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▶ Double-blind placebo-controlled evaluation of the PROMETA™ protocol for methamphetamine dependence.

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The US company which owns and markets the controversial PROMETA proprietary combination of drugs for methamphetamine dependence funded a rigorous trial by independent researchers; the result was a no-better-than-placebo verdict, another negative in the search for drugs to counter stimulant dependence.

Summary After cannabis, the powerful stimulant methamphetamine is the most abused illicit drug worldwide, with 15–16 million regular users, yet there are no approved medications for the treatment of methamphetamine dependence.

A proprietary system of treatment for methamphetamine dependence, the PROMETA™ protocol, combines medications purported to normalise brain systems altered by chronic stimulant use along with psychosocial treatment designed to minimise withdrawal symptoms, prevent relapse and reduce cravings. Of the three medications in the protocol, flumazenil is the principal element. Among other effects, the drug works via the GABA neurotransmitter system to block the action of benzodiazepine tranquilisers and sleeping pills. Medically it is used to reverse deep sedation and as an antidote to benzodiazepine overdose. A second element is gabapentin, an anti-convulsant which also acts on the GABA system and which has been used as an analgesic. It has been reported to reduce craving and other subjective effects of cocaine. Last is hydroxyzine hydrochloride, an anti-anxiety drug which has been widely used in the management of withdrawal from substance dependence.

The featured study was conducted when this protocol was being heavily publicised and was subject to a great deal of debate and controversy in drug abuse, investment and

news media circles. Proponents were buoyed by anecdotal reports and uncontrolled studies, while opponents cited the lack of data from placebo-controlled trials. In just such a trial, the study aimed to evaluate the efficacy and safety of this protocol in the treatment of methamphetamine dependence. It was funded by the company which owns the protocol, which also referred people seeking treatment via its call centre to the researchers and trained the researchers in the protocol to ensure their implementation matched the company's specification. The company played no other part in the study.

The study recruited adults seeking treatment for methamphetamine abuse or dependence and who had used the drug on at least four of the last 30 days. The 120 eligible for and who agreed to join the study were allocated to one of three clinics which offered a 40-day medication regimen beginning with five infusions (at two clinics on an inpatient basis) plus 14 weekly sessions of cognitive-behavioural therapy over the roughly 15 weeks of the trial. For a randomly selected half of the patients, the medication was the PROMETA™ protocol; the other half were given identical but inactive placebo preparations (except that they too were offered the anti-anxiety agent hydroxyzine hydrochloride, not considered a key element of the protocol). The study based its findings on the 111 patients who at least began the medication/placebo regimens. Typically they were white single men in employment who on average had used methamphetamine more than every other day and had used for about 10 years. Over 8 in 10 were on probation or parole and most had a history of physical and sexual abuse.

Main findings

Just half the 60 patients allocated to the protocol stayed in the study until the end of the 40-day medication phase and 18 to the end of the study. Corresponding figures for placebo patients were 42 and 26. At no point (until the end of the medication infusion phase, of all medication, or of the study) were there any statistically significant differences between PROMETA™ and placebo patients in the proportions of weekly urine tests which indicated no methamphetamine use, or in the proportions of patients with three consecutive methamphetamine-free tests. Proportions of methamphetamine-free urine tests increased over the course of the study, but to the same degree regardless of whether the active protocol was administered or a placebo.

This general picture was replicated by the patients' own accounts of their methamphetamine use, by the end of the study among retained patients averaging just four to five days a month, regardless of whether real mdeication had been taken. Craving for methamphetamine too fell roughly equally over the course of the study and retention or compliance with taking medication did not significantly differ. Safety concerns were few. No adverse occurrences or experiences were deemed definitely related to the study drugs, and only one was probably related.

The authors' conclusions

Under the conditions of this study, treatment with the combination medication protocol was no more effective than placebo in reducing methamphetamine use or craving or keeping patients in treatment. The results were negative and clear: active medication and placebo groups showed no statistically significant differences in drug use as measured by urine testing or self-report, or in self-reported craving. Both groups substantially reduced their reported methamphetamine use. The placebo group remained

in the study for on average about 17 days longer than the medication group, not a statistically significant difference after age had been taken in to account. There were no clinically relevant differences in the pattern or severity of adverse events that would imply a greater risk in either group.

These findings differ from those of another randomised and placebo-controlled trial of a similar medication combination, which did find reductions in methamphetamine use associated with the protocol. A possible explanation could be the influence of the marketing campaign which occurred during the featured trial, which may have elevated the placebo effect. Inpatient hospitalisation for infusion at two of the sites may have also contributed to a strong placebo effect. Consistent with this explanation, at the end of treatment at one of the clinics twice as many patients believed they had received active medication as believed they had received a placebo. Regardless of whether they actually did receive active medication, these patients were twice as likely to be abstinent at the end of the study. Perhaps too the psychosocial components of the treatment were stronger in the featured study.

FINDINGS These findings, which do not even hint at a positive impact from a (in the USA) fairly widely implemented treatment, represent another blow to attempts to find pharmacological solutions to dependence on stimulant drugs. At the same time, among the minority of patients who stayed in the study to be assessed, they are a testament to the power of the patient's desire to get better and the impact of psychological and social influences – in particular, the belief that they are receiving a treatment which works, even if in reality it is an inactive placebo.

The more positive earlier trial referred to by the authors lasted just 30 days, and even then, by the end the gains associated with the active medication had nearly evaporated. In the final week patients who had received active medication said they had used methamphetamine on 41% of days, those given placebo, 44%, a minimal difference. After day six of the trial urine test results did not significantly differ between the two sets of patients. The report on the study says it was "double-blind', presumably meaning that both investigators and patients did not know which patient was in which group, but how blinding was achieved is not detailed, nor whether it successfully hid who got what, and whether medical staff too were blinded is unclear. From the featured study, it seems that anything which enabled patients to deduce or guess whether they had been given active medication could have accounted for the positive results. Possibly too, the fact that in the featured study the great majority of patients were under criminal justice supervision gave those who could get better such a strong incentive to do so that the drugs made no further difference. How many might have been in this position in the earlier trial was not reported.

The one seizure in the featured study is consistent with the warning from a commentator on the study that "the adverse effects of this medication combination, especially the risk of seizures associated with flumazenil, merits caution, especially in view of the frequent comorbidity of seizures in methamphetamine users".

The evaluated protocol has been the subject of considerable controversy in the USA. Attempts have also been made to gain a foothold in the UK. The confidential protocol is marketed by a US healthcare services management company which does not manufacture or distribute the medications. Rather than a new drug, it combines in what the company describes as "a unique dosing algorithm" several medications approved by US

authorities, but not for the treatment of substance dependence. According to the company, the treatment programme it markets which features the protocol is "the only outpatient program to uniquely combine medical and psychosocial therapy into one integrated program". Apparently the company changed its name (1 2) in March 2011 from Hythiam to Catasys which now markets a similar treatment under the trade name OnTrak™.

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