Commentary

New medications for the treatment of cocaine dependence

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Summary. Cocaine dependence continues to be a significant public health problem in the United States and in Europe. Regular cocaine use has not declined significantly in the United States since 1992 and has been rising in the European Union. Although counseling remains the treatment of choice for cocaine dependence, many cocaine dependent patients do not respond completely to drug counseling. Therefore, the development of effective medications for the treatment of cocaine dependence is a research priority. Progress in the understanding of the neurobiology of cocaine dependence has led to the discovery of several promising medications that have already shown encouraging results in controlled clinical trials. Other promising compounds are just now becoming available for clinical trials. Among the medications in clinical trials, modafinil may be helpful in promoting an initial period of stable abstinence. For the prevention of relapse, medications that block cocaine euphoria or reduce cocaine craving have shown promise. Potential relapse-prevention medications include disulfiram and GABAergic medications such as gamma-vinyl GABA, tiagabine and topiramate. Finally, a vaccine capable of stimulating the production of cocaine specific antibodies has shown promise in preliminary studies for the prevention of relapse to cocaine use. Newer medications not yet included in clinical trials, but promising nonetheless, include: dopamine D3 receptor antagonists, neurokinin 1 receptor antagonists, and n-acetylcysteine.

Key words: cocaine dependence, pharmacotherapy, new medications, withdrawal, relapse prevention.

INTRODUCTION

Developing new medications for the treatment of cocaine dependence continues to be a research priority. In the United States, the number of current users of cocaine has remained relatively stable over the past five years [1]. While in Europe, the most recent data suggests an overall increase in the use of cocaine. Population surveys carried out in a number of countries have recorded a marked increase in use among young people since the mid-1990s. In addition, indicators of cocaine availability in Europe, including the number of seizures of the drug and the amount seized, have increased dramatically [2].

Although progress has been made in developing new psychosocial treatments for cocaine dependence, psychotherapy alone does not provide substantial benefit for many patients [3-5].

Thus, medications have been sought to augment psychosocial treatment. Although there are currently no medications approved for the treatment of cocaine dependence either in Europe or in the US, progress in the understanding of the neurobiology of cocaine dependence has led to the discovery of several promising medications that have already shown encouraging results in controlled clinical trials and newer medications are becoming available.

ABSTINENCE INITIATION

In the treatment of addictions there are two goals for medications, first to help patients attain an initial period of abstinence, and then to assist patients avoid relapse. Medications for cocaine dependence are being developed to achieve both of these goals.

Among the most promising medications for abstinence initiation is modafinil. Modafinil is a medication approved for the treatment of narcolepsy. It may be useful for abstinence initiation in cocaine dependent patients by several mechanisms of action, including, reduction of cocaine withdrawal symptoms, reduction in cocaine craving, or a reduction in cocaine-induced euphoria. As a mild stimulant, modafinil may be able to reduce cocaine withdrawal symptoms [6]. Modafinil enhances glutamate-neurotransmission [7]. It may therefore be efficacious for cocaine dependence by ameliorating glutamate

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depletion seen in chronic cocaine users [6]. Improved baseline glutamatergic tone in the nucleus accumbens prevents reinstatement of cocaine self-administration in an animal model of relapse [8].

Modafinil was found to block the euphoric effects of cocaine in three independent human laboratory studies [9-11]. First, Dackis *et al.* conducted a double-blind, placebo-controlled cocaine / modafinil interaction trial. In this trial, cocaine dependent patients were placed on modafinil 200 mg, 400 mg, or placebo and then challenged with 30 mg of IV cocaine. Pretreatment with modafinil significantly blunted cocaine induced euphoria in one of the subjective measures [10]. In a separate, but very similar, human laboratory trial, Malcolm and colleagues found that modafinil at both 400 and 800 mg significantly reduced visual analogue scale ratings of "high", "any drug effect", and "worth in dollars" compared to cocaine alone [9]. Most recently, hart and colleagues evaluated the effect of modafinil on the self-administration of cocaine in a human laboratory trial. In this trial, the effects of modafinil maintenance (0, 200, and 400 mg/day) on response to smoked cocaine (0, 12, 25, and 50 mg) were examined in nontreatment-seeking cocaine-dependent individuals (n = 8). Cocaine significantly increased self-administration, subjective-effect ratings, and cardiovascular measures; modafinil at both doses (200 and 400 mg/day) markedly attenuated these effects [11].

A double blind, placebo-controlled pilot trial of modafinil involving 62 cocaine dependent patients was completed in 2004. In this trial, modafinil-treated patients submitted significantly more cocaine metabolite-free urine samples compared to placebo-treated patients (42% *vs* 22%). Modafinil-treated patients were also rated as more improved compared to placebo-treated patients [12].

The results of the pilot trial were recently replicated in a larger multicenter trial involving 210 cocaine dependent patients. In this 16-week trial, cocaine dependent patients were treated with modafinil 200 mg daily, modafinil 400 mg daily, or placebo. In contrast to the pilot trial, in which none of the patients were both cocaine and alcohol dependent, in this trial 41% of the patients were both alcohol and cocaine dependent. In the group as a whole, modafinil was not superior to placebo in promoting abstinence from cocaine. However, among patients who were not also alcohol dependent, both doses of modafinil were superior to placebo for promoting abstinence from cocaine [13]. In cocaine dependent patients without alcohol dependence, two clinical trials have shown modafinil to be efficacious. There are two more large-scale double-blind, placebo-controlled clinical trials of modafinil ongoing at this time.

RELAPSE PREVENTION

After patients have attained a period of abstinence, then the more difficult phase of treatment begins, relapse prevention. Examples of pharmacological strategies for cocaine relapse prevention include blocking cocaine-induced euphoria or reducing cocaine craving. New insights into the effects of cocaine on the brain reward system have resulted in several promising relapse prevention medications.

The mesocortical dopamine system plays a central role in the reinforcing effects of cocaine [14-17]. Mesocortical dopaminergic neurons receive modulatory inputs from both GABergic and glutaminergic neurons. GABA is primarily an inhibitory neurotransmitter in the central nervous system, and activation of GABAergic neurons tends to decrease activation in the dopaminergic reward system. Preclinical trials of medications that foster GABAergic neurotransmission have suggested that these compounds reduce the dopamine response to both cocaine administration and to conditioned reminders of prior cocaine use [18-20]. GABAergic medications also reduce the self-administration of cocaine in animal models [21, 22]. Therefore, GABAergic medications could prevent relapse either by blocking cocaine-induced euphoria or by reducing craving caused by exposure to conditioned reminders of prior cocaine use. Some promising GABAergic medications include, gamma-vinyl GABA (GVG), tiagabine and topiramate.

GVG is an antiepileptic that has been in use in many countries throughout the world for a number of years. It is an irreversible inhibitor of GABA transaminase and thus elevates brain GABA concentrations. Preclinical trials of GVG have been promising. GVG has been shown to block cocaine and cocaine cue induced increases in nucleus accumbens dopamine [19, 23]. GVG has been shown to block cocaine self-administration in rodents [22].

There have been two clinical trials of GVG for the treatment of stimulant dependence. They were both small open-label trial involving 20 and 30 patients respectively, with either cocaine or amphetamine dependence [24, 25]. In these trials, treatment completers showed significant reductions in drug use. In the first trial 8 of 20 patients completed the trial and reported drug free periods ranging from 46-58 days. In the second trial, 18 subjects completed the trial. Out of the these 18 subjects, 16 submitted drug tests negative for amphetamine and cocaine for the last 6 weeks of the trial. GVG has not been approved for use in the USA due to an associa-

tion between the use of GVG and visual field defects. Data suggest that visual field defects associated with GVG occur after relatively long term exposure and brief treatments may be safely conducted [26]. In addition, perimetry was conducted in the second clinical trial of GVG for methamphetamine and cocaine dependence and the data showed no visual field defects as a result of this short-term exposure [27]. Large-scale, well-controlled trials of GVG for cocaine dependence are planne Tiagabine is another GABAergic medication that may be promising for the treatment of cocaine dependence. Tiagabine is a selective blocker of the presynaptic GABA reuptake transporter type 1,and it is currently approved for the treatment of seizures [28]. Tiagabine was found to be well tolerated and moderately effective for improving abstinence in a pilot study that included 45 cocaine and opiate dependent patients participating in a methadone maintenance program. In this 10-week trial, the number of cocaine metabolite free urine samples increased by 33% in the group treated with tiagabine 24 mg daily, and decreased by 14% in the placebo treated group [29]. In a more recent trial, Gonzalez compared tiagabine to gabapentin and placebo in 76 cocaine and opiate dependent patients maintained on methadone. In this trial, tiagabine at 24 mg daily was superior to both placebo and gabapentin in promoting cocaine abstinence [30]. However, Winhusen and colleagues failed to find tiagabine (20 mg daily) to be superior to placebo in 79 cocaine dependent patients in a 12 week double-blind, placebo-controlled trial [31].

Topiramate may be an excellent medication for relapse prevention based on its effects on both GABA neurotransmission and glutamate neurotransmission. Topiramate increases cerebral levels of GABA, and facilitates GABA neurotransmission [32, 33]. Topiramate also inhibits glutamate neurotransmission through a blockade of AMPA/kainate receptors [34]. In animal models of cocaine relapse, blockade of AMPA receptors in the nucleus accumbens prevented reinstatement of cocaine self-administration [35].

In a 13-week, double-blind, placebo-controlled pilot trial of topiramate for cocaine dependence involving 40 cocaine dependent patients, topiramate-treated patients were significantly more likely to be abstinent during the last 5 weeks of the trial compared to placebo-treated patients [36]. In addition, among patients who returned for at least one visit after receiving medications, topiramate-treated patients were significantly more likely to achieve at least 3 weeks of continuous abstinence from cocaine compared to placebo-treated patients (59% *vs* 26%), and topiramate-treated patients were significantly more likely than placebo-treated patients to be rated very much improved at their last visit (71% *vs* 32%) [36].

Disulfiram is a promising cocaine relapse prevention medication with a unique mechanism of action. Disulfiram (Antabuse) is an established medicine used for the treatment of alcohol dependence. It causes a characteristic unpleasant reaction when alcohol is ingested due to blockade of the enzyme aldehyde dehydrogenase and the subsequent build-up of acetaldehyde.

In addition to its effects on alcohol metabolism, disulfiram also blocks the enzymatic degradation of cocaine and dopamine and leads to extremely high cocaine and dopamine levels when cocaine is ingested [37, 38]. This does not increase the cocaine induced high, as one might expect, but rather it makes the high less pleasant by increasing the associated anxiety [37, 39]. There are now four published trials showing that disulfiram reduces cocaine use in cocaine dependent patients [4, 40-42]. More recently, the combination of disulfiram and naltrexone was found to be better than placebo in promoting sustained abstinence from both cocaine and alcohol in patients with dual cocaine and alcohol dependence [43].

The last of the promising relapse prevention therapies is a vaccine capable of stimulating the production of cocaine-specific antibodies. The vaccine (TA-CD) works by stimulating the production of cocaine-specific antibodies that bind to cocaine molecules and prevent them from crossing the blood-brain barrier. Since cocaine is inhibited from entering the brain, its euphoric and reinforcing effects are reduced. Animal trials of TA-CD have shown that the vaccine produces cocaine specific antibodies and decreases self-administration of cocaine in rodents [44].

Human trials of TA-CD have been promising. Outcome data from two early human trials suggested that the vaccine was well tolerated, capable of stimulating high antibody titers, and it reduced the euphoric effects of cocaine [45, 46]. In a double-blind, placebo-controlled trial conducted in 114 cocaine and opiate dependent patients maintained on methadone, patients treated with the vaccine were significantly more likely to achieve abstinence from cocaine in the first 10 weeks of treatment [47].

NEWER MEDICATIONS FOR COCAINE DEPENDENCE NOT YET INCLUDED IN CONTROLLED CLINICAL TRIALS

There are several new compounds that have been identified in preclinical trials as potentially useful for the treatment of cocaine dependence but have not yet been studied in controlled clinical trials. These medications include neurokinin

1 receptor antagonists, dopamine D3 receptor antagonists and n-acetylcysteine. These medications are potential relapse prevention medications that may reduce cocaine induced euphoria, craving for cocaine, or relapse to cocaine caused by stress.

NK1 receptor (NK1R) antagonists, such as aprepitant, may be useful for the treatment of cocaine dependence. Substance P is a neuropeptide that has been implicated in the response to stress, as well as reward-related behaviors. Substance P and its preferred receptor, NK1R are highly expressed in brain areas involved in stress response and drug reward such as the hypothalamus, amygdala, and nucleus accumbens [48]. Blockade of central NK1R results in antidepressant-related and anxiolytic-like activity in several animal models [49]. NK1R antagonists have been shown to reduce symptoms of social anxiety [50] and the NK1R antagonist MK-869 was shown to be superior to placebo in the treatment of major depression [51]. That the NK1R is involved in drug reward is first suggested by the fact that genetically altered mice without NK1R showed reduced alcohol consumption compared to wild type controls [52]. NK1R antagonists also reduce striatal dopamine release provoked by cocaine administration [53]. Finally activation of central NK1R induces reinstatement of cocaine seeking behavior [54].

The evidence supporting a direct effect of NK1R antagonists on cocaine reward is mixed. There is at least one trial in which the NK1R antagonist WIN51708 blocked the acquisition of sensitization to repeated doses of cocaine [55]. However, in a series of other trials, NK1R antagonists did not block cocaine induced increases in locomotor activity, cocaine self-administration, or cocaine-induced reinstatement of drug seeking behavior [54, 56]. In addition, in mice with a genetic deletion of NK1R, neither the locomotor activating effects of cocaine were altered, nor was sensitization altered [57].

Although NK1R antagonists may not have a significant impact on cocaine reward, their effects on stress reduction may make them useful in preventing relapse, primarily through reductions in stress-induced craving and relapse. Stress has been shown to be a powerful inducer of cocaine craving and relapse. In human laboratory trials, stress has been shown to provoke cocaine craving, and patients who exhibited more stress-induced craving and had greater corticotropin and cortisol response to stress relapsed sooner in a 90-day period after discharge from inpatient treatment [58]. In clinical trials it has been shown that patients who exhibit more cocaine withdrawal symptoms have worse outcomes in outpatient treatment compared to cocaine dependent patients without cocaine withdrawal symptoms [59, 60]. Thus, NK1R antagonists may be useful in reducing stress induced craving and relapse in cocaine dependent patients.

Dopamine is, of course, central to the reinforcing effects of all drugs of abuse, including alcohol and cocaine. Among the first medications considered for the treatment of cocaine dependence were dopamine antagonists. There are two main groups of dopamine receptors, the D1-D5 family and the D2-D3 family. Several representatives of antagonists to both groups of dopamine receptors have been evaluated for cocaine dependence treatment and have not been found to be efficacious. D1 receptor antagonists such as ecopipam were simply ineffective. D2 antagonists, although sometimes effective at reducing either cocaine or cue induced craving in human laboratory studies, either had intolerable side effects or simply were not effective in clinical trials [61-65].

Dopamine D3 receptor (D3R) antagonists may be different. The high concentration of D3R in limbic structures suggests that these receptors may be most important in drug reward and addiction [66]. D3R have the highest affinity of all dopamine receptors for exogenous dopamine, again suggesting a predominant role for these receptors in reward and addiction [67, 68]. The net effect of D3 antagonism is a slight increase in dopaminergic tone, which may be useful in chronic cocaine users who generally have decreased dopaminergic tone [66]. Thus D3R antagonism may be a better strategy than D1 or D2 receptor blockade for the treatment of cocaine dependence.

The preclinical trials with D3R antagonists predict clinical usefulness. In almost every animal model of addiction, D3R antagonists appear to be useful for the treatment of cocaine dependence. First, the D3R antagonist SB277011 blocked both the acquisition and expression of cocaine induced conditioned place preference [69]. D3R antagonists also reduced cocaine-induced reinstatement of self-administration as well as conditioned cue induced reinstatement of cocaine self-administration [69, 70]. D3R antagonists lowered the breakpoint in progressive ratio self-administration models [71]. Finally D3R antagonists reduced stress-induced reinstatement of cocaine self-administration [72]. Clinical trials with D3R antagonists are currently being planned.

The last of the promising medications ready for controlled clinical trials is n-acetylcysteine. N-acetylcysteine (NAC) is an amino acid and a cysteine prodrug. Preclinical, and some early pilot clinical trials have suggested that it may be an effective medication for the treatment of addictive disorders. Preclinical studies have suggested that levels of glutamate in the nucleus accumbens mediate reward-seeking behavior [73, 74]. Low

levels of extracellular glutamate in the nucleus accumbens are associated with chronic cocaine exposure. Through stimulation of the cysteine-glutamate antiporters, NAC may increase extracellular glutamate. This in turn modulates the release of glutamate in response to drug taking via stimulation of metabotropic glutamate autoreceptors. This reduction in glutamate release may block drug seeking behaviors and drug craving. In rats, NAC pretreatment blocked the reinstatement of drug seeking behavior induced by cocaine or conditioned cues of cocaine [75]. In a human laboratory trial, NAC reduced cocaine craving in non-treatment seeking cocaine dependent men and women [76]. In an open-label trial, NAC was found to be safe and well tolerated in cocaine dependent patients [77].

CONCLUSIONS

Currently, there are no medications that are FDA approved for the treatment of stimulant dependence. However, recent advances in the understanding of the processes involved in cocaine addiction have allowed researchers to identify several promising new candidate medications. Many of these have already shown promise in double blind, placebo-controlled clinical trials and there are newer medications that are just now becoming available for clinical trials. It seems highly likely that in the near future there will be effective pharmacological treatments for cocaine dependence.

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