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Commentary on Ling et al: Double-blind Placebo-Controlled Evaluation of the PROMETA™ Protocol for Methamphetamine Dependence

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Keywords

Methamphetamine; stimulant; clinical trial

Ling et al. tested the efficacy and safety of the PROMETA protocol for the treatment of methamphetamine addiction in a double-blind, placebo-controlled study (1). The PROMETA protocol has been widely promoted as a treatment for alcohol, cocaine, and methamphetamine addiction although its safety and efficacy have not been definitively evaluated in rigorous clinical trials. Ling et al. report that the PROMETA protocol was no more effective than placebo in reducing either methamphetamine use or craving for methamphetamine. The protocol includes a combination of flumazenil, gabapentin, and hydroxyzine. Flumazenil is a benzodiazepine antagonist typically used for benzodiazepine overdose (2). Gabapentin, on the other hand, is used for treatment of seizures and pain, possibly acts by inhibiting the $\alpha_2\delta$ type of calcium receptors, although the exact mechanism of action is unclear (3). Hydroxyzine is an H_1 -histaminic receptor antagonist with anticholinergic effects (4). The authors deserve credit for successfully testing the safety and efficacy of this challenging protocol. This study raises several additional questions some of which are summarized below:

The first question is related to the justification for this study. Neither the components of the PROMETA medication cocktail nor the sequence and time-course of their administration is supported by any scientific rationale. Presumably, the resources used for this study could have been used to conduct studies with a clearer scientific rationale. On the other hand, the PROMETA protocol has been widely used in specialized clinics as a treatment of alcohol, cocaine, and methamphetamine addiction without systematic studies supporting its safety and efficacy. The trial is thus warranted to test this practice. Further, in a previous double-blind, placebo-controlled-study, Urschel et al reported that the PROMETA protocol reduced methamphetamine use as well as craving (5). Because the Urschel study was only a 30 day study, there was a need for further studies with longer treatment duration to test the safety and efficacy of PROMETA combination in methamphetamine users. Thus, although a clear scientific rationale was lacking, the widespread use of the protocol and some preliminary findings supporting its efficacy sufficiently justified this clinical trial.

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A second issue is the high placebo response as potential limitation of this study. Ling et al. commented that in one of the site the study participants, who thought they had received active medication, irrespective of the actual treatment they received, were twice as likely as those who thought they had received placebo to submit negative urines at the end of the study. These findings are consistent with a high placebo response which is commonly observed in pharmacotherapy trials for depression, pain, and schizophrenia (6). Placebo response also seems to be a function of the likelihood of receiving the active medication such that higher placebo responses are observed if the chances of being assigned to active treatment is more than 50 percent (7). The high placebo response was somewhat unexpected in this patient population and might be, at least partly, attributed to the positive media coverage and promotion for the PROMETA protocol. Importantly, high placebo response rate may reduce the power of this study to detect treatment differences and should be considered as a potential limitation of the study.

A third issue is the need to translate these research findings into clinical practice. One would expect that the negative results of the Ling study would discourage further use of PROMETA treatment for methamphetamine addiction. Further, the adverse effects of this medication combination, especially the risk of seizures associated with flumazenil merits caution, especially in view of the frequent co-morbidity of seizures in methamphetamine users (8). However, since the PROMETA protocol has been actively promoted and widely used even in the absence of robust scientific evidence supporting its efficacy, it remains to be seen if these negative findings will deter promoters of PROMETA from continuing their aggressive marketing of this protocol. It is incumbent upon the scientific community to disseminate these study findings to clinicians and patients to encourage caution in the further use of this unproven and risky treatment.

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