and damage to the hair shafts. On a recent trip to China, I found it disturbing that young and adult Chinese people in the cities were using lead-based hair dyes to make their hair darker to mimic Western fads. Media attention has encouraged some Chinese manufacturers to omit the labeling of lead content in these products. In adult patients, multisystem disease due to lead toxicity should be considered when symptoms and signs are abdominal pain, hemolytic anemia, neurologic dysfunction (mononeuropathy including headache), gout, or renal insufficiency. Questions about hair dyes need to be included in the medical history.

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In reply: We thank Dr Brown for drawing attention to an unusual cause of anemia that can affect elderly persons. Although the magnitude of risk from hair dyes is uncertain,[1-3] environmental exposure to lead is common enough that lead intoxication should routinely be considered in the differential diagnosis of unexplained anemia, especially in patients from outside the United States.[4] In addition to the paint and toys mentioned by Dr Brown, nonoccupational sources of lead exposure have included ceramic glazes[5] (a potential danger for nursing home residents participating in ceramic arts programs[6]), traditional medicines,[7] cosmetics (especially kohl-based eyeliner[8]), candy,[9] metal lunchboxes,[10] and several others. Although the peripheral blood smear often reveals basophilic stippling in lead intoxication, this test is neither specific nor highly sensitive, and other assays such as blood lead and erythrocyte zinc protoporphyrin measurements might be necessary to make the diagnosis.[11]

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Treatment of Methamphetamine Dependence

To the Editor: We wish to draw attention to several issues in the article entitled "Open-Label Study of a Proprietary Treatment Program Targeting Type A γ-Aminobutyric Acid Receptor Dysregulation in Methamphetamine Dependence" by Urschel et al.[1] We believe there are serious shortcomings in the design and interpretation of the study and that the conclusion that the Prometa protocol shows efficacy in methamphetamine treatment is misleading.

First, the percentage of patients who responded positively in this open-label trial is comparable to the percentage who responded to placebo in a double-blind, placebo-controlled study using one of the drugs in the Prometa protocol. Heinzerling et al[2] at the University of California, Los Angeles, conducted a 16-week randomized, placebo-controlled, double-blind trial of 2 γ-aminobutyric acid (GABA)ergic medications, baclofen (20 mg 3 times a day) and gabapentin (800 mg twice daily), for the treatment of methamphetamine dependence. Eighty-eight patients were randomized, and outcome measures included many of the same measures used by Urschel et al. Although most of the study patients improved during the 16-week treatment period, neither gabapentin nor baclofen was superior to placebo. We compared the placebo response in the study by Heinzerling et al with the treatment outcome data from Urschel et al, which had only an active treatment condition. In Heinzerling's study, 64% of the placebo-treated group provided methamphetamine-free urine samples by the end of the trial; in Urschel's study, 65% of patients had methamphetamine-free urine samples. This suggests that the response to the Prometa protocol in the study by Urschel et al is likely to be at the level of a placebo condition. Like Urschel et al, Heinzerling et al observed declines in craving during the study period, but again these were not significantly different from placebo.

Second, the authors attribute the apparent effectiveness of their treatment to the effects of one of the constituent medications, flumazenil. However, there is little scientific evidence that the neurotransmitter system on which flumazenil acts (type A GABA [$GABA_A$]) is involved in either the direct effects of methamphetamine or the adaptations resulting from methamphetamine use. Methamphetamine does not bind to $GABA_A$ receptors, there is no evidence that it directly or indirectly affects GABA neurotransmission, and there is no evidence that $GABA_A$ receptors are dysregulated in methamphetamine addiction. Thus, implying that the Prometa program alters $GABA_A$ receptor function, structure, or regulation is premature and potentially misleading.

Third, the psychosocial component is described both as "participants learn coping skills and work to implement the

lifestyle and behavior changes needed to promote abstinence and reduce risk of relapse" and as "The weekly sessions were intended to allow data collection and to keep participants engaged in the study. No specific psychotherapy or specific drug-abuse counseling was provided." These are mutually contradictory descriptions.

We urge caution before accepting claims of efficacy for the Prometa protocol. A risk of open-label trials is that apparent decreases in problematic drug use might be attributed to the treatment, whereas in fact it is comparable to placebo. Moreover, we should be cautious in interpreting outcomes that do not have a neurobiologic basis. Thus, the conclusion reached by Urschel et al, "The results of this open-label trial suggest that this proprietary treatment program is a promising outpatient medical treatment for methamphetamine dependence" is inaccurate and misleading. Urschel et al note that placebo-controlled trials of GABAergic drugs are needed, and we agree. However, they fail to make clear that double-blind, placebo-controlled trials with components of the Prometa protocol have already been conducted, and these controlled studies do not suggest efficacy against methamphetamine addiction. Until positive evidence from adequate peer-reviewed, placebo-controlled trials is available, the Prometa protocol should not be considered an effective treatment of methamphetamine addiction.

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In reply: We are surprised by the response from Mendelson et al, and we address the numerous errors in their letter.

A large portion of their letter discusses a study by Heinzerling et al that showed neither baclofen nor gabapentin had statistically significant effects in decreasing methamphetamine use. Mendelson et al correctly point out that the percentage of patients who responded to active treatment in our study is similar to the percentage of those who responded to either active treatment or placebo in the study by Heinzerling et al. They suggest that a placebo response (in our open uncontrolled study, a response unrelated to pharmacological intervention) could have accounted for the findings reported in our article.

Although benefit unrelated to drug treatment is always a possibility in an uncontrolled study (we acknowledged this important limitation in our article), it is difficult to see how the results reported by Heinzerling et al affect interpretation of our results. There appears to be a critical difference between the characteristics of patients enrolled and retained in the 2 trials. At baseline, 94% of our study participants had positive urine drug screen (UDS) results. During the pretreatment screening period in the Heinzerling et al study, 38% to 55% of placebo-treated patients had UDS results negative for methamphetamine. In addition, the completion rate for our trial (72%) was higher than that for any group in the Heinzerling et al study (60% for baclofen, 35% for gabapentin, 41% for placebo). Heinzerling et al point out that 64% (38% by their more conservative approach to estimation after correction for dropouts) of placebo-treated patients had negative UDS results at end point. If we are correct in comparing this result with the data shown in Figure 3 for the screening period, there was essentially no change from baseline in the rate of methamphetamine-positive UDS results for placebo-treated patients during their study (ie, no placebo effect). This is clearly different from our results in which treatment, admittedly confounded by a potential placebo effect, resulted in a 44% absolute reduction in positive UDS results from baseline. Even after correction for dropouts in the same manner as Heinzerling et al, the percentage of negative UDS results at end point would still be 36% vs 6% at baseline, an absolute decline of 30%. Thus, although the end point results for placebo-treated patients studied by Heinzerling et al and those who received active treatment in our study might be similar, the changes from baseline differ greatly, probably because of differences in the patients enrolled in the 2 trials.

Mendelson et al also question that flumazenil might play a key role in the treatment-associated benefits observed in our study. Contrary to their statement, there is evidence that both amphetamine and another stimulant, cocaine, might affect GABAergic neurotransmission. Zhang et al[1] have recently