by KYLE M. KAMPMAN, MD

Dr. Kampman is Associate Professor at the Department of Psychiatry, University of Pennsylvania School of Medicine; and the Medical Director, University of Pennsylvania Treatment Research Center, Philadelphia, Pennsylvania.

New Medications for the Treatment of Cocaine Dependence

ABSTRACT

Cocaine dependence continues to be a significant public health problem in the United States. Although some cocaine-dependent patients will respond well to drug counseling, for many, standard psychosocial treatment is inadequate. Therefore, the development of an effective medication for the treatment of cocaine dependence is a research priority. However, despite many years of research, no medication has emerged as consistently effective for the treatment of cocaine dependence. 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. Among more severely addicted patients, propranolol 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 GABAergic medications, such as baclofen, tiagabine, and topiramate, and the glutamatergic medication, modafinil. Surprisingly, an old treatment for alcohol dependence, disulfiram, may also have efficacy for cocaine relapse prevention. 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.

ADDRESS CORRESPONDENCE TO:
Kyle M. Kampman MD, Medical Director, University of Pennsylvania Treatment Research Center
3900 Chestnut Street, Philadelphia, PA 19104
Phone: (215) 222 3200 x109; Fax: (215) 386 6770; E-mail: kampman_k@mail.trc.upenn.edu

INTRODUCTION

Developing new medications for the treatment of cocaine dependence continues to be a research priority in the United States for the simple reason that, despite many years of effort, we still do not have a truly effective treatment for this very serious disease. Although progress has been made in developing new psychosocial treatments for cocaine dependence, for many patients, psychotherapy alone does not provide substantial benefit.[1–3] Thus, medications have been sought to augment psychosocial treatment. Despite many years of research, no medication has emerged as consistently effective.[4] However, 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.

COCAINE WITHDRAWAL AND ABSTINENCE INITIATION

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

The presence of cocaine withdrawal symptoms may make it difficult for cocaine users to attain a period of initial abstinence. Cocaine withdrawal symptoms include dysphoric mood, fatigue, sleep disturbance, appetite changes, and irritability. In several studies, it has been demonstrated that patients who enter treatment with severe cocaine withdrawal symptoms are more likely to drop out of treatment prematurely and are less likely to attain abstinence from cocaine in outpatient treatment programs.[2,5–7] Poor treatment outcomes may be due to the fact that cocaine-dependent patients who have cocaine withdrawal symptoms experience cocaine differently. Several investigators have noted that cocaine-dependent patients who experience cocaine withdrawal symptoms report a greater high from experimentally administered cocaine.[8–10] The increased euphoria experienced by patients with cocaine withdrawal syndrome may make it more difficult for them to give up cocaine.

Propranolol. The beta-blocker, propranolol, appears to be promising for the treatment of patients who present for treatment with severe cocaine withdrawal symptoms. Beta blockers are primarily used to treat angina and hypertension, though they are often used to control anxiety and agitation.[11,12] During cocaine withdrawal, patients are sensitive to the effects of adrenalin and noradrenalin, and this may contribute to the anxiety and restlessness they feel.[13] As a beta-blocker, propranolol may be able to reduce the anxiety associated with cocaine withdrawal as well as reduce some of the more uncomfortable symptoms of cocaine craving. Beta-blockers may also be able to reduce some of the rewarding properties of cocaine. In a human laboratory trial, the beta blocker carvedilol reduced cocaine self-administration in nontreatment-seeking, cocaine-dependent subjects.[14]

There have been three clinical trials conducted with propranolol for the treatment of cocaine dependence. First, in an open pilot trial,[15] propranolol was shown to be safe and well tolerated by cocaine-dependent patients. In addition, propranolol-treated subjects were more likely to be retained in a seven-week outpatient treatment program compared to a historical control group (80% vs. 47%, respectively).[15] In a subsequent double-blind, placebo-controlled trial involving 108 cocaine dependent subjects,[16] propranolol improved treatment retention and decreased cocaine use among subjects who entered treatment with severe cocaine withdrawal symptoms. Most recently, propranolol appeared to promote periods of extended abstinence from cocaine in a trial of 199 severely addicted cocaine-dependent subjects who entered treatment with severe cocaine withdrawal symptoms.[17] Thus, beta-blockers, like propranolol, may be effective in assisting more severely addicted cocaine-dependent subjects attain a period of initial abstinence.

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.[18–21] 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.[22–24] GABAergic medications also reduce the self-administration of cocaine in animal models.[25,26] So, 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 baclofen, tiagabine, and topiramate.

Baclofen. Baclofen is GABA B agonist used as a muscle relaxant. As a GABA agonist, baclofen may reduce the amount of dopamine released into the nucleus accumbens as a result of cocaine stimulation or cocaine craving.

In a human laboratory study, baclofen decreased the craving response provoked by exposure to conditioned reminders (cues) of prior cocaine use.[27] In addition, baclofen has been shown to blunt the characteristic pattern of brain activation associated with cocaine cue-induced craving.[28]

Clinical trial data with baclofen have also been promising. In a 16-week, double-blind, placebo-controlled, pilot trial, baclofen significantly improved the probability of submitting a cocaine metabolite-free urine sample among baclofen-treated subjects compared to placebo-treated subjects.[29] Baclofen appeared to be particularly useful among subjects who continued to use cocaine during a two-week baseline phase prior to starting medications.[29]

Tiagabine. 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.[30] 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 percent in the group treated with tiagabine 24mg daily and decreased by 14 percent in the placebo-treated group.[31]

Topiramate. 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 subjects, topiramate-treated subjects were significantly more likely to be abstinent during the last five weeks of the trial compared to placebo-treated subjects.[36] In addition, among subjects who returned for at least one visit after receiving medications, topiramate-treated subjects were significantly more likely to achieve at least three weeks of continuous abstinence from cocaine compared to placebo-treated subjects (59% vs. 26%), and topiramate-treated subjects were significantly more likely than placebo-treated subjects to be rated very much improved at their last visit (71% vs. 32%).[36]

Disulfiram. Disulfiram is a promising cocaine relapse prevention medication. Disulfiram is an established medicine used for the treatment of alcohol dependence. It causes a characteristic unpleasant

In the treatment of addictions there are two goals for medications: To help patients attain an initial period of abstinence and to assist patients avoid relapse.

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.[40–43]

Modafinil. Modafinil is a medication approved for the treatment of narcolepsy. It enhances glutamate-neurotransmission.[44] Modafinil may be efficacious for cocaine dependence by ameliorating glutamate depletion seen in chronic cocaine users.[45] Improved baseline glutamatergic tone in the nucleus accumbens prevents reinstatement of cocaine self-administration in an animal model of relapse.[46] In addition, modafinil was found to block the euphoric effects of cocaine in two independent human laboratory studies.[47,48] Thus, modafinil may be effective for relapse prevention due several mechanisms of action.

A double-blind, placebo-controlled trial of modafinil involving 62 cocaine dependent subjects was recently completed. Modafinil-treated subjects submitted significantly more cocaine metabolite-free urine samples compared to placebo-treated subjects (42% vs. 22%). Modafinil-treated subjects were also rated as more improved compared to placebo-treated subjects.[49]

TA-CD. The last of the promising relapse prevention therapies to be discussed is not a medicine, but 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.[50]

Human trials of TA-CD have been promising. In one of the first human trials of the vaccine, TA-CD was given to 34 cocaine-dependent subjects on an inpatient treatment unit. In that trial, a series of three vaccinations resulted in high antibody titers and the vaccine was well tolerated.[51] More recently, two different doses of TA-CD were tested in cocaine dependent subjects participating in a 12-week outpatient treatment program. Preliminary outcome data from that trial suggested that the vaccine reduced the euphoric effects of cocaine and the higher dose was associated with more cocaine abstinence compared to the lower dose.[52]

CONCLUSION

Currently, there are no medications that are FDA approved for the treatment of cocaine 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 virtually all of them are undergoing confirmatory testing in one or more trials. It seems highly likely that in the near future there will be effective pharmacological treatments for cocaine dependence.

REFERENCES

1. Caroll K. Behavioral therapies for co-occurring substance use and mood disorders. *Biol Psychiatry* 2004;56:778–84.
2. Kampman KM, Alterman AI, Volpicelli JR, et al. Cocaine withdrawal symptoms and initial urine toxicology results predict treatment attrition in outpatient cocaine dependence treatment. *Psychology Addict Behav* 2001;15:52–9.
3. Alterman A, McKay J, Mulvaney F, McLellan A. Prediction of attrition from day hospital treatment in lower socioeconomic cocaine-dependent men. *Drug Alcohol Depend* 1996;40:227–33.
4. Vocci F, Ling W. Medications development: Successes and challenges. *Pharmacol Ther* 2005; In press.
5. Kampman KM, Volpicelli JR, McGinnis DE, et al. Reliability and validity of the cocaine selective severity assessment. *Addict Behav* 1998;23:49–61.
6. Mulvaney FD, Alterman AI, Boardman CR, Kampman K. Cocaine abstinence symptomatology and treatment attrition. *J Subst Abuse Treat* 1999;16:129–35.
7. Kampman KM, Volpicelli JR, Mulvaney FD, et al. Cocaine withdrawal severity and urine toxicology results from treatment entry predict outcome in medication trials for cocaine dependence. *Addict Behav* 2002;27:251–60.
8. Uslaner J, Kalechstein, A, Richter T, et al. Association of depressive symptoms during abstinence with the subjective high produced by cocaine. *Am J Psychiatry* 1999;156:1444–46.
9. Newton T, Kalechstein A, Tervo K, Ling W. Irritability following abstinence from cocaine predicts euphoric effects of cocaine administration. *Addict Behav* 2003;28:817–21.
10. Sofuoglu M, Dudish-Poulsen S, Brown S, Hatsukami D. Association of cocaine withdrawal symptoms with more severe dependence and enhanced subjective response to cocaine. *Drug Alcohol Depend* 2003;69:273–82.
11. Kathol R, Noyes R, Slymen D, et al. Propranolol in chronic anxiety disorders. *Arch Gen Psychiatry* 1980;37:1361–5.
12. Liebowitz M, Gorman J, Fryer A, et al. Pharmacotherapy of social phobia: An interim report of a placebo-controlled comparison of phenelzine and atenolol. *J Clin Psychiatry* 1988;49:252–7.
13. McDougle C, Black J, Malison R, et al. Noradrenergic dysregulation during discontinuation of cocaine use in addicts. *Arch Gen Psychiatry* 1994;51:713–9.
14. Sofuoglu M, Brown S, Babb D, et al. Carvedilol affects the physiological and

behavioral response to smoked cocaine in humans. *Drug Alcohol Depend* 2000;60:69–76.
15. Kampman KM, Rukstalis M, Ehrman R, et al. Open trials as a method of prioritizing medications for inclusion in controlled trials for cocaine dependence. *Addict Behav* 1999;24:287–91.
16. Kampman KM, Volpicelli JR, Mulvaney FD, et al. Effectiveness of propranolol for cocaine dependence may depend on cocaine withdrawal symptom severity. *Drug Alcohol Depend* 2001;63:69–78.
17. Kampman K. The combination of amantidine and propranolol for the treatment of cocaine-dependent patients with severe cocaine withdrawal symptoms. Orlando, FL: The College on Problems of Drug Dependence Annual Meeting, 2005.
18. Dworkin SI, Smith JE. Neurobehavioral pharmacology of cocaine. In: Clouet D, Ashgar K, Brown R, eds. *Mechanisms of Cocaine Abuse and Toxicity.* National Institute on Drug Abuse Research Monograph #88. Washington, DC: US Government Printing Office, 1988:185–98.
19. Goeders NE, Dworkin SI, Smith JE. Neuropharmacological assessment of cocaine self-administration into the medial prefrontal cortex. *Pharmacol Biochem Behav* 1986;24:1429–40.
20. Koob G, Vaccarino F, Amalric M, Bloom F. Positive reinforcement properties of drugs: search for neural substrates. In: Engel J, Oreland L (eds). *Brain Reward Systems and Abuse.* New York, NY: Raven Press, 1987:35–50.
21. Roberts DCS, Koob GF, Klonoff P, Figiber HC. Extinction and recovery of cocaine self-administration following 6-hydroxydopamine lesions of the nucleus accumbens. *Pharmacol Biochem Behav* 1980;12:781–7.
22. Dewey SL, Chaurasia CS, Chen C, et al. GABAergic attenuation of cocaine-induced dopamine release and locomoter activity. *Synapse* 1997;25:393–8.
23. Dewey S, Smith G, Logan J, et al. GABAergic inhibition of endogenous dopamine release measured in vivo with 11c- raclopride and positron emission tomography. *J Neurosci* 1992;12:3773–80.
24. Gerasimov MR, Ashby CR, Gardner EL, et al. Gamma-vinyl-GABA inhibits methamphetamine, heroin, or ethanol-induced increases in nucleus accumbens dopamine. *Synapse* 1999;34:11–9.
25. Kushner SA, Dewey SL, Kornetsky C. The irreversible g -aminobutyric acid (GABA) transaminase inhibitor g -vinyl-GABA blocks cocaine self-administration in rats. *J Pharmacol Exp Ther* 1999;290:797–802.
26. Roberts DC, Andrews MM, Vickers GJ. Baclofen attenuates the reinforcing effects of cocaine in rats. *Neuropsychopharmacology* 1996;15:417–23.
27. Childress AR, Mozley PD, McElgin W, et al. Limbic activation during cue-induced craving. *Am J Psychiatry* 1999;156:11–8.
28. Childress AR. A stone unturned: The promise of GABAergic modulation in cocaine dependence treatment. In: Harris L (ed). *Problems of Drug Dependence 1999: Proceedings of the 61st Annual Scientific Meeting.* The College on Problems of Drug Dependence. NIDA Research Monograph 180. Washington DC: US Government Printing Office, 2000.
29. Shoptaw S. Outcomes when using the GABA-B agonist baclofen in human cocaine users. In: Harris L (ed). *Problems of Drug Dependence 1999: Proceedings of the 61st Annual Scientific Meeting.* The College on Problems of Drug Dependence. NIDA Research Monograph 180. Washington DC: US Government Printing Office, 2000.
30. Schachter S. Tiagabine. *Epilepsia* 1999;40:S17–S22.
31. Gonzalez G, Sevarino K, Sofuoglu M, et al. Tiagabine increases cocaine-free urines in cocaine-dependent methadone treated patients: Results of a randomized pilot study. *Addiction* 2003;98:1625–32.
32. Kuzniecky R, Hetherington H, Ho S, et al. Topiramate increases cerebral GABA in healthy humans. *Neurology* 1998;51:627–9.
33. Petroff OA, Hyder F, Mattson RH, Rothman DL. Topiramate increases brain GABA, homocarnasine, and pyrrolidinone in patients with epilepsy. *Neurology* 1999;52:473–8.
34. Gibbs J, Sombati S, DeLorenzo R, Coulter D. Cellular actions of topiramate: blockade of kainate-evoked inward currents in cultured hippocampal neurons. *Epilepsia* 2000;Suppl 1.
35. Cornish JL, Kalivas PW. Glutamate transmission in the nucleus accumbens mediates relapse in cocaine addiction. *J of Neurosci* 2000;20:1–5.
36. Kampman KM, Pettinati H, Lynch K, et al. A pilot trial of topiramate for the treatment of cocaine dependence. *Drug Alcohol Depend* 2004;75:233–40.
37. McCance-Katz E, Kosten T, Jatlow P. Disulfiram effects on acute cocaine administration. *Drug Alcohol Depend* 1998;52:27–39.
38. Karamanakos P, Pappas P, Stephanou P, Marselos M. Differentiation of disulfiram effects on central catecholamines and hepatic ethanol metabolism. *Pharmacol Toxicol* 2001;88:106–10.
39. Hameedi F, Rosen M, McCance-Katz E, et al. Behavioral, physiological, and pharmacological interaction of cocaine and disulfiram in humans. *Biol Psychiatry* 1995;37:560–3.
40. Caroll K, Nich C, Ball S, McCance E, Rounsaville B. Treatment of cocaine and alcohol dependence with psychotherapy and disulfiram. *Addiction* 1998;93:713–27.
41. Petrakis I, Caroll K, Nich C, et al. Disulfiram treatment for cocaine dependence in methadone-maintained opioid addicts. *Addiction* 2000;95:219–28.
42. George T, Chawarski M, Pakes J, et al. Disulfiram versus placebo for cocaine dependence in buprenorphine-maintained subjects: A preliminary trial. *Biol Psychiatry* 2000;47:1080–6.
43. Caroll K, Fenton L, Ball S, et al. Efficacy of disulfiram and cognitive behavioral therapy in cocaine dependent outpatients: A randomized placebo-controlled trial. *Arch Gen Psychiatry* 2004;61:264–72.
44. Touret M, Sallanon-Moulin M, Fages C, et al. Effects of modafinil-induced wakefulness on glutamine synthetase regulation in the rat brain. *Brain Res Mol Brain Res* 1994;26:123–8.
45. Dackis C, O'Brien CP. Glutamatergic agents for cocaine dependence. *Ann NY Acad Sci* 2003;1003:328–45.
46. Baker D, McFarland K, Lake R, et al. N-acetyl cysteine-induced blockade of cocaine-induced reinstatement. *Ann NY Acad Sci* 2003;1003:349–51.
47. Malcolm R, Donovan C, Devane A, et al. Influence of modafinil, 400- or 800mg/day on subjective effects of intravenous cocaine in nontreatment seeking volunteers. *Drug Alcohol Depend* 2002;66:S110.
48. Dackis CA, Lynch KG, Yu,E, et al. Modafinil and cocaine: A double-blind, placebo-controlled drug interaction study. *Drug Alcohol Depend* 2003;70:29–37.
49. Dackis C, Kampman K, Lynch K, et al. A double-blind, placebo-controlled trial of modafinil for cocaine dependence. *Neuropsychopharmacology* 2005;30:205–11.
50. Kantak KM CS, Lipman EG, Bond J, et al. Evaluation of anti-cocaine antibodies and a cocaine vaccine in a rat self-administration model. *Psychopharmacology* [Berl] 2000;148:251–62.
51. Kosten T, Rosen M, Bond J, et al. Human therapeutic cocaine vaccine: Safety and immunogenicity. *Vaccine* 2002;20:1196–1204.
52. Martell B, Mitchell E, Poling J, et al. Vaccine pharmacotherapy for the treatment of cocaine dependence. *Biol Psychiatry* 2005;58:158–64.

DRUG TRADE NAME KEY

BACLOFEN
(Lioresal®, Novartis)

DISULFIRAM
(Antabuse®, Odyssey Pharmaceuticals, Inc.)

MODAFINIL
(Provigil®, Cephelon)

PROPRANOLOL
(Inderal®, AstraZeneca)

TA-CD
(cocaine vaccine, Xenova Group)

TOPIRAMATE
(Topamax®, Ortho-McNeil Pharmaceutical)