with little input from clinical practitioners. It reflects mainly the methods and concepts valued by academic researchers who do not interact with patients. It would be unfortunate if the official psychiatric diagnostic manual mirrored this bias, to the detriment of patient care.

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## Disulfiram: An Anticraving Substance?

TO THE EDITOR: We read with interest the Treatment in Psychiatry article by Bankole A. Johnson, D.Sc., M.D. (1), published in the June 2010 issue of the *Journal*. Hereby, we would like to briefly comment on the author's statements regarding disulfiram.

Disulfiram has been used for more than 50 years as an aversion therapeutic agent in the treatment of alcohol dependence (2). However, categorizing disulfiram as a "psychological pill" does not encompass the whole potential of the substance, since emerging evidence suggests that it also possesses anticraving properties (3). Besides its well-known mechanism of action (i.e., aldehyde dehydrogenase inhibition), disulfiram also inhibits dopamine beta-hydroxylase, leading to an increase of dopamine concentrations while decreasing concentrations of norepinephrine in the brain (4). Since dopaminergic transmission in the ventral striatal reward system is suggested to play a key role in the development of addictive disorders and craving (5, 6) and reduced activation of this system has been shown in alcohol dependence (7), cocaine dependence (8), and nonsubstance-related addictions such as pathological gambling (9), disulfiram could be hypothesized as a common treatment option for these disorders. In cocaine dependence, disulfiram has already shown preliminary efficacy in reducing craving and relapse rates (10). Furthermore, in a patient with alcohol dependence and comorbid pathological gambling, treatment with disulfiram led to a significant reduction in alcohol craving and urges to gamble as well as to maintenance of abstinence from both alcohol and gambling for more than 12 months (11). In alcohol dependence, most of the clinical trials conducted with disulfiram have possessed significant methodological shortcomings and have not measured changes in alcohol craving under treatment (2). Therefore, to evaluate the potential of disulfiram as an anticraving agent also in alcohol dependence, further randomized controlled trials would be needed.

### References

1. Johnson BA: Medication treatment of different types of alcoholism. Am J Psychiatry 2010; 167:630–639
2. Suh JJ, Pettinati HM, Kampman KM, O'Brien CP: The status of disulfiram: a half of a century later. J Clin Psychopharmacol 2006; 26:290–302
3. Barth KS, Malcolm RJ: Disulfiram: an old therapeutic with new applications. CNS Neurol Disord Drug Targets 2010; 9:5–12
4. Vaccari A, Saba PL, Ruiu S, Collu M, Devoto P: Disulfiram and diethyldithiocarbamate intoxication affects the storage and release of striatal dopamine. Toxicol Appl Pharmacol 1996; 139:102–108
5. Heinz A, Siessmeier T, Wrase J, Hermann D, Klein S, Grusser SM, Flor H, Braus DF, Buchholz HG, Grunder G, Schreckenberger M, Smolka MN, Rosch F, Mann K, Bartenstein P: Correlation between dopamine $D_{(2)}$ receptors in the ventral striatum and central processing of alcohol cues and craving. Am J Psychiatry 2004; 161:1783–1789
6. Frascella J, Potenza MN, Brown LL, Childress AR: Shared brain vulnerabilities open the way for nonsubstance addictions: Carving addiction at a new joint? Ann N Y Acad Sci 2010; 1187:294–315
7. Beck A, Schlagenhauf F, Wustenberg T, Hein J, Kienast T, Kahnt T, Schmack K, Hagele C, Knutson B, Heinz A, Wrase J: Ventral striatal activation during reward anticipation correlates with impulsivity in alcoholics. Biol Psychiatry 2009; 66:734–742
8. Asensio S, Romero MJ, Palau C, Sanchez A, Senabre I, Morales JL, Carcelen R, Romero FJ: Altered neural response of the appetitive emotional system in cocaine addiction: an fMRI study. Addict Biol 2010; 15:504–516
9. Reuter J, Raedler T, Rose M, Hand I, Glascher J, Buchel C: Pathological gambling is linked to reduced activation of the mesolimbic reward system. Nat Neurosci 2005; 8:147–148
10. Pani PP, Trogu E, Vacca R, Amato L, Vecchi S, Davoli M: Disulfiram for the treatment of cocaine dependence. Cochrane Database Syst Rev 2010:CD007024
11. Mutschler J, Buhler M, Grosshans M, Diehl A, Mann K, Kiefer F: Disulfiram, an option for the treatment of pathological gambling? Alcohol Alcohol 2010; 45:214–216

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## Response to Müller and Banas Letter

TO THE EDITOR: I thank Drs. Müller and Banas for their interesting comments. Recently, I compiled an updated synopsis on the actions, effects, and efficacy of disulfiram in the treatment of alcohol dependence (1). Disulfiram can be an effective agent for treating alcohol dependence, but this is limited to populations where there is high compliance with adhering to the medication (2) or where subjects have been directly supervised (2, 3). Since the behavioral effects of monitoring alcohol consumption and direct supervision are quite powerful in helping to maintain abstinence, it is these elements that are associated with any potential efficacy for disulfiram as a treatment for alcohol dependence. As such, its effect as a "psychological pill" is the predominant mode of action.

Disulfiram is associated with an increase in acetaldehyde levels, which in and of itself appears to be reinforcing (4). While I concur with Drs. Müller and Banas that disulfiram has been shown to inhibit dopamine beta-hydroxylase

(5), thereby increasing dopamine levels, presumably in the cortico-mesolimbic dopamine system (which is the primary circuit for the expression of alcohol reinforcement and abuse liability) (6), this pharmacological effect is quite weak and is not its principal mode of action.

Furthermore, this effect of disulfiram on the cortico-mesolimbic dopamine circuit would be to increase, not decrease, reinforcement and abuse liability. In essence, the proposal would be for disulfiram to "substitute" for the effects of alcohol. Hence, both of its proposed mechanisms of action—on alcohol metabolism and on dopamine metabolism—would tend to argue against an effect as an anticraving agent. Furthermore, to my knowledge, there is no compelling body of research that would support the use of disulfiram as a substitute for alcohol. Indeed, there is no strong clinical evidence that a substitution agent would be an important treatment for alcohol dependence. Instead, the most important research studies have focused on developing medications that are neuromodulators of dopamine levels in the cortico-mesolimbic dopamine system, thereby decreasing the drive, urge, or propensity to use alcohol. These so-called anticraving agents are the hallmarks of promising new treatments for alcohol dependence.

Although preliminary evidence has been proposed for disulfiram as a treatment agent for cocaine dependence, this has not been established in subsequent studies, and the need for high doses, which have been associated with significant toxicity, is a safety limitation that precludes such use (7). Furthermore, the potential effect of disulfiram on pathological gambling is based on a single case report (8) and a letter to a journal editor (9). It would, therefore, appear preliminary to propose disulfiram as an important treatment for pathological gambling.

In closing, disulfiram has a place in the treatment of alcohol dependence in individuals with high compliance or for whom medication adherence can be observed to occur during direct supervision. With such high monitoring and supervision, there are likely to be marked improvements in drinking behavior (10), and it is reasonable to question whether disulfiram adds much over and above these behavioral approaches. In my view, it seems rather odd that a drug that has been used in practice for almost 60 years still requires even more studies to establish convincingly its efficacy for the treatment of alcohol dependence.

### References


1. Johnson BA: Disulfiram, in Encyclopedia of Psychopharmacology. Edited by Stolerman IP. Berlin, Springer-Verlag, 2010, pp 413–416
2. Brewer C, Meyers RJ, Johnsen J: Does disulfiram help to prevent relapse in alcohol abuse? CNS Drugs 2000; 14:329–341
3. Suh JJ, Pettinati HM, Kampman KM, O'Brien CP: The status of disulfiram: a half of a century later. J Clin Psychopharmacol 2006; 26:290–302
4. Peana AT, Muggironi G, Diana M: Acetaldehyde-reinforcing effects: a study on oral self-administration behavior. Front Psychiatry 2010; 1(article 23):1–6
5. Goldstein M, Anagnoste B, Lauber E, McKeregham MR: Inhibition of dopamine-beta-hydroxylase by disulfiram. Life Sci 1964; 3:763–767
6. Weiss F, Porrino LJ: Behavioral neurobiology of alcohol addiction: recent advances and challenges. J Neurosci 2002; 22:3332–3337
7. Elkashef A, Vocci F: Pharmacotherapy of cocaine addiction, in Addiction Medicine: Science and Practice. Edited by Johnson BA. New York, Springer, 2010, pp 1017–1028
8. Mutschler J, Bühler M, Grosshans M, Diehl A, Mann K, Kiefer F: Disulfiram, an option for the treatment of pathological gambling? Alcohol Alcohol 2010; 45:214–216
9. Mutschler J, Bühler M, Diehl A, Mann K, Kiefer F: Disulfiram: an old drug with new potential in the treatment of pathological gambling? Med Hypotheses 2010; 74:209–210
10. Johnson BA: Update on neuropharmacological treatments for alcoholism: scientific basis and clinical findings. Biochem Pharmacol 2008; 75:34–56


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## Circadian Rhythm Disturbances Associated With Psychiatric Symptoms in a Patient With a Pineal Region Tumor

To the Editor: We read with interest the Clinical Case Conference by Vijay A. Mittal, Ph.D., et al (1), published in the September 2010 issue of the *Journal*. The case concerned a young man with a pineal region tumor who presented prodromal obsessive-compulsive behaviors and psychotic symptoms. We recently provided treatment in a similar case, involving a young patient who had circadian rhythm disturbances in relation to a pineal tumor.

**"Ivan" was a 19-year-old Caucasian man who presented to our sleep service 6 years after insertion of a ventriculo-peritoneal shunt, followed by resection of and chemotherapy and radiotherapy for a secreting germ cell pineal tumor, which were performed in 2001. No recurrence of the tumor was shown at follow-up assessment.**

**Shortly after insertion of the shunt, the patient exhibited insomnia, a severely disturbed sleep-wake cycle, and fragmentation of nocturnal sleep. In June 2004, he developed paranoid ideas and bipolar disorder. Treatment was started, and when the patient was seen by us in December 2007, he was receiving treatment with clorazepate dipotasique (40 mg), olanzapine (7.5 mg), and escitalopram (20 mg). His school performance had been severely affected, and he stayed at home and was socially isolated. He complained of severe fatigue and described his sleep as not restful.**

**Polysomnography, performed at the beginning of October 2007 under psychotropic treatment, showed light fragmented sleep, and actigraphy showed an irregular sleep-wake cycle, with abnormally raised nocturnal activity. Twenty-four hour urinary 6-sulfatoxymelatonin levels were barely detectable with absence of the typical 24-hour sleep-wake cycle. Treatment with controlled-release melatonin was started in October 2007. The patient's sleep rapidly stabilized, with restoration of a regular sleep-wake cycle and marked improvement of psychotic symptoms, permitting progressive withdrawal of psychotropic medication between January and April 2008. Further sleep analyses, performed in mid-November 2007, showed restoration of slow-wave sleep, with diminished sleep fragmentation, and actigraphy confirmed restoration of a normal sleep-wake cycle. Treatment with**