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Efficacy of Contingency Management for Cocaine Dependence Treatment: A Review of the Evidence

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Abstract: Cocaine dependence causes serious individual and social harm and a considerable proportion of substance related treatment capacity is devoted to cocaine dependent persons. In the absence of approved pharmacotherapies, other treatments for cocaine dependence should be explored. In this review, the efficacy of Contingency Management (CM), a promising behavior therapy using operant conditioning, is evaluated for the treatment of cocaine dependence. A systematic evaluation of 19 studies with a total of 1,664 patients showed that CM - in combination with standard cognitive behavioral or other psychological interventions – (1) increases cocaine abstinence, (2) improves treatment retention during and after group-based or individual psychological treatment, (3) is of benefit in pharmacotherapy trials, and (4) that CM may act synergistically with pharmacotherapy. This suggests that CM is a promising add-on intervention for cocaine dependence treatment. Therefore, it is advocated to include CM in standard treatment programs for cocaine dependence and future pharmacotherapy research. Future larger studies are deemed necessary to replicate these promising results, now often lacking statistical significance.

Keywords: Cocaine dependence, abstinence, treatment retention, contingency management, voucher-based reinforcement, pharmacotherapy.

1. INTRODUCTION

Cocaine dependence causes considerable physical, psychological and social harm [1]. In 2009 the estimate of last year cocaine users reached 20 million people worldwide [2]. In the US, Canada and Europe about half a million patients are annually treated for cocaine dependence. Of all European countries, Spain has the highest proportional treatment demand for cocaine-related problems, directly followed by the Netherlands where 30% of the total capacity of drug treatment is consumed by cocaine dependent patients [2]. The number of patients entering drug treatment primarily for cocaine-related problems has been increasing in Europe for several years. Based on 17 countries that have provided data across the period 2004–2009, the number of cocaine dependent patients increased from about 38,000 in 2004 to around 55,000 in 2009 [3]. Similar developments have been reported in the rest of the world [2]. Therefore, there is a growing need to improve the efficacy of cocaine dependence treatment. Currently, no proven-effective pharmacological treatment for cocaine dependence is available [4]. However, psychological interventions have demonstrated some efficacy. Psychosocial or behavioral treatment methods, like the community reinforcement approach (CRA), 12-step counseling or facilitation (TSF), and cognitive behavioral therapy (CBT) have all shown some efficacy in the treatment of cocaine dependent patients [5]. One of the more promising approaches, in terms of retention and cocaine use reduction, is Contingency Management (CM), which is generally applied in conjunction with other psychosocial or behavioral treatments [6,7]. Contingency Management is a form of operant conditioning and based on the provision of alternative positive reinforcers when abstaining from cocaine dependence: For instance, a financial bonus is given to stop cocaine use behavior and to promote abstinent behavior. However, negative reinforcers or punishment can be applied as well, e.g. extra chores (positive punishment) or the cancelation of a theater visit (negative punishment) (see Table **1**). CM can also be used in combination with pharmacotherapy to enhance the success of medication in cocaine dependence (for reviews see [8] and [9]).

Despite recommendations by The National Institute of Drug Abuse (NIDA) [10] and the Substance Abuse and Mental Health Services Administration (SAMHSA) [11], and despite empirical evidence of several meta-analyses indicating medium size effectiveness of CM [6,7], CM is not (widely) implemented in treatment programs for substance dependence. This might be due to the slow pace of introducing new evidenced-based treatments into normal practice and possibly due to the extra expense of CM to existing treatment. Moreover, for cocaine dependence treatment with CM, most of the evidence, including the

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Table 1. Types of Contingency Management

Method	Positive Stimulus	Negative Stimulus
Reinforcement: Increase desirable behavior	Positive *Reinforcement*: Delivery of a desired consequence contingent on desirable behavior	Negative *Reinforcement*: Removing an aversive or confining circumstance contingent on desirable behavior
Punishment: Decrease undesirable behavior	Positive *Punishment*: Punishing consequence contingent on evidence of undesirable behavior	Negative *Punishment*: Removing a positive circumstance or condition contingent on evidence of undesirable behavior

meta-analyses mentioned earlier, comes from studies with cocaine dependent patients maintained on methadone [12-14].

However, patients maintained on methadone may be very different from patients with a primary diagnosis of cocaine dependence in terms of their dependence characteristics and the presence of comorbid physical and mental disorders and the level of social impairment. These differences make generalization of CM efficacy between these groups of substance abusers questionable. Therefore, this paper specifically reviews CM efficacy for the treatment of patients with cocaine dependence without a co-morbid diagnosis of opioid dependence. Additionally, no meta-analytical approach was undertaken for several reasons. First, because of clinical and methodological heterogeneity observed in studies included for this review and other systematic reviews [6,7], aggregate data synthesis was not considered. Second, the selective inclusion of data for aggregate data synthesis can cause overestimation of effect sizes. Moreover, all included studies for this review report multiple outcomes and time points, but tend to report mainly statistical significant findings. This makes selection of data for aggregate data synthesis challenging and disputable. Therefore, we do not undertake a meta-analytic approach in this systematic review of the efficacy of CM for cocaine dependence treatment. However, all treatment studies focusing on the effects of CM alone and on the effects of CM in combination with other behavioral interventions or with pharmacological interventions are included in this review.

2. METHODS

2.1. Search Strategy

MEDLINE, EMBASE and PsychINFO databases were searched using either one of the following keywords: "contingency management" OR "CM" OR "contingent" OR "voucher-based reinforcement" OR "VBRT" AND "cocaine" until December 2011.

2.2. Inclusion and Exclusion Criteria

A total of 473 unique articles were retrieved. However, studies were excluded when patients had (comorbid) opioid dependence (DSM-IV), used methadone, were diagnosed with severe mental or neurological disorders (e.g. psychosis, dementia), when the article was not written in English or when the studies were not randomized controlled trials (RCTs). Only 15 articles were left for evaluation (Fig. **1**). Four additional articles were retrieved via cross-references resulting in a total of 19 articles eligible for review. Of these 19 articles, 12 examined CM efficacy for cocaine dependence treatment in combination with psychological treatment and 7 examined CM efficacy or its added value to pharmacotherapy. Three of the identified articles presented additional or follow-up data of the original studies; therefore 16 unique studies were identified.

In the studies retrieved, retention and abstinence were the main primary outcome parameters and therefore secondary outcome measures are not discussed in this review. Retention is defined by the number of patients retained in treatment over time. Cocaine abstinence is measured by the time to relapse to cocaine use, or in other words, abstinence duration. The number of cocaine negative urines is often used as an objective proxy measure for abstinence. All studies objectively quantified cocaine use by urine analysis.

2.3. Statistical Analysis

Statistical data was taken from the original studies and presented in similar fashion. In some cases statistical data was recalculated in order to be more comprehensive. When not reported, Risk Ratios (RRs) with 95% confidence intervals (CIs) were calculated for continuous abstinence in the CM supplemented interventions compared to standard treatment or any intervention without CM. The end-point for continuous abstinence was preferably the end of treatment. To determine RRs, contingency tables containing events for both CM and control interventions were created using population percentages or "individual patient plots" [15,27]. In studies with sampling zeros, the zero-cells were given a value of "0.5". The Cox Logit method was used to calculate RRs when studies only reported χ^2 without proportions. To provide insight in the clinical significance of the reviewed interventions the Number Needed to Treat (NNT) was calculated in a similar fashion to the RRs, and indicated the number of patients to be treated with additional CM to the control intervention in order to successfully retain abstinence during the same treatment period. Effect sizes for pharmacological studies combined with CM were only determined if these effects could be accounted for by CM interventions, not when other (pharmacological) interventions accounted for the results. In general, differences between groups or treatments were considered significant when the p-value was ≤ 0.05. Statistical analyses were made using Comprehensive Meta-Analysis 2.0 statistical software.

3. RESULTS

One study (N=120 patients) compared Treatment as Usual (TAU) to TAU+CM; three original studies compared

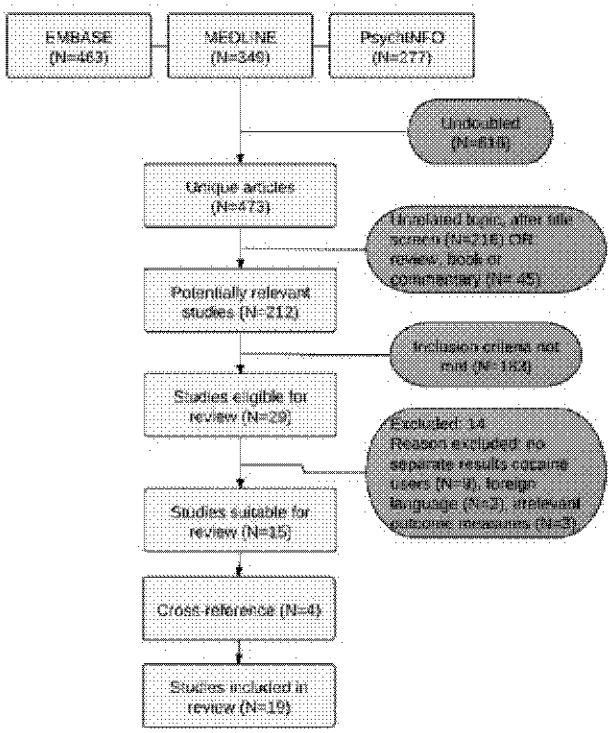

Fig. (1). Flow chart of studies included in this review.

CRA+CM to TAU (N=198) and one papers provided additional data; one study (N=145) compared CRA or TAU with contingent or non-contingent incentives; three original studies compared CRA+CM to CRA only or to CRA with non-contingent incentives (N=168), one paper provided additional data; and one study compared CRA+CM to CM (N=100). Finally, one follow-up study, containing data of 2 included studies (N=78), is discussed in combination with the original study (Table **2**). The seven studies concerning the combination of CM with pharmacotherapy (N=933) are separately discussed in Section 4: Pharmacotherapy Supplementary to CM.

3.1. Standard Treatment Only Versus Standard Treatment with CM

Petry *et al.* [15] investigated the added value of CM to a combination of TSF and CBT, in this study referred to as TAU. During this 12 week RCT (N=120) TAU in combination with high-value CM, but not with low-value CM, resulted in significant longer periods of abstinence compared to TAU alone ($p<0.05$). Also the percentage of drug-free specimens was significantly higher in the TAU + high-value CM group compared to TAU ($p<0.01$) and TAU + low-value CM ($p<0.05$). Continuous abstinence during 12 weeks was increased compared to TAU in low-value CM (RR=8.33, 95% CI=0.47-147.7, p=0.15) and in high-value CM (RR=13.82, 95% CI=0.81-234.9, p=0.07). In order to treat one patient effectively (Number Needed to Treat), i.e. continuous abstinence during 12 weeks of treatment, 6 patients should receive high-value CM compared to a NNT of 10 in low-value CM. No differences between groups were observed in the average number of weeks in treatment ($p>0.60$). These results suggest that addition of CM to TAU has no added effect on treatment retention, but is superior to TAU alone in terms of continuous and overall abstinence and that these results may be dependent on the magnitude of the financial reinforcement.

3.2. CRA+ CM versus Standard Treatment

Higgins *et al.* [16] compared CRA+CM versus 12-step facilitation (TSF) in a 24 week RCT (N=38) and demonstrated a higher retention rate in the CRA+CM group compared to the TSF group (58% *vs* 11%; $p<0.01$). In addition, longer periods of abstinence were reported from week 4-16 in the CM compared to the TSF condition (74-42% *vs* 16-5%; p=0.005), but no lasting treatment effect was observed after 24 weeks of treatment. In contrast, the number of abstinent patients was significantly higher in the CRA+CM group throughout week 3-24 ($p<0.05$). Continuous abstinence during 16 weeks was increased in the CRA+CM group compared to the TSF group (RR=8, 95% CI=1.11-57.9, $p<0.05$), which resulted in a NNT of 3. Interestingly, switching the vouchers to lottery tickets after week 12 significantly reduced the costs, but did not lower the efficacy [16]. At follow-up 12 months later [17], abstinence point prevalence when missing patients were excluded was 92% in the CRA+CM group versus 69% in the TSF group (no *p-value* reported). However, in the intention-to-treat analysis no significant differences in abstinence at 9 and 12 months were found. In addition, a meta-analysis [18] of the data from one earlier non-randomized trial [19] and the above described RCT [16] demonstrated a RR for cocaine abstinence of 3.75 (95% CI=1.79–7.87) in the first 4 weeks of CRA treatment and a RR of 5.09 (95% CI=1.63–15.86) between weeks 4 and 16 of treatment, clearly indicating that CRA in combination with CM is a more effective treatment than TSF. The studies cited so far were all conducted in the US. In addition, two studies have been performed in Spain so that CM can be evaluated in a different cultural context and community setting. Garcia-Rodriguez *et al.* [20] compared CRA+CM with either low- or high-value vouchers (with a 1:2 value ratio) with standard outpatient CBT group therapy in a RCT (N=96). Cocaine positive urines were more frequent in the CBT group than in the CM groups with low and high-value vouchers (12% in CBT *vs* 4% in low-value voucher group *vs* 3% in the high-value voucher group; p=0.02). In addition, continuous abstinence over 24 weeks was significantly higher in the CRA plus high-value vouchers (RR=1.79, 95% CI=0.89-3.61, p=0.10) and low-value (RR=1.58, 95% CI=0.65-3.83, p=0.32) vouchers group compared to standard CBT (37.9% *vs* 33.3% *vs* 21.2%, $p<0.01$). The NNT was 6 for the high-value condition and 8 for the low-value condition. Mean continuous abstinence duration was also higher in the CM groups compared to the standard treatment group (p=0.02). No statistically significant differences between the two CRA plus vouchers groups were observed, although a trend in favor of higher value incentives was observed. In a second randomized controlled trial (N=64) from Spain [21,22], retention rates were significantly higher in the CRA+CM compared to the standard CBT group (66% *vs* 29%, p=0.003). The CRA+CM group had a higher 12-month continuous abstinence rate compared to the CBT group (35% *vs* 17%; RR= 2.01, 95% CI=0.83-4.87, p=0.12) and a NNT comparable to Garcia-Rodriguez *et al.* of 6. Moreover, CRA+CM treatment resulted in longer periods of abstinence

(25.7±17.4 *vs* 15.2±18.1 weeks, p=0.02) and a higher abstinence rate at 12 months (59% *vs* 26%, p=0.008).

In summary, these data show that CM as an add-on intervention to CRA is superior to TSF and to standard CBT, but these studies do not allow us to draw firm conclusions about the efficacy of CM as a stand-alone in the treatment of cocaine dependence.

3.3. CRA with CM Versus CRA Alone or CRA with Non-Contingent Incentives

Three trials have assessed the efficacy of CM as an add-on intervention to CRA for the treatment of cocaine dependence. Higgins *et al.* [23] randomly assigned 40 patients to two intervention groups, one receiving CRA+CM and one "control" group receiving CRA only. The addition of CM to CRA resulted in a 20-40% increase of continuous abstinence during week 5 to 20, which was twice the number of abstinent weeks on average (11.7±2.0 weeks *vs* 6.0±1.5 weeks, p=0.03). At week 20, continuous abstinence was increased by addition of CM (RR=6, 95% CI=0.79-45.42, p=0.08), which related to a NNT of 4, for this treatment period. The combination of CM and CRA also increased the adherence after 24 weeks by 35% (p=0.03). A follow-up of this sample [17] indicated a trend towards longer post-treatment abstinence in the CRA+CM compared to the CRA only group (p=0.11). Furthermore, Higgins *et al.* [23] hypothesized that cocaine use during the first week of treatment was associated with poor outcome. The data showed that there was no difference in attrition rates among patients who abstained early in treatment, in the voucher group compared to the non-voucher group. However, the use of vouchers significantly decreased attrition rates in those who still used in the first week of treatment. Although continuous abstinence was significantly increased by CM (p=0.03), there was no interaction between intervention groups and first week urine analysis outcomes on continuous abstinence (p=0.92). This combination of results suggests that prognosis can be based on early treatment urine analysis and that CM is likely to especially increase retention in patients with a poor prognosis (i.e. those who are still using cocaine in the early treatment phase), but that CM does not influence continuous abstinence in this problematic subgroup.

In order to assess the added value of contingent incentives to CRA, in another study, Higgins *et al.* [24] compared CRA plus contingent vouchers (i.e. CM) with CRA plus non-contingent vouchers (N=70). As compared to CRA with non-contingent vouchers, continuous abstinence rates using CRA with contingent vouchers were significantly higher in weeks 12 through 16, but at other time points only a trend favoring contingent vouchers was seen. The number of continuous abstinent patients during the 24 weeks of treatment was only significantly higher for the contingent voucher condition compared to the non-contingent condition between week 12 and 16 (RR=2.65, 95% CI=1.18-5.93, p=0.02), and not between 16-24 weeks (RR=1.67, 95% CI=0.76-3.62). At other time intervals and during the 1-year follow-up only a trend was seen favoring the contingent condition (p values ranging from 0.09 to 0.20). However, patients who were abstinent during treatment tended to remain abstinent during follow-up (p=0.02). Point prevalence of cocaine abstinence throughout the one-year follow-up was significantly higher in the contingent condition but tended to increase in *both* conditions across follow-up assessments (p=0.04). No differences in retention rates were observed during treatment and follow-up, showing that contingent vouchers directly reinforce sustained cocaine abstinence during and after treatment of cocaine dependence. Roozen *et al.* [18] pooled the data of these two studies [23,24] and found an overall effect between 4–16 weeks for cocaine abstinence of RR=1.73 (95% CI=1.04–2.88), indicating that CRA in combination with contingent incentives is more effective with regard to cocaine abstinence than CRA alone or in combination with non-contingent incentives.

Finally, results of a recent one-year Spanish RCT in 58 subjects showed a small but non-significant higher retention in cocaine dependence in the CRA+CM group compared to the CRA only group [25]. More importantly, continuous abstinence during the first 12 weeks of treatment was significantly higher in the CRA+CM group compared to the CRA only group (72% *vs* 38%; RR=1.91, 95% CI=1.14-3.20, p=0.01). With a clinically relevant NNT of 3, this intervention seems effective. However, the statistical and clinical difference between the two groups was no longer significant after 24 weeks (RR=1.1, 95% CI=0.56-2.18, p=0.79 NNT=29) [26] and after 12 months (RR=1.13, 95% CI=0.51-2.51, p=0.77) [25]. During the 12 months of treatment significantly (p=0.002) less cocaine positive urine samples were seen in the CRA+CM group (cocaine negative urines: 96% ± 7.2) compared to CRA only group (cocaine negative urines: 79% ± 25.7).

In conclusion, these data show that the added value of CM to CRA is most prominent during the first months of treatment and that the effect is likely to become smaller over time. In addition, some of the data suggest that addition of CM to CRA might be especially important in patients with a tendency to relapse early during treatment. Again, it should be noted that these studies do not allow us to make firm conclusions about the efficacy of CM as a stand-alone treatment.

3.4. CRA or Standard Treatment with Contingent or Non-Contingent Incentives

One RCT (N=145) [27] compared CRA to TSF (regarded as TUA) in combination with contingent (i.e. CM) and non-contingent incentives. Although the study focused on pregnant women or women with young children, it can be of use to interpret the added value of CM in both CRA and TSF conditions in specific populations where a high health risk for both the addicted patient and her child or children exists. The longest periods of abstinence (p<0.01) and a higher percentage of cocaine negative urines (p<0.01) were seen in the CM conditions compared to the non-contingent conditions. No differences in abstinence duration (p=0.75) of urine analysis results (p=0.99) were seen between CRA and TSF. After 12 weeks the CM condition was both favoured in the CRA (RR=9.86, 95% CI=0.56-173.9, p=0.12) and in the TSF (RR=7, 95% CI=0.91-54.1, p=0.06) intervention groups, however, at the end of treatment (24 weeks) no patient achieved to maintain continuously abstinent. Retention rates were non-significantly higher in contingent

compared to non-contingent incentives (p=0.15) and in CRA compared to TSF (p=0.19).

In summary, these data support the added value of CM when combined with CRA or TSF, but do not suggest a greater efficacy of CRA compared to TSF. Together with some of the data described before, these data suggest that non-contingent conditions only increase retention, whereas CM increases both retention and abstinence.

3.5. CRA with CM Versus CM Alone

CM has been developed as an intervention preferably to be used in combination with other interventions. However, a randomized controlled trial (N=100) by Higgins *et al.* [28], in which CRA+CM was compared to CM alone gives some information on the potential effect of CM as a stand-alone treatment. After 12 weeks of treatment, 78% in the CRA+CM group and 51% in the CM only group did not use cocaine (RR=1.52; 95% CI=1.12-2.07, p=0.001). Other periodic assessments during 24 weeks of treatment and a one-year follow-up assessment did not show significant differences in abstinence, and were not reported. The NNT could not be determined, as no control intervention for CM was included. The average of cocaine-negative specimens in the CRA+CM group was significantly higher compared to the CM alone group (p=0.004), indicating reduced cocaine use in the CRA+CM group compared to the CM alone group. Retention at 12 and 24 weeks was 87% and 65% in the CRA+CM group compared to 51% and 33% in the CM alone group (p's<0.01).

These findings indicate that CRA together with CM is superior to CM alone with regard to early treatment attrition and relapse, but does not benefit long-term abstinence. Interestingly, this single study indicates some potential of CM as a stand-alone treatment, to produce prolonged behavioral changes (i.e. cocaine abstinence) independent of additional behavioral interventions and after CM discontinuation. This is in contradiction to the original theory of Higgins *et al.* [28] claiming that a combination of CRA and CM would lead to sustained abstinence, where CM would initiate early, short-term cocaine abstinence and CRA would induce healthy lifestyle changes resulting in long-term abstinence post-treatment.

Together, CRA+CM is superior to CM alone in terms of early treatment (<12 weeks) continuous and average abstinence and it is associated with prolonged retention, up to 24 weeks. Although CM alone may decrease post-treatment cocaine use, but needs to be further investigated together with a appropriate control group (e.g. standard treatment). However, this study does suggests that CM is more effective when applied in combination with another intervention, such as CRA [28].

4. PHARMACOTHERAPY SUPPLEMENTARY TO CM

CM apparently has an added value to other behavioral treatments, as it increases both retention and abstinence in combination with CRA or other forms of TAU. Possibly, this beneficial effect of CM can also be established in combination with pharmacological approaches used in the treatment of cocaine dependence. Seven studies outlined below have investigated the added value of CM to dopaminergic, serotonergic, and glutamatergic agents and to opioid antagonist medications in cocaine dependence treatment (Table **3**).

Cocaine increases synaptic dopamine levels in the mesocorticolimbic system by blocking the dopamine transporter (DAT) on the presynaptic neuron. Whereas increased synaptic dopamine release contributes to the acute reinforcing effects of cocaine [29], it is hypothesized that chronic cocaine exposure produces depletion of dopamine [30]. As such, increasing or restoring dopaminergic neurotransmission, may be a successful pharmacological treatment approach for cocaine dependence [31]. Furthermore, as serotonin and glutamate are known to play a role in cocaine addiction [32], the therapeutic potential of drugs associated with these neurotransmitters has also been evaluated in the treatment of cocaine dependence. Finally, some preclinical studies have shown that opioid antagonists can reduce the reinforcing effect of cocaine [56] and therefore the therapeutic effects of opioid antagonists have been tested in cocaine dependent patients.

4.1. Dopaminergic Agents

Levodopa (L-DOPA) is a precursor of dopamine and suppletion of dopamine by levodopa administration could resolve low dopamine levels in the brain of cocaine dependent patients. In three randomized, double-blind trials levodopa/carbidopa alone did not reduce cocaine use or craving compared to placebo [39,40]. However, the combination of dopamine suppletion with behavioral therapy yielded more promising results. In a large (N=161) double-blind RCT [31] with six treatment arms the effects of levodopa and placebo in combination with each of the following strategies was evaluated: Clinical Management (ClinMan), CBT or CM. Treatment with levodopa in combination with CM resulted in significantly fewer cocaine-positive urines compared to placebo + CM (40% *vs* 77%, respectively), and significantly longer periods of consecutive abstinence compared to almost all other treatments (except levodopa + ClinMan). No data on continuous abstinence were reported. In another RCT (N=136), Schmitz *et al.* examined the effect of different CM conditions in combination with levodopa or placebo using three different CM targets: abstinence (cocaine-negative urines), medication compliance and attendance [33]. It was concluded that CM had an added effect on levodopa treatment only when abstinence was reinforced and not if attendance and medication compliance were reinforced.

Together, these results suggest the presence of a specific synergy between levodopa and CM targeted at abstinence.

4.2. Serotonin Agents

There is currently very little empirical support for the use of antidepressants in the treatment of cocaine dependence, although further studies are justified to test the possible effects of the 5-HT_3 receptor antagonist ondansetron [4]. In a placebo-controlled double-blind trial [41], the selective 5-HT

Table 2. Overview of Efficacy Studies for Contingency Management Cocaine Dependence Treatment

Study			Interventions	Results	
Ref	**Type & Duration**	**N=**	**Types**	**Abstinence**	**Retention**
3.1 Standard Treatment only or with CM					
[15]	RCT 12wks	120	(A) ST+high value CM (B) ST+low value CM (C) ST (TSF/CBT)	Continuous abstinence: At wk 12: (C) *vs* (B) RR=8.33, 95% CI=0.47-147.7 (p=0.15), (C) *vs* (A) RR=13.82, 95% CI=0.81-234.9 (p=0.07) Continuous period of abstinence: Longest in (A) *vs* (C) (p<0.05) and (B) *vs* (C) (p=0.09) Mean neg. urines±SD: (A) 84.2±26.8%, *vs* (B) 66.4 ± 40.8% (p<0.05) and (C) 62.3±41.5% (p<0.01). (B) *vs* (C) = p>0.65	Mean period of retention (wks ±SD): (A) 6.7±4.1, (B) 6.2±4.1 and (C) 6.2±4.1 (p>0.60)
3.2 CRA + CM vs Standard Treatment					
[16]	RCT 24wks	38	(A) CRA+CM (B) TSF	Continuous abstinence: wk 4: (A)74% *vs* (B)16%, at wk 8: 68% *vs* 11%, wk 16: 42% *vs* 5% (RR=8, 95% CI=1.11-57.9, p=0.04) Abstinence rate: In wk 3-24 higher in (A) (p<0.05)	Continuous period of retention: 12 wks: (A) 84% *vs* (B) 26%, 24 wks: (A) 58% *vs* (B) 11% (p<0.01)
[20]	RCT 24wks	96	(A) CRA+high value CM (B) CRA+low value CM (C) ST (CBT)	Continuous abstinence: (A): mo 1 93.1%, mo 3 72.4%, mo 6 37.9% (RR=1.79, 95% CI=0.89-3.61, p=0.10) (B): mo 1 86.7%, mo 3 60.0%, mo 6 33.3% (RR=1.58, 95% CI=0.65-3.83, p=0.32) (C): mo1 79.9%, mo 3 42.3%, mo 6 21.2% Mean of total neg. urines : (A): 97.07%, (B): 96.09%, (C): 88.45%	Continuous period of retention: (A): mo 1 96.6%, mo 3 79.3%, mo 6 69%, (B): mo 1 93.3%, mo 3 66.7%, mo 6 53.3%, (C): mo 1 86.5%, mo 3 53.8%, mo 6 36.5% Mean period of retention (wks ±SD): (A): 19.2±7.6, (B): 17.1±8.4, (C): 14.4±8.5
[21,22]	RCT 1 year	64	(A) CRA+CM (B) ST (CBT)	Continuous abstinence: At mo 12 (A) 34.5% *vs* (B)17.1 % (RR= 2.01, 95% CI=0.83-4.87, p=0.12) Mean neg. urines±SD: (A) 95.7±7.2% *vs* (B) 85.5±20.9% (p=0.01) Mean longest period of abstinence (wks±SD): 25.7±17.4 *vs* 15.2±18.1, (p =0.02) Abst. rate: at mo 12 (A) 58.6% *vs* (B) 25.7%, (p=0.008)	Continuous period of retention: mo 12 (A) 65.5% *vs* (B) 28.6% (p=0.003) Mean period of retention (wks ±SD): (A) 35.7±18 *vs* (B) 20.6±18.3 (p=0.002)
3.3 CRA with CM vs CRA only or with non-contingent incentives					
[23]	RCT 24wks	40	(A) CRA+CM (B) CRA	Continuous abstinence: (A) 70%, 55%, 30 % *vs* (B) 50%, 15%, 5% in wk 5, 10 and 20 (RR=6, 95% CI=0.79-45.42, p=0.08). Mean period of abstinence (wks±SD): wk 1-24: (A) 11.7±2.0 *vs* (B) 6.0±1.5 (p=0.03) Abstinence rate: at wk 24 (A) 80% *vs* (B) 75% (p=0.70)	Continuous period of retention: 12 wks: 90% (A) *vs* 65% (B) (p=0.06) 24 wks: 75% (A) *vs* 40% (B) (p=0.03) Mean period of retention (wks ±SD): 21±1.5(A) *vs* 15.7±2.0(B) (p=0.04)
[24]	RCT 24wks	70	(A) CRA+CM (B) CRA+N-CM	Continuous period of abstinence: wks 12-15 RR= 2.65, 95% CI= 1.18-5.93, 16-24 wks RR= 1.67, 95% CI=0.76-3.62. During FU period (1,5 yrs): (A) favoured (χ2=5.24, p=0.02) Abs. rate: greater in (A) (χ2= 4.12, p = .04)	Continuous period of retention: 12 wks: (A)72% *vs* (B)79% 24 wks: 56% *vs* 53% Retention at FU (1,5 yrs): (A) 89% to 97% *vs* (B) 82% to 97% (no p-value)
[25,26]	RCT 1 year	58	(A) CRA+CM (B) CRA	Continuous abstinence: 12 wks: (A) 72.4% *vs* (B) 37.9% (RR=1.91, 95% CI=1.14-3.20, p=0.01) 24 wks: (A) 37.9%, *vs* (B) 34.5% (RR=1.1, 95% CI=0.56-2.18, p=0.79) 1 yr: (A) 31% *vs* (B) 27.6% (RR=1.13, 95% CI=0.51-2.51, p=0.77) Mean neg. urines±SD: 1-6 mo (A) 97.1±6.3% *vs* (B) 79.7±25.8%, (p=0.001), 7-12 mo (A) 95.7±7.2% *vs* (B) 79.3±25.7% (p=0.002)	Continuous period of retention: 1 yr: (A) 65.5% *vs* (B) 48.3% (p = 0.28)

(Table 2) contd…..

Study			Interventions	Results	
Ref	**Type & Duration**	**N=**	**Types**	**Abstinence**	**Retention**
3.4 CRA or Standard Treatment with contingent or non-contingent incentives					
[27]	RCT 24wks	145	(A) CRA+CM (B) CRA+N-CM (C) TSF+CM (D) TSF+N-CM	Continuous abstinence: (A) *vs* (B) RR=9.86, 95% CI=0.56-173.9 (p=0.12), (C) *vs* (D) RR=7, 95% CI=0.91-54.1 (p=0.06) Mean longest period of abstinence (wks±SD): CM= 4.6±5.4 *vs* N-CM= 2.5±3.0 (p<0.01), CRA *vs* TSF (p=0.75) Mean neg. urines±SD: CM=38.6±28.5% *vs* N-CM=24.7±28.7% (p<0.01), CRA *vs* TSF (p=0.93)	No significant difference between CM and N-CM (p=0.15) or between CRA and TSF (p=0.19), or interaction between the two factors (p =0.99)
3.5 CRA with CM vs CM only					
[28]	RCT 24wks	100	(A) CRA+CM (B) CM only	Abstinence rate: at wk 12 (A) 78% *vs* (B) 51% (RR=1.52; 95% CI=1.12-2.07), no significant differences from 24 wks –24 mos (FU) Mean neg. urines±SD (60 samples): (A) 35.6±18.9 *vs* (B) 24.0± 20.7 (p= .004), in percentage: (A) 59.3±31.5% *vs* (B) 40±34,5%	Continuous period of retention: 12 wks: (A) 84% *vs* (B) 51% 24 wks: 65% *vs* 33% Retention during FU: at 2 yrs (A) 86% to 98% *vs* (B) 73% to 92%, at 1,5 yrs: 90% *vs* 75% (p=0.05)
Follow-up studies					
[16,17]	-	78	-	Abstinence rate: [16]: at mo 9 and mo 12 88% and 92%(A) *vs* 69% and 69% (B) [23]: at mo 9 and mo 12 70%(A) *vs* 65%(B) and 65%(A) *vs* 60%(B), respectively.	Continuous period of retention: [16]: mo 12: (A) 65.5% *vs* (B) 28.6% (p=0.003)

reuptake blocker (SSRI) fluoxetine (20 or 40 mg) proved to be ineffective in the treatment of cocaine dependence when administered in combination with non-contingent psychological treatment. However, in a subsequent placebo-controlled double-blind trial (N=81), three different daily doses of fluoxetine (0 mg – placebo –, 20 or 40 mg) were administered contingent on cocaine negative urines for 6 weeks in this 14 week trial. Cocaine-dependent subjects receiving 40 mg of fluoxetine had fewer (p=0.03) cocaine positive urine samples during the take-home dose contingency than patients who received placebo or 20 mg fluoxetine [34]. Therefore the combination of fluoxetine and CM may be beneficial when fluoxetine alone is not sufficient to improve treatment of cocaine dependence.

Citalopram is another SSRI used to treat major depression. Moeller *et al.* performed a double-blind RCT (N=76) with cocaine dependent patients who all received CM and CBT [35]. Their results showed some significant effects of citalopram compared to placebo: fewer cocaine positive urines (p=0.002), a time by treatment interaction (p=0.04) suggesting increased abstinence following longer treatment, and an increased number of uninterrupted negative urine samples (RR=2.38; 95% CI=1.15–4.91, p=0.02). In terms of retention no statistically significant differences between citalopram and placebo treated subjects were found, suggesting that therapy retention was probably due to CM and increased abstinence was due to citalopram.

Finally, the naturally occurring essential amino acid tryptophan is a precursor of serotonin. Following oral intake of tryptophan, the brain level of serotonin increases [42]. Tryptophan administration in rats has been shown to decrease cocaine intake [43,44]. To evaluate the effect of tryptophan in humans, Jones *et al.* performed a double-blind RCT (N=183) using contingent and non-contingent groups in a 2x2 study design [36]. Tryptophan had no significant effect on continuous abstinence periods or relapse prevention, suggesting that tryptophan is ineffective in cocaine dependence treatment. No differences were seen between CM in combination with tryptophan or placebo. However, contingent-vouchers significantly increased average abstinence (p<0.05) and attenuated average cocaine use compared to non-contingent vouchers (p<0.05). No data on continuous abstinence over the trial period was published.

In summary, these findings suggest that (in some cases) antidepressants may become effective in the treatment of cocaine dependence only in combination with CM and that CM might also be an effective treatment in itself, in the context of a medication trial.

4.3. Other Agents

Although earlier animal studies indicated positive effects of the glutamatergic receptor antagonist memantine on relapse [45,46], it showed no effect on cocaine use in pateints with cocaine dependence [47]. When CM was added to memantine in a 12 week RCT (N=112) [37], including a 2-week placebo lead in, again no significant difference in cocaine use between 40 mg daily memantine and placebo was observed. However, abstinence after the placebo lead in (44%) was a significant predictor (p =0.01) of subsequent cocaine abstinence (i.e. a minimum of 3 consecutive weeks of abstinence) during the trial. This suggests the existence of a subgroup of early-responders and a CM resistant subgroup, which is probably most in need of (effective) medication. Between these subgroups no difference in medication effects were observed.

Table 3. Overview of Pharmacotherapy and Contingency Management Combined Studies

Study*		Interventions		Results	
Ref & *Drug*	N=	Types		Abstinence	Retention
4.1 Dopaminergic agents					
[31] *Levodopa*	161	(A) ClinMan + drug (B) CBT + (A) (C) CM + (B)	(D) ClinMan + placebo (E) CBT + (D) (F) CM + (E)	Consecutive amount neg. urines: higher in (C) compared to other treatments (except A) (p's<0.05). Mean pos. urines: CM 59% *vs* CBT 84%, drug 61.6% *vs* placebo 79.1%	No significant differences in dropout rates by medication, $\chi^2(1) = 3.12$, $p = 0.0770$, therapy, $\chi^2(2) = .6172$, $p = 0.7345$, or their interaction, $\chi^2(2) = 1.0164$, $p = 0.60$
[33] *Levodopa*	136	*All CBT + ClinMan* (A) CM-URINE + drug (B) CM-ATT. + drug (C) CM-MEDIC. + drug	(D) CM-URINE + placebo (E) CM-ATT. + placebo (F) CM-MEDIC.+ placebo	ORs for pos. urines: (A) *vs* (B) (OR 26.38, CI 1.74–398.95) and *vs* (C) (OR 13.50, CI 1.24–149.02). No sig. difference between (D), (E) and (F)	No significant difference in medication *vs* placebo (F (1, 2,322) = 0.05, p <0.82) Higher in CM-ATTEND condition (log rank χ^2= 3.01, p =0.08)
4.2 Serotonin agents					
[34]** *Fluoxetine*	81	(A) contingent placebo (B) contingent 20mg/d (C) contingent 40mg/d		Total neg. urines: significant effect of dosage increase (p=0.03) corresponding with abstinence. No effect for time, no interaction effect of time and medication on cocaine use	No significant difference among groups (X^2 (2, N=54) =1.31, p=0.52)
[35] *Citalopram*	157	(A) CBT + CM + 20mg/d (B) CBT + CM + placebo		Continuous abstinence preriods: 2.38x higher in (A) (p=0.02, CI 1.15–4.91) Effect of treatment: F=9.3, df=1,67, p=0.002 Treatment by time interaction: F=4.1, df=1,665, p=0.04	No significant difference (A) and (B) (KM log rank = 0.66, p=0.42)
[36]** *Tryptophan*	199	(A) CM + 8mg/d (B) N-CM + 8mg/d	(C) CM + placebo (D) N-CM + placebo	Avg: CM favored over N-CM (F=4.98; df= 1,17; p < 0.05), Continuous abstinence period: CM favored over N-CM (F=8.54; df= 1,17; p < 0.05), No sig. effect tryptophan *vs* placebo	No significant differences among groups (X^2 =0.203, df=1, p=0.65)
4.3 Other agents					
[37]** *Memantine*	112	*2 wk CM lead-in (A)+(B)* (A) CM + BT + 40mg/d (B) CM + BT + placebo		No difference (A) and (B) in proportional cocaine using days (X^2 = 0.03, p = 0.87)	No significant difference (A) and (B) (X^2 = 0.89, p=0.83)
[38] *Naltrexone*	87	(A) CBT + 100 mg/d (B) CBT+CM + 100 mg/d	(C) CBT+ placebo (D) CBT+CM + placebo	Pos. urines: no significant difference between (A) though (D)	No significant difference among groups (X^2 (3) = 1.52, p = 0.68)

*All studies are RCTs and 12 weeks of duration; **14 weeks of duration.

The opioid antagonist naltrexone is an approved treatment for the treatment of alcohol dependence at a standard dose of 50 mg/d. However, naltrexone is ineffective as a stand-alone therapy [48] or in combination with relapse prevention or TSF [49] in reducing substance use in patients with co-occurring cocaine and alcohol dependence. In a RCT (N=87) by Schmitz *et al.* [50] no differences in cocaine use between high dosage naltrexone (100 mg/d) and placebo was found, nor did the combination with CM and CBT influence treatment retention or medication adherence throughout treatment groups. The lack of CM efficacy in this study may be due to co-occurring alcohol dependence, which is consistent with the results obtained by Grassi *et al.* [51]. Studies in cocaine-dependent samples without alcohol dependence are needed to examine the potential effect of naltrexone in combination with CM in cocaine-only-dependent patients.

In summary, CM has no added value in the treatment of cocaine or cocaine-alcohol dependent patients with memantine or naltrexone.

4.4. Clinical Trials in Progress

Several clinical trials are being conducted which combine pharmacotherapy studies with CM (Table **4**). Medication or placebo with contingent and non-contingent incentive groups are evaluated using a 2x2 cross-over design [34, 36]. As can be concluded from the finished trials discussed above, contingent incentives can successfully promote abstinence, so this CM type provides a suitable pharmacotherapy testing condition in which patients are motivated to stop cocaine use. A non-contingent incentive comparison condition likely will support high retention rates across groups, diminishing

Table 4. Clinical Trials in Progress

NCT Number	Interventions		Outcomes
NCT00350870 Completed	1. Disulfiram 2. Placebo	3. Disulfiram plus CM 4. Placebo plus CM	Reduction in cocaine use measured by self report and urine toxicology results
NCT01526538 Recruitment in progress	1. CM with d-cycloserine 2. CM with placebo		Post-treatment continuous abstinence
NCT00617201 Completed	1. CM with atomoxetine 2. CM with placebo		Post-treatment continuous abstinence

the likelihood of trial insensitivity caused by attrition. A placebo-controlled trial, investigating disulfiram in combination with CBT+CM or CBT only for the treatment of cocaine dependence (ClinicalTrials.gov; NCT00350870), is expected to be published shortly. Other trials in progress are currently conducted at Johns Hopkins University (ClinicalTrials.gov; NCT01526538) and the University of Kentucky (ClinicalTrials.gov; NCT00617201).

4.5. Compounds Suggested for Future Study

Several excellent reviews on pharmacological treatment of cocaine dependence have recently been published [4,52-54]. Based on the currently available studies, potential first line treatments include bupropion, (lis)dexamphetamine and disulfiram [4]. In cocaine dependent patients without a comorbid diagnosis of alcohol dependence, modafinil is a promising treatment. Modafinil, a wakefulness enhancing compound and mild stimulant, may be useful for abstinence initiation as it reduces cocaine withdrawal symptoms, cocaine craving, and cocaine-induced euphoria [54]. Modafinil could also be provided contingent on abstinence as take-home doses [14,34]. A similar design could be considered for dexamphetamine and lisdexamphetamine, a form of dexamphetamine only active via oral administration [55], and for bupropion.

Other potent compounds for relapse prevention are disulfiram, mainly for treatment of patients with dual cocaine and alcohol dependence [4] and a cocaine vaccine [4,54]. If these compounds prove to be effective in cocaine relapse prevention, they could be applied in combination with contingent monetary reinforcement therapy. In conclusion, it is suggested that compounds like bupropion, (lis)dexamphetamine, modafinil, disulfiram and possibly a cocaine vaccine are investigated in CM enhanced trials. Some of these compounds could be given as a medication-take home doses, rewarding patients in similar fashion to methadone-maintained patients (e.g. [14]), others can be given on a monetary reward basis in a 2x2 design (e.g. [34, 36]).

5. DISCUSSION

This review specifically reviewed the efficacy of CM for the treatment of cocaine dependence. Treatment retention seems to be uninfluenced by addition of CM to TAU [15]. However, in terms of continuous and overall abstinence, combining CM with TAU seems superior to TAU alone. These results may be dependent on reward magnitude of the contingent reinforcer, where higher value incentive is linked to better results [15,20]. The combination CM with CRA is superior to TSF and/or CBT [20,21,23] or CRA alone [23,25,26]; especially during the first 12 weeks and to a much lesser extent until 24 weeks after the start of treatment. This translates into not significant RRs that approximate 1 and a larger NNT, e.g. 2.9 after 12 weeks compared to 29 at 24 weeks [25,26]. Addition of CM to CRA increases retention in outpatient treatment settings, and continuous and mean abstinence rates [23,25,26]. Extension of treatment programs up to one year are not associated with better effects in terms of long term continuous abstinence, but do show decreased overall cocaine use and lower attrition rates even after discontinuation of CM targeted at cocaine abstinence [21,25]. This implies that relapses may occur but that CM treatment will result in increased numbers of patients regaining abstinence after relapse, which is reflected in overall cocaine use. No difference in efficacy is observed between CRA and TSF under either CM or non-contingent conditions, but addition of CM to both behavior treatments increases abstinence [27]. Together, these results suggest similar efficacy of TSF, CBT and CRA, but increased efficacy, mainly during the first 12 weeks of treatment, when these treatments are combined with CM. These results also suggest clinical significance with a NNT between 3 and 8. Unfortunately, these figures seldom go together with statistical significant RRs. The use of non-contingent incentives results in increased retention rates as well, although without improved abstinence rates [23,27]. In conclusion, CM seems an effective add-on therapy to existing psychological treatments. However, statistical significance is often lacking for primary outcome measures, probably due to small sample size. Therefore, larger RCT are needed.

Contingency Management as a stand-alone therapy needs to be investigated more extensively in a design with an appropriate control group, but does show some beneficial in- and post-treatment effects [17,24,28]. CM alone may have the potential to change behavior independent of additional behavioral interventions. This would mean that CM not only enhances extrinsic motivation, elicited by external stimuli, but may also stimulate intrinsic motivation by changes in behavior that persist over time. However, more evidence in support of this hypothesis is needed. Furthermore, effectiveness of CM is largest when contingent incentives directly reinforce cocaine abstinence. Other targets of contingent reinforcement, like medication compliance or treatment adherence, are less productive or not effective at all [33]. Hence, behavioral and pharmacological strategies should reinforce cocaine abstinence using CM. In addition, CM offered in a group setting [20,21,26] seems to be equally

effective across outcome measures compared to individually offered CM [15,16,24,27,28]. Therefore, group-based CM appears to be a more cost-effective alternative than individual CM.

CM is also a promising approach as an add-on in the pharmacological treatment of cocaine dependence. Levodopa [31] and citalopram [35] showed significant effects on cocaine use only in the context of CM. These results suggest that CM may have added value in pharmacological attempts to treat cocaine dependence. However, these pharmacological studies generally failed to provide data on continuous abstinence or data on the effect of combined interventions. This made it often impossible to evaluate CM efficacy in terms of RRs and NNT. Furthermore, the study design of theses studies could be improved by adding a non-contingent incentive group (e.g. [34,36]), which decreases differences in retention rates across groups and thus will allow for better validity of trials, by eliminating differences in attrition in the contingent and non-contingent group. In itself, the fact that CM leads to lower attrition levels is also a beneficial treatment effect, since longer treatment retention may provide for better long-term effects. It should be noted that early in-treatment cocaine users with a poor prognosis [37] can be motivated with *contingent* incentives to remain in therapy, but that CM does not help them in abstaining from cocaine use [23]. Therefore, this subgroup seems to require adjuvant pharmacotherapy that is effective in promoting long-term cocaine abstinence. In future trials, the benefits of contingent and non-contingent incentives to treat cocaine dependence should be evaluated in combination with promising compounds like modafinil, (lis)dexamphetamine, bupropion, disulfiram and possibly cocaine vaccines.

There are several limitations to this review and general points of criticism to CM. Studies performed in the US are clearly distinct from those in Spain, because about half of the American participants are crack cocaine users, whereas European participants use cocaine almost exclusively via nasal administration (snorting). Crack cocaine and nasal cocaine use may differ in addictive potential. In addition, treatment-seeking behavior may be different between the two continents, but this is not described in the studies reviewed. Moreover, in contrast to group-based therapy in European studies, American studies exclusively refer to individual treatment. Although results are comparable for both types of therapy, these differences obscure a proper comparison. Furthermore, most studies allowed and promoted the use of disulfiram (as part of CRA). As discussed previously, disulfiram could be effective in cocaine dependence treatment (for a review see [4]) and may therefore be a confounder for study outcome. Indeed, two trials included significantly more disulfiram users [16] or only disulfiram users in the CM groups [28]. Other studies failed to mention the possible use of disulfiram [21,22,25,26] or reported incomplete data on disulfiram use [24]. Also, the wide variety of variables used as outcome measures and combination of interventions impedes comparison of data between studies and pooling of the data, this makes both interpretation of statistical and clinical significance challenging. Finally, some practical problems with CM remain. First, CM treatment is linked to additional costs of approximately €40 per week per patient. However, costs can be reduced by switching from contingent monetary reinforcers to contingent lottery tickets [16,23,24], which cost a fraction, but do not diminish the treatment effect. Second, different types of CM delivery (Table **1**) can be used to enhance abstinence at reduced costs. For example, similar to the methadone take-home-dose model, the dexamphetamine or bupropion take-home-dose model could be used in cocaine dependence treatment, which makes the use of monetary reinforcers redundant. Third, implementation of CM into standard treatment needs additional training of personnel in CM administration. Despite these uncertainties and practical issues, the current evidence discussed in this review leads us to strongly advocate addition of CM to the current standard treatments for cocaine dependence and in future cocaine pharmacotherapy trials.

Future Research Questions:

- Results regarding Contingency Management (CM) as an intervention for cocaine dependence suggest that CM has an add-on effect when combined with treatment as usual. The effect of CM as a stand-alone treatment has to be investigated in larger randomized clinical trials, with appropriate control groups.
- To reduce treatment attrition and to boost abstinence, future research should include both contingent and non-contingent, "control", study arms.
- Promising compounds like modafinil, (lis)dexamphetamine, bupropion, disulfiram, and possibly a cocaine vaccine are candidates for cocaine dependence treatment. It would be interesting to evaluate the efficacy of pharmacological interventions combined with CM.
- The cost effectiveness of CM-added treatment in cocaine dependence treatment should be evaluated.

Key Learning Objectives:

- The addition of (Contingency Management) CM to several other treatments available for cocaine dependence (e.g., Community Reinforcement Approach, Cognitive Behavioral Therapy, pharmacotherapy) tends to increase abstinence and decreases attrition in comparison to these interventions without CM. Especially during the first 12 weeks of treatment, CM increases efficacy, whereas effects are smaller or absent after this time.
- Individual and group-based CM treatments seem equally effective. Introduction of group-based CM may reduce treatment costs associated with CM.
- CM provides a potent platform to study psychological and pharmacological interventions, separately or combined. In both psychological and pharmacological intervention studies the addition of non-contingent groups could provide appropriate "control" groups, whereas in pharmacological intervention studies contingent incentives seems to specifically enhance drug efficacy.
- In both psychological and pharmacological interventions contingent incentives that directly reinforce cocaine abstinence seem more effective, whereas other targets of incentives, like medication compliance or treatment adherence seem less effective.
- Extra costs of approximately €40 per week per patient accompany the addition of CM to existing treatments. Some candidate drugs may be fit to serve as reinforcer, similar to contingent methadone doses in methadone maintained patients, promoting abstinence and treatment retention in cocaine dependence treatment.

ABBREVIATIONS

abst. = Abstinence

avg. = Average

BT = Behavioral therapy

CBT = Cognitive Behavioral Treatment

ClinMan = Clinical Management

CM = Contingency Management

CM-ATT = CM-Attendance

CM-MEDIC = CM-Medication

CRA = Community Reinforcement Approach

FU = Follow-Up

mo(s) = Month(s)

N-CM = Non-contingent incentive

neg. = Negative

OR = Odds Ratio

pos. = Positive

pt(s) = Patient(s)

ret. = Retention

RR = Relative Risk/Risk Ration

RCT = Randomized Controlled Trial

SD = Standard Deviation

TAU = Treatment as usual

TSF = Twelve-Step Facilitation

wk(s) = Week(s)

yr(s) = Year(s)

CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

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REFERENCES

[1] van Amsterdam J, Opperhuizen A, Koeter M, van den Brink W. Ranking the harm of alcohol, tobacco and illicit drugs for the individual and the population. Eur Addict Res 2010; 16(4): 202-7.

[2] UNODC. World Drug Report. United Nations Office on Drugs and Crime; May 2011; pp. 1-272. Report No.: E.11.XI.10.

[3] EMCDDA. 2011 Annual report on the state of the drugs problem in the European Union. European Monitoring Centre for Drugs and Drug Addiction: Lisbon 2011.

[4] van den Brink W. Evidence-based Pharmacological Treatment of Substance use Disorders and Pathological Gambling. Curr Drug Abuse Rev 2012; 5(1): 3-31.

[5] Knapp WP, Soares BGO, Farrel M, Lima MS. Psychosocial interventions for cocaine and psychostimulant amphetamines related disorders. Cochrane Database Syst Rev 2007; (3): CD003023.

[6] Prendergast M, Podus D, Finney J, Greenwell L, Roll J. Contingency management for treatment of substance use disorders: a meta-analysis. Addiction 2006; 101(11): 1546-60.

[7] Lussier JP, Heil SH, Mongeon JA, Badger GJ, Higgins ST. A meta-analysis of voucher-based reinforcement therapy for substance use disorders. Addiction 2006; 101(2): 192-203.

[8] Carroll KM, Rounsaville BJ. A perfect platform: combining contingency management with medications for drug abuse. Am J Drug Alcohol Abuse 2007; 33(3): 343-65.

[9] Stitzer ML, Vandrey R. Contingency management: utility in the treatment of drug abuse disorders. Clin Pharmacol Ther 2008; 83(4): 644-7.

[10] National Institute on Drug Abuse (NIDA). Principles of Drug Addiction Treatment. NIH publication 1999.

[11] Rawson R. Treatment for Stimulant Use Disorders Treatment Improvement Protocol (TIP) Series. 1999.

[12] Stine SM, Burns B, Kosten T. Methadone dose for cocaine abuse. 9th ed. US: American Psychiatric Ass US 1991

[13] Stine SM, Freeman M, Burns B, Charney DS, Kosten TR. Effect of methadone dose on cocaine abuse in a methadone program. Am J Addict 1992; 1(4): 294-303.

[14] Stitzer ML, Iguchi MY, Felch LJ. Contingent take-home incentive: effects on drug use of methadone maintenance patients. J Consult Clin Psychol. 1992 Dec;60(6):927–34.

[15] Petry NM, Tedford J, Austin M, Nich C, Carroll KM, Rounsaville BJ. Prize reinforcement contingency management for treating cocaine users: how low can we go, and with whom? Addiction 2004; 99(3): 349-60.

[16] Higgins ST, Budney AJ, Bickel WK, Hughes JR, Foerg F, Badger G. Achieving cocaine abstinence with a behavioral approach. Am J Psychiatry 1993; 150(5): 763-9.

[17] Higgins ST, Budney AJ, Bickel WK, Badger GJ, Foerg FE, Ogden D. Outpatient behavioral treatment for cocaine dependence: One-year outcome. Exp Clin Psychopharmac: Am Psychol Assoc 1995 ;3(2): 205-12.

[18] Roozen HG, Boulogne JJ, van Tulder MW, van den Brink W, De Jong CAJ, Kerkhof AJFM. A systematic review of the effectiveness of the community reinforcement approach in alcohol, cocaine and opioid addiction. Drug Alcohol Depend 2004; 74(1): 1-13.

[19] Higgins ST, Delaney DD, Budney AJ, *et al.* A behavioral approach to achieving initial cocaine abstinence. Am J Psychiatry 1991; 148(9): 1218-24.

[20] Garcia-Rodriguez O, Secades-Villa R, Higgins ST, *et al.* Effects of voucher-based intervention on abstinence and retention in an outpatient treatment for cocaine addiction: a randomized controlled trial. Exp Clin Psychopharmacol 2009; 17(3): 131-8.

[21] Secades-Villa R, Garcia-Rodriguez O, Garcia-Fernandez G, Sanchez-Hervas E, Fernandez-Hermida JR, Higgins ST. Community reinforcement approach plus vouchers among cocaine-dependent outpatients: twelve-month outcomes. Psychol Addict Behav 2011; 25(1): 174-9.

[22] Secades-Villa R, Garcia-Rodriguez O, Higgins ST, Fernandez-Hermida JR, Carballo JL. Community reinforcement approach plus vouchers for cocaine dependence in a community setting in Spain: Six-month outcomes. J Subst Abuse Treat 2008; 34(2): 202-7.

[23] Higgins ST, Budney AJ, Bickel WK, Foerg FE, Donham R, Badger GJ. Incentives improve outcome in outpatient behavioral treatment of cocaine dependence. Arch Gen Psychiatry 1994; 51(7): 568-76.

[24] Higgins ST, Wong CJ, Badger GJ, Ogden DE, Dantona RL. Contingent reinforcement increases cocaine abstinence during outpatient treatment and 1 year of follow-up. J Consult Clin Psychol 2000; 68(1): 64-72.

[25] Garcia-Fernandez G, Secades-Villa R, Garcia-Rodriguez O, *et al.* Long-term benefits of adding incentives to the community reinforcement approach for cocaine dependence. Eur Addict Res 2011; 17(3): 139-45.

[26] Garcia-Fernandez G, Secades-Villa R, Garcia-Rodriguez O, Sanchez-Hervas E, Fernandez-Hermida JR, Higgins ST. Adding voucher-based incentives to community reinforcement approach improves outcomes during treatment for cocaine dependence. Am J Addict 2011; 20(5): 456-61.

[27] Schottenfeld RS, Moore B, Pantalon MV. Contingency management with community reinforcement approach or twelve-step facilitation drug counseling for cocaine dependent pregnant women or women with young children. Drug Alcohol Depend 2011; 118(1): 48-55.

[28] Higgins ST, Sigmon SC, Wong CJ, *et al.* Community reinforcement therapy for cocaine-dependent outpatients. archives of general psychiatry. JAMA 2003; 60(10): 1043-52.

[29] Volkow N. Drug dependence and addiction, III: Expectation and brain function in drug abuse. Am J Psychiatry 2004; 161(4): 621.

[30] Dackis CA, Gold MS. New concepts in cocaine addiction: the dopamine depletion hypothesis. Neurosci Biobehav Rev 1985; 9(3): 469-77.

[31] Schmitz JM, Mooney ME, Moeller FG, Stotts AL, Green C, Grabowski J. Levodopa pharmacotherapy for cocaine dependence: choosing the optimal behavioral therapy platform. Drug Alcohol Depend 2008; 94(1-3): 142-50.

[32] Kalivas PW. Neurobiology of Cocaine addiction: implications for new pharmacotherapy. Am J Addict 2007; 16(2): 71-8.

[33] Schmitz JM, Lindsay JA, Stotts AL, Green CE, Moeller FG. Contingency management and levodopa-carbidopa for cocaine treatment: a comparison of three behavioral targets. Exp Clin Psychopharmacol 2010; 18(3): 238-44.

[34] Schmitz JM, Rhoades HM, Elk R, Creson D, Hussein I, Grabowski J. Medication take-home doses and contingency management. Exp Clin Psychopharmacol 1998; 6(2): 162-8.

[35] Moeller FG, Schmitz JM, Steinberg JL, *et al.* Citalopram combined with behavioral therapy reduces cocaine use: a double-blind, placebo-controlled trial. Am J Drug Alcohol Abuse 2007; 33(3): 367-78.

[36] Jones HE, Johnson RE, Bigelow GE, Silverman K, Mudric T, Strain EC. Safety and efficacy of L-tryptophan and behavioral incentives for treatment of cocaine dependence: a randomized clinical trial. Am J Addict 2004; 13(5): 421-37.

[37] Bisaga A, Aharonovich E, Cheng WY, *et al.* A placebo-controlled trial of memantine for cocaine dependence with high-value voucher incentives during a pre-randomization lead-in period. Drug Alcohol Depend 2010; 111(1-2): 97-104.

[38] Schmitz JM, Lindsay JA, Green CE, Herin DV, Stotts AL, Gerard Moeller F. High-dose naltrexone therapy for cocaine-alcohol dependence. Am J Addict 2009; 18(5): 356-62.

[39] Shoptaw S, Watson DW, Reiber C, *et al.* Randomized controlled pilot trial of cabergoline, hydergine and levodopa/carbidopa: Los Angeles Cocaine Rapid Efficacy Screening Trial (CREST). Addiction 2005; 100 Suppl 1: 78-90.

[40] Mooney ME, Schmitz JM, Moeller FG, Grabowski J. Safety, tolerability and efficacy of levodopa-carbidopa treatment for cocaine dependence: two double-blind, randomized, clinical trials. Drug Alcohol Depend 2007; 88(2-3): 214-23.

[41] Grabowski JJ, Rhoades HH, Kirby KK, 7. Fluoxetine is ineffective for treatment of cocaine dependence or concurrent opiate and cocaine dependence: two placebo-controlled double-blind trials. J Clin Psychopharmacol 1995; 15(3): 163-74.

[42] Fernstrom JD, Wurtman RJ. Brain serotonin content: physiological dependence on plasma tryptophan levels. Science 1971; 173(3992): 149-52.

[43] Carroll ME, Lac ST, Asencio M, Kragh R. Intravenous cocaine self-administration in rats is reduced by dietary L-tryptophan. Psychopharmacology (Berl.). 1990;100(3):293–300.

[44] McGregor A, Lacosta S, Roberts DC. L-tryptophan decreases the breaking point under a progressive ratio schedule of intravenous cocaine reinforcement in the rat. Pharmacol. Biochem. Behav 1993; 44(3): 651-5.

[45] Maldonado C, Rodríguez-Arias M, Miñarro J, 5. Effect of memantine and CNQX in the acquisition, expression and reinstatement of cocaine-induced conditioned place preference. Prog Neuropsychopharmacol Biol Psychiatry 2007; 31(4): 932–9.

[46] Newman JL, Beardsley PM. Effects of memantine, haloperidol, and cocaine on primary and conditioned reinforcement associated with cocaine in rhesus monkeys. Psychopharmacology (Berl.). 2006; 185(2): 142-9.

[47] Collins EDE, Vosberg SKS, Foltin RWR, 5. The effects of acute pretreatment with high-dose memantine on the cardiovascular and behavioral effects of cocaine in humans. Exp Clin Psychopharmacol 2007; 15(3): 228-37.

[48] Hersh D, Van Kirk JR, Kranzler HR. Naltrexone treatment of comorbid alcohol and cocaine use disorders. Psychopharmacology (Berl.) 1998; 139(1-2): 44-52.

[49] Schmitz JM, Stotts AL, Sayre SL, DeLaune KA, Grabowski J. Treatment of cocaine-alcohol dependence with naltrexone and relapse prevention therapy. Am J Addict 2004; 13(4): 333–41.

[50] Schmitz JM, Lindsay JA, Green CE, Herin DV, Stotts AL, Moeller FG. High-dose naltrexone therapy for cocaine-alcohol dependence. Am J Addict 2009; 18(5): 356-62.

[51] Grassi MCM, Cioce AMA, Nencini PP, 5. Short-term efficacy of Disulfiram or Naltrexone in reducing positive urinalysis for both cocaine and cocaethylene in cocaine abusers: a pilot study. Pharmacol Res 2007; 55(2): 117-21.

[52] Somaini L, Donnini C, Raggi MA, *et al.* Promising medications for cocaine dependence treatment. Recent Pat CNS Drug Discov 2011; 6(2): 146-60.

[53] Karila L, Reynaud M, Aubin H-J, *et al.* Pharmacological treatments for cocaine dependence: is there something new? Curr. Pharm. Des 2011; 17(14): 1359-68.

[54] Kampman K. What's new in the treatment of cocaine addiction? Curr Psychiatry Rep 2010; 12: 441-7.

[55] Blick SKA, Keating GM. Lisdexamfetamine. Paediatr Drugs 2007; 9(2): 12-35; discussion 136-8

[56] Ramsey NFN, van Ree JMJ. Intracerebroventricular naltrexone treatment attenuates acquisition of intravenous cocaine self-administration in rats. Pharmacol. Biochem. Behav 1991; 40(4): 807-10.

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