

## Long-term methadone maintenance reduces protracted symptoms of heroin abstinence and cue-induced craving in Chinese heroin abusers

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### Abstract

**Background:** Cession of heroin use may be followed by a protracted-abstinence (PA) syndrome consisting of craving, negative mood, and physiological changes. PA symptoms have rarely been compared between drug-free and methadone-maintained former heroin users after similar lengths of heroin abstinence.

**Methods:** Seventy former heroin users were included in one of four groups: in day 15–45 of methadone maintenance therapy (short-term MMT), in month 5–6 of MMT (long-term MMT), opiate-free for 15–45 days after methadone-assisted heroin detoxification (short-term post-methadone), and opiate-free for 5–6 months after methadone-assisted heroin detoxification (long-term post-methadone). PA symptoms (negative mood, dyssomnia, somatization, and craving), and blood pressure and pulse were assessed pre- and post-neutral videotape and pre- and post-heroin videotape.

**Results:** Dyssomnia and the total PA score were worst in short-term post-methadone participants, mood was best in long-term MMT participants, and cue-induced craving was least severe in long-term MMT participants. Blood pressure and pulse did not differ across groups.

**Conclusions:** Even after acute withdrawal, the first months of heroin abstinence after methadone-assisted detoxification may be more difficult in terms of cue-induced craving and other PA symptoms than the first months of heroin abstinence during MMT. Our findings add to the literature supporting MMT for prevention of cue-induced heroin craving.

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**Keywords:** Heroin dependence; Methadone maintenance; Craving; Protracted withdrawal symptoms; Mood; Somatization; Dyssomnia

There exist numerous references in the literature to a protracted-abstinence (PA) syndrome extending beyond the acute withdrawal phase following discontinuation of illicit opioids. Clinicians have generally described the components as craving (Dole, 1968), negative mood or anhedonia (Krupitsky et al., 2002a,b), and altered physiological parameters (Martin and Jasinski, 1969) that temporally follow acute withdrawal. The PA syndrome has sometimes been called “protracted withdrawal,” but the use of that term has been discouraged because not all PA symptoms are opposite those of intoxication and because some PA symptoms may reflect lingering toxic effects or unmasked preexisting conditions (Satel et al., 1993).

Surprisingly, there seem to be few studies in which PA symptoms are directly compared between drug-free and methadone-

maintained former heroin users. Such studies would help to determine whether drug-free former heroin users spend some time in greater discomfort than methadone-maintained former heroin users even after acute withdrawal symptoms have resolved. This would be worth knowing in order to inform treatment decisions and to help prepare patients for the first weeks or months of abstinence. A search of the Medline and PsycInfo databases from 1950 to 2007 uncovered several studies in which drug-free and methadone-maintained former heroin users were compared in terms of personality (Cohen et al., 2005) or neuropsychological performance (Prosser et al., 2006), but only one that compared abstinence symptoms (Judson and Goldstein, 1982). In that study, 16 former heroin users were assessed while stabilized on methadone (with at least 13 weeks of heroin abstinence) at a mean dosage of 69 mg/day (range 30–100 mg/day), then assessed again at least 6 months after detoxification, with current heroin abstinence verified by urinalysis (and no use for 6 months by self-

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report). Results generally showed more symptomatology while on methadone than while drug-free; many of the symptoms appeared to be side effects of methadone (sweating, constipation, and sexual dysfunction), but craving was also higher while on methadone than while drug-free. Measures of negative mood (unhappiness, nervousness) did not differ significantly at the two time points and actually tended to be worse at the drug-free time point.

In the present study, we have attempted to extend prior findings by testing former heroin users at more than one time point (though in a between-groups design) during methadone maintenance or during a drug-free state following methadone-assisted detoxification. In addition to assessing abstinence symptoms by questionnaire, we used a laboratory procedure to assess cue-induced craving. We hypothesized that symptoms of PA would be lower in MMT patients than in currently unmedicated former heroin users and would further decrease with greater time in MMT.

## 1. Methods and materials

### 1.1. Subjects

Seventy male subjects were selected for inclusion in one of four groups based on their treatment status: (1) former heroin users currently in day 15–45 of methadone maintenance therapy (short-term MMT); (2) former heroin users currently in month 5–6 of MMT (long-term MMT); (3) former heroin users who had undergone methadone-assisted heroin detoxification and had been opiate-free for 15–45 days (short-term post-methadone); (4) former heroin users who had undergone methadone-assisted heroin detoxification and had been opiate-free for 5–6 months (long-term post-methadone). For inclusion in the MMT or post-methadone groups, participants were required to have met Diagnostic and Statistical Manual of Mental Disorders ([American Psychiatric Association, 2000](#)) criteria for opioid dependence in the past 12 months, as assessed by the Structured Clinical Interview for the DSM-III-R (SCID). Both MMT and post-methadone subjects were required to have negative urine toxicology screening tests (excluding methadone in the MMT group) at the time of study enrollment and urine drug screens were conducted weekly after enrollment. The MMT subjects were recruited from the MMT Program of Beijing Ankan Hospital, Beijing City and the post-methadone subjects were recruited from the Addiction Treatment Center of Beijing Ankan Hospital, Beijing City. Inclusion criteria were: (1) DSM-IV criteria for heroin dependence; (2) 18–45 years old; (3) without use of cocaine and other drugs. Exclusion criteria were: (1) current or past psychiatric illness other than heroin dependence; (2) neurological signs and/or history of neurological disease; (3) history of head trauma; (4) history of cardiovascular or endocrinologic disease; (5) current medical illness.

Eighteen subjects were recruited in the short-term post-methadone group (mean age=35.2 years old [SD=7.8]). Eighteen subjects were recruited in the long-term post-methadone group (mean age=32.3 years old [SD=5.7]). Seventeen subjects were recruited in the short-term MMT group (mean age=37.2 years old

[SD=5.5]). Seventeen subjects recruited in the long-term MMT group (mean age=36.5 years old [SD=5.3]) who had been in MMT for 5–6 months (confirmed by urine toxicology). Drug-use characteristics are presented in [Table 2](#).

All participants gave written informed consent after having the purpose of the study explained to them by the investigators. The study was approved by the National Institute on Drug Dependence, Peking University.

### 1.2. PA symptoms

The PA symptoms assessed included three components: somatization, negative mood, and dyssomnia; each component was assessed by a separate questionnaire. The somatization questionnaire consisted of eight questions, rated on a scale of zero (no effect) to four (strongest). The questionnaire asked about the following symptoms: (1) panic, (2) bodily malaise, (3) restlessness, (4) musculoskeletal pain, (5) sluggishness, (6) yawning, tearing, and runny nose, (7) gooseflesh, (8) loss of appetite. The negative-mood questionnaire consisted of four questions, rated on a scale of zero (no effect) to four (strongest). The questionnaire asked about the following symptoms: (1) dysphoria, (2) loneliness, (3) loss of interest in daily activities, and (4) irritability. The dyssomnia questionnaire consisted of five questions, rated on a scale of zero (no effect) to four (strongest). The questionnaire asked about the following symptoms: (1) insufficient sleep duration, (2) difficulty falling asleep, (3) restless sleep, (4) early awakening, and (5) dizziness on awakening.

### 1.3. Stimulus videotapes

There were two kinds of videotapes: neutral and heroin-related, each 5 min in length. The neutral videotape involved scenes that were non-emotional in content, such as birds, flowers, or trees. Heroin-related videotapes included heroin-use scenes.

### 1.4. Craving measures

Craving was also assessed by a 10-point visual analog scale (VAS) ([Sinha et al., 1999, 2000](#)), which participants marked as 1 (“not at all”) to 10 (“extremely high”) in response to the question, “How much do you feel urge to use heroin?” Craving ratings were obtained at baseline and immediately after exposure to neutral or heroin videotape.

### 1.5. Pulse rate and blood pressure measures

Acquisition and on-line analysis were accomplished with a Grass Model 7 polygraph. Blood pressure was measured on line with an SD-700 monitor (IBS Corporation, Mass., USA). Pulse rate was measured continuously with a sensor attached to the subject's finger and connected to an SD-700 monitor.

### 1.6. Test sessions

Subjects were scheduled for a battery of tests at four time points: pre-neutral videotape, post-neutral videotape, pre-heroin

videotape and post-heroin videotape. All subjects completed the PA questionnaires before each test. Baseline measures of blood pressure, pulse, and heroin craving were taken during 5 min of rest. They subjects watched a neutral videotapes for 5 min (neutral condition). The neutral condition was followed by another heroin-related videotape for 5 min (heroin-related condition). Following each condition, measures of blood pressure, pulse, and heroin craving were taken again. The order of the tests is listed in Table 1.

### 1.7. Statistical analysis

All data are reported as mean±SD for each participant. Reactivity to cues was assessed using change scores from baseline for craving ratings. Between-group comparisons were analyzed using one-way analysis of variance (ANOVA) and post hoc *t* tests if the omnibus *F* was significant. Within-group comparisons were analyzed using repeated-measures ANOVA and post hoc *t* tests if the omnibus *F* was significant. *p* values less than or equal to 0.05 were judged statistically significant. The analyses were performed with SPSS 13.0.

## 2. Results

### 2.1. Subject characteristics

As shown in Table 2, there were no significant differences between groups on demographic measures. Duration of heroin abuse in the MMT groups was significantly higher than in the post-methadone groups ( $p=0.002$ ). Given that our purpose was to assess MMT's effectiveness on PA symptoms and craving, this difference rendered our comparisons more stringent.

### 2.2. Protracted-abstinence symptoms

For somatization, there was no significant difference between groups [ $F(3, 66)=2.297, p=0.086$ ] (Fig. 1a). There were significant group differences in dyssomnia [ $F(3, 66)=9.382, p<0.001$ ] and total score [ $F(3, 66)=6.339, p=0.001$ ], each with a similar pattern: symptoms were higher in the short-term post-methadone group than in any of the other 3 groups (Fig. 1c–d). There was also a significant group difference in negative mood [ $F(3, 66)=3.763, p=0.015$ ], with a different pattern: Symptoms were

Table 1  
Schedule of assessments

–0:05 min Subjects arrived in laboratory room. Demographic questionnaire, PA symptoms scale.

#### Neutral video (condition 1)

0:00 min Baseline period: on-line pulse and blood pressure, craving score  
0:05 min Neutral video shown  
0:10 min On-line pulse and blood pressure, craving score  
0:15 min 10-min relaxation period

#### Heroin-cue video (condition 2)

0:25 min Baseline period: on-line pulse and blood pressure, craving score  
0:30 min Heroin-cue video shown  
0:35 min On-line pulse and blood pressure, craving score

Table 2  
Demographic and clinical characteristics of subjects

| Characteristic                               | Short-term post-methadone (n=18) | Long-term post-methadone (n=18) | Short-term MMT (n=17) | Long-term MMT (n=17) | <i>p</i> value from ANOVA |
|--|----------------------------------|---------------------------------|-----------------------|----------------------|---------------------------|
| Age (years±SD)                               | 35.2±7.8                         | 32.3±5.7                        | 37.2±5.5              | 36.5±5.3             | 0.094                     |
| Years of education (±SD)                     | 9.2±2.1                          | 10.0±3.3                        | 9.2±1.9               | 11±2.6               | 0.130                     |
| Duration of heroin use (years±SD)            | 6.9±4.7                          | 7.2±4.7                         | 11.6±4.0              | 10.5±3.3             | 0.002 <sup>a</sup>        |
| Average heroin dose (g/day±SD)               | 0.7±0.7                          | 0.5±0.4                         | 0.9±0.4               | 0.8±0.4              | 0.249                     |
| Average money spent on heroin (US \$/day±SD) | 65.8±58.5                        | 46.0±31.9                       | 65.7±26.1             | 64.6±34.1            | 0.285                     |
| Average methadone dose (mg/day±SD)           |                                  |                                 | 48.5±10.3             | 41.2±15.6            |                           |

<sup>a</sup> Significant difference between methadone-maintenance groups and protracted-abstinence groups.

similar in the two post-methadone groups, lower in each of the two MMT groups than in the long-term post-methadone group, and also lower in the long-term MMT group than in the short-term post-methadone group (Fig. 1b).

### 2.3. Craving scores

Change scores for cue-induced heroin craving differed across groups [ $F(3, 66)=4.247, p=0.008$ ]; the long-term MMT group was significantly less responsive than either of the post-methadone groups (Fig. 2). In within-group comparisons, there were no significant differences in craving scores of pre-neutral videotape, post-neutral videotape, or pre-heroin videotape, but scores were significantly greater for post-heroin videotape ( $p<0.05$ ; data not shown).

### 2.4. BP and PR

Blood pressure and pulse did not differ between groups at any time point tested (data not shown).

## 3. Discussion

We assessed cue-induced craving and other symptoms of protracted abstinence (PA) in methadone-maintained and post-methadone participants after differing lengths of abstinence from heroin. We found that dyssomnia and the total PA score were worst in short-term post-methadone participants, mood was best in long-term MMT participants, and cue-induced craving was least severe in long-term MMT participants. Thus, our results generally suggest that PA is more severe during the first 5–6 months of a drug-free, post-methadone state than during the first 5–6 months of methadone maintenance.

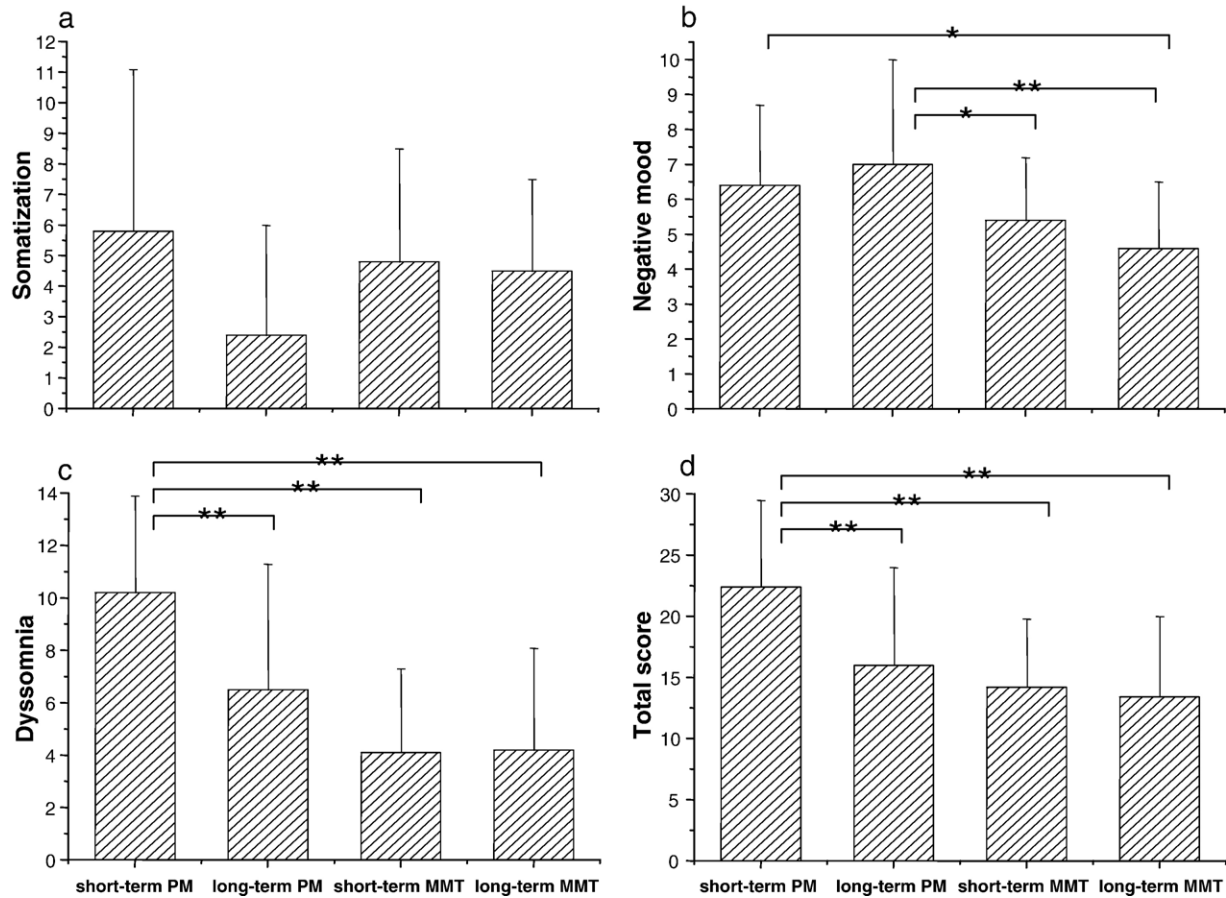


Fig. 1. Protracted-abstinence-symptom ratings. a, somatization; b, negative mood; c, dysomnia; d, total score. Horizontal bars show results of post hoc *t* tests: \* $p < 0.05$ ; \*\* $p < 0.01$ . See text for omnibus *F* values.

These results differ somewhat from the results of the only similar published study we were able to find (Judson and Goldstein, 1982). In that study, self-reported heroin craving was greater during methadone maintenance than when assessed in the same participants 6 months after detoxification. MMT participants in that study had been abstinent from heroin for a minimum of only 13 weeks; in our study, (cue-induced) craving in MMT participants did not become lower than in other groups until 5–6 months of abstinence. Thus, the discrepancy may be attributable to more elapsed time since the last use of heroin in our long-term MMT group.

Even in our long-term MMT group, cue-induced craving was not blocked completely, nor was there a significant diminution in somatization (in fact, there was a nonsignificant tendency for somatization to be lowest in the long-term post-methadone group). The modesty of methadone's effects in our participants is probably attributable to the fact that, per clinic policy, the mean dose was low—less than 50 mg/day. Methadone is most effective in the range of 80 to 120 mg daily (Dole and Nyswander, 1965; Donny et al., 2005; Faggiano et al., 2003; Strain et al., 1999). Still, the fact that group differences were seen even at such low maintenance doses of methadone may, in some respects, strengthen our findings.

Methadone maintenance as a treatment for opioid dependency has been advocated since the pioneering work of Dole and

Nyswander (Dole and Nyswander, 1965; Dole, 1967). Benefits of MMT include reductions in unemployment, drug-related mortality, infectious disease (including HIV and other blood-borne infections), and criminal behavior (Cooper et al., 1983; Davoli et al., 1993; Gearing and Schweitzer, 1974; Gronbladh et al., 1990; Muraskin, 1988; Patti et al., 1993; Senay, 1985; Tims, 1984) (Cooper, 1989; Marmor et al., 1987). The present results confirm

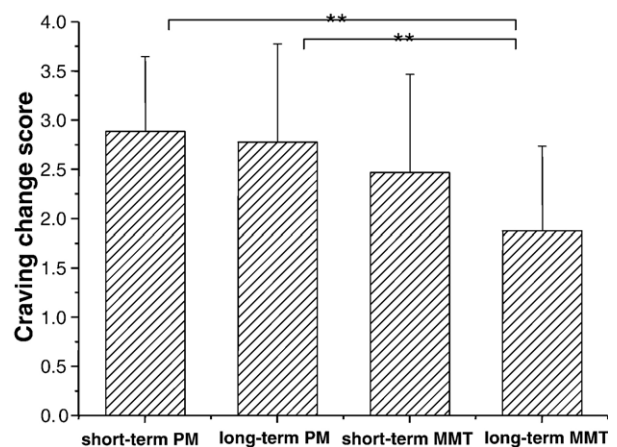


Fig. 2. Change scores for heroin craving post-heroin video. Horizontal bars show results of post hoc *t* tests: \* $p < 0.05$ ; \*\* $p < 0.01$ . See text for omnibus *F* values.



that methadone maintenance decreases cue-induced craving for heroin.

This study does have some limitations. Participants were not randomly assigned to the MMT and post-methadone groups, so some undetected preexisting group differences cannot be ruled out. In the cue sessions, only one order of presentation was used: neutral videotapes first, followed by heroin videotapes. This was done in order to prevent carryover effects from the heroin videotapes. Lastly, we tested only men, who may differ from women in subjective and physiological responses to drug cues (Carroll et al., 2004; Yu et al., 2007); therefore, replication in women is needed.

These limitations notwithstanding, our findings suggest that the first several months of heroin abstinence after methadone-assisted detoxification may be more difficult in terms of cue-induced craving and other PA symptoms than the first several months of heroin abstinence during MMT. Further studies are needed to determine whether the same holds true for drug-free former heroin users who have undergone a taper from long-term methadone maintenance rather than the short detoxification used here, and to compare symptomatology over longer time frames than the ones studied here. Still, our findings add to the large body of literature supporting the use of MMT for prevention of cue-induced heroin craving.

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