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Reduction in methamphetamine induced sensitization and reinstatement after combined pergolide plus ondansetron treatment during withdrawal

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Abstract

We have previously found the 5-HT_3 receptor antagonist ondansetron to be useful in reducing cocaine self-administration and cocaine induced sensitization in rats when given during cocaine withdrawal. More recently we have found the combination of the dopamine agonist pergolide plus ondansetron, 3.5 h later, to reverse cocaine sensitization and associated changes in NMDA and AMPA receptors. Here we tested this drug combination in 1) a methamphetamine sensitization model and 2) a reinstatement model after intravenous methamphetamine self-administration using a nose-poke task. We found pergolide plus ondansetron given from days 3–7 of methamphetamine withdrawal to reverse methamphetamine induced sensitization and attenuate reinstatement. We hypothesize that pergolide may evoke a methamphetamine associated memory and that ondansetron can disrupt its reconsolidation. These data suggest that pergolide plus ondansetron treatment may be useful as a therapy to reduce relapse in methamphetamine abusers.

Keywords: Methamphetamine; Sensitization; Reinstatement; Ondansetron; Pergolide; Withdrawal; Nose-poke

1. Introduction

Methamphetamine abuse continues to rise while there are no Food and Drug Administration (FDA) approved medications for this problem. Previous strategies have focused on testing compounds which block amine transporters or bind dopamine receptors as well as other targets (Vocci and Ling, 2005). We have found the 5-HT_3 receptor antagonist ondansetron to be useful in reducing cocaine sensitization (King et al., 2000; Davidson et al., 2002a) and self-administration on a progressive ratio schedule (Davidson et al., 2002a). Importantly, ondansetron was effective when given after the self-administration schedule, during the acute cocaine withdrawal period, where it reduced cocaine intake on the following day. Ondansetron had no effect on self-administration when given on its own (Davidson et al., 2002a, 2004). Thus ondansetron was effective when given not before cocaine, as is usually the case, but 3.5 h after cocaine, during acute cocaine withdrawal.

The fact that ondansetron appears to be most useful in rodent models of drug abuse when given during the acute cocaine withdrawal is problematic from a treatment perspective. It is unlikely that stimulant addicts will be available for treatment during the acute withdrawal period and giving cocaine as part of a drug therapy would also be an issue. For this reason we have tested a cocaine-like drug as a substitute. This maintenance-type pharmacotherapy, which we have found useful in reducing cocaine sensitization (Zhang et al., 2007) consists of first giving a dopamine agonist (pergolide) in order to 1) simulate part of the action of methamphetamine by stimulating dopamine D_1 receptor mediated pathways and 2) evoke a mild stimulant-like effect followed by a withdrawal period. We then gave ondansetron, 3.5 h later, during the putative acute withdrawal. We hypothesized that ondansetron can disrupt a type of "reconsolidation" process, which may involve dopamine D_1 receptor activation (Sherry et al., 2006), leading to a less addicted brain (Lee et al.,

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2005, 2006; Millar and Marshall, 2005). That is, the drug associated memories of methamphetamine may be evoked by pergolide, and their reconsolidation, a period when the memory is particularly labile, is then disrupted by ondansetron. One mechanism by which ondansetron could disrupt memory reconsolidation is by inhibiting protein kinases such as extracellular signal-regulated kinase (ERK) which is essential to memory reconsolidation (Svensson et al., 2006; Girault et al., 2007).

There are other considerations for using pergolide as a substitute for methamphetamine: first, pergolide is not only a direct agonist at dopamine D_1/D_2 receptors but also is a partial 5-HT_2 receptor agonist, and thus is expected to better match the mixed dopamine/5-HT indirect agonist profile of methamphetamine. Second, the clinical profile of pergolide is well-established because it has been used in the treatment of Parkinson's and other neuropsychiatric disorders (Langtry and Clissold, 1990). We propose that pergolide, when followed in the acute withdrawal by the 5-HT_3 receptor antagonists ondansetron, will attenuate methamphetamine induced sensitization and drug-seeking behavior. Our treatment strategy is to maintain the "desensitized" state with continued treatment thus facilitating methamphetamine abstinence.

In the present study, we use the behavioral sensitization model as a high throughput screen where we can test a number of pharmacotherapies relatively quickly. Pharmacotherapies which are useful in the sensitization model are then tried in our more time consuming i.v. self-administration extinction and reinstatement model.

2. Methods

2.1. Methamphetamine sensitization experiment

2.1.1. Animals

Adult male Sprague–Dawley rats, initially weighing 300–320 g (Charles River Laboratories), were acclimated to the vivarium on a 12-h light/dark cycle (light, 7 AM to 7 PM). One week later, they were housed in pairs in plastic cages according to the "Guide for Care and Use of Laboratory Animals". The following procedures were approved by the Duke University Institutional Animal Use and Care Committee.

2.1.2. Methamphetamine pretreatment

The animals were implanted with Alza Osmotic pumps (model 2ML1, Alza Corporation, Palo Alto, CA) filled with (+)-methamphetamine hydrochloride (Sigma, St. Louis, MO) to provide 25 mg/kg/day dosing. The pumps were primed by warming in a water bath at 37 °C for 3 h and modified by adding a microdialysis fiber to disperse the drug over a wider surface area. Surgery: the animals were anesthetized by brief methoxyflurane inhalation. A 2 cm vertical incision and a large subcutaneous pocket were made on the dorsal surface. The pump was implanted into this pocket with the delivery portal toward the head. The incision was closed with metal surgical autoclips. Daily methamphetamine injections: methamphetamine was injected (1 ml/kg, s.c.) at 1, 2, 4, 6, 6, and 6 mg/kg/day for 6 days, starting the day after surgery. Daily injections were given to produce a methamphetamine spike. The combination of methamphetamine minipump plus daily s.c. injection can be considered a good model of the human escalating binge dosing profile. In humans the half-life of methamphetamine is long thus bingers have relatively steady plasma methamphetamine levels, with spikes when methamphetamine is taken. In rodents methamphetamine has a short half-life thus minipumps can be used to provide longer plasma methamphetamine coverage. The relevance of methamphetamine dosing regimens in rodents has been reviewed (Davidson et al., 2001; Cho et al., 2001). On day 7, the minipumps were removed and the residual amount of methamphetamine was measured to make sure the pump worked.

2.1.3. Experimental groups

One group of rats received a methamphetamine minipump plus methamphetamine s.c. injection and then underwent 9 days of withdrawal. Another group of rats received a saline minipump plus daily s.c. saline injection, also followed by 9 days of withdrawal. On day 10 of withdrawal these rats received one of 3 treatments. 1) DMSO (1%) plus saline; 2) pergolide (0.1 mg/kg) plus saline or 3) pergolide plus ondansetron (0.2 mg/kg), thus there were 6 groups in total ($n=11–20$). The second injections were all given 3.5 h after the first injection. These doses were chosen as we have found them to be effective in attenuating cocaine sensitization and self-administration (Davidson et al., 2002a; Zhang et al., 2007). All injections were given at 1 ml/kg. Pergolide (Sigma, St Louis, MO) was dissolved in 10% DMSO, then diluted1:10 with sterile 0.9% saline before use. Ondansetron hydrochloride dihydrate was obtained from the Duke Pharmacy and diluted 1:10 with sterile 0.9% saline prior to use. Table 1 summarizes the treatments.

2.1.4. Acute methamphetamine challenge and behavioral rating

On day 28 of methamphetamine withdrawal animals, in their home cages, were taken from the vivarium to the laboratory where they were allowed to acclimate for 60 min. After acclimation behavioral ratings were taken every 5 min. After the first 3 ratings, animals were injected with 0.5 mg/kg methamphetamine (i.p. 1 ml/kg), behavior was monitored over the next 60 min. Behavioral ratings (Table 2) were taken as previously described (Davidson et al., 2002b). Behavioral ratings were given at 5 min intervals with 20 s observation period for each rat. Locomotor activity is not reported as methamphetamine induced stereotypies decrease ambulations making interpretation of this data difficult (Segal and Mandel, 1974).

2.1.5. Statistical analysis of behavioral rating data

Total ratings over the 60 min post methamphetamine challenge were analyzed. The behavioral rating data is ordinal and therefore it was analyzed using non parametric Kruskal–Wallis ANOVA on ranks. There was no difference ($H(2)=0.047$, $P=0.977$) between the 3 saline control groups: (1) saline pump and DMSO plus saline injections (mean ± S.E.M = 84 ± 9); (2) saline pump and pergolide plus saline (82 ± 5) and (3) saline

Table 1
Treatment and testing schedules for the 2 experiments

Experiment	Day				
	1	2–7	8–14	15–19	28
Sensitization	Minipumps 1) meth 2) saline for 7-days	Daily s.c. injections of meth or saline	Withdraw	a) D/S b) P/S c) P/O	Challenge with 0.5 mg/kg meth
Experiment	Day				
	1–5	8–12	15–19	22–23	24–26
Extinction and reinstatement	Autoshape+FR1	FR5	1) D/S 2) P/O	Extinction	Reinstatement 0.1, 0.2, 0.4 mg/kg meth

For the methamphetamine sensitization experiment minipumps were implanted for 7 days, during which daily s.c. injections were also given. Rats were withdrawn for 8 days then treated with a) DMSO plus saline (D/S); b) pergolide plus saline (P/S) or pergolide plus ondansetron (P/O). Rats were tested for behavioral sensitization on day 28 of methamphetamine withdrawal. For the extinction and reinstatement experiment rats were first trained to nose-poke for i.v. methamphetamine using autoshaping, then FR1 and finally FR5 schedules of reinforcement. They were then treated with either 1) DMSO plus saline (D/S) or 2) pergolide plus ondansetron (P/O). After a 2 day extinction period rats were injected with 0.1–0.4 mg/kg methamphetamine s.c. to reinstate methamphetamine seeking behavior.

pump and pergolide plus ondansetron (87±5) thus we combined these 3 groups to give a single control group.

2.2. Methamphetamine self-administration experiment

2.2.1. Animals

Adult male Sprague–Dawley rats (~300 g) were acclimated to the vivarium on a reverse12 h light/dark cycle (light between 7 PM–7 AM) for 1 week prior to surgery. They were housed in pairs and had free access to food and water. The following procedures were approved by the Duke University Institutional Animal Use and Care Committee.

2.2.2. Surgery

Animals were anesthetized (pentobarbital 50 mg/kg i.p.), shaved and an incision made above the jugular vein. A catheter was fed from the jugular to an opening between the shoulder blades. A 0.047 in. o.d, 0.025 in. i.d. catheter (Silastic) was inserted through the vein towards the heart. The other end of the catheter was fed through the dorsal incision to an infusion harness (CIH95, Instech). Rats were then housed alone.

Table 2
Behavioral rating scale

Score	Classification	Definition
1	Asleep	Lying down, eyes closed
2	Almost asleep	Lying down, eyes partially shut
3	Dystonia	Lying down, abnormal posture, tense muscles
4	Inactive	Lying down, eyes open, infrequent sniffing
5	In place oral behavior	Lying down, oral movements (e.g. yawning)
6	Grooming	Grooming of face, body, or groin
7	Normal active movement	Investigation or sniffing of cage, rearing
8	Hyperactive	Running with rapid jerky positional changes
9	Slow-patterned movement	Repetitive exploration of the cage under normal activity
10	Fast-patterned movement	Intense, rapid repetitive exploration of cage
11	Hyper-reactive	Jumpy or jerky violent movements

To examine methamphetamine induced behavioral activation we rated rats behavior. Each rat is examined visually every 5 min for 20 s and the predominant behavior is noted.

2.2.3. Test apparatus

This consisted of Med Associates rat boxes inside sound attenuating boxes. The inner box had 2 Med Associates nose-poke holes (2 cm diameter) situated at each ends 9 cm above floor level. A photobeam detector was located at each hole so that interruption of the beam (nose-poke) was registered by computer. The contingent hole was fitted with a white light at the back which denoted when methamphetamine was available. The presence of a "house light" in the test chamber indicated an open session, and went off when the session closed or during the 20 s post reinforcement time-out (to avoid overdose). The Med Associates operating system controlled the syringe pumps.

2.2.4. Training

7 days after surgery the rat was introduced to the test apparatus and given 2–3 days of autoshaping (Carroll and Lac, 1993) where the white light behind the contingent nose-poke hole went on as the rat was given a free (non-contingent) methamphetamine infusion (0.05 mg/kg/infusion). During these days rats were also able to earn an infusion on a fixed-ratio (FR) FR1 schedule where each nose-poke in the contingent hole earned a methamphetamine infusion. A maximum of only 50 infusions per session was allowed to avoid overdose. Animals were then trained on the FR1 schedule for 2–3 days. In the second week of testing, animals worked under an FR5 schedule of reinforcement (5 nose-pokes needed for each infusion) for 0.1 mg/kg/infusion, again with a maximum of 50 infusions. The final 3 days of FR5 testing was used as the "baseline" measurement of responding. These sessions finished at 50 infusions or 5 h, whichever came first.

2.2.5. Treatment

After 3 days of methamphetamine withdrawal in their home cages we treated rats for 5 days with first pergolide (0.1 mg/kg s.c.) followed 3.5 h after with ondansetron (0.2 mg/kg s.c.; P/O in the figures). These doses were used as we found them to be useful in

reversing methamphetamine sensitization (see below). Control rats received corresponding DMSO (1%) plus saline injections. Three days after the last pergolide plus ondansetron dose we reintroduced rats to the testing chamber for their first extinction session.

2.2.6. Extinction and reinstatement

The previously contingent nose-pokes were no longer paired with drug delivery. All other variables were as during the testing phase except that, since no methamphetamine could be self-administered, the 50 infusion limit was removed in order to observe the full extent of drug-seeking behavior. Session time was again limited to 5 h. During the first day, animals received no treatment prior to the session. On the second day a s.c. saline injection was given prior to testing (1 ml/kg). Day 3, 4, and 5 consisted of 1 ml/kg subcutaneous injections of 0.1, 0.2 and 0.4 mg/kg s.c. methamphetamine respectively prior to testing. It should be noted that we have used a short, 2-day extinction period which reduces responding by greater than 50%. Other groups use longer periods of extinction, but many days (10–20) are needed in order to get responding to very low levels. The clinical relevance of extinction has been questioned as it bears little relationship to drug abstinence. Further, extinction itself may normalize stimulant induced changes in protein levels (Self et al., 2004). Thus as a compromise we used a shorter extinction period, resulting in a dramatic decrease in responding, which allows us to use reinstatement drug-seeking behavior as a measure of relapse potential. Table 1 summarizes the treatment, training and testing timeline.

2.2.7. Data analysis for reinstatement experiment

The baseline data were analyzed using *T*-test. Responding during reinstatement was expressed as a percentage of the second extinction day and analyzed using a 2-way repeated measure ANOVA (one factor repetition) using SigmaStat software. All pairwise multiple comparisons used the Holm-Sidak method. Significance was set at $P<0.05$. Values presented are means±S.E.M.s.

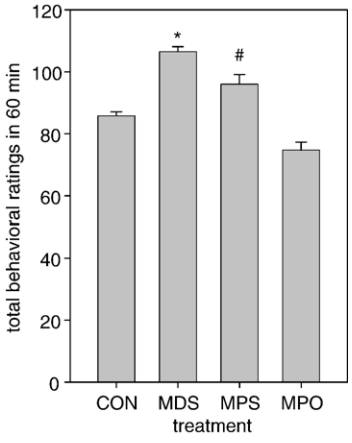

Fig. 1. Acute methamphetamine challenge. Behavioral ratings are taken every 5 min. After 15 min a challenge dose of methamphetamine is given (0.5 mg/kg i.p.) and ratings are recorded for the next 60 min. Methamphetamine pretreated rats given DMSO and saline (MDS) show a sensitized response to the challenge dose, but methamphetamine treated rats given pergolide plus ondansetron (MPO) are not sensitized. Methamphetamine rats treated with pergolide plus saline (MPS) are not different from controls (CON) or MDS, but are more sensitized versus the MPO group. *significantly different from controls and MPO ($P<0.05$). #significantly different from MPO ($P<0.05$). $N=14$–40.

Table 3
Baseline data prior to reinstatement

Treatment	Average daily dose (mg/kg)	Weight (g)	Training pokes		Extinction pokes
			Correct	Incorrect	
Controls	3.04±0.32	307±4	187±9	11±3	52±7
Pergolide/ondansetron	2.84±0.22	313±9	197±30	38±22	73±16

There were no significant differences in drug history (average daily dose self-administered), rat weight at end of training, number of correct or incorrect pokes at the end of training, or in the extent of extinction (all $P>0.25$). Values are means±S.E.M.s, $n=5$ for both groups. Controls received DMSO plus saline (D/S) injections.

3. Results

3.1. Reversal of sensitization

The 7-day methamphetamine treatment regimen caused behavioral sensitization to the acute methamphetamine challenge on day 28 of withdrawal. This sensitization was reversed by pergolide plus ondansetron treatment, but not by pergolide alone (Fig. 1). Comparing the behavioral ratings for the 4 groups, there was a significant effect of treatments: $H(3)=26.2$, $P<0.001$. Multiple comparisons using Dunn's method revealed that the methamphetamine plus DMSO and saline group (M–DS) showed increased stereotypies versus both the control ($Q=3.76$, $P<0.05$) and methamphetamine plus pergolide and ondansetron (M–PO) group ($Q=4.75$, $P<0.05$), but was not different from the methamphetamine plus pergolide alone (M–PS) group ($Q=1.47$, $P>0.05$). The methamphetamine plus pergolide alone group exhibited greater behavioral activation versus the methamphetamine plus pergolide and ondansetron group ($Q=3.06$, $P<0.05$), but not the control group ($Q=1.88$, $P>0.05$).

3.2. Baseline self-administration data

At the end of training, there was no difference between the 2 groups in the rat weights, average daily methamphetamine dose self-administered or number of nose-pokes during baseline sessions (Table 3). That is, prior to pharmacotherapy treatment, both groups were very similar. There was also no difference in the degree of extinction between the 2 groups ($P=0.26$); the total number of nose-pokes in the contingent hole on the second extinction day were 52±7 (range 32–69) for the controls and 73±16 (range 21–118) for the pergolide plus ondansetron group.

3.3. Reinstatement of methamphetamine seeking behavior

There were significant overall effects of pergolide plus ondansetron treatment ($F(1, 29)=5.767$; $P<0.05$), methamphetamine reinstatement dose ($F(2, 29)=12.293$; $P<0.001$) and their interaction ($F(2, 29)=4.038$; $P<0.05$). Pergolide plus

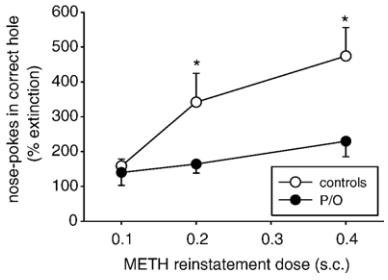

Fig. 2. Nose-poke behavior was evoked using injections of methamphetamine (0.1–0.4 mg/kg s.c.). Rats treated with pergolide plus ondansetron (P/O) had a reduced response to methamphetamine in this reinstatement paradigm. Values are means ± S.E.M.s, $n = 5$ for both groups. Controls received DMSO plus saline injections.

ondansetron treatment attenuated methamphetamine induced reinstatement. Overall, there was a dose dependency with the 0.4 mg/kg injection evoking most methamphetamine seeking behavior. Within the control group there was a clear dose-dependent effect, however within the pergolide plus ondansetron group the dose-response curve was flat. Examining each reinstatement dose of methamphetamine, there was no difference in responding between controls and pergolide plus ondansetron at the low methamphetamine dose (0.1 mg/kg) but there was a clear reduction in methamphetamine seeking in the pergolide plus ondansetron group at both 0.2 ($P < 0.05$) and 0.4 ($P < 0.01$) mg/kg doses (Fig. 2).

3.4. Reinstatement of non-contingent nose-pokes

There were no significant differences between the controls and pergolide plus ondansetron groups in the number of non-contingent nose-pokes on any extinction or reinstatement day ($P = 0.616$) suggesting that pergolide plus ondansetron treatment selectively attenuates methamphetamine seeking behavior and not general activity or nose-poking per se.

4. Discussion

Because i.v. self-administration experiments are costly and time consuming, we first tested the putative pharmacotherapies in our behavioral sensitization model. The relevance of sensitization to drug abuse and self-administration has been reviewed (Schenk and Partridge, 1997; Robinson and Berridge, 2001). The pergolide plus ondansetron treatment was more effective than pergolide alone in reducing methamphetamine sensitization (Fig. 1). Our previous studies suggest that ondansetron is not effective in self-administration models when given alone (Davidson et al., 2002a). Thus we only examined the combination therapy of pergolide plus ondansetron in the present self-administration study.

We found that 5 days of treatment, during early methamphetamine withdrawal, with pergolide followed 3.5 h later with ondansetron, can attenuate methamphetamine induced behavioral sensitization and reinstatement of methamphetamine seeking behavior. These data support our previous data using ondansetron in cocaine self-administering and cocaine sensitized rats (Davidson et al., 2002a, 2004; Zhang et al., 2007). Thus 5-HT_3 receptor mechanisms may be important, at least for the consolidation of sensitization and self-administration behavior during early methamphetamine withdrawal. Ondansetron has previously been used in i.v. cocaine self-administration (Peltier and Schenk, 1991; Lane et al., 1992) and conditioned place-preference (Cervo et al., 1996) with little effect. However in all of these cases ondansetron was given prior to the test session. It should be remembered that ondansetron has a short half-life in rodents (12 min; Saynor and Dixon, 1989) and thus if given prior to a test session one may not expect it to have a consistent effect especially if, as we hypothesize, it alters processes that occur after the administration of the stimulant.

The acute stimulant withdrawal period may represent a treatment window. For example, consolidation of sensitization may be attenuated by disrupting certain neuroplastic mechanisms. These mechanisms may include phosphorylation of NMDA or AMPA receptor subunits in limbic brain regions, which are not only markers of psychostimulant sensitization (Loftis and Janowsky, 2002) but may be important in mediating long-term changes associated with addiction (Kalivas and Volkow, 2005). Recently, we have found ondansetron given in the acute pergolide withdrawal to reverse specific NMDA and AMPA phosphorylation changes in limbic brain regions after cocaine (Zhang et al., 2007). Possible mechanisms behind these 5-HT3 receptor effects could include attenuation of protein kinases, which may decrease NR2B or GluR1 receptor subunit phosphorylation.

In the present self-administration study we only tested the combination treatment of pergolide plus ondansetron. We did not test the effects of pergolide or ondansetron alone. Previous clinical studies have suggested that pergolide monotherapy is not efficacious in stimulant abuse (Malcolm et al., 2000). Ondansetron alone may have some clinical use in cocaine (Johnson et al., 2006) but not methamphetamine addicts (Johnson et al., 2004) but our previous data suggest that ondansetron is most useful in attenuating cocaine self-administration (Davidson et al., 2002a) or reversing cocaine sensitization (Zhang et al., 2007) when given in the acute cocaine or pergolide withdrawal period. Further, the data presented here show that the combination treatment of pergolide plus ondansetron is more effective than pergolide alone in reversing methamphetamine sensitization. Thus, although we cannot state definitively that pergolide or ondansetron alone would not be effective treatments for drug induced relapse, our previous data suggest that the combination treatment is most effective. This treatment regimen also fits with current thinking on the disruption of reconsolidation processes as a treatment for drug addiction (Lee et al., 2005, 2006).

It is noted that sensitization was reduced 2 weeks after the pergolide plus ondansetron treatment while reinstatement was evoked 5–7 days after our pergolide plus ondansetron treatment. Despite this, we still found the pergolide plus ondansetron treatment to be effective in both models. These data are in agreement with our previous studies which have found ondansetron to be effective for a number days after dosing stopped (King et al., 2000; Davidson et al., 2002a, 2004). Thus the pergolide plus ondansetron treatment could be given as a maintenance treatment for methamphetamine or

cocaine abusers. However, if methamphetamine associated memory reconsolidation was disrupted, then perhaps only a few days of inpatient treatment would be required, further studies are needed to explore this possibility.

Johnson et al. (2006) recently reported that ondansetron improved days off in cocaine abusers but we believe our new pergolide plus ondansetron paradigm, will provide a better maintenance treatment for stimulant abusers. We note that pergolide may not be the optimal dopamine agonist for human use due to its large volume of distribution and long half-life (Thalamas et al., 2005). As well, pergolide has recently been found to have cardiotoxic effects (Schade et al., 2007). This makes its use less appealing, although the dose used in the present study (0.1 mg/kg) is small. Regardless, pergolide plus ondansetron treatment may be useful in methamphetamine abusers in early abstinence.

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