ADDICTIVE DISORDERS & THEIR TREATMENT

Volume 18, Number 2
June 2019

Is Trazodone Contramid Useful in Inducing Patients to Refrain From Using Cocaine After Detoxification, so Avoiding Early Relapse? A Case Series

Icro Maremmani, MD,†‡ Vincenza Spera, MD,§ Angelo G.I. Maremmani, MD,†‡‖ Marco Carli, MD,¶ and Marco Scarselli, MD¶*

Abstract

Objectives:
So far, no specific medication has been approved by international drug regulatory agencies for the treatment of cocaine use disorder (CoUD). The reward deficiency syndrome (dysphoric-depressive) was originally described as an outcome after detoxification; it is now considered to be one of the possible routes to relapsing behavior.

Materials and Methods:
We describe the case of 9 consecutive patients affected by mono CoUD. They voluntarily stopped cocaine use for almost 2 weeks, after daily use for almost 2 months, entering into a dysphoric-depressive syndrome and experiencing a high level of craving for cocaine. All patients received trazodone contramid once a day, at bedtime, at an initial dose of 150 mg the first week, upgraded to 300 mg starting with the second week of treatment; they were followed up for 6 months.

Results:
Only 1 patient failed to complete 6-month follow-up, relapsing many times into cocaine use during the observational period. Another patient completed the follow-up while improving his psychiatric symptoms but relapsing 3 times into cocaine use. In total, 7/9 patients (77.8%) improved their psychiatric symptoms and, 6 months after starting therapy, remained cocaine-detoxified.

Conclusions:
The present case series shows that trittico contramid is probably able to positively modify psychopathologic symptomatology and cocaine craving in CoUD patients who voluntarily stopped cocaine use but were at high risk of early relapse. The current need is for controlled clinical trials to confirm the safety and efficacy of trittico contramid in avoiding early relapse in cocaine self-detoxified patients.

Key Words: trittico contramid, cocaine use disorder (CoUD), reward deficit syndrome, avoiding relapse

(*Addict Disord Their Treatment* 2019;18:105–112)

To date, no specific medication has been approved by international drug regulatory agencies for the treatment of cocaine use disorder (CoUD). So far, only 4 therapeutic strategies are available for the pharmacological treatment of substance use disorder patients.

The first strategy comprises maintenance (long-term) treatments using long-acting agonist-replacement therapies that mimic the drug of abuse (cross-tolerant). This kind of approach is feasible when agonist drugs are neither toxic nor addictive, either in the short or the long term. The property of normalizing the abnormalities produced by chronic intoxication may provide further advantages. This strategy is followed in the agonist-maintenance treatment for heroin addiction (agonist opioid treatment). The second strategy moves in the opposite direction; it includes maintenance therapy based on substances that block the effects of the abused substances (antagonists). This strategy is used against substances that act mainly by affecting one single receptor system. No craving control is provided. If baseline craving is low, this strategy may be effective, as the lack of reinforcement may gradually detach the individual from the substance. The foremost example is naltrexone when used for the treatment of heroin addiction. The third strategy consists of maintenance therapies with drugs that have some anticraving properties but do not produce cross-tolerance. These options are currently available for the treatment of alcohol and cocaine abuse (eg, dopaminergic agents). The fourth strategy involves the use of medications that interfere with the metabolism of the used substance. Its rejection may be favored, or its effects

From the *Vincent P. Dole Dual Disorder Unit, Department of Specialty Medicine, Santa Chiara University Hospital; §School of Psychiatry; ¶Department of Translational Research and New Technologies, University of Pisa; ‡G. De Lisio Institute of Behavioral Sciences, Pisa; †Association for the Application of Neuroscientific Knowledge to Social Aims (AU-CNS), Pietrasanta, Lucca; ‖Department of Psychiatry, North-Western Tuscany Region, NHS Local Health Unit, Versilia Zone, Viareggio, Italy, EU.

I.M. served as Board Member for Indivior, Molteni, Mundipharma, D&A Pharma, and Lundbeck. The remaining authors declare no conflict of interest.

Reprints: Icro Maremmani, MD, Vincent P. Dole Dual Disorder Unit, Department of Specialty Medicine, Santa Chiara University Hospital, University of Pisa, Via Roma, 67 56100 Pisa, Italy, EU (e-mail: icro.maremmani@med.unipi.it).

DOI: 10.1097/ADT.0000000000000157

altered, so replacing the expected reward with unpleasant, aversive effects. Disulfiram treatment for alcoholism is the best example of this strategy.[1]

Apart from the presence of these therapeutic strategies, no medication is actually able to provide a maintenance (long-term) treatment by utilizing long-acting cocaine, including the use of agonist-replacement therapies. This approach has been successfully used in treating opiate and nicotine addiction, but not cocaine addiction. One of the major obstacles is the cocaine-like addictive potential of agonist-replacement therapies. Similarly, at the moment there is no evidence supporting the use of substances that block the effects of cocaine, such as dopamine receptor antagonists. Likewise, we have no substances that interfere with the cocaine metabolism by favoring its rejection, or altering its effects, so replacing the expected reward with unpleasant, aversive effects. A cocaine vaccine is now being developed, but its results are still not completely satisfactory.[2] In theory, options currently available for the treatment of cocaine abuse are long-term therapies with drugs that have some anticraving properties, but do not produce cross-tolerance, such as antidepressant or dopamine agonist treatment,[3,4] but there is no current evidence supporting the clinical use of antidepressants in the treatment of CoUD patients.[5] In addition, the use of psychostimulants for cocaine dependence has been extensively attempted, but their efficacy is not entirely clear, and the results have been contradictory.[6]

Neuroimaging studies have clearly mapped the metabolic changes in specific areas associated with subjective craving and drug-related cueing: the extent of metabolic changes in the orbitofrontal and anterior cingulated cortex areas is directly related to the intensity of cue-induced craving.[7–13] In contrast, neuroimaging studies on the brains of abstinent individuals with a history of chronic addictive use reveal a reduced level of baseline metabolism in the same areas.[9,13–18] Such metabolic "depression" also includes responses to normal, biologically relevant stimuli, such as food-related or sexual cues[19] and to decision-making challenges in certain experimental settings.[20,21] To sum up, chronically exposed individuals who have developed drug addiction show they are hypersensitive to drug-related stimuli, while they are less responsive to other sources of direct stimulation or cueing. Most of the changes are closely linked with the dopaminergic system. Dopamine does, in fact, play a crucial role in reward and in drug addiction, and most of the drugs of abuse strongly increase dopamine release in the ventral striatum. A variety of substances share a common tropism for the dopaminergic system involved in the dynamics of reward. Starting with an initial increase in dopamine release and pulsatility, the reward system of cocaine users is gradually hampered. In fact, in the chronic phase, cocaine-addicted individuals show a significant decrease in dopaminergic activity, especially in relation to drug-induced dopamine release. Indeed, in the striatum, both a lower level of available dopamine and a reduced number of D2 receptors have been documented in addicted individuals.[22–26]

In the light of these convergences, a common treatment principle for addictive disorders can now be proposed. This consists in resorting to prodopaminergic drugs, if possible by acting through the specific target system of the abused drug, while avoiding specific antagonists and general antidopaminergic drugs. While the former line of action should succeed in replacing damaged functions and controlling craving, the 2 latter categories tend to exacerbate craving and impede the reversal of reward deficiency and susceptibility to stress. Unfortunately, the efficacy of antidepressants, dopamine partial agonist antipsychotic agents, dopaminergic agents, such as psychostimulants, and mood stabilizers, used as anticraving therapy, even though promising, has not yet been sufficiently demonstrated.[5,27–29]

The reward deficiency syndrome (RDS) was originally described as an outcome of chronic alcohol and stimulant abuse. In part, it is linked with the a-motivational syndrome[30] displayed as an expression of chronic cannabis intoxication, but it is also closely related to the postwithdrawal syndrome, which is described by Martin and colleagues as an enduring pathologic state in abstinent detoxified opiate addicts.[31–33]

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From a withdrawal-related point of view, through each detoxification cycle the patient, in cases of cocaine acute withdrawal, experiences a later, enduring drug-free state featuring symptoms of hypophoria, looming as an acquired discomfort correlated with the absence of drug-related stimulation. Hypophoria includes somatic, vegetative (sleep), mood, and anxiety symptoms such as susceptible or irritable (depressed) mood, amplified pain perception, inability to perform simple tasks and make normal efforts, and inability to experience reward in any way other than substance use. This syndrome closely resembles the subthreshold symptoms of dysthymia and the residual symptoms of chronic bipolar disorder.[1,34] This is one of the possible routes to relapsing behavior.

Both depressive symptoms and RDS can be controlled by the administration of serotoninergic agents,[35] tricyclic antidepressants, or dopaminergic agonists.[36] However, one of the major issues raised by these medications is the possible induction of a switch by the patient from a depressive state to mania. There is, in fact, some evidence that substance use increases during manic phases, at least in dual disorder heroin use disorder/bipolar patients.[37] In contrast, the relationship between bipolar disorder and substance use disorder is well known.[38] To treat depressive symptoms and/or RDS in CoUD patients, after cocaine self-detoxification, we therefore need no-switching, sedative-antidepressant medications.

Trazodone is a second-generation antidepressant belonging to the class of serotonin receptor antagonists and reuptake inhibitors that have been approved for the treatment of major depressive disorder (MDD) since the 1970s. Trazodone's mechanism of action derives from its potentiation of serotoninergic activity in the central nervous system both through the inhibition of neuronal reuptake of serotonin, and through serotonin transporter blocking and antagonism action at 5-HT-2A/2C serotonin receptors. The antagonistic property of trazodone at 5-HT2C receptors may, in part, mediate its antidepressant effects by increasing the release of dopamine and noradrenaline in the prefrontal cortex.[39] Among other actions, Trazodone blocks α1- and α2-adrenergic receptors, H1 receptors, and has minimal anticholinergic effects. These pharmacodynamic properties help to overcome several adverse effects like sexual dysfunction, insomnia, and anxiety, which are often associated with selective serotonin reuptake inhibitors and serotonin–noradrenaline reuptake inhibitors antidepressants. Several clinical trials involving patients with MDD have proved the efficacy of trazodone when compared with tricyclic antidepressants, selective serotonin reuptake inhibitors and serotonin–noradrenaline reuptake inhibitors.[40]

There are different formulations of trazodone, including immediate-release and extended-release tablets. Trazodone contramid, which was approved by the FDA in February 2010 for MDD, is a once-daily extended-release formulation (available in 150 and 300 mg bisectable tablets) that allows trazodone to be released over 24 hours. It may be started at a dose (150 mg) that is already potentially effective as an antidepressant, and that can be titrated up to 225 mg first and to 300 mg afterward, every 3 to 4 days. Both clinical trials and clinical practice have proved trazodone's efficacy for MDD. Because of its mechanism of action, it may be particularly useful in patients with MDD and concomitant symptoms of insomnia, anxiety, irritability, or agitation. Contramid technology allows an improvement in tolerability and therapeutic compliance by avoiding the peaks and troughs in serum concentration usually seen with the immediate-release formulation, so helping patients reach target antidepressant doses while minimizing adverse events. Its sedative effect may be useful in self-detoxified hypophoric patients to avoid switching and relapse.[41] Cocaine-induced euphoria was not altered by trazodone pretreatment, although feelings of tension and shakiness after cocaine administration were lowered.[42]

MATERIALS AND METHODS

In this report, we describe the case history of 9 consecutive patients affected by CoUD according to the diagnostic criteria of the Diagnostic and statistical manual of mental disorders-5 (DSM-5);[43]

after daily use for almost 2 months, these patients voluntarily stopped their use of cocaine for almost 2 weeks, without achieving complete well-being. In particular, they continued to experience cocaine craving, sleep disturbances, depressed mood and anxiety, even if they did not meet the DSM-5 criteria for a full affective disorder or anxiety disorder. We followed up our patients for at least 6 months because no patient has reached 6-month cocaine abstinence, after previous self-detoxifications. All patients received trazodone contramid once a day, at bedtime, at an initial dose of 150 mg the first week and 300 mg starting with the second week of treatment. All patients were checked every week by a psychiatrist working in addiction medicine. No specific psychotherapies were initiated but counseling was provided. Diagnosis of CoUD was formulated in accordance with the criteria of DSM-5. Substance use was assessed every week by radioimmunologic assay tests for cocaine and stimulants, performed on patient urine specimens. The presence of cocaine metabolites, or a refusal to deliver urine specimens, were considered as proof of relapsing behavior. Mental status (mood, anxiety, and sleep disturbance) and cocaine craving were assessed at baseline with a 6-point scale (ranging from normal to severe). The intermediate evaluations and the last one were assessed using a 7-point scale (ranging from very much improved to very much worse), using baseline status as reference. All the clinical examinations were performed by the same psychiatrist, who was an expert in addiction medicine. Patients who relapsed into cocaine intake, or were follow-up noncompleters, were defined as nonresponders.

CASE SERIES

Patient 1

A 20-year-old man was admitted to our clinic after 3-week cocaine abstinence and after 6 months of reported daily use before becoming abstinent. The patient had started to use cocaine when he was 16 years old and continuous use started immediately afterward. The length of cocaine dependence was 4 years. Four months was the last, longest cocaine-free period. At the baseline psychiatric examination, he showed moderate depressed mood and moderate anxiety. His sleep pattern was markedly altered. Cocaine craving was markedly present. He completed 6-month therapy without relapsing into cocaine use. At 6-month examination, his mood was very much improved, whereas anxiety was only minimally improved. The sleep pattern was very much improved, and craving was improved too. The patient showed nearly complete remission of all psychiatric symptoms without important side-effects.

Patient 2

A 33-year-old man was admitted to our clinic after 2-week cocaine abstinence and after 7 months of reported daily use before becoming abstinent. The patient began to use cocaine when he was 23 years old and began continuous use when he was 26. The length of cocaine dependence was 7 years. Five months was the last and longest cocaine-free period. At the baseline psychiatric examination, he showed marked depressed mood and marked anxiety. His sleep pattern was markedly altered. Cocaine craving was severe. He completed 6-month therapy without relapsing into cocaine use. At 6-month examination mood was very much improved and anxiety was much improved too. The sleep pattern was very much improved, and the level of craving too showed much improvement. The patient showed nearly complete remission of all psychiatric symptoms without significant side-effects.

Patient 3

A 41-year-old man was admitted to our clinic after 4-week cocaine abstinence and after 6 months of reported daily use before becoming abstinent. The patient began his first use of cocaine at the age of 20 and continuous use when he was 22. The length of cocaine dependence was 19 years. Six months was the last and longest cocaine-free period. At the baseline psychiatric examination, he showed marked depressed mood and marked anxiety. His sleep was markedly altered. Cocaine craving was severe.

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He completed 6-month therapy without relapsing into cocaine use. At 6-month examination, mood, anxiety and sleep patterns were very much improved. Cocaine craving was much improved. The patient showed nearly complete remission of all psychiatric symptoms without major side-effects.

Patient 4

A 28-year-old man was admitted to our clinic after 2 weeks of cocaine abstinence and after 4 months of reported daily use before becoming abstinent. The patient began to use cocaine at the age of 15, and continuous use started 3 years later. The length of cocaine dependence was 10 years. Four months was the last and longest cocaine-free period. At the baseline psychiatric examination, he was markedly ill regarding depressed mood, anxiety, sleep disturbances, and cocaine craving. He completed 6-month therapy without relapsing into cocaine use. At the 6-month follow-up examination, mood was very much improved, but anxiety was unchanged. Both sleep pattern and cocaine craving were much improved. The patient showed nearly complete remission of all psychiatric symptoms without any major side-effects.

Patient 5

A 30-year-old woman was admitted to our outpatient clinic after a 2-week period of cocaine abstinence and after 6 previous months of reported daily use before becoming abstinent. The patient began her first use of cocaine at the age of 23 and continuous use started 3 years later. The length of cocaine dependence was 4 years. Three months was the last and longest cocaine-free period. At the baseline psychiatric evaluation, she showed severe depressed mood and marked anxiety. Her sleep disturbances and cocaine craving were severe. She completed 6-month therapy, relapsing 3 times into cocaine use. At 6-month examination mood and anxiety were much improved, whereas sleep pattern and cocaine craving showed only minimal improvement. The patient showed no important side-effects.

Patient 6

A 25-year-old man was admitted to our clinic after 5 weeks of cocaine abstinence and after 8 months of reported daily use before becoming abstinent. The patient started to use cocaine for the first time when he was 18 years old, and continuous use began when he was 20. The length of cocaine dependence was 5 years. Two months was the last and longest cocaine-free period. At the baseline psychiatric evaluation, he showed severe depressed mood and marked anxiety. His sleep was markedly disturbed, and cocaine craving markedly present. He completed 6-month therapy without relapsing into cocaine use. At the 6-month examination his mood was minimally improved, while anxiety was minimally worse. The sleep pattern was much improved, and craving was very much improved. The patient showed slight improvement, which did not alter his patient care status regarding affective disturbances, except sleep disturbances, without any major side-effects. His condition was very much improved on the addiction side.

Patient 7

A 45-year-old man was admitted to our clinic after 4-week cocaine abstinence and after 8-month reported daily use before becoming abstinent. The patient began the first use of cocaine at the age of 19, starting continuous use immediately afterward. Length of cocaine dependence was 26 years. Three months was the last and longest cocaine-free period. At the baseline psychiatric evaluation, he showed severe depressed mood and anxiety. His sleep was severely disturbed. Cocaine craving was markedly present. He completed 6-month therapy without relapsing into cocaine use. At the 6-month examination, mood was very much improved, and anxiety was much improved too. The sleep pattern was much improved, while cocaine craving was very much improved. The patient showed nearly complete remission of all psychiatric symptoms without any important side-effects.

Patient 8

A 47-year-old man was admitted to our clinic after 2 weeks of abstinence

and after 12 months of reported daily use before becoming abstinent. The patient began his first use of cocaine when he was 20 years old and continuous use when he was 22. Length of cocaine dependence was 25 years. Three months was the last and longest cocaine-free period. At the baseline psychiatric evaluation, he showed severe depressed mood and severe anxiety. His sleep was markedly disturbed. Cocaine craving was severe. He did not complete 6-month therapy and relapsed into cocaine use many times. At the 2-month examination, mood, anxiety, and sleep disturbances were minimally improved. Cocaine craving was unchanged. Therapeutic effect was only minimal regarding the psychiatric symptoms and the patient's addiction status had deteriorated.

Patient 9

A 19-year-old woman was admitted to our clinic after 2 weeks of cocaine abstinence and after 2 months of reported daily use before becoming abstinent. The patient began her first use of cocaine when she was 15 and continuous use when she was 18. The length of cocaine dependence was 1 year. Two months was the last and longest cocaine-free period. At the baseline psychiatric evaluation, mood and anxiety were both markedly impaired. Her sleep disturbance was severe as well as her cocaine craving. She completed 6-month therapy without relapsing into cocaine use. At the 6-month examination, mood and anxiety were only minimally improved, but sleep pattern and cocaine craving were much improved. Efficacy on addictive problems (sleep and craving) was conspicuous, and side-effects did not significantly interfere with her functional skills.

Only 1 patient did not complete 6-month follow-up, relapsing many times into cocaine use during the observational period. For this patient, trittico contramid's therapeutic effect was minimal regarding depressive symptoms and the patient's addiction status had become worse. One patient completed the follow-up while improving his psychiatric symptoms but relapsed 3 times into cocaine use. In total, 2/9 patients (22.2%), relapsed into cocaine use and were considered nonresponders. In contrast,

TABLE 1. 6-Month Outcomes of Treatment With Trittico Contramid of 9 Consecutive Self-detoxified Cocaine Use Disorder Patients Showing Psychiatric Symptoms and Craving for Cocaine

			Symptomatologic Outcomes				
	Completer	Responder	Mood	Anxiety	Sleep	Cocaine Craving	Efficacy Index*
Patient 1	Yes	Yes	+++	+	+++	+	Marked-none
Patient 2	Yes	Yes	+++	++	+++	++	Marked-none
Patient 3	Yes	Yes	+++	+++	+++	++	Marked-none
Patient 4	Yes	Yes	+++	=	++	+++	Marked-none
Patient 5	Yes	No	++	++	+	+	Marked-do not interfere
Patient 6	Yes	Yes	+	−	++	+++	Minimal-do not interfere
Patient 7	Yes	Yes	+++	+++	++	+++	Marked-none
Patient 8	No	No	+	+	+	=	Minimal-do not interfere
Patient 9	Yes	Yes	+	+	++	+++	Marked-do not interfere

*The efficacy index is the ratio between therapeutic effects and side-effects.
− Indicates minimally worse; +, minimally improved; ++, much improved; +++, very much improved; =, unchanged.

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7/9 patients (77.8%) improved their psychiatric symptoms and 6 months after therapeutic baseline remained cocaine-detoxified; they were therefore considered responders.

Table 1 summarizes outcomes at baseline. Craving for cocaine had very much improved in 3 patients (33.3%), had much improved in 3 (33.3%), showed only minimally improvement in 2 (22.2%), whereas no change was observed in 1 patient (11.1%). Mood disturbances had greatly improved in 5 patients (55.6%), were much improved in 1 patient (11.1%) and only minimally improved in 3 patients (33.3%). Anxiety had greatly improved in 1 patient (11.1%), was much improved in 3 (33.3%), only minimally improved in 3 (33.3%), was unchanged in 1 patient (11.1%) and minimally worse in 1 patient (11.1%). Sleep disturbances were very much improved in 3 patients (33.3), much improved in 4 (44.4%), and only minimally improved in 2 (22.2%) patients. Craving for cocaine did not show any relation psychopathologic symptoms. In fact, partial correlations between craving and psychopathologic symptoms, after correction by accounting for craving and psychopathologic symptom baseline severity, did not show significant correlations in cases of mood symptoms ($r = 0.25$; $P = 0.586$), anxiety ($r = 0.05$; $P = 0.912$), or sleep disturbances ($r = 0.40$; $P = 0.371$). Psychopathologic symptoms improved during treatment in all patients.

DISCUSSION

The present case series shows that trittico contramid is probably able to positively modify psychopathologic symptomatology and cocaine craving in CoUD patients who stopped cocaine use without achieving sufficient well-being. Interestingly the action against cocaine craving proved to be unrelated to the improvement of psychiatric symptomatology.

The use of trittico contramid may be efficient in helping highly motivated CoUD patients who stopped cocaine use despite consequent psychopathologic discomfort and craving persistence. It is possible that in patients who have already achieved complete abstinence from cocaine, but in whom craving for cocaine, mood, anxiety, and sleep disturbance occur, the utilization of trittico contramid may help to avoid a postdetoxification discomfort that would place patients at risk of resuming cocaine intake. Thus, controlled clinical trials in a larger population to confirm the safety and efficacy of trittico contramid in treating cocaine postdetoxification discomfort are warranted.

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