist, and gabapentin, a GABA-transaminase inhibitor, have been evaluated in an RCT study (Heinzerling *et al.* 2006). In this study, neither baclofen nor gabapentin were better than placebo based on a general sample. However, in the post hoc analysis, baclofen was better than placebo in reducing methamphetamine use in a subgroup of those with high adherence to medication, whereas gabapentin was not. A more potent GABA agonist was recommended for future studies (Heinzerling *et al.* 2006). Topiramate is a GABA agonist and also a non-NMDA receptor antagonist that stabilizes neurons and the downstream release of DA in the mesocorticolimbic region. It has been increasingly studied in substance abuse disorders. However, a study of topiramate in methamphetamine users surprisingly reported that topiramate enhanced the subjective effect of an acute dose of intravenous methamphetamine in a small-scale human laboratory study (Johnson *et al.* 2007). Nevertheless, the results of an RCT with a larger sample size have not yet been published [ClinicalTrials.gov Identifier: NCT00345371]. Vigabatrin can irreversibly inhibit GABA transaminase and rapidly elevate brain GABA concentrations. In an open-label trial, vigabatrin effectively reduced methamphetamine and/or cocaine use (Brodie *et al.* 2005). In another phase I clinical trial, vigabatrin was well tolerated but not effective in attenuating the subjective effect when treated with a pre-methamphetamine dose (De La Garza *et al.* 2009). Data from a phase II study with a larger sample size have not been published [ClinicalTrials.gov identifier: NCT00730522]. Flumazenil, a benzodiazepine receptor antagonist, which is thought to reverse the change in GABAA receptor plasticity caused by methamphetamine exposure, has been found to significantly reduce methamphetamine craving when combined with the GABA transmission enhancer gabapentin in a controlled study (Urschel *et al.* 2011).

Opioid antagnonists and calcium channel blockers

Naltrexone is an opioid antagonist; in an RCT study, naltrexone significantly reduced methamphetamine use and craving (Jayaram-Lindstrom *et al.* 2008). However, in a recent small-scale clinical trial, Naltrexone plus NAC failed to show any benefit in reducing amphetamine use and craving (Grant *et al.* 2010). Several RCT studies are underway and may further demonstrate the effect of opioid antagonists in treating amphetamine dependence.

Calcium channel antagonists have the potential to attenuate cocaine-induced dopamine output in the striatum and thus are proposed as a possible treatment for amphetamine dependence. Though open-label trials have found that isradipine (Johnson *et al.* 1999, Johnson *et al.* 2005) and amlodipine (Batki *et al.* 2002) attenuated the subjective effect of and craving for methamphetamine, a controlled study failed to find an effect of amlodipine (Batki *et al.* 2001). So far, no RCTs on isradipine have been reported.

Agonist-like Therapies

DA receptor agonists and metabolism inhibitors

Encouraged by the success of partial or full agonists of opioid and nicotinic receptors in treating opioid and nicotine dependence respectively, DA receptor agonists have also been proposed as candidates for the treatment of stimulant dependence (Bergman 2008). Aripiprazole is one such candidate, based on its partial agonist effect at D2, although it also partially antagonizes 5-HT1A and 5-HT2A. Unfortunately, one RCT comparing aripiprazole, methylphenidate and placebo unexpectedly found that the aripiprazole group provided more positive urine samples compared with the placebo group (Tiihonen *et al.* 2007).

Although the dopamine-beta-hydroxylase inhibitor disulfiram showed promising results in cocaine dependence studies, exploration of its use in amphetamine dependence has only just begun. One open-label small-scale clinical trial has just been completed and the results are not yet known [ClinicalTrials.gov identifier: NCT00731133]. Another candidate metabolism inhibitor is the monoamine oxidase B inhibitor selegiline, which was shown to be safe when used together with intravenous methamphetamine in a human laboratory study (Newton *et al.* 2005). No RCT has evaluated the efficacy of selegiline in amphetamine dependence.

Stimulant replacement therapy

Methylphenidate is a dopamine reuptake inhibitor, and has been studied in cocaine dependence. Only one RCT has tested the effectiveness of methylphenidate for treating methamphetamine dependence, in which it significantly reduced intravenous amphetamine use compared with patients who received a placebo

(Tiihonen *et al.* 2007). Further studies with methylphenidate have been planned (Karila *et al.* 2010). Dextroamphetamine is a monoamine releaser and can increase extracellular DA, NE and 5-HT levels. Dextroamphetamine-SR significantly reduced withdrawal symptoms and craving in two RCT studies (Longo *et al.* 2010, Galloway *et al.* 2011) and increased treatment retention or compliance (Shearer *et al.* 2001, Longo *et al.* 2010). However, dextroamphetamine-SR did not significantly reduce methamphetamine use at a dose of 60 mg/d (Galloway *et al.* 2011), but showed a trend at a higher dose of 110 mg/d (Longo *et al.* 2010). Based on these results, a higher dosage of dextroamphetamine-SR was speculated to benefit a subgroup of patients characterized with severe withdrawal symptoms (Galloway *et al.* 2011).

Bupropion is a dopamine and norepinephrine reuptake inhibitor that shows a stimulant effect in animals. Two RCTs have been performed on bupropion. It was effective in reducing methamphetamine use in participants with low-to-moderate methamphetamine dependence (Elkashef *et al.* 2008). More clinical trials are still in processing [ClinicalTrials.gov identifier: NCT00572234]. Modafinil is another stimulant that may be useful in the treatment of cocaine dependence. However, in four recent RCTs, modafinil at both 200mg/d (Shearer *et al.* 2009, Anderson *et al.* 2011) and 400mg/d (Heinzerling *et al.* 2010, Anderson *et al.* 2011) failed to demonstrate efficacy in attenuating methamphetamine use, craving or retention in a general sample, but showed some effect in high-compliance patients (Shearer *et al.* 2009, Anderson *et al.* 2011) or heavy users (Heinzerling *et al.* 2010) Nevertheless, because of the attractive actions of modafinil on the central nervous system, clinical trials at a higher dosage are ongoing [ClinicalTrials.gov identifier: NCT01354470 and NCT00630097].

Anti-withdrawal Symptoms

The acute phase of amphetamine withdrawal is characterized by disturbed sleep, depressive symptoms, anxiety and craving (McGregor *et al.* 2005). Medications that can alleviate depression, anxiety and improve sleep, such as antidepressants, are thought to have the potential to alleviate acute withdrawal symptoms and thus can help to maintain abstinence from amphetamine. So far, only amineptine and mirtazapine have been tested in RCTs for treating amphetamine withdrawal symptoms. Amineptine showed limited benefit in reducing amphetamine use but has been removed from the market because of the risk of abuse (Jittiwutikan *et al.* 1997, Srisurapanont *et al.* 1999, Shoptaw *et al.* 2009). The results of mirtazapine RCTs, however, were contradictive. Mirtazapine is a noradrenergic and specific serotonergic antidepressant that also has sedative and anxiolytic properties. Acute mirtazapine reduces the latency and increases the duration of sleep. A small controlled clinical trial indicated that mirtazapine improved self-reported withdrawal symptoms, hyper arousal and anxiety symptoms at 3 and 14 days after amphetamine cessation (Kongsakon *et al.* 2005). However, in another 5-week RCT, mirtazapine did not facilitate retention or reduce withdrawal symptoms, while anxiety symptoms and sleep disturbance tended to be worse in a group of out-patients (Cruickshank *et al.* 2008). SSRIs such as fluoxetine (Batki *et al.* 2000), paroxetine (Piasecki *et al.* 2002)

and sertraline (Shoptaw *et al.* 2006), and tricyclic antidepressants (TCAs) such as imipramine (Galloway *et al.* 1996) also failed to prove their efficacy in reducing amphetamine use and improving depressive symptoms. Ondansetron is a 5-HT3 receptor antagonist that may decrease dopamine activity in the cortico-mesolimbic region. An 8-week multi-centre RCT reported that ondansetron was not superior to placebo in attenuating methaphetamine use, retention and craving (Johnson *et al.* 2008).

Summary

So far, no medication has been proven to be effective for the treatment of amphetamine dependence, although pharmacotherapy studies for amphetamine dependence are still in the early stages. Based on these findings, naltrexone and dextroamphetamine have shown some positive results, and dextroamphetamine is promising for treating heavy methamphetamine users. Bupropion and modafinil have possible benefits in selected patients (Elkashef *et al.* 2008, Karila *et al.* 2010). Atypical antipsychotics should be prescribed with caution when treating patients with methamphetamine/amphetamine dependence (Bergman 2008). Although existing studies are not encouraging, treatment medications for amphetamine dependence have been developing rapidly in recent years (Elkashef *et al.* 2008). Further studies should target broader mechanism actions, such as actions mediated by the nicotinic acetylcholine receptor (nAChR) (Crunelle *et al.* 2010), cannabinoid-1 (CB-1) receptor, dopamine D3, corticotropin-releasing factor and opioid receptors (Elkashef *et al.* 2008).

Hallucinogens

Hallucinogens are a broad spectrum of substances that alter the perception of reality. The most commonly used or abused hallucinogens include 3, 4-Methylenedioxymethamphetamine (MDMA or ecstasy) and lysergic acid diethylamide (LSD). Phencyclidine (PCP) and the related agent ketamine are technically dissociative anaesthetics, but share many characteristics with hallucinogens (Leshner 2001, Suzuki & Halpern 2009); the latter has been the most abused drug in Hong Kong since 2000 (Narcotics Division 2009).

LSD

LSD is a 5-HT_{2a} agonist that leads to mood swings and altered sensations and feelings. The subjective effects of LSD are unpredictable and vary with the dosage and the "stateset" of the user, including their mood, expectations, personality and surroundings. Sometimes these feelings are uncomfortable and are referred to as a "bad trip", which may be one of the reasons that LSD users tend to stop using it voluntarily. LSD is not considered to cause withdrawal symptoms, though tolerance will develop quickly (Leshner 2001). No clinical trial has examined the treatment of LSD abuse or dependence (Suzuki & Halpern 2009).

MDMA

MDMA is a substrate for monoamine transporter proteins. It is an amphetamine-analogue substance but also has a hallucinogenic effect. MDMA and its metabolite can stimulant efflux of 5-HT and, to a lesser extent, DA and NE. Acute use of MDMA dose-dependently elevates extracellular levels of 5-HT and DA, while long-term use of MDMA leads to depletion of 5-HT and dysfunction of 5-HT transporters and the plastics of 5-HT neuron terminals (Baumann & Rothman 2008). Although withdrawal symptoms in MDMA users are rare, MDMA abuse and dependence were initially recognized in DSM-IV (Diagnostic and Statistical Manual of Mental Disorders *DSM-IV-TR* Fourth Edition) and remained in DSM-IV-TR (Diagnostic and Statistical Manual of Mental Disorders *DSM-IV-TR* Fourth Edition (Text Revision)) (Suzuki & Halpern 2009). "Compulsive use" and "escalating use" are thought to be the two main characteristics of MDMA dependence (Degenhardt *et al.* 2010), which is associated with sensitization of dopaminergic responses leading to down-regulation of 5-HT in the inhibition of DA release (Schenk 2011). No RCT study has been performed on MDMA dependence (Suzuki & Halpern 2009). Based on its actions on 5-HT and/or NE transporters, agents that block 5-HT transporters, such as SSRIs, are speculated to block the effect of MDMA. Studies in this field are in the early stages of clinical trial (Hysek *et al.* 2011, Hysek *et al.* 2011).

PCP and Ketamine

The effects of PCP and ketamine are mediated by the glutamine transmitter, which is involved in the perception of pain, response to the environment and memory. Both drugs act as an NMDA receptor antagonist, although ketamine is less potent than PCP (Leshner 2001). NMDA antagonists may enhance glutaminergic transmission by disinhibiting glutamine release and the cortical hyperglutaminergic state may subsequently stimulate the release of monoamines, including dopamine, which may explain their addictive potential (Ross & Peselow 2009). Withdrawal symptoms have been reported in subjects with PCP dependence (Leshner 2001) and ketamine dependence (Jansen & Darracot-Cankovic 2001). PCP or ketamine abuse is less common in western cultures, and the majority of ketamine abusers are poly-drug abusers (Suzuki & Halpern 2009), thus clinical trials for the treatment of PCP or ketamine abuse/dependence are rare. However, it has been suggested that treatments for other types of drug addiction may be expanded to hallucinogens addiction (Suzuki & Halpern 2009).

Cannabis

Cannabis is the most commonly abused drug in America, but is less popular in Hong Kong (Narcotics Division 2009). Delta-9-tetrahydrocannabinol (THC) is the

main active ingredient in marijuana, which binds to the cannabinoid receptors (CBRs) and is responsible for many of the known effects of cannabis. THC has a similar affect to endogenous cannabinoids and the endocannabinoid system is involved in brain development and many mental and physical functions. THC also stimulates brain cells to release dopamine, which causes the feeling of "euphoria" or "high". Long-term use of cannabis may cause addition and withdrawal symptoms, making cannabis hard to quit. Frequently reported withdrawal symptoms include anxiety, sleep difficulty, irritability and craving (Volkow 2009). Currently, medication strategies for cannabis abuse/dependence involve targeting these withdrawal symptoms, trying agents useful for other drug abuse, or targeting the endocannabinoid system to attenuate the reinforcing effect of cannabis (Vandrey & Haney 2009).

RCTs on cannabis abuse/dependence are limited and most results come from human laboratory studies or open-label clinical trials. Dronabino, a CBRs agonist, has shown by far the most promising effect in treating cannabis dependence (Vandrey & Haney 2009). In preliminary studies, dronabino significantly removed cannabis withdrawal symptoms (Haney *et al.* 2004) (Budney *et al.* 2007), and could prevent relapse when combined with lofexidine (Haney *et al.* 2008). In a recently published RCT study, dronabino significantly reduced withdrawal symptoms with a higher retention rate compared with placebo, but the difference in cannabis use was not significant between groups and a higher dosage and treatment combination was recommended (Levin *et al.* 2011).

Bupropion was reported to be ineffective in treating cannabis withdrawal symptoms (Carpenter *et al.* 2009) and even worsened mood symptoms (Haney *et al.* 2001). Similar results were found for divalproex, a mood stabilizer (Haney *et al.* 2004). Mirtazapine (Haney *et al.* 2010), baclofen (Haney *et al.* 2010) and nefazadone (Haney *et al.* 2003, Carpenter *et al.* 2009) also failed to attenuate cannabis use, though they could improve a subset of withdrawal symptoms. However, other medications showed some positive results, including lithium carbonate (Winstock *et al.* 2009), NAC (Gray *et al.* 2010), lofexidine (Haney *et al.* 2008) and fluoxetine (Cornelius *et al.* 1999). A small-scale controlled clinical trial demonstrated a trend for buspirone, a non-benzodiazepine anxiolytic, to reduce anxiety and cannabis use, and facilitate abstinence (McRae-Clark *et al.* 2009). Trials of the CBRs antagonist rimonabant helped patients to maintain abstinence from cannabis. However, the results were inconsistent and further study and controlled clinical trials are needed (Vandrey & Haney 2009). The mu-opioid receptor antagonist naltrexone disappointingly increased the subjective and cardiovascular effects of cannabis in heavy marijuana smokers (Cooper & Haney 2010). Due to the prevalence of cannabis abuse in western cultures, studies in this field are active. More medications are planned or undergoing testing (Vandrey & Haney 2009, Weinstein & Gorelick 2011).

Summary and Future Directions

Most rigorous pharmacological therapies have concentrated on cocaine dependence. There have been fewer studies on amphetamine/methamphetamine dependence and even fewer on other abused drugs, such as cannabis or hallucinogens. Although several agents are common to the dozens of medications or compounds that have been evaluated, their mental or physical side effects and the potential for abuse have so far limited their usage to well-managed and carefully monitored clinical experiments. Apart from the efficacy of these medications, low motivation for treatment and heterogeneous study samples are major obstacles for clinical trials in detecting their efficacy. Nevertheless, efforts in developing appropriate pharmacological therapies are increasing. Along with advances in understanding the biological basis of addiction, more receptors have been identified as treatment targets and new therapies are under development.

Pharmacotherapy Adjunct to Psychological Therapy

The etiology of SUDs includes both psychosocial and biological factors, thus the optimal therapy should combine both biological and pharmacological treatments. As mentioned previously in this paper, in SUD patients, bingeing and euphoria or withdrawal and craving drive their drug use and prevent long-term abstinence. Pharmacotherapy that amends the neuro-basis of euphoria, withdrawal symptoms and craving can theoretically free patients from drug addiction in the long term. However, treatment retention in pharmacotherapy clinical trials is low and poor compliance leads to negative or weak results. Combining pharmacotherapy with psychosocial therapy will enhance patient retention and medication compliance and foster the learning of new skills, thus enhancing the effect of pharmacotherapy (Swift & Leggio 2009).

Contingency management (CM) can significantly increase treatment retention (Lussier *et al.* 2006). A study examined the combined effect of the dopamine enhancer levodopa/carbidopa with different psychotherapies – clinical management (ClinMan), ClinMan + Cognitive Behavioural Therapy (CBT) and ClinMan + CBT + CM – and found that only the last of these showed effectiveness in favour of levodopa/carbidopa (Schmitz *et al.* 2008). Another study evaluated the dopamine-enhancing effects on the reinforcement effect of CM by comparing levodopa or placebo with one of three CM conditions: CM to reinforce negative urine samples, CM to reinforce medication or CM to reinforce attendance at appointments. All three behaviours – negative urine samples, taking medication and attending appointments – were influenced by the CM condition. Evidence of levodopa-enhancing effects was found only in the CM condition that reinforced cocaine-negative urine samples. One explanation for this result is that dopamine enhances the salient CM reward effect only when the reward effect of cocaine is reduced (Schmitz *et al.* 2010). Likewise, CM has shown addictive effects in cocaine abuse treatment when combined with antidepressants (Kosten *et al.* 2003) and bupropion (Poling *et al.* 2006).

CBT is another strong evidence-based psychosocial therapy. A series of studies has evaluated the effect of CBT combined with therapeutic medication. RP with naltrexone reduced cocaine-positive urine samples significantly more than RP or naltrexone alone (Schmitz *et al.* 2001). The antidepressant citalopram combined with CBT + CM improved the percentage of negative urine samples compared with placebo (Moeller *et al.* 2007). Disulfiram adjunct to CBT reduced cocaine use more than other treatment, but only in patients without alcohol problems (Carroll *et al.* 2004). Medication adjunct to psychosocial therapy for treating alcohol, nicotine and opiate dependence has proved to be successful, although data on other types of drug addiction are lacking. Nevertheless, psychosocial therapy combined with pharmacotherapy is expected to produce a better efficacy profile (Kampman 2010).

Vaccine Therapy

Vaccine therapy is a new direction for treating addiction. The rationale for this treatment is that antibodies will bind with the abused drug and form a macromolecular immunological complex that may block the passage of the drug via the blood-brain barrier. Therefore, the reinforcing effects of the drug will be extinguished over a relatively long period. Based on this theory, vaccine therapy may help to maintain abstinence and motivate addicts to retain in a treatment programme (Montoya 2008, Orson *et al.* 2008). Drug vaccine therapy has undergone testing for decades, and vaccines for cocaine and nicotine have now been developed and tested in clinical trials. Vaccines for PCP, morphine and methamphetamine have been studied in preclinical experiments (Gentry *et al.* 2010, Kinsey *et al.* 2010). Clinical trials of a cocaine vaccine, succinylnorcocaine, covalent to cholera B (SNC-rCTB), have consistently found that high antibody groups had significantly more drug-free urine samples. However, the main limitation of vaccine therapy is the response variability. In all of these clinical trials, only about 30% of subjects elicited the target antibody concentration (Kosten & Biegel 2002, Martell *et al.* 2005, Martell *et al.* 2009). Recently, a new treatment was developed that combines enzyme treatment with the vaccine, which may further reduce the drug's access to the brain (Kinsey *et al.* 2010). Studies on alternative adjuvants and new vaccine constructs are ongoing (Kinsey *et al.* 2010).

Traditional Medicine Therapy

Traditional Herbal Remedies

Explorations of potential treatments using traditional herbal remedies are increasing and more than 200 traditional herbs have been tested. The majority of these studies focus on alcohol, opiate or nicotine dependence, with a small number of studies on cocaine or methamphetamine dependence (Min *et al.* 2007). However, most studies are in the preclinical stage and well-designed clinical trials are very few. No RCTs have been performed on stimulant addiction, such as cocaine and methamphetamine (Lu *et al.* 2009). Basic research on several herbal components have already shown promising results in animal models, including ginseng, withania somnifera, thunbergia laurifolia linn and corydolis yanhusuo. These herbal components display a modulatory action on the DA system and stimulant-induced behaviours (Lu *et al.* 2009). The therapeutic effects of two frequently studied hallucinogenic herbs, ibogaine and ayahuasca, are still being debated (Labate & Cavnar 2011). However, a main component of ayahuasca is N,N-dimethyltryptamine (DMT), which was identified as a sigma receptor agonist in the latest study

(Fontanilla *et al.* 2009) and may have similar effects to stimulants such as cocaine (Katz *et al.* 2011). In summary, the effectiveness of traditional herbs has not been confirmed (Lu *et al.* 2009).

Acupuncture

The use of acupuncture for relieving withdrawal symptoms in the detoxification stage in heroin addicts has been thoroughly studied. A five-point auricular protocol was formulated by the National Acupuncture Detoxification Association (NADA) and has been widely accepted in clinical practice and research (Cui *et al.* 2008). However, evidence for the efficacy of acupuncture in cocaine or other stimulant addiction is less substantial and elicits mix results (Bullock *et al.* 1999, Avants *et al.* 2000, Margolin *et al.* 2002). Though many factors, including the treating context, dose and patients' belief about acupuncture, may confound the results of a clinical trial, acupuncture is not expected to form a stand-alone therapy for addiction but may be included as a component of a treatment programme (Shwartz *et al.* 1999, Margolin 2003). Further study on this treatment should examine how it can be integrated effectively into other treatments (Margolin 2003).

Conclusion

In psychotropic addiction treatment, psychosocial therapy plays the primary role. Evidence-based psychosocial treatments have been established. However, only 70% of patients are able to complete the treatment programme and one third of them achieve abstinence after treatment. Treatment compliance and relapse are tough problems in addiction treatment. However, as addiction is now viewed as a chronic disorder, similar to other chronic diseases that need lifelong treatment such as diabetes and hypertension, we cannot expect short-term treatment for addiction to generate long-term effects. The framework for a long-term care model has been proposed and is now being developed, and the transition from an acute care model to a continuing care model is being explored. Pharmacotherapy is another type of relapse prevention in drug addiction treatment that has the potential to achieve long-term abstinence. Though no medication has been proven to be effective for the treatment of psychotropic substance abuse, research in this area, and in the development of novel treatment methods such as immunological therapy, is thriving. Several medications have emerged with promising treatment effects. The integration of novel pharmacotherapy and psychosocial therapy within a continuing care system is the goal for the future.

List of Abbreviations

$	US Dollar
5-HT	Serotonin
AA	Alcohol Anonymous
AC	Acute care model
ADHD	Attention-deficit hyperactivity disorder
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
APA	American Psychiatric Association
CA	Cocaine Anonymous
CB-1	Cannabinoid-1 receptor
CB-CBT	Computer- based training in CBT
CBRs	Cannabinoid receptors
CBT	Cognitive-behaviour therapy
ClinMan	Clinical management
CM	Contingency management
CMA	Crystal Meth Anonymous
CRA	Community reinforcement approach
CRF	Corticotropin-releasing factor
DA	Dopamine
DEC	Drug Endangered Children
DMT	N,N-dimethyltryptamine
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders *DSM-IV-TR* Fourth Edition
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders *DSM-IV-TR* Fourth Edition (Text Revision)
EF	Educational-feedback
FDA	US Food and Drug Administration
GABA	Gamma-aminobutyric acid
GHQ-28	General Health Questionnaire-28
IR	Immediate release
LDX	Lisdexamfetamine
LSD	lysergic acid diethylamide
MA	Methamphetamine
MAO-B	Monoamine oxidase type B
MDMA	3, 4-Methylenedioxymethamphetamine
MI	Motivational interviewing
MPH	Methylphenidate
MTC	Modified therapeutic communities
NA	Narcotics Anonymous
NA	Nucleus accumbens
NAC	N-Acetyl cysteine
nAChR	Nicotinic acetylcholine receptor
NDNA	The National Acupuncture Detoxification Association
NE	Norepinephrine
NIDA	National Institute of Drug Abuse

NMDA	N-methyl-D-aspartic acid
PCP	Phencyclidine
PFC	Prefrontal cortex
RCT	Randomized controlled trials
RM	Recovery management Model
RP	Relapse prevention
SDS	Severity of Dependence Score
SHG	Self-help group
SNC-rCTB	Succinylnorcocaine covalently to cholera B
SR	Sustain release
SSRI	Serotonin reuptake Inhibitor
SUDs	Substance use disorders
TCAs	Tricyclic antidepressants
TCs	Therapeutic communities
THC	Delta-9-tetrahydrocannabinol
TM	Telephone monitoring
TMC	Telephone monitoring and counseling
VTA	Ventral tegmental area

References

Addolorato G., Abenavoli L., Leggio L. *et al.* (2005) How many cravings? Pharmacological aspects of craving treatment in alcohol addiction: a review. *Neuropsychobiology* 51, 59-66.

Akerele E. & Levin F.R. (2007) Comparison of olanzapine to risperidone in substance-abusing individuals with schizophrenia. *Am J Addict* 16, 260-8.

Alan Marlatt G. & Bowen S.W. (2009) Relapse prevention:evidence base and future directions. *Evidence-based addiction treatment* (ed. Miller P.M.), pp. 217-232. Elsevier/Academic Press, Berlington, MA.

Alvarez Y., Farre M., Fonseca F. *et al.* (2010) Anticonvulsant drugs in cocaine dependence: a systematic review and meta-analysis. *J Subst Abuse Treat* 38, 66-73.

Amato L., Minozzi S., Pani P.P. *et al.* (2007) Antipsychotic medications for cocaine dependence. *Cochrane Database of Systematic Reviews*, CD006306.

Anderson A.L., Li S.H., Biswas K. *et al.* (2011) Modafinil for the treatment of methamphetamine dependence. *Drug Alcohol Depend*.

Anderson A.L., Reid M.S., Li S.H. *et al.* (2009) Modafinil for the treatment of cocaine dependence. *Drug Alcohol Depend* 104, 133-9.

Avants S.K., Margolin A., Holford T.R. *et al.* (2000) A randomized controlled trial of auricular acupuncture for cocaine dependence. *Arch Intern Med* 160, 2305-12.

Baker A., Lee N.K., Claire M. *et al.* (2005) Brief cognitive behavioural interventions for regular amphetamine users: a step in the right direction. *Addiction* 100, 367-78.

Barry D. & Petry N.M. (2009) Cognitibe behavioral treatment for substance use disorders. *Evidence-based addiction treatment* (ed. Miller P.M.), pp. 159-173. Elsevier/Academic Press, Berlington, MA.

Barry D., Sullivan B. & Petry N.M. (2009) Comparable efficacy of contingency management for cocaine dependence among African American, Hispanic, and White methadone maintenance clients. *Psychol Addict Behav* 23, 168-74.

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, 582-590.

Batki S.L. (2002) Review: antidepressants are not effective for cocaine dependence. *Evid Based Ment Health* 5, 82-3.

Batki S.L., Bui L., Mendelson J. *et al.* (2002) Methamphetamine-amlodipine interactions: preliminary analysis (abstract). *Drug and Alcohol Dependence* 66.

Batki S.L., Moon J., Delucchi K. *et al.* (2000) Methamphetamine quantitative urine concentrations during a controlled trial of fluoxetine treatment. Preliminary analysis. *Ann N Y Acad Sci* 909, 260-3.

Batki S.L., Moon J., Delucchi K. *et al.* (2001) Amlodipine treatment of methamphetamine dependence a controlled outpatient trial: preliminary analysis. . *Drug and Alcohol Dependence* 63, 12.

Baumann M.H.& Rothman R.B. (2008) Neurobiology of 3, 4-methylenedioxymethamphetamine. *Neurochemistry of abused drugs* (ed. Karch S.B.), pp. 119-135. CRC Press, New York.

Bergman J. (2008) Medications for stimulant abuse: agonist-based strategies and preclinical evaluation of the mixed-action D-sub-2 partial agonist aripiprazole (Abilify). *Exp Clin Psychopharmacol* 16, 475-83.

Blum K., Chen T.J., Downs B.W. *et al.* (2009) Neurogenetics of dopaminergic receptor supersensitivity in activation of brain reward circuitry and relapse: proposing "deprivation-amplification relapse therapy" (DART). *Postgraduate medicine* 121, 176-196.

Bonn-Miller M.O., Vujanovic A.A. & Drescher K.D. (2011) Cannabis use among military veterans after residential treatment for posttraumatic stress disorder. *Psychol Addict Behav* 25, 485-91.

Brodie J.D., Case B.G., Figueroa E. *et al.* (2009) Randomized, double-blind, placebo-controlled trial of vigabatrin for the treatment of cocaine dependence in Mexican parolees. *Am J Psychiatry* 166, 1269-77.

Brodie J.D., Figueroa E., Laska E.M. *et al.* (2005) Safety and efficacy of gamma-

vinyl GABA (GVG) for the treatment of methamphetamine and/or cocaine addiction. *Synapse* 55, 122-5.

Budney A.J., Higgins S.T., Radonovich K.J. *et al.* (2000) Adding voucher-based incentives to coping skills and motivational enhancement improves outcomes during treatment for marijuana dependence. *J Consult Clin Psychol* 68, 1051-61.

Budney A.J., Moore B.A., Rocha H.L. *et al.* (2006) Clinical trial of abstinence-based vouchers and cognitive-behavioral therapy for cannabis dependence. *J Consult Clin Psychol* 74, 307-16.

Budney A.J., Vandrey R.G., Hughes J.R. *et al.* (2007) Oral delta-9-tetrahydrocannabinol suppresses cannabis withdrawal symptoms. *Drug Alcohol Depend* 86, 22-9.

Bullock M.L., Kiresuk T.J., Pheley A.M. *et al.* (1999) Auricular acupuncture in the treatment of cocaine abuse. A study of efficacy and dosing. *J Subst Abuse Treat* 16, 31-8.

Burke B.L., Arkowitz H.& Menchola M. (2003) The efficacy of motivational interviewing: a meta-analysis of controlled clinical trials. *J Consult Clin Psychol* 71, 843-61.

Caldeiro R.M., Meredith C.W., Saxon A.J. *et al.* (2009) Pharmacological Approaches to the treatment of substance use disorders. *Pharmacology and Treatment of Substance Abuse* eds. Cohen l.M., Collins F.L., Young A.M. *et al.*). Taylor & Francis Group, New York.

Carpenedo C.M., Kirby K.C., Dugosh K.L. *et al.* (2010) Extended voucher-based reinforcement therapy for long-term drug abstinence. *Am J Health Behav* 34, 776-87.

Carpenter K.M., McDowell D., Brooks D.J. *et al.* (2009) A preliminary trial: double-blind comparison of nefazodone, bupropion-SR, and placebo in the treatment of cannabis dependence. *Am J Addict* 18, 53-64.

Carroll K.M. (1998) A cognitive-behavioral approach: Treating cocaine addiction (NIH Publication 98-4308).Rockville, MD: National Institute on Drug Abuse;.

Carroll K.M., Ball S.A., Martino S. *et al.* (2008) Computer-assisted delivery of cognitive-behavioral therapy for addiction: a randomized trial of CBT4CBT. *Am J Psychiatry* 165, 881-8.

Carroll K.M., Ball S.A., Martino S. *et al.* (2009) Enduring effects of a computer-assisted training program for cognitive behavioral therapy: a 6-month follow-up of CBT4CBT. *Drug Alcohol Depend* 100, 178-81.

Carroll K.M., Ball S.A., Nich C. *et al.* (2006) Motivational interviewing to improve treatment engagement and outcome in individuals seeking treatment for substance abuse: a multisite effectiveness study. *Drug Alcohol Depend* 81, 301-12.

Carroll K.M., Fenton L.R., Ball S.A. *et al.* (2004) Efficacy of disulfiram and cognitive behavior therapy in cocaine-dependent outpatients: a randomized placebo-controlled trial. *Arch Gen Psychiatry* 61, 264-72.

Carroll K.M., Nich C., Ball S.A. *et al.* (2000) One-year follow-up of disulfiram and psychotherapy for cocaine-alcohol users: sustained effects of treatment. *Addiction* 95, 1335-49.

Carroll K.M., Nich C., Ball S.A. *et al.* (1998) Treatment of cocaine and alcohol dependence with psychotherapy and disulfiram. *Addiction* 93, 713-27.

Carroll K.M., Rounsaville B.J., Gordon L.T. *et al.* (1994) Psychotherapy and pharmacotherapy for ambulatory cocaine abusers. *Arch Gen Psychiatry* 51, 177-87.

Carroll K.M., Rounsaville B.J., Nich C. *et al.* (1994) One-year follow-up of psychotherapy and pharmacotherapy for cocaine dependence. Delayed emergence of psychotherapy effects. *Arch Gen Psychiatry* 51, 989-97.

Carroll K.M., Sairam K., Olliff S.P. *et al.* (1996) Case report: paravesical suture granuloma resembling bladder carcinoma on CT scanning. *Br J Radiol* 69, 476-8.

Castells X., Casas M., Perez-Mana C. *et al.* (2010) Efficacy of psychostimulant drugs for cocaine dependence. *Cochrane Database Syst Rev*, CD007380.

Castells X., Casas M., Vidal X. *et al.* (2007) Efficacy of central nervous system

stimulant treatment for cocaine dependence: a systematic review and meta-analysis of randomized controlled clinical trials. *Addiction* 102, 1871-87.

Childress A.R., Ehrman R., Roshenow D. *et al.* (1992) Classically conditioned factors in drug dependence. *Substance abuse, a comprehensive textbook* eds. Lowinson J.H., Ruiz P. & Millman R.B.), pp. 56-69. Williams & Wilkins, Philadelphia.

Cooper Z.D. & Haney M. (2010) Opioid antagonism enhances marijuana's effects in heavy marijuana smokers. *Psychopharmacology (Berl)* 211, 141-8.

Copeland J., Swift W., Roffman R. *et al.* (2001) A randomized controlled trial of brief cognitive-behavioral interventions for cannabis use disorder. *J Subst Abuse Treat* 21, 55-64; discussion 65-6.

Cornelius J.R., Salloum I.M., Haskett R.F. *et al.* (1999) Fluoxetine versus placebo for the marijuana use of depressed alcoholics. *Addict Behav* 24, 111-4.

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

Cruickshank C.C., Montebello M.E., Dyer K.R. *et al.* (2008) A placebo-controlled trial of mirtazapine for the management of methamphetamine withdrawal. *Drug Alcohol Rev* 27, 326-33.

Crunelle C.L., Miller M.L., Booij J. *et al.* (2010) The nicotinic acetylcholine receptor partial agonist varenicline and the treatment of drug dependence: a review. *Eur Neuropsychopharmacol* 20, 69-79.

Cui C.L., Wu L.Z. & Luo F. (2008) Acupuncture for the treatment of drug addiction. *Neurochem Res* 33, 2013-22.

D'Amico E.J., Miles J.N., Stern S.A. *et al.* (2008) Brief motivational interviewing for teens at risk of substance use consequences: a randomized pilot study in a primary care clinic. *J Subst Abuse Treat* 35, 53-61.

Dackis C.A., Kampman K.M., Lynch K.G. *et al.* (2005) A double-blind, placebo-controlled trial of modafinil for cocaine dependence. *Neuropsychopharmacology* 30, 205-11.

De La Garza R., 2nd, Zorick T., Heinzerling K.G. *et al.* (2009) The cardiovascular and subjective effects of methamphetamine combined with gamma-vinyl-gamma-aminobutyric acid (GVG) in non-treatment seeking methamphetamine-dependent volunteers. *Pharmacol Biochem Behav* 94, 186-93.

De Leon G., Sacks S., Staines G. *et al.* (2000) Modified therapeutic community for homeless mentally ill chemical abusers: treatment outcomes. *Am J Drug Alcohol Abuse* 26, 461-80.

DeFulio A., Donlin W.D., Wong C.J. *et al.* (2009) Employment-based abstinence reinforcement as a maintenance intervention for the treatment of cocaine dependence: a randomized controlled trial. *Addiction* 104, 1530-8.

Degenhardt L., Bruno R. & Topp L. (2010) Is ecstasy a drug of dependence? *Drug Alcohol Depend* 107, 1-10.

Denis C., Lavie E., Fatseas M. *et al.* (2006) Psychotherapeutic interventions for cannabis abuse and/or dependence in outpatient settings. *Cochrane Database Syst Rev* 3, CD005336.

Dennis M.L., Foss M.A. & Scott C.K. (2007) An eight-year perspective on the relationship between the duration of abstinence and other aspects of recovery. *Eval Rev* 31, 585-612.

Dennis M.L., Scott C.K. & Funk R. (2003) An experimental evaluation of recovery management check-ups (RMC) for people with chronic substance use disorders. *Eval Program Plann*, 339-352.

Donovan D.M., Rosengren D.B., Downey L. *et al.* (2001) Attrition prevention with individuals awaiting publicly funded drug treatment. *Addiction* 96, 1149-60.

Donovan D.M. & Wells E.A. (2007) 'Tweaking 12-Step': the potential role of 12-Step self-help group involvement in methamphetamine recovery. *Addiction* 102 Suppl 1, 121-9.

Dunn C., Deroo L. & Rivara F.P. (2001) The use of brief interventions adapted from motivational interviewing across behavioral domains: a systematic review. *Addiction* 96, 1725-42.

Dutra L., Stathopoulou G., Basden S.L. *et al.* (2008) A meta-analytic review of

psychosocial interventions for substance use disorders. *Am J Psychiatry* 165, 179-87.

Elkashef A., Fudala P.J., Gorgon L. *et al.* (2006) Double-blind, placebo-controlled trial of selegiline transdermal system (STS) for the treatment of cocaine dependence. *Drug Alcohol Depend* 85, 191-7.

Elkashef A., Vocci F., Hanson G. *et al.* (2008) Pharmacotherapy of methamphetamine addiction: an update. *Subst Abus* 29, 31-49.

Elkashef A.M., Rawson R.A., Anderson A.L. *et al.* (2008) Bupropion for the treatment of methamphetamine dependence. *Neuropsychopharmacology* 33, 1162-70.

Epstein D.H., Hawkins W.E., Covi L. *et al.* (2003) Cognitive-behavioral therapy plus contingency management for cocaine use: findings during treatment and across 12-month follow-up. *Psychol Addict Behav* 17, 73-82.

Feeney G.F., Connor J.P., Young R.M. *et al.* (2006) Improvement in measures of psychological distress amongst amphetamine misusers treated with brief cognitive-behavioural therapy (CBT). *Addict Behav* 31, 1833-43.

Festinger D.S., Marlowe D.B., Dugosh K.L. *et al.* (2008) Higher magnitude cash payments improve research follow-up rates without increasing drug use or perceived coercion. *Drug Alcohol Depend* 96, 128-35.

Fiorentine R. (1999) After drug treatment: are 12-step programs effective in maintaining abstinence? *Am J Drug Alcohol Abuse* 25, 93-116.

Fiorentine R. & Hillhouse M.P. (2000) Drug treatment and 12-step program participation: the additive effects of integrated recovery activities. *J Subst Abuse Treat* 18, 65-74.

Focchi G.R., Leite M.C., Andrade A.G. *et al.* (2005) Use of dopamine agonist pergolide in outpatient treatment of cocaine dependence. *Substance use & misuse* 40.

Fontanilla D., Johannessen M., Hajipour A.R. *et al.* (2009) The hallucinogen N,N-dimethyltryptamine (DMT) is an endogenous sigma-1 receptor regulator. *Science* 323, 934-7.

Galloway G.P., Buscemi R., Coyle J.R. *et al.* (2011) A randomized, placebo-controlled trial of sustained-release dextroamphetamine for treatment of methamphetamine addiction. *Clin Pharmacol Ther* 89, 276-82.

Galloway G.P., Newmeyer J., Knapp T. *et al.* (1996) A controlled trial of imipramine for the treatment of methamphetamine dependence. *J Subst Abuse Treat* 13, 493-7.

Garcia-Fernandez G., Secades-Villa R., Garcia-Rodriguez O. *et al.* (2011) Adding voucher-based incentives to community reinforcement approach improves outcomes during treatment for cocaine dependence. *Am J Addict* 20, 456-61.

Garcia-Rodriguez O., Secades-Villa R., Higgins S.T. *et al.* (2009) Effects of voucher-based intervention on abstinence and retention in an outpatient treatment for cocaine addiction: a randomized controlled trial. *Exp Clin Psychopharmacol* 17, 131-8.

Gaval-Cruz M. & Weinshenker D. (2009) mechanisms of disulfiram-induced cocaine abstinence: antabuse and cocaine relapse. *Mol Interv* 9, 175-87.

Gentry W.B., Ruedi-Bettschen D. & Owens S.M. (2010) Anti-(+)-methamphetamine monoclonal antibody antagonists designed to prevent the progression of human diseases of addiction. *Clin Pharmacol Ther* 88, 390-3.

George T.P., Chawarski M.C., Pakes J. *et al.* (2000) Disulfiram versus placebo for cocaine dependence in buprenorphine-maintained subjects: a preliminary trial. *Biol Psychiatry* 47, 1080-6.

Glatz A.C., Ehrlich M., Bae R.S. *et al.* (2002) Inhibition of cocaine self-administration by fluoxetine or D-fenfluramine combined with phentermine. *Pharmacol Biochem Behav* 71, 197-204.

Glynn L.H. & Moyers T.B. (2009) Motivational interviewing for addictions. *Evidence-based addiction treatment* (ed. Miller P.M.), pp. 177-187. Elsevier/Academic Press, Berlington, MA.

Goldberg A. (2007) A collaborative model for community action against methamphetamine. *J Psychoactive Drugs* Suppl 4, 327-35.

Gorelick D.A., Kim Y.K., Bencherif B. *et al.* (2005) Imaging brain mu-opioid

receptors in abstinent cocaine users: time course and relation to cocaine craving. *Biol Psychiatry* 57, 1573-82.

Grabowski J., Rhoades H., Schmitz J. *et al.* (2001) Dextroamphetamine for cocaine-dependence treatment: a double-blind randomized clinical trial. *J Clin Psychopharmacol* 21, 522-6.

Grabowski J., Rhoades H., Silverman P. *et al.* (2000) Risperidone for the treatment of cocaine dependence: randomized, double-blind trial. *J Clin Psychopharmacol* 20, 305-10.

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

Grabowski J., Roache J.D., Schmitz J.M. *et al.* (1997) Replacement medication for cocaine dependence: methylphenidate. *J Clin Psychopharmacol* 17, 485-8.

Grant J.E., Odlaug B.L. & Kim S.W. (2010) A double-blind, placebo-controlled study of N-acetyl cysteine plus naltrexone for methamphetamine dependence. *Eur Neuropsychopharmacol* 20, 823-8.

Gray K.M., Watson N.L., Carpenter M.J. *et al.* (2010) N-acetylcysteine (NAC) in young marijuana users: an open-label pilot study. *Am J Addict* 19, 187-9.

Grella C.E., Stein J.A., Weisner C. *et al.* (2010) Predictors of longitudinal substance use and mental health outcomes for patients in two integrated service delivery systems. *Drug Alcohol Depend* 110, 92-100.

Haile C.N., Kosten T.R. & Kosten T.A. (2009) Pharmacogenetic treatments for drug addiction: cocaine, amphetamine and methamphetamine. *Am J Drug Alcohol Abuse* 35, 161-177.

Hamilton J.D., Nguyen Q.X., Gerber R.M. *et al.* (2009) Olanzapine in cocaine dependence: a double-blind, placebo-controlled trial. *Am J Addict* 18, 48-52.

Haney M., Hart C.L., Vosburg S.K. *et al.* (2010) Effects of baclofen and mirtazapine on a laboratory model of marijuana withdrawal and relapse. *Psychopharmacology (Berl)* 211, 233-44.

Haney M., Hart C.L., Vosburg S.K. *et al.* (2008) Effects of THC and lofexidine in a human laboratory model of marijuana withdrawal and relapse. *Psychopharmacology (Berl)* 197, 157-68.

Haney M., Hart C.L., Vosburg S.K. *et al.* (2004) Marijuana withdrawal in humans: effects of oral THC or divalproex. *Neuropsychopharmacology* 29, 158-70.

Haney M., Hart C.L., Ward A.S. *et al.* (2003) Nefazodone decreases anxiety during marijuana withdrawal in humans. *Psychopharmacology (Berl)* 165, 157-65.

Haney M., Rubin E. & Foltin R.W. (2011) Aripiprazole maintenance increases smoked cocaine self-administration in humans. *Psychopharmacology (Berl)* 216, 379-87.

Haney M., Ward A.S., Comer S.D. *et al.* (2001) Bupropion SR worsens mood during marijuana withdrawal in humans. *Psychopharmacology (Berl)* 155, 171-9.

Hanley M.J. & Kenna G.A. (2008) Quetiapine: treatment for substance abuse and drug of abuse. *Am J Health Syst Pharm* 65, 611-8.

Harris D.S., Everhart T., Jacob P., 3rd *et al.* (2009) A phase 1 trial of pharmacologic interactions between transdermal selegiline and a 4-hour cocaine infusion. *BMC Clin Pharmacol* 9, 13.

Harris G.C.& Aston-Jones G. (1993) Beta-adrenergic antagonists attenuate withdrawal anxiety in cocaine- and morphine-dependent rats. *Psychopharmacology (Berl)* 113, 131-6.

Hart C.L., Haney M., Vosburg S.K. *et al.* (2007) Smoked cocaine self-administration is decreased by modafinil. *Neuropsychopharmacology* 33, 761-768.

Heinzerling K.G., Shoptaw S., Peck J.A. *et al.* (2006) Randomized, placebo-controlled trial of baclofen and gabapentin for the treatment of methamphetamine dependence. *Drug Alcohol Depend* 85, 177-84.

Heinzerling K.G., Swanson A.N., Kim S. *et al.* (2010) Randomized, double-blind, placebo-controlled trial of modafinil for the treatment of methamphetamine dependence. *Drug Alcohol Depend* 109, 20-9.

Herin D.V., Rush C.R. & Grabowski J. (2010) Agonist-like pharmacotherapy for stimulant dependence: preclinical, human laboratory, and clinical studies. *Ann*

N Y Acad Sci 1187, 76-100.

Hettema J., Steele J. & Miller W.R. (2005) Motivational interviewing. *Annu Rev Clin Psychol* 1, 91-111.

Higgins S.T. (2006) Extending contingency management to the treatment of methamphetamine use disorders. *Am J Psychiatry* 163, 1870-2.

Higgins S.T., Badger G.J. & Budney A.J. (2000) Initial abstinence and success in achieving longer term cocaine abstinence. *Exp Clin Psychopharmacol* 8, 377-86.

Higgins S.T., Budney A.J., Bickel W.K. *et al.* (1993) Achieving cocaine abstinence with a behavioral approach. *Am J Psychiatry* 150, 763-9.

Higgins S.T., Delaney D.D., Budney A.J. *et al.* (1991) A behavioral approach to achieving initial cocaine abstinence. *Am J Psychiatry* 148, 1218-24.

Higgins S.T. & Rogers R.E. (2009) Contingency management and the community reinforcement approach. *Evidence-based addiction treatment* (ed. Miller P.M.), pp. 249-262. Elsevier/Academic Press, Berlington, MA.

Higgins S.T., Sigmon S.C., Wong C.J. *et al.* (2003) Community reinforcement therapy for cocaine-dependent outpatients. *Arch Gen Psychiatry* 60, 1043-52.

Higgins S.T., Wong C.J., Badger G.J. *et al.* (2000) Contingent reinforcement increases cocaine abstinence during outpatient treatment and 1 year of follow-up. *J Consult Clin Psychol* 68, 64-72.

Houtsmuller E.J., Notes L.D., Newton T. *et al.* (2004) Transdermal selegiline and intravenous cocaine: safety and interactions. *Psychopharmacology (Berl)* 172, 31-40.

Hser Y.-I.& Anglin M.D. (2011) Addiction treatment and recovery careers. *Addiction recovery management* eds. Kelly J.F. & White W.L.), pp. 9-29. Humana Press, New York.

Hser Y.I., Stark M.E., Paredes A. *et al.* (2006) A 12-year follow-up of a treated cocaine-dependent sample. *J Subst Abuse Treat* 30, 219-26.

Hubbard R.L., Craddock S.G. & Anderson J. (2003) Overview of 5-year followup outcomes in the drug abuse treatment outcome studies (DATOS). *J Subst*

Abuse Treat 25, 125-34.

Humphreys K., Huebsch P.D., Finney J.W. *et al.* (1999) A comparative evaluation of substance abuse treatment: V. Substance abuse treatment can enhance the effectiveness of self-help groups. *Alcohol Clin Exp Res* 23, 558-63.

Humphreys K. & Moos R. (2001) Can encouraging substance abuse patients to participate in self-help groups reduce demand for health care? A quasi-experimental study. *Alcohol Clin Exp Res* 25, 711-6.

Humphreys K. & Moos R.H. (2007) Encouraging posttreatment self-help group involvement to reduce demand for continuing care services: two-year clinical and utilization outcomes. *Alcohol Clin Exp Res* 31, 64-8.

Hysek C.M., Brugger R., Simmler L.D. *et al.* (2011) Effects of the alpha2-adrenergic agonist clonidine on the pharmacodynamics and pharmacokinetics of 3,4 methylenedioxymethamphetamine in healthy volunteers. *J Pharmacol Exp Ther*.

Hysek C.M., Simmler L.D., Ineichen M. *et al.* (2011) The norepinephrine transporter inhibitor reboxetine reduces stimulant effects of MDMA ("ecstasy") in humans. *Clin Pharmacol Ther* 90, 246-55.

Jansen K.L. & Darracot-Cankovic R. (2001) The nonmedical use of ketamine, part two: A review of problem use and dependence. *J Psychoactive Drugs* 33, 151-8.

Jayaram-Lindstrom N., Hammarberg A., Beck O. *et al.* (2008) Naltrexone for the treatment of amphetamine dependence: a randomized, placebo-controlled trial. *Am J Psychiatry* 165, 1442-8.

Jittiwutikan J., Srisurapanont M. & Jarusuraisin N. (1997) Amineptine in the treatment of amphetamine withdrawal: a placebo-controlled, randomised, double-blind study. *J Med Assoc Thai* 80, 587-92.

Johnson B.A., Ait-Daoud N., Elkashef A.M. *et al.* (2008) A preliminary randomized, double-blind, placebo-controlled study of the safety and efficacy of ondansetron in the treatment of methamphetamine dependence. *Int J Neuropsychopharmacol* 11, 1-14.

Johnson B.A., Roache J.D., Ait-Daoud N. *et al.* (2005) Effects of isradipine, a dihydropyridine-class calcium-channel antagonist, on d-methamphetamine's subjective and reinforcing effects. *Int J Neuropsychopharmacol* 8, 203-13.

Johnson B.A., Roache J.D., Ait-Daoud N. *et al.* (2007) Effects of acute topiramate dosing on methamphetamine-induced subjective mood. *Int J Neuropsychopharmacol* 10, 85-98.

Johnson B.A., Roache J.D., Bordnick P.S. *et al.* (1999) Isradipine, a dihydropyridine-class calcium channel antagonist, attenuates some of d-methamphetamine's positive subjective effects: a preliminary study. *Psychopharmacology (Berl)* 144, 295-300.

Johnston L.D., O'Malley P.M., Bachman J.G. *et al.* (2010) Monitoring the future national survey results on drug use, 1975–2010. Volume I: Secondary school students. *Ann Arbor: Institute for Social Research, The University of Michigan*.

Kahn R., Biswas K., Childress A.R. *et al.* (2009) Multi-center trial of baclofen for abstinence initiation in severe cocaine-dependent individuals. *Drug Alcohol Depend* 103, 59-64.

Kalivas P.W. (1993) Neurotransmitter regulation of dopamine neurons in the ventral tegmental area. *Brain Res Brain Res Rev* 18, 75-113.

Kalivas P.W. (2007) Neurobiology of cocaine addiction: implications for new pharmacotherapy. *Am J Addict* 16, 71-8.

Kalivas P.W., McFarland K., Bowers S. *et al.* (2003) Glutamate transmission and addiction to cocaine. *Ann N Y Acad Sci* 1003, 169-75.

Kalivas P.W., Volkow N. & Seamans J. (2005) Unmanageable motivation in addiction: a pathology in prefrontal-accumbens glutamate transmission. *Neuron* 45, 647-50.

Kalivas P.W. & Volkow N.D. (2011) New medications for drug addiction hiding in glutamatergic neuroplasticity. *Mol Psychiatry*.

Kampman K.M. (2010) What's new in the treatment of cocaine addiction? *Curr Psychiatry Rep* 12, 441-7.

Kampman K.M., Alterman A.I., Volpicelli J.R. *et al.* (2001) Cocaine withdrawal

symptoms and initial urine toxicology results predict treatment attrition in outpatient cocaine dependence treatment. *Psychol Addict Behav* 15, 52-9.

Kampman K.M., Dackis C., Lynch K.G. *et al.* (2006) A double-blind, placebo-controlled trial of amantadine, propranolol, and their combination for the treatment of cocaine dependence in patients with severe cocaine withdrawal symptoms. *Drug Alcohol Depend* 85, 129-37.

Kampman K.M., Pettinati H., Lynch K.G. *et al.* (2004) A pilot trial of topiramate for the treatment of cocaine dependence. *Drug Alcohol Depend* 75, 233-40.

Kampman K.M., Pettinati H., Lynch K.G. *et al.* (2003) A pilot trial of olanzapine for the treatment of cocaine dependence. *Drug Alcohol Depend* 70, 265-73.

Kampman K.M., Rukstalis M., Pettinati H. *et al.* (2000) The combination of phentermine and fenfluramine reduced cocaine withdrawal symptoms in an open trial. *J Subst Abuse Treat* 19, 77-9.

Kampman K.M., Volpicelli J.R., Mulvaney F. *et al.* (2001) Effectiveness of propranolol for cocaine dependence treatment may depend on cocaine withdrawal symptom severity. *Drug Alcohol Depend* 63, 69-78.

Karila L., Gorelick D., Weinstein A. *et al.* (2008) New treatments for cocaine dependence: a focused review. *Int J Neuropsychopharmacol* 11, 425-38.

Karila L., Weinstein A., Aubin H.J. *et al.* (2010) Pharmacological approaches to methamphetamine dependence: a focused review. *Br J Clin Pharmacol* 69, 578-92.

Katz J.L., Su T.P., Hiranita T. *et al.* (2011) A Role for Sigma Receptors in Stimulant Self Administration and Addiction. *Pharmaceuticals (Basel)* 4, 880-914.

Kay-Lambkin F.J., Baker A.L., Kelly B. *et al.* (2011) Clinician-assisted computerised versus therapist-delivered treatment for depressive and addictive disorders: a randomised controlled trial. *Med J Aust* 195, S44-50.

Kay-Lambkin F.J., Baker A.L., Lewin T.J. *et al.* (2009) Computer-based psychological treatment for comorbid depression and problematic alcohol and/or cannabis use: a randomized controlled trial of clinical efficacy. *Addiction* 104, 378-88.

Kelly J.F. & Moos R. (2003) Dropout from 12-step self-help groups: prevalence, predictors, and counteracting treatment influences. *J Subst Abuse Treat* 24, 241-50.

Kennedy A., Wood A.E., Saxon A.J. *et al.* (2008) Quetiapine for the treatment of cocaine dependence: an open-label trial. *J Clin Psychopharmacol* 28, 221-4.

Kinsey B.M., Kosten T.R. & Orson F.M. (2010) Anti-cocaine vaccine development. *Expert Rev Vaccines* 9, 1109-14.

Kleber H.D., Weiss R.D., Anton R.F., Jr. *et al.* (2007) Treatment of patients with substance use disorders, second edition. American Psychiatric Association. *Am J Psychiatry* 164, 5-123.

Knapp W.P., Soares B.G., Farrel M. *et al.* (2007) Psychosocial interventions for cocaine and psychostimulant amphetamines related disorders. *Cochrane Database Syst Rev*, CD003023.

Knight J.R., Sherritt L., Van Hook S. *et al.* (2005) Motivational interviewing for adolescent substance use: a pilot study. *J Adolesc Health* 37, 167-9.

Kongsakon R., Papadopoulos K.I. & Saguansiritham R. (2005) Mirtazapine in amphetamine detoxification: a placebo-controlled pilot study. *Int Clin Psychopharmacol* 20, 253-6.

Koob G.F. & Nestler E.J. (1997) The neurobiology of drug addiction. *J Neuropsychiatry Clin Neurosci* 9, 482-97.

Kosten T., Oliveto A., Feingold A. *et al.* (2003) Desipramine and contingency management for cocaine and opiate dependence in buprenorphine maintained patients. *Drug Alcohol Depend* 70, 315-25.

Kosten T.R. & Biegel D. (2002) Therapeutic vaccines for substance dependence. *Expert Rev Vaccines* 1, 363-71.

Kuczenski R., Segal D.S., Cho A.K. *et al.* (1995) Hippocampus norepinephrine, caudate dopamine and serotonin, and behavioral responses to the stereoisomers of amphetamine and methamphetamine. *J Neurosci* 15, 1308-17.

Labate B.C. & Cavnar C. (2011) The expansion of the field of research on ayahuasca: some reflections about the ayahuasca track at the 2010 MAPS "Psychedelic

Science in the 21st Century" conference. *Int J Drug Policy* 22, 174-8.

LaRowe S.D., Myrick H., Hedden S. *et al.* (2007) Is cocaine desire reduced by N-acetylcysteine? *Am J Psychiatry* 164, 1115-1117.

Laudet A., Stanick V. & Sands B. (2007) An exploration of the effect of on-site 12-step meetings on post-treatment outcomes among polysubstance-dependent outpatient clients. *Eval Rev* 31, 613-46.

Laudet A.B. & White W.L. (2008) Recovery capital as prospective predictor of sustained recovery, life satisfaction, and stress among former poly-substance users. *Subst Use Misuse* 43, 27-54.

Lee N.K. & Rawson R.A. (2008) A systematic review of cognitive and behavioural therapies for methamphetamine dependence. *Drug Alcohol Rev* 27, 309-17.

Leshner A.I. (2001) Hallucinogens and dissociative drugs including LSD, PCP, ketamine, dextromethorphan. *National institute on drug abuse research report series*.

Levin F.R., Evans S.M., Brooks D.J. *et al.* (2007) Treatment of cocaine dependent treatment seekers with adult ADHD: double-blind comparison of methylphenidate and placebo. *Drug Alcohol Depend* 87, 20-9.

Levin F.R., Evans S.M., Brooks D.J. *et al.* (2006) Treatment of methadone-maintained patients with adult ADHD: double-blind comparison of methylphenidate, bupropion and placebo. *Drug Alcohol Depend* 81, 137-48.

Levin F.R., Mariani J.J., Brooks D.J. *et al.* (2011) Dronabinol for the treatment of cannabis dependence: a randomized, double-blind, placebo-controlled trial. *Drug Alcohol Depend* 116, 142-50.

Lima M.S., Reisser A.A., Soares B.G. *et al.* (2003) Antidepressants for cocaine dependence. *Cochrane Database Syst Rev*, CD002950.

Loebl T., Angarita G.A., Pachas G.N. *et al.* (2008) A randomized, double-blind, placebo-controlled trial of long-acting risperidone in cocaine-dependent men. *J Clin Psychiatry* 69, 480-6.

Longo M., Wickes W., Smout M. *et al.* (2010) Randomized controlled trial of dexamphetamine maintenance for the treatment of methamphetamine

dependence. *Addiction* 105, 146-54.

Lu L., Liu Y., Zhu W. *et al.* (2009) Traditional medicine in the treatment of drug addiction. *Am J Drug Alcohol Abuse* 35, 1-11.

Luigjes J., van den Brink W., Feenstra M. *et al.* (2011) Deep brain stimulation in addiction: a review of potential brain targets. *Mol Psychiatry*.

Lussier J.P., Heil S.H., Mongeon J.A. *et al.* (2006) A meta-analysis of voucher-based reinforcement therapy for substance use disorders. *Addiction* 101, 192-203.

Magill M. & Ray L.A. (2009) Cognitive-behavioral treatment with adult alcohol and illicit drug users: a meta-analysis of randomized controlled trials. *J Stud Alcohol Drugs* 70, 516-27.

Majer J.M., Jason L.A., Ferrari J.R. *et al.* (2011) 12-Step involvement among a U.S. national sample of Oxford House residents. *J Subst Abuse Treat* 41, 37-44.

Malcolm R., Kajdasz D.K., Herron J. *et al.* (2000) A double-blind, placebo-controlled outpatient trial of pergolide for cocaine dependence. *Drug Alcohol Depend* 60, 161-8.

Margolin A. (2003) Acupuncture for substance abuse. *Curr Psychiatry Rep* 5, 333-9.

Margolin A., Kleber H.D., Avants S.K. *et al.* (2002) Acupuncture for the treatment of cocaine addiction: a randomized controlled trial. *JAMA* 287, 55-63.

Margolin A., Kosten T.R., Avants S.K. *et al.* (1995) A multicenter trial of bupropion for cocaine dependence in methadone-maintained patients. *Drug Alcohol Depend* 40, 125-31.

Martell B.A., Mitchell E., Poling J. *et al.* (2005) Vaccine pharmacotherapy for the treatment of cocaine dependence. *Biol Psychiatry* 58, 158-64.

Martell B.A., Orson F.M., Poling J. *et al.* (2009) Cocaine vaccine for the treatment of cocaine dependence in methadone-maintained patients: a randomized, double-blind, placebo-controlled efficacy trial. *Arch Gen Psychiatry* 66, 1116-23.

Martin G. & Copeland J. (2008) The adolescent cannabis check-up: randomized trial of a brief intervention for young cannabis users. *J Subst Abuse Treat* 34, 407-14.

Martino S., Carroll K.M., Nich C. *et al.* (2006) A randomized controlled pilot study of

motivational interviewing for patients with psychotic and drug use disorders. *Addiction* 101, 1479-92.

Maude-Griffin P.M., Hohenstein J.M., Humfleet G.L. *et al.* (1998) Superior efficacy of cognitive-behavioral therapy for urban crack cocaine abusers: main and matching effects. *J Consult Clin Psychol* 66, 832-7.

McCambridge J. & Strang J. (2004) The efficacy of single-session motivational interviewing in reducing drug consumption and perceptions of drug-related risk and harm among young people: results from a multi-site cluster randomized trial. *Addiction* 99, 39-52.

McCambridge J. & Strang J. (2005) Deterioration over time in effect of Motivational Interviewing in reducing drug consumption and related risk among young people. *Addiction* 100, 470-8.

McCance E.F. (1997) Overview of potential treatment medications for cocaine dependence. *NIDA Res Monogr* 175, 36-72.

McGregor C., Srisurapanont M., Jittiwutikarn J. *et al.* (2005) The nature, time course and severity of methamphetamine withdrawal. *Addiction* 100, 1320-9.

McKay J.R., Lynch K.G., Coviello D. *et al.* (2010) Randomized trial of continuing care enhancements for cocaine-dependent patients following initial engagement. *J Consult Clin Psychol* 78, 111-20.

McKay J.R., McLellan A.T., Alterman A.I. *et al.* (1998) Predictors of participation in aftercare sessions and self-help groups following completion of intensive outpatient treatment for substance abuse. *J Stud Alcohol* 59, 152-62.

McKay J.R., Van Horn D., Oslin D.W. *et al.* (2011) Extended telephone-based continuing care for alcohol dependence: 24-month outcomes and subgroup analyses. *Addiction* 106, 1760-9; discussion 1770-1.

McKee S.A., Carroll K.M., Sinha R. *et al.* (2007) Enhancing brief cognitive-behavioral therapy with motivational enhancement techniques in cocaine users. *Drug Alcohol Depend* 91, 97-101.

McRae-Clark A.L., Carter R.E., Killeen T.K. *et al.* (2009) A placebo-controlled trial of buspirone for the treatment of marijuana dependence. *Drug Alcohol Depend*

105, 132-8.

Meredith C.W., Jaffe C., Yanasak E. *et al.* (2007) An open-label pilot study of risperidone in the treatment of methamphetamine dependence. *J Psychoactive Drugs* 39, 167-72.

Miller W.R.& Rollnick S. (2002) *Motivational Interviewing: Preparing People for Change*. second edn., Guilford Press, New York.

Miller W.R., Yahne C.E. & Tonigan J.S. (2003) Motivational interviewing in drug abuse services: a randomized trial. *J Consult Clin Psychol* 71, 754-63.

Min X., Lee D.T., Jinhua X. *et al.* (2007) A database on treating drug addiction with traditional Chinese medicine. *Addiction* 102, 282-8.

Minozzi S., Amato L., Davoli M. *et al.* (2008) Anticonvulsants for cocaine dependence. *Cochrane Database of Systematic Reviews*, Art. No.: CD006754. DOI:10.1002/14651858.CD006754.pub2.

Moeller F.G., Schmitz J.M., Herin D. *et al.* (2008) Use of stimulants to treat cocaine and methamphetamine abuse. *Curr Psychiatry Rep* 10, 385-91.

Moeller F.G., Schmitz J.M., Steinberg J.L. *et al.* (2007) Citalopram combined with behavioral therapy reduces cocaine use: a double-blind, placebo-controlled trial. *Am J Drug Alcohol Abuse* 33, 367-78.

Monti P.M., Miranda R., Jr., Nixon K. *et al.* (2005) Adolescence: booze, brains, and behavior. *Alcohol Clin Exp Res* 29, 207-20.

Montoya I.D. (2008) Immunotherapies for drug addictions. *Adicciones* 20, 111-115.

Mooney M.E., Herin D.V., Schmitz J.M. *et al.* (2009) Effects of oral methamphetamine on cocaine use: a randomized, double-blind, placebo-controlled trial. *Drug and Alcohol Dependence* 101, 34-41.

Mooney M.E., Schmitz J.M., Moeller F.G. *et al.* (2007) Safety, tolerability and efficacy of levodopa-carbidopa treatment for cocaine dependence: two double-blind, randomized, clinical trials. *Drug Alcohol Depend* 88, 214-23.

Narcotics Division. (2009) The Narcotics Division (ND) of the Security Bureau, The government of Hong Kong Special Administrative Region. Central Registry of Drug Abuse Fifty-ninth Report.

Nejtek V.A., Avila M., Chen L.A. *et al.* (2008) Do atypical antipsychotics effectively treat co-occurring bipolar disorder and stimulant dependence? A randomized, double-blind trial. *Journal of Clinical Psychiatry* 69, 1257-1266.

Nejtek V.A., Avila M., Chen L.A. *et al.* (2008) Do atypical antipsychotics effectively treat co-occurring bipolar disorder and stimulant dependence? A randomized, double-blind trial. *J Clin Psychiatry* 69, 1257-66.

Newton T.F., De La Garza R., 2nd, Fong T. *et al.* (2005) A comprehensive assessment of the safety of intravenous methamphetamine administration during treatment with selegiline. *Pharmacol Biochem Behav* 82, 704-11.

Obert J.L., McCann M.J., Marinelli-Casey P. *et al.* (2000) The matrix model of outpatient stimulant abuse treatment: history and description. *J Psychoactive Drugs* 32, 157-64.

Oliveto A., Poling J., Mancino M.J. *et al.* (2009) Sertraline Delays Relapse in Recently Abstinent Cocaine-Dependent Patients with Depressive Symptoms(1). *Addiction*.

Olmstead T.A.& Petry N.M. (2009) The cost-effectiveness of prize-based and voucher-based contingency management in a population of cocaine- or opioid-dependent outpatients. *Drug Alcohol Depend* 102, 108-15.

Orson F.M., Kinsey B.M., Singh R.A. *et al.* (2008) Substance abuse vaccines. *Ann N Y Acad Sci* 1141, 257-69.

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

Petry N.M. (2010) Contingency management treatments: controversies and challenges. *Addiction* 105, 1507-9.

Petry N.M., Alessi S.M., Hanson T. *et al.* (2007) Randomized trial of contingent prizes versus vouchers in cocaine-using methadone patients. *J Consult Clin Psychol* 75, 983-91.

Petry N.M., Alessi S.M., Marx J. *et al.* (2005) Vouchers versus prizes: contingency management treatment of substance abusers in community settings. *J Consult Clin Psychol* 73, 1005-14.

Petry N.M. & Martin B. (2002) Low-cost contingency management for treating cocaine- and opioid-abusing methadone patients. *J Consult Clin Psychol* 70, 398-405.

Petry N.M., Martin B. & Simcic F., Jr. (2005) Prize reinforcement contingency management for cocaine dependence: integration with group therapy in a methadone clinic. *J Consult Clin Psychol* 73, 354-9.

Petry N.M., Peirce J.M., Stitzer M.L. *et al.* (2005) Effect of prize-based incentives on outcomes in stimulant abusers in outpatient psychosocial treatment programs: a national drug abuse treatment clinical trials network study. *Arch Gen Psychiatry* 62, 1148-56.

Pettinati H.M., Kampman K.M., Lynch K.G. *et al.* (2008) Gender differences with high-dose naltrexone in patients with co-occurring cocaine and alcohol dependence. *J Subst Abuse Treat* 34, 378-90.

Pettinati H.M., Kampman K.M., Lynch K.G. *et al.* (2008) A double blind, placebo-controlled trial that combines disulfiram and naltrexone for treating co-occurring cocaine and alcohol dependence. *Addict Behav* 33, 651-67.

Piasecki M.P., Steinagel G.M., Thienhaus O.J. *et al.* (2002) An exploratory study: the use of paroxetine for methamphetamine craving. *J Psychoactive Drugs* 34, 301-4.

Pier Paolo Pani, Emanuela Trogu, Rosangela Vacca *et al.* (2010) Disulfiram for the treatment of cocaine dependence. *Cochrane Database of Systematic Reviews*.

Plebani J.G., Lynch K.G., Yu Q. *et al.* (2011) Results of an initial clinical trial of varenicline for the treatment of cocaine dependence. *Drug Alcohol Depend*.

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. *Arch Gen Psychiatry* 63, 219-28.

Preston K.L., Ghitza U.E., Schmittner J.P. *et al.* (2008) Randomized trial comparing two treatment strategies using prize-based reinforcement of abstinence in cocaine and opiate users. *J Appl Behav Anal* 41, 551-63.

Rash C.J., Olmstead T.A. & Petry N.M. (2009) Income does not affect response to

contingency management treatments among community substance abuse treatment-seekers. *Drug Alcohol Depend* 104, 249-53.

Rawson R.A., Huber A., Brethen P. *et al.* (2002) Status of methamphetamine users 2-5 years after outpatient treatment. *J Addict Dis* 21, 107-19.

Rawson R.A., Huber A., McCann M. *et al.* (2002) A comparison of contingency management and cognitive-behavioral approaches during methadone maintenance treatment for cocaine dependence. *Arch Gen Psychiatry* 59, 817-24.

Rawson R.A., Marinelli-Casey P., Anglin M.D. *et al.* (2004) A multi-site comparison of psychosocial approaches for the treatment of methamphetamine dependence. *Addiction* 99, 708-17.

Rawson R.A., McCann M.J., Flammino F. *et al.* (2006) A comparison of contingency management and cognitive-behavioral approaches for stimulant-dependent individuals. *Addiction* 101, 267-74.

Rawson R.A., Shoptaw S.J., Obert J.L. *et al.* (1995) An intensive outpatient approach for cocaine abuse treatment. The Matrix model. *J Subst Abuse Treat* 12, 117-27.

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

Roache J.D., Grabowski J., Schmitz J.M. *et al.* (2000) Laboratory measures of methylphenidate effects in cocaine-dependent patients receiving treatment. *J Clin Psychopharmacol* 20, 61-8.

Roache J.D., Kahn R., Newton T.F. *et al.* (2011) A double-blind, placebo-controlled assessment of the safety of potential interactions between intravenous cocaine, ethanol, and oral disulfiram. *Drug Alcohol Depend*.

Roll J.M., Petry N.M., Stitzer M.L. *et al.* (2006) Contingency management for the treatment of methamphetamine use disorders. *Am J Psychiatry* 163, 1993-9.

Ross S. & Peselow E. (2009) The neurobiology of addictive disorders. *Clin Neuropharmacol* 32, 269-76.

Rothman R.B. & Baumann M.H. (2006) Balance between Dopamine and Serotonin Release Modulates Behavioral Effects of Amphetamine-Type Drugs. *Annals of the New York Academy of Sciences*, 245-260.

Rothman R.B., Baumann M.H., Dersch C.M. *et al.* (2001) Amphetamine-type central nervous system stimulants release norepinephrine more potently than they release dopamine and serotonin. *Synapse* 39, 32-41.

Rothman R.B., Blough B.E. & Baumann M.H. (2008) Dual Dopamine Serotonin Releasers as Potential Medications for Stimulant and Alcohol Addictions. *Progress in brain research*, 385-406.

Rush C.R., Vansickel A.R., Lile J.A. *et al.* (2009) Evidence-based treatment of amphetamine dependence: behavioral and pharmacological approaches. *Pharmacology and Treatment of Substance Abuse* eds. Cohen l.M., Collins F.L., Young A.M. *et al.*). Taylor & Francis Group, NewYork.

Sacks S., Banks S., McKendrick K. *et al.* (2008) Modified therapeutic community for co-occurring disorders: a summary of four studies. *J Subst Abuse Treat* 34, 112-22.

Sacks S., McKendrick K., Sacks J.Y. *et al.* (2008) Enhanced outpatient treatment for co-occurring disorders: main outcomes. *J Subst Abuse Treat* 34, 48-60.

Sacks S., Sacks J.Y., McKendrick K. *et al.* (2004) Modified TC for MICA offenders: crime outcomes. *Behav Sci Law* 22, 477-501.

Schenk S. (2011) MDMA ("ecstasy") abuse as an example of dopamine neuroplasticity. *Neurosci Biobehav Rev* 35, 1203-18.

Schiffer W.K., Azmoodeh M., Gerasimov M. *et al.* (2003) Selegiline potentiates cocaine-induced increases in rodent nucleus accumbens dopamine. *Synapse* 48, 35-8.

Schmitz J.M., Lindsay J.A., Green C.E. *et al.* (2009) High-dose naltrexone therapy for cocaine-alcohol dependence. *Am J Addict* 18, 356-62.

Schmitz J.M., Lindsay J.A., Stotts A.L. *et al.* (2010) Contingency management and levodopa-carbidopa for cocaine treatment: a comparison of three behavioral targets. *Exp Clin Psychopharmacol* 18, 238-44.

Schmitz J.M., Mooney M.E., Moeller F.G. *et al.* (2008) Levodopa pharmacotherapy for cocaine dependence: choosing the optimal behavioral therapy platform. *Drug Alcohol Depend* 94, 142-50.

Schmitz J.M., Stotts A.L., Rhoades H.M. *et al.* (2001) Naltrexone and relapse prevention treatment for cocaine-dependent patients. *Addict Behav* 26, 167-80.

Schmitz J.M., Stotts A.L., Sayre S.L. *et al.* (2004) Treatment of cocaine-alcohol dependence with naltrexone and relapse prevention therapy. *Am J Addict* 13, 333-41.

Scott C.K. & Dennis M.L. (2009) Results from two randomized clinical trials evaluating the impact of quarterly recovery management checkups with adult chronic substance users. *Addiction*, 959-971.

Secades-Villa R., Garcia-Rodriguez O., Garcia-Fernandez G. *et al.* (2011) Community reinforcement approach plus vouchers among cocaine-dependent outpatients: twelve-month outcomes. *Psychol Addict Behav* 25, 174-9.

Secades-Villa R., Garcia-Rodriguez O., Higgins S.T. *et al.* (2008) Community reinforcement approach plus vouchers for cocaine dependence in a community setting in Spain: six-month outcomes. *J Subst Abuse Treat* 34, 202-7.

Shearer J., Darke S., Rodgers C. *et al.* (2009) A double-blind, placebo-controlled trial of modafinil (200 mg/day) for methamphetamine dependence. *Addiction* 104, 224-33.

Shearer J., Wodak A., Mattick R.P. *et al.* (2001) Pilot randomized controlled study of dexamphetamine substitution for amphetamine dependence. *Addiction* 96, 1289-96.

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

Shoptaw S., Huber A., Peck J. *et al.* (2006) Randomized, placebo-controlled trial of sertraline and contingency management for the treatment of methamphetamine dependence. *Drug Alcohol Depend* 85, 12-8.

Shoptaw S., Reback C.J., Peck J.A. *et al.* (2005) Behavioral treatment approaches for

methamphetamine dependence and HIV-related sexual risk behaviors among urban gay and bisexual men. *Drug Alcohol Depend* 78, 125-34.

Shoptaw S., Yang X., Rotheram-Fuller E.J. *et al.* (2003) Randomized placebo-controlled trial of baclofen for cocaine dependence: preliminary effects for individuals with chronic patterns of cocaine use. *J Clin Psychiatry* 64, 1440-8.

Shoptaw S.J., Kao U., Heinzerling K. *et al.* (2009) Treatment for amphetamine withdrawal. *Cochrane Database Syst Rev*, CD003021.

Shwartz M., Saitz R., Mulvey K. *et al.* (1999) The value of acupuncture detoxification programs in a substance abuse treatment system. *J Subst Abuse Treat* 17, 305-12.

Sigmon S.C. & Higgins S.T. (2006) Voucher-based contingent reinforcement of marijuana abstinence among individuals with serious mental illness. *J Subst Abuse Treat* 30, 291-5.

Silverman K., Wong C.J., Needham M. *et al.* (2007) A randomized trial of employment-based reinforcement of cocaine abstinence in injection drug users. *J Appl Behav Anal* 40, 387-410.

Simpson D.D., Joe G.W. & Broome K.M. (2002) A national 5-year follow-up of treatment outcomes for cocaine dependence. *Arch Gen Psychiatry* 59, 538-44.

Simpson D.D., Joe G.W., Fletcher B.W. *et al.* (1999) A national evaluation of treatment outcomes for cocaine dependence. *Arch Gen Psychiatry* 56, 507-14.

Sindelar J., Elbel B. & Petry N.M. (2007) What do we get for our money? Cost-effectiveness of adding contingency management. *Addiction* 102, 309-16.

Smelson D.A., 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. *J Subst Abuse Treat* 27, 45-9.

Soares B., Lima Reisser A.A., Farrell M. *et al.* (2010) WITHDRAWN: Dopamine agonists for cocaine dependence. *Cochrane Database Syst Rev*, CD003352.

Soares B.G., Lima M.S., Reisser A.A. *et al.* (2003) Dopamine agonists for cocaine dependence. *Cochrane Database Syst Rev*, CD003352.

Srisurapanont M., Jarusuraisin N. & Jittiwutikan J. (1999) Amphetamine withdrawal:

II. A placebo-controlled, randomised, double-blind study of amineptine treatment. *Aust N Z J Psychiatry* 33, 94-8.

Stitzer M.L., Petry N.M. & Peirce J. (2010) Motivational incentives research in the National Drug Abuse Treatment Clinical Trials Network. *J Subst Abuse Treat* 38 Suppl 1, S61-9.

Stoops W.W., Lile J.A. & Rush C.R. (2010) Monetary alternative reinforcers more effectively decrease intranasal cocaine choice than food alternative reinforcers. *Pharmacol Biochem Behav* 95, 187-91.

Sullivan C.J., McKendrick K., Sacks S. *et al.* (2007) Modified therapeutic community treatment for offenders with MICA disorders: substance use outcomes. *Am J Drug Alcohol Abuse* 33, 823-32.

Suzuki J.& Halpern J.H. (2009) Hallucinogens. *Pharmacology and Treatment of Substance Abuse* eds. Cohen l.M., Collins F.L., Young A.M. *et al.*), pp. 393-414. Taylor & Francis Group, New York.

Swift R.& Leggio L. (2009) Adjunctive pharmacotherapy in the treatment of alcohol and drug dependence. *Evidence-based addiction treatment* (ed. Miller P.M.). Elsevier/Academic Press, Berlington, MA.

Szerman N., Peris L., Mesias B. *et al.* (2005) Reboxetine for the treatment of patients with Cocaine Dependence Disorder. *Hum Psychopharmacol* 20, 189-92.

The Marijuana Treatment Project Research Group. (2004) Brief treatments for cannabis dependence: findings from a randomized multisite trial. *J Consult Clin Psychol* 72, 455-66.

Tiihonen J., Kuoppasalmi K., Fohr J. *et al.* (2007) A comparison of aripiprazole, methylphenidate, and placebo for amphetamine dependence. *Am J Psychiatry* 164, 160-2.

Timko C. & DeBenedetti A. (2007) A randomized controlled trial of intensive referral to 12-step self-help groups: one-year outcomes. *Drug Alcohol Depend* 90, 270-9.

Torrens M., Fonseca F., Mateu G. *et al.* (2005) Efficacy of antidepressants in substance use disorders with and without comorbid depression. A systematic

review and meta-analysis. *Drug Alcohol Depend* 78, 1-22.

Urschel H.C., 3rd, Hanselka L.L. & Baron M. (2011) A controlled trial of flumazenil and gabapentin for initial treatment of methylamphetamine dependence. *J Psychopharmacol* 25, 254-62.

Vandrey R., Bigelow G.E. & Stitzer M.L. (2007) Contingency management in cocaine abusers: a dose-effect comparison of goods-based versus cash-based incentives. *Exp Clin Psychopharmacol* 15, 338-43.

Vandrey R. & Haney M. (2009) Pharmacotherapy for cannabis dependence: how close are we? *CNS Drugs* 23, 543-53.

Volkow N.D. (2009) Marijuana abuse. *National institute on drug abuse research report series*.

Volkow N.D. & Swanson J.M. (2003) Variables that affect the clinical use and abuse of methylphenidate in the treatment of ADHD. *American Journal of Psychiatry* 160, 1909-1918.

Walker D.D., Stephens R., Roffman R. *et al.* (2011) Randomized controlled trial of motivational enhancement therapy with nontreatment-seeking adolescent cannabis users: a further test of the teen marijuana check-up. *Psychol Addict Behav* 25, 474-84.

Weinstein A.M. & Gorelick D.A. (2011) Pharmacological treatment of cannabis dependence. *Curr Pharm Des* 17, 1351-8.

Weiss R.D., Griffin M.L., Gallop R.J. *et al.* (2005) The effect of 12-step self-help group attendance and participation on drug use outcomes among cocaine-dependent patients. *Drug Alcohol Depend* 77, 177-84.

White W. & McLellan A.T. (2008) Addiction as a chroinc disease: messages for clients, families and referral sources. *Counselor* 9, 24-33.

White W.L. & Kelly J.F. (2011) Recovery management: What if we really believed that addiction was a chronic disorder? *Addiction recovery management* eds. Kelly J.F. & White W.L.). Humana Press, New York.

Williams R.J., Goodale L.A., Shay-Fiddler M.A. *et al.* (2004) Methylphenidate and dextroamphetamine abuse in substance-abusing adolescents. *Am J Addict* 13,

381-9.

Winstock A.R., Lea T. & Copeland J. (2009) Lithium carbonate in the management of cannabis withdrawal in humans: an open-label study. *J Psychopharmacol* 23, 84-93.

Winzelberg A. & Humphreys K. (1999) Should patients' religiosity influence clinicians' referral to 12-step self-help groups? Evidence from a study of 3,018 male substance abuse patients. *J Consult Clin Psychol* 67, 790-4.