Modafinil: A Useful Medication for Cocaine Addiction? Review of the Evidence from Neuropharmacological, Experimental and Clinical Studies

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Abstract: Cocaine addiction is a chronic relapsing disorder associated with severe medical and psychosocial complications. However, there are no approved medications for cocaine dependent individuals. Modafinil, a medication that differs chemically and pharmacologically from other central nervous system stimulants, has been suggested to be potentially useful for this complex disorder. The present paper aims to critically review the published evidence from laboratory and clinical studies on modafinil for cocaine addiction, including discussion of its pharmacological characteristics and how it may relate with cocaine neurobiology. Whilst its exact mechanism of action remains to be elucidated, different neurotransmitter systems have been implicated, including modulation on dopamine, glutamate/GABA, noradrenaline and the hypocretin/orexin system, but it is possible that modafinil acts by a synergistic combination of mechanisms. With a favourable pharmacokinetic profile, it appears to have a low abuse potential. Laboratory and clinical studies provide consistent, albeit preliminary, evidence of the potential usefulness of modafinil for cocaine dependent patients. Not only there is no evidence of pharmacokinetic interactions between modafinil and cocaine, but in addition cocaine induced euphoria and cardiovascular effects appear to be attenuated by modafinil. Furthermore, modafinil has been shown to decrease cocaine self-administration. In addition, modafinil treated patient are more likely to achieve protracted abstinence than placebo treated patients. However, further research is needed to confirm these findings.

Keywords: Modafinil, cocaine, cytochrome P450, dopamine, glutamate, craving, abuse liability.

INTRODUCTION

Cocaine addiction is a chronic relapsing disorder that constitutes a grave public health problem worldwide, associated with severe medical and psychosocial complications [1]. Over the last two decades an increasing number of studies have advanced our understanding on the neurobiological basis of this complex disorder and many efforts are being made towards the development of efficacious pharmacotherapies. While, there are still no approved medications for cocaine dependent individuals, several pharmacological strategies, including disulfiram, tiagabine, topiramate, or modafinil have shown preliminary evidence of efficacy in clinical trials [2-4].

Cocaine, like other psychostimulants of high abuse potential, produces a brief, intense euphoria, experienced as a "rush" of pleasure lasting several seconds followed by minutes of persistent but lower level euphoria, and a strong craving. Due to physiological reward effects of cocaine, repeated use occurs as a means of again achieving such intense euphoria [5]. Often it leads to compulsive binge patterns lasting up to a few days, followed by episodes of cocaine withdrawal [6]. Enhanced dopamine transmission in the nucleus accumbens has been widely regarded as the primary neuropharmacological target for cocaine-induced reinforcing effects [5, 7, 8]. However, other neurotransmitter systems appear to be involved in the persistence of cocaine-seeking behaviour, the vulnerability to relapse, as well as in cue-elicited craving. Glutamate transmission in the nucleus accumbens appears to be essential for cocaine-induced craving and glutamate plays a key role in the processes underlying the development and maintenance of addiction and in precipitating relapse [9-11]. Furthermore, repeated cocaine administration has been found to be associated with a depletion of extracellular glutamate levels [10, 12, 13].

Modafinil (2-diphenylmethyl-sulfinyl-2 acetamide), a novel wake-promoting agent, is chemically and pharmacologically distinct from amphetamine-like and other central nervous system (CNS) stimulants. It was originally approved by the Food and Drug Administration (FDA) for the treatment of narcolepsy, obstructive sleep apnea, and shift work sleep disorders [14]. However, due to its tolerability and its broad mode of action modafinil is frequently used and studied for off-label indications in general medicine and psychiatry, particularly in attention deficit hyperactivity disorder (ADHD), as an adjunct to antidepressants for depression, or in the recovery from general anaesthesia [15-18]. Additionally, increasing evidence suggests the potential use of modafinil in the treatment of cocaine dependent patients [4].

The present paper aims to critically review the published evidence from laboratory and clinical studies on modafinil

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for cocaine addiction, including discussion of its pharmacological characteristics and how it may relate with cocaine neurobiology. This may be of particular relevance for both clinicians and researchers considering the dimension of the current cocaine epidemic and the on-going search for effective medications.

METHODS

A comprehensive search from a range of electronic databases was conducted for the period from the introduction of modafinil to August 2007. The primary search was conducted on PubMed using solely the term "modafinil" which resulted in 565 articles. Of the total number of retrieved papers, 145 corresponded to clinical trials, including 98 randomized control trials, 114 to reviews, including two meta-analysis, 10 to editorials, and 51 to letters. A secondary search were then conducted with the key words "modafinil" and "cocaine" which resulted in 24 articles, as follows: five preclinical studies in animals, eight laboratory studies in humans (all of them randomized controlled trials), including two pharmacokinetic studies, two clinical trials (including an open study and a randomized controlled trial), six reviews, and three letters. Additional searches were conducted from other specialised electronic databases, including Cochrane Library, and EMBASE. In addition, references in empirical articles and narrative and meta-analytic reviews were used for further potential sources of articles. There were no restrictions on the identification or inclusion of studies in terms of publication status, language and design type. However, abstracts of presentations to specialist meetings and conferences were not included.

PHARMACOLOGICAL CHARACTERISTICS

Pharmacodynamic Actions

Whilst several studies have evidenced that modafinil acts differently from other CNS stimulants such as amphetamine and methylphenidate [15, 19-22] its exact mode of action remains to be elucidated. *In vivo* and *in vitro* studies have implicated different neurotransmitter systems and it is possible that it acts by a synergistic combination of mechanisms. It appears that many of its neurochemical actions overlap with those of cocaine.

One of the main hypotheses on how modafinil may exert its therapeutic effects appears to be through its ability to enhance glutamate release and inhibit GABAergic release in various brain regions [23, 24]. In addition, the apparent neuroprotective effects of modafinil seem to be best explained by the attenuation of glutamate-induced excitotoxicity in cortical neurons [25]. The dopamine system has been implicated as well in modafinil´s mechanism of action. An increase in extracellular dopamine levels without an increase in its release has been reported and proposed to play an important role in modafinil´s wake-promoting actions [26]. It has also been suggested that modafinil behaves as a weak dopamine re-uptake inhibitor, with similar properties to the atypical antidepressant bupropion [27, 28]. It would increase dopaminergic transmission by binding weakly to the dopamine transporter [29]. However, in a recent study, modafinil was described to inhibit dopaminergic neurons through an agonistic action at D_2-like receptors, therefore suggesting a unique site of action for modafinil [30].

Another proposed mechanism to explain modafinil´s wake-promoting and stimulating effects is through activation of central noradrenergic transmission, either by directly stimulating the receptors due to alpha 1B-adrenergic agonist effects or associated to indirect inhibition of noradrenaline reuptake in noradrenergic terminals on sleep-promoting neurons [31, 32]. Modafinil also appears to activate noradrenergic neurons in the locus coeruleus involved in arousal and pupillary control, without affecting extracoerulear noradrenergic neurons involved in cardiovascular and salivary regulation [33]. Additionally, modafinil has been reported to regulate cortical serotoninergic transmission by increasing serotonin release without being involved in the reuptake process [34]. Finally, the hypocretin/orexin system has also been implicated in the mechanism of action of modafinil. Hypocretins/orexins are neuropeptides, produced in the lateral hypothalamus, involved in various hypothalamic mechanisms, such as energy homeostasis and neuroendocrine functions and can increase as well the release of GABA and glutamate [35]. Modafinil has been shown to activate these orexin containing hypothalamic neurons [22].

Pharmacokinetics

Absorption and Distribution

Modafinil is readily absorbed following single or multiple oral doses, reaching peak plasma concentrations approximately 2-4 hours after administration [36, 37]. Food has no significantly effects on its bioavailability, although absorption can be delayed by approximately one hour when taken concurrently with food [14]. Steady-state plasma concentrations are achieved within 2-4 days [38]. Modafinil is widely distributed in body tissue; it is moderately bound to plasma proteins (roughly 60% of the dose), mainly to albumin [36].

Metabolism and Elimination

Modafinil is extensively metabolised in the liver (90%), largely *via* amide hydrolysis, with lesser contributions from cytochrome P450 (CYP)-mediated oxidative pathways to two major metabolites, modafinil acid and modafinil sulfone [36]. Renal excretion accounts for 80% of elimination of modafinil. Less than 10% of the dose is excreted unchanged in the urine. D-modafinil enantiomer is eliminated three times faster than L-modafinil [39]. The elimination half-life is approximately 12-15 hours [38]. Modafinil acid is the major urinary metabolite, which accounts for 31% to 60% of the dose, although there are at least other six inactive metabolites present in lower concentrations in urine [37,38]. None of these metabolites appear to contribute to modafinil's therapeutic effects [36]. Urine alkalinisation has no effect on the elimination of modafinil [14]. Whilst severe chronic renal failure does not seem to significantly influence the pharmacokinetics of modafinil, in patients with cirrhosis of the liver the oral clearance of modafinil has been reported to decrease by about 60% and the steady state concentration to double compared to normal patients [14]. Consequently, the dose of modafinil should be reduced to one-half in patients with severe hepatic impairment. Similarly, it can be reduced as well in the elderly due to the physiological lower plasma clearance observed with aging. This decrease of the clearance rate of modafinil with age appears to be more pro-

nounced in males, but also young females have a faster clearance rate than young males [37].

Drug Interactions

In daily practice, modafinil is frequently co-administered with other medications and psychostimulants abusers often continue taking drugs while on medication. Therefore, understanding the potential for drug-drug interactions and the inhibition or induction of cytochrome P450 drug-metabolizing enzymes by modafinil could be of clinical relevance. In contrast, pharmacological agents that induce or inhibit cytochrome P450 activity are unlikely to have major effects on the pharmacokinetics of modafinil [36].

In vitro studies have evidenced that modafinil, at pharmacologically relevant concentrations, causes a potent, reversible inhibition solely of CYP2C19 in human liver microsomes [36, 40]. Medications that are largely metabolized by the CYP2C19 isoenzyme, including diazepam, propranolol, phenytoin, omeprazole, lansoprazole may have prolonged elimination when administered concomitantly with modafinil and may therefore require dosage reduction and monitoring for toxicity [14, 40, 41]. The clinical relevance of the CYP2C19 is underpinned by a case report of a narcoleptic patient chronically treated with clomipramine whose blood concentrations of clomipramine and its metabolite showed a significant dose-dependent and reversible increase after commenced on modafinil [42]. As the patient was a poor metabolizer of the CYP2D6 isoenzyme, which is primarily responsible for the biotransformation of clomipramine [43], the pharmacokinetic interaction was attributed to inhibition of CYP2C19 metabolizing enzyme. This finding may become significant when modafinil is co-administered with certain tricyclic antidepressants or with selective serotonin reuptake inhibitors in patients deficient in the CYP2D6 isoenzyme (approximately, 7-10% of the Caucasian population) and where the CYP2C19 acts as a secondary metabolic pathway [44].

In vitro, modafinil produces a modest, but concentration-dependent, induction of CYP1A2, CYP3A4, and CYP2B6 in human liver microsomes [40, 45]. However, the only clinically significant interactions observed have been with ethinylestradiol and triazolam, apparently through induction of CYP3A4, primarily in the gastrointestinal system, rather than in the liver, as reported in a single-blind placebo-controlled drug interaction study where chronic administration of modafinil (400 mg) was found to significantly reduce triazolam and to a lesser extent ethinylestradiol levels [46]. Dose adjustments may be necessary for patients being treated with these and similar medications. Caution is advised when medications with a narrow therapeutic margin, and metabolised predominantly or exclusively by this enzyme, such as cyclosporine A, are administered concomitantly with modafinil, as the apparent small induction of CYP3A4 caused by modafinil may lower its effectiveness, as described in the case of a patient whose cyclosporine blood levels decreased by 50% with modafinil [47].

A concentration-related suppression of CYP2C9 activity *in vitro* has also been reported [40]. This could have potential clinical relevance in relationship to warfarin, a drug with a narrow therapeutic index and primarily metabolized by the CYP2C9 isoenzyme. However, no significant changes in the pharmacokinetic profiles of R- and S- warfarin in 28 healthy subjects given a single dose of racemic warfarin (5 mg) were observed following chronic administration of modafinil in a placebo-controlled, single-blind study [48].

Results from interaction studies in healthy volunteers assessing a number of pharmacokinetic parameters have shown that simultaneous administration of modafinil and methylphenidate did not cause significant alterations in the steady-state pharmacokinetics of either drug, despite sporadic differences in plasma concentrations between medications [49, 50]. Similarly, two further randomized open-label studies evaluated the potential interactions between modafinil and dextroamphetamine in healthy volunteers, showing that although there was a slightly greater incidence of adverse events when modafinil and dextroamphetamine were administered together, simultaneous administration of both compounds did not alter the pharmacokinetic parameters of either drug [51, 52].

Contraindications, Safety and Tolerability

Modafinil appears only contraindicated in patients with known hypersensitivity to modafinil or its inactive ingredients [14]. The rare occurrence of severe cutaneous adverse reactions associated with modafinil treatment, including erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, and drug rash with eosinophilia and systemic symptoms have been reported, consistent with a drug hypersensitivity syndrome [14, 18, 53]. Whilst not explicitly contraindicated, modafinil should be used with caution in patients with a history of angina, cardiac ischemia or recent history of myocardial infarction. It should be best avoided in patients with left ventricular hypertrophy, or patients who have developed the mitral valve prolapse syndrome when previously taking CNS stimulants. Modafinil is not recommended in pregnancy and breast-feeding.

Safety and tolerability of modafinil as a wake-promoting agent has been assessed in a large report that combined data from six randomized, double-blind controlled trials [54]. A total of 1529 outpatients received modafinil 200, 300, or 400 mg or placebo once daily for up to 12 weeks for excessive sleepiness (hypersomnolence) associated with shift work sleep disorder, obstructive sleep apnea, or narcolepsy. Overall, modafinil was well tolerated compared to placebo. There were 27 medication-related serious adverse events reported (modafinil, n = 18; placebo, n = 9). The most common adverse events were headache (34% vs 23% for modafinil and placebo, respectively), and nausea (11% vs 3%). In addition, among modafinil-treated patients, clinically significant increases in diastolic or systolic blood pressure were infrequent (n = 9 and n = 1, respectively, < 1% of patients), while one patient in the modafinil group and one in the placebo group had a clinically significant increase in heart rate. New clinically meaningful electrocardiogram abnormalities were rare with modafinil (n = 2) and placebo (n = 4). Similarly, in a double-blind controlled trial of modafinil for cocaine dependence [63] the most common side-effects and with at least twice the incidence than in placebo-treated patients, included: nausea (23%), upper respiratory symptoms (17%), anxiety (13%), tachycardia (13%), urinary tract infection (10%), dizziness (7%), reduced appetite (7%), racing thoughts (7%), and dry mouth (7%).

ABUSE LIABILITY

Due to its psychostimulant actions, there have been questions about the abuse potential of modafinil, particularly since his use has broadened to a variety of psychiatric, neurological, and medical illnesses. There has been actually some controversy on this subject in the specialized literature [55, 56]. This originates partly from the FDA approved product monograph where it states that it produces "psychoactive and euphoric effects, alterations in mood, perception, thinking and feelings typical of other CNS stimulants" and it adds that modafinil "is reinforcing, as evidenced by its self-administration in monkeys previously trained to self-administer cocaine" [14]. However, data from preclinical and clinical studies suggest that modafinil lacks the abuse potential of amphetamine and methylphenidate, two other medications used for the treatment of narcolepsy or ADHD. Additionally, brain areas activated by modafinil appear to differ from those activated by amphetamine and methylphenidate, suggesting modafinil has a distinct mechanism of action from other CNS stimulants [21, 22]. In a drug-discrimination experiment with six cocaine-trained rats, only at the two highest doses in four of the six animals was modafinil discriminated as cocaine, with about 67% correct responding, while a wider dosage range *d*-amphetamine and *l*-ephedrine were discriminated 100% and 82% of the times as cocaine, respectively [57]. In a further experiment, modafinil, *d*-amphetamine and *l*-ephedrine were compared to saline and cocaine conditions for reinforcing effects in rhesus monkeys maintained on intravenous cocaine self-administration [57]. The results showed that modafinil, like other abused stimulants, can serve as a reinforcer albeit at very high doses. Indeed, modafinil proved to be over 200 times less potent than *d*-amphetamine and approximately 15 times less potent than *l*-ephedrine.

Modafinil failed to prove to be pharmacologically equivalent to methylphenidate, and did not appear to have the toxic or reinforcing effects that may lead to abuse in a double-blind study, with 25 adult male polysubstance abusers, conducted to assess the abuse potential of modafinil using methylphenidate as a reference [58]. Results from a further experiment designed to assess acute behavioural effects of oral modafinil, cocaine, and placebo in nine subjects with recent histories of cocaine use showed that cocaine, but not modafinil, produced stimulant-like self-reported drug effects and therefore adds to the evidence suggesting that modafinil has minimal abuse potential [59]. In another double-blind study, six volunteers with a recent cocaine use history participated in an experiment conducted to assess whether a range of oral doses of cocaine (50, 100, and 150 mg), modafinil (200, 400, and 600 mg), and placebo shared discriminative-stimulus and self-reported effects with 150 mg cocaine [60]. Methylphenidate (60 mg) and triazolam (0.5 mg) were included as positive and negative controls. Cocaine and methylphenidate, but not modafinil or triazolam, produced cocaine-like discriminative-stimulus, subject-rated, and cardiovascular effects. Only one study with 12 women with a history of polysubstance abuse reported that these could discriminate some amphetamine-like effects of modafinil 200 mg and 800 mg relative to placebo [61], therefore suggesting that women may be more prone to perceive modafinil as rewarding. It appears, however, that modafinil´s reinforcing effects are influenced by behavioural demands following drug administration, similar to those of other stimulant drugs [62].

To sum up, results from preclinical and clinical abuse liability studies indicate that modafinil has some potential for abuse. However, there are no convincing reports of modafinil producing drug-induced euphoria, which can lead to addiction. To date there has been no indication of excessive use or abuse in clinical samples among individuals with cocaine abuse or dependence [56, 63-65]. Furthermore, discontinuation of modafinil is not associated with withdrawal emergent adverse events, nor is related with amphetamine-like withdrawal symptoms [66]. Preclinical studies in drug-naïve animals using intravenous self-administration and place conditioning tests support the evidence that modafinil lacks reinforcing or rewarding effects and did not modify the effects of cocaine and overall suggests that it does not possess an addictive potential in naïve animals [67]. When evaluating the abuse potential of modafinil it is also important to consider that it is practically insoluble in water and therefore reduces the likelihood to be injected. In addition, it is highly unstable or degrades when heated at temperatures above 180^{o}C and consequently prevents it from being smoked like cocaine or methamphetamine [57, 60, 66]. Considering all this evidence it is not surprising that the FDA/Drug Enforcement Administration included modafinil in the less restrictive schedule IV, rather than in schedule II along with methylphenidate and other stimulants.

MODAFINIL FOR COCAINE ADDICTION: EVIDENCE FROM LABORATORY AND CLINICAL STUDIES

Laboratory Studies

Several experimental studies of human cocaine abusers have assessed the usefulness of modafinil as a potential pharmacotherapy for cocaine addiction (Table **1**) [68-71]. The earliest of these reports was a within-subjects study with seven cocaine-dependent subjects [68]. In order to evaluate the safety of modafinil in combination with cocaine subjects first received open-label cocaine (30 mg) intravenously and then were treated for four days with modafinil (200 or 400 mg/day) or placebo in randomized double-blind sequences prior to three subsequent cocaine infusions. Co-administration of modafinil and a single dose of intravenous cocaine failed to show significant changes in blood pressure (BP), pulse, temperature, or electrocardiogram measures. In addition, both active doses of modafinil were associated with significant reductions of cocaine-induced euphoria as observed by the decreases in the "Amphetamine" scale of the Addiction Research Center Inventory. Similar findings were seen in a further 22-day cocaine-modafinil interaction trial with 12 non-treatment seeking, cocaine dependent individuals who received random sets of intravenous infusions of saline or cocaine (20 and 40 mg); modafinil was given in a single-blind manner at 0 mg, 400 mg, or 800 mg per day [69]. Consistent with the previous study, no significant hemodynamic interactions between cocaine and modafinil were found. In addition, modafinil was associated with an attenuation of cocaine-induced increases of heart rate (HR) and systolic BP. Interestingly, modafinil 800 mg/day did not appear to be superior over 400 mg/day dose, suggesting a

possible "ceiling" effect for modafinil on cocaine subjective effects as measured using three visual analog scales. Blood samples from the 12 subjects participating in this study were analyzed to assess whether modafinil influences the pharmacokinetics of intravenous cocaine [70]. Although long-term administration of both 400 and 800 mg/day modafinil significantly decreased systemic exposure to cocaine during the first 180 minutes following intravenous cocaine administration, there was no evidence of significant changes in total AUC, clearance or elimination half-life of cocaine and consequently for a potentially harmful pharmacokinetic interaction between modafinil and cocaine.

More recently, Hart *et al.* [71] evaluated during a 48-day inpatient/outpatient double-blind, crossover study the effects of modafinil maintenance (200, 400 mg/day) or placebo on response to smoked cocaine self-administration (0, 12, 25, and 50 mg) in a group of eight non-treatment seeking cocaine-dependent volunteers. Both active modafinil maintenance doses significantly decreased cocaine self-administration of the two larger doses (25 and 50 mg, $p<0.03$ for both maintenance doses). In addition, modafinil maintenance significantly attenuated cocaine dose dependent increases in heart rate, systolic and diastolic BP, and subjective responses. In all these experimental studies side-effects of modafinil were mild and did not result in any subject drop-out or any dose reduction.

Particular attention deserves the attenuation of the increased HR and BP induced by cocaine, consistently reported in the different laboratory studies with cocaine dependent individuals following concomitant administration of cocaine and modafinil at clinically relevant doses [68, 69, 71]. This finding might have potential clinical implications considering the severe cardiovascular complications associated with cocaine abuse [72]. Consequently, it would appear that modafinil may confer some protection from the vasoconstrictive and heart rate effects of cocaine abuse. However, whilst some double-blind, randomized, placebo-controlled studies have failed to show any significant changes in HR or BP following modafinil administration [73] and although it is an infrequent side-effect in randomized controlled clinical trials of modafinil [18, 54], some studies have described significant increases in HR and BP

Table 1. Modafinil for Cocaine Dependence Summary from Laboratory and Clinical Studies

Authors and Year	Study Design	Comparative Condition	Sample	Duration	Key Results
Laboratory Studies					
Dackis *et al.*, 2003 [68]	Randomized, double blind, controlled drug interaction study involving iv administration of open-label cocaine (30 mg)	Modafinil (200, 400 mg/day) or placebo	7 cocaine dependent volunteers	16 days	No significant changes in BP, pulse, temperature, or ECG measures with co-administration of modafinil and iv cocaine. Both modafinil doses were associated with significant reductions of cocaine-induced euphoria.
Donovan *et al.*, 2005 [70]	Open-label, escalating dose, modafinil-cocaine interaction study. Double-blind randomized iv cocaine (20 or 40mg) or saline.	Modafinil (400, 800 mg/day) or placebo	12 non-treatment seeking, cocaine dependent volunteers	21 days	No evidence for a potentially harmful pharmacokinetic interaction between modafinil and cocaine.
Malcolm *et al.*, 2006 [69]	Randomized blinded infusions of saline, 20mg and 40mg iv cocaine. Modafinil or placebo was given open label	Modafinil (400, 800 mg/day) or placebo	12 non-treatment seeking, cocaine dependent volunteers	22 days	No significant hemodynamic interactions between cocaine and modafinil. Cocaine-induced increases of HR or systolic BP attenuated by modafinil.
Hart *et al.*, 2008 [71]	Double-blind, crossover study on response to smoked cocaine self-administration (0, 12, 25, and 50 mg).	Modafinil maintenance (200, 400 mg/day) or placebo	8 non-treatment seeking cocaine-dependent volunteers	48 days	Both modafinil doses significantly decreased cocaine self-administration. Both doses significantly attenuated subjective and cardiovascular responses raised by cocaine.
Clinical Studies					
Malcolm *et al.*, 2002 [65]	Case report	None	4 stimulant abusers, 1 of them with ADHD and heavy cocaine abuse	Several months	Reduction in craving and in cocaine use, and improvement of his cognitive problems.
Dackis and O'Brien, 2003 [77]	Open-label	Modafinil 200 or 400 mg/day + twice-weekly CBT	17 cocaine-dependent subjects	8 weeks	High levels of cocaine abstinence associated with modafinil treatment in cocaine dependent patients experiencing severe cocaine withdrawal at baseline
Dackis *et al.*, 2005 [63]	Double-blind randomized controlled trial	Modafinil (400 mg/day) or placebo + twice-weekly CBT	62 treatment-seeking cocaine-dependent patients	8 weeks	Significantly more BE-negative urine samples and more likely to achieve prolonged abstinence ($\geq$ 3 weeks) with modafinil than with placebo.

iv: intravenous; ECG: Electrocardiogram; HR: Heart Rate; BP: Blood Pressure; ARCI: Addiction Research Center Inventory ; CBT: cognitive behavioural therapy; BE: Benzoylecgonine.

with modafinil [74, 75]. Therefore, as mentioned earlier, caution is advised when using modafinil in patients with cardiovascular disease.

Clinical Studies

Further evidence on the potential utility of modafinil for psychostimulant abuse and specifically for cocaine addiction comes from clinical reports and a randomized placebo-controlled trial (Table **1**) [63, 65, 76, 77]. Initial interest on the potential usefulness of modafinil for cocaine abusers came from a case series of stimulant abusers that included a patient treated with modafinil for ADHD and heavy cocaine abuse who showed an improvement in his cognitive problems and a reduction in craving and in cocaine use [64]. Similarly, a reduction of craving for amphetamines and an improvement of comorbid anxiety and depression were described in a patient with social phobia and amphetamine dependence who previously failed to improve on trials of a variety of medications [76].

An 8-week open-label trial with twice weekly cognitive-behavioural therapy (CBT) reported high levels of cocaine abstinence and treatment retention in a group of 17 cocaine dependent patients with severe cocaine withdrawal [77]. Based on this preliminary report, as well on the results from laboratory studies, Dackis *et al.* [63] conducted an 8-week outpatient double-blind controlled trial to further assess whether modafinil would improve clinical outcome in cocaine-dependent patients. Cocaine abstinence as measured by urine benzoylecgonine (BE) levels was the primary efficacy measure. Sixty-two treatment-seeking cocaine dependent individuals were randomized to receive modafinil 400 mg/day or matching placebo tablets, while receiving manual-guided, twice-weekly CBT. Whilst there was no evidence that modafinil, which was well tolerated, reduced cocaine craving, nor that it reversed cocaine withdrawal, patients in the modafinil group provided significantly more BE-negative urine samples ($p=0.03$) and were more likely to achieve prolonged abstinence (3 weeks or more) ($p=0.05$) than placebo-treated patients over the eight weeks of follow-up. Consistent with other studies [68, 69], the authors reported that modafinil blunted cocaine-induced euphoria in patients receiving standardized psychosocial treatment as well. Finally, a recent systematic review and meta-analysis evaluated all randomized controlled clinical trials of CNS stimulants for the treatment of cocaine dependence [78]. Although, none of five CNS stimulants included in the review decreased dropout rate, cocaine use or craving compared to placebo, secondary analyses of dexamphetamine and modafinil were described as promising, supporting further research with these agents.

Another area where modafinil may have a significant impact to the treatment of substance use disorders in general and of cocaine addiction in particular is through its apparent neurocognitive effects. It has been suggested that modafinil may have a neuroprotective effect, attenuating glutamate-induced excitotoxicity in cortical neurons [25]. It has also been reported that it selectively improves neuropsychological task performance in healthy volunteers, adult patients with ADHD, as well as in patients with schizophrenia [79-81]. The positive effects observed on specific neuropsychological tests particularly in patients with ADHD [80] suggests an inhibition of impulsive responding, which may allow for other cognitive processes to enter into the decision-making process and enhance the ability to decide whether to use or not [3]. Modafinil has also been found to improve cognitive functions in several domains dependent on prefrontal cortex and cognitive control, and compared to placebo, administration of modafinil is associated with greater activation of the dorsolateral prefrontal cortex [82, 83]. The dorsolateral prefrontal cortex, with projections to the prefrontal cortex, amygdala, nucleus accumbens and ventral tegmental area, is involved in reward, motivation, cue-elicited craving and decision making circuits providing the substrate for integration of cognitive control (choice) and motivationally relevant information and the inhibitory control over seductive options fostering the promise of immediate reward [84]. Furthermore, in cocaine-addicted individuals it has been suggested that reduced frontal lobe metabolism could explain important clinical phenomena such as denial and the loss of control [85]. Therefore, cocaine addicted patients taking modafinil would then, at least hypothetically, have more cognitive resources to avoid psychostimulant use, to engage in psychosocial treatments, and to reach better cocaine use outcomes. In addition, modafinil has been reported to have some antidepressant properties [17, 86], which can be of relevance as well considering that milder depressive symptoms lasting for approximately two weeks are typical of cocaine withdrawal [87], and that mild depressive symptoms may increase subjective and physiological effects of cocaine [88]. Consequently, there would be blunting of cocaine effects if they begin to relapse while taking the medication. Finally, the presence of moderate-to-severe depressive symptoms is a good predictor of relapse to substance use at three-months after treatment completion [89].

CONCLUSIONS

Modafinil, a medication originally licensed for narcolepsy and neurochemically unrelated to other CNS stimulants, emerges as a reasonable candidate in the pharmacological treatment of cocaine addiction based on the increasing and so far solid evidence from laboratory studies and reports with clinical samples. Its stimulatory and activating effects may be useful to counteract the feelings of fatigue, anhedonia, and low mood that may appear during cocaine withdrawal. Under controlled conditions, modafinil has been shown to blunt cocaine-induced euphoria, which in turn may prevent cocaine priming, and to attenuate cocaine associated increases in cardiovascular responses [68, 69], while lacking any potentially harmful interactions when administered concomitantly [70]. Furthermore, modafinil has been found to decrease cocaine self-administration [71]. It has minimal abuse potential and is well tolerated in cocaine abusing population [63]. Nonetheless, it appears that its efficacy in cocaine dependent patients is increased when combined with psychosocial treatments. Finally, its effects on neurocognitive functions may be relevant to facilitate the individuals´ ability to control impulsive responding.

Considering its clinical and pharmacological profile, the question arises as to whether modafinil could be potentially useful as well for other substance use disorders, particularly for psychostimulant abuse, including methamphetamine abuse or even nicotine dependence. Finally, considering the elevated prevalence of other mental disorders among indi-

viduals with cocaine dependence another issue that needs to be addressed is whether modafinil could be potentially useful for dually diagnosed cocaine abusers. A reasonable target patient group appears to be those with comorbid ADHD and cocaine abuse. Moreover, considering the findings from a recent randomized placebo controlled trial showing that add-on modafinil may improve depressive symptoms in patients with bipolar disorder [86], other dually diagnosed cocaine dependent individuals may benefit from it as well.

Further research is needed to validate this initial findings and particularly further randomized controlled trials are required to explore the usefulness of modafinil in different subgroups of cocaine dependent individuals.

Key Learning Objectives:

- To learn about the mode of action of modafinil.
- To get a good understanding of the drug-drug interactions and the inhibition or induction of cytochrome P450 drug-metabolizing enzymes by modafinil.
- To learn whether or not modafinil has any abuse potential and understand the rationale behind it.
- To get a good understanding of the evidence proving from laboratory studies and from clinical reports on the potential usefulness and efficacy of modafinil for cocaine addiction.
- To learn some other beneficial effects of modafinil that may have a significant impact to the treatment of cocaine dependent individuals.

Future Research Questions:

- Further randomized controlled trials are needed to replicate the so far solid but limited data from clinical samples.
- Further research is required to evaluate the usefulness of modafinil in different subgroups of cocaine dependent individuals.
- Can modafinil be potentially useful as well for other substance use disorders, particularly for psychostimulant abuse, including methamphetamine abuse or even nicotine dependence?
- Considering the high prevalence of comorbid psychiatric disorders among individuals with cocaine dependence, another question to be addressed is whether modafinil can be useful for dually diagnosed cocaine abusers, particularly for those with comorbid ADHD, or those with comorbid bipolar disorder.

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