Additional methadone increases craving for heroin: a double-blind, placebo-controlled study of chronic opiate users receiving methadone substitution treatment

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Abstract
Aims. To assess the acute-on-chronic effects of methadone on drug craving, mood and cognitive and psychomotor functioning in patients on long-term methadone substitution treatment. Design and participants. A double-blind, cross-over design was used to compare the effects of a 33% increase in patient's daily dosage of methadone with a matched placebo linctus. Eighteen patients completed the study; all were assessed pre- and post-drug on two separate testing days. Findings. Methadone significantly increased both positive craving (expected positive effects) and negative craving (expected relief of withdrawal discomfort) for heroin. Patients were unable to distinguish between methadone and placebo treatments. No differences between treatments emerged in cognitive or psychomotor effects. In terms of mood, patients were more alert and more contented following placebo than following methadone. Conclusions. Additional methadone may "prime" cravings for heroin in methadone substitution patients.

Introduction
Methadone is the most widely used pharmacological treatment for people dependent on opioids, with methadone substitution programmes remaining popular in many Countries since the advent of HIV and MDS (Gossop & Grant, 1991; Ball & Ross, 1991). Despite its widespread use, relatively little is known of the acute on chronic effects of methadone on drug craving, cognitive function and mood. Methadone is an opiate agonist acting at μ opioid receptors (Koob, 1992). It is well absorbed with oral bioavailability of 90% (Sawe, 1986) and peak plasma concentration being reached 2-4 hours after oral administration (Koob, 1992). Its plasma elimination half-life is 16-24 hours in opioid-naive people, but in chronic users extends to 24-48 hours) showing considerable individual variation (Tennant, 1987). This variation in how individuals metabolize the drug may contribute to differences in withdrawal symptoms reported by patients on methadone substitution following acute daily dosage (Dyer & White, 1997).

Tolerance to the various effects of most centrally acting drugs builds up over repeated use. However, tolerance may develop at different rates to the drug's differing effects. For example, with benzodiazepines, tolerance to sedative effects develops faster than tolerance to anxiolytic or cognitive effects (Curran, 1991). Tolerance to the euphoric and analgesic effects of opioids such as methadone is thought to develop over repeated use (Gossop, 1987) but it is not clear whether tolerance also builds up to methadone's other effects. The prescribed dose is seldom escalated within treatment settings, but patients may obtain extra methadone as well as other opioids outside the treatment setting.

Studies of the effects of methadone on mood have focused predominantly on mood-related opiate withdrawal symptoms and craving. Musselman & Kell (1995) report improvements over a period of 8 months in anxiety and dysthymia in 71 patients enrolled in a methadone maintenance programme. However, it was not clear from this study whether patients' mood was stabilizing over time on methadone or whether patients were also using illicit drugs. Hiltunen et al (1995) found plasma levels of methadone over a 24-hour period correlated with self-rated levels of anxiety and irritability, although lack of placebo control hinders interpretation of the self report data. Dawe & Gray (1995) compared methadone to clonidine in 16 detoxifying opiate addicts. No significant difference in the effects of these two drugs was
found in terms of people’s desire to use heroin either for its pleasant effect or for alleviating unpleasant mood or feelings.

Drug craving is a central concern for most addicts and for many theoretical conceptualizations of drug dependence. Recently, Tiffany (1992, 1997) has produced a critique of research on drug craving at both a conceptual and an empirical level. At a conceptual level, he has proposed a cognitive processing model of drug craving and drug use. At an empirical level, he has developed several multi-item questionnaires for the reliable assessment of craving in different drug using groups. The most recent scale is the 'heroin craving questionnaire' (HCQ) (Tiffany et al., 1999). The HCQ was initially validated in a sample of 230 heroin users who were not trying to stop using heroin. It has also been used in research with opiate users in the United Kingdom (Weinstein et al., 1998). The HCQ assesses five components of craving for heroin: (i) desire to use (ii) intention to use (iii) anticipation of positive outcome (iv) relief from withdrawal and dysphoria and (v) lack of control over use. Factors (iii) and (iv) correspond, respectively, to positive and negative craving.

Given current concerns about "drug driving" and road traffic accidents, it is also important to know whether methadone impairs the psychomotor skills and speed of reaction time which are central to driving skills. Patients taking other prescribed psychotropics such as benzodiazepines and certain antidepressants are warned about deleterious effects of these drugs on driving and on operating machinery. In reviewing the literature on the cognitive effects of a wide range of opioids, Zaeny (1995) points out that most studies of methadone have methodological problems such as lacking appropriate controls, using small numbers of participants, not allowing for patients’ polydrug use and often relying on one or two arbitrarily selected cognitive tests (especially DSST). One exception is a study by Rothenberg et al (1977) which assessed the effects of two doses of methadone (5 mg, 10 mg) and placebo in 12 patients on methadone substitute treatment and in 12 healthy volunteers. The drug impaired the performance of healthy volunteers on both simple and choice reaction-time tasks, but did not affect the performance of patients, implying that tolerance to the psychomotor or sedative effects of methadone builds up during maintenance treatment.

If maintenance patients become differentially tolerant over long-term use to the effects of methadone on drug craving, mood, cognitive and psychomotor function) then an acute increase in methadone dose should affect measures of these four aspects differentially. Therefore the present study was designed to assess the acute-on-chronic effects of methadone on these measures in maintenance patients. The increased dose was selected as a percentage (33%) increase of each individual's total daily dose. The 33% increase was considered to be the highest dosage useable whilst minimizing any risk of respiratory depression in the outpatient population assessed. The increase was additional to the patient's normal, once-daily dose of methadone. A double-blind, balanced cross-over design was chosen to compare additional methadone with a carefully matched placebo. Of central concern was whether patients' craving, mood, cognitive and psychomotor function changed following additional methadone compared with additional placebo. Our hypothesis was that the increased dose would have global sedative effects which could affect performance across a range of tasks, rather than specific effects on particular cognitive processes. It was also predicted that sedative effects would be apparent following methadone on the subjective mood rating scale employed. In terms of drug craving, the literature does not support a unidirectional hypothesis. Pharmacologically, one would expect a reduction in craving for heroin following additional methadone. However, an opposite effect (increased craving) would be predicted from studies where a drug "primes" craving for more of that drug (e.g. Hodgson, Rankin & Stockwell, 1979).

To test during peak methadone effect, assessments were administered before and 3-4 hours following the additional treatments (Koob, 1992). A range of measures were employed to assess the effects of this increase on craving, cognitive and psychomotor function and mood.

Methods
Participants
Patients over 18 years of age were included who had been taking prescribed methadone for a minimum of 6 months and who had been on the same dose in the 20-100 mg per day range for the previous 4 weeks. In addition, participants needed to have basic literary skills and be able and willing to give informed
consent. Patients were excluded if they had any past history of severe head injury or organic cognitive dysfunction. Eighteen participants fulfilling our inclusion criteria were recruited via their key workers and completed all assessments on both testing days.
The project took place at the Camden and Islington Substance Misuse Services, an out-patient service with over 2000 registered patients, most of whom are classified as opiate-dependent and polydrug users. Ethical approval was given by the ethics committees of University College London and of Camden and Islington Community Health Services NHS Trust. All participants gave written, informed consent.

Design
A double-blind, placebo-controlled, cross-over design was employed with participants being assigned randomly to treatment order (methadone or placebo on the first testing day). Testing occurred pre-drug and then began again 3 hours post-drug on each test day. Versions of tests were counterbalanced across subjects and design.
Participants attended two separate sessions with a 1-week "washout" period between. They were informed that a urine sample would required and breath alcohol levels would be measured on each day. Participants were assured that results of these tests (and all other information obtained in the study) were confidential and would not be reported to their key workers.

Drugs
Methadone formulated in linctus and placebo (the same linctus without methadone) was purchased from Martindale Pharmaceuticals. Eight drops of peppermint essence were added to each dose to give the same taste to methadone and placebo syrups. A hospital pharmacist dispensed both methadone (33% of each participant's daily prescribed dose) and a matched quantity of placebo linctus.

Procedure
A battery of tests was administered at four time-points (pre- and post-drug on each test day). Two additional scales (heroin craving questionnaire and "guess on treatment") were given only at the post-drug testings. Participants arrived at the same time on each test day (either 9 or 10 a.m.) and had taken their daily dose of methadone approximately 40-80 minutes beforehand. The waiting time between test sessions was filled partly by chatting and giving participants time to relax. In addition, on the first test day, this time was also used for administering the National Adult Reading Test (NART) and a drug use questionnaire. One the second test day, participants also watched a video.
A range of tests were used to determine the effect of methadone on mood, cognitive and psychomotor functioning, and craving for heroin. Order of test administration is given in Table 1.

National Adult Reading Test (NART). This test was administered once to provide an estimate of premorbid intellectual function (Nelson, 1982).

Table 1. Order of test administration

Screening tests each day
   Urine sample
   Breathalyser
Tests given pre- and post-drug
   Immediate prose recall
      1. Mood rating scale
      2. Digit symbol substitution test (DSST)
      3. Simple reaction time test
      4. Finger-tapping test
      5. Digit cancellation test
6. Delayed prose recall
Tests given post-drug
Word-stem completion
Heroin craving questionnaire
Guess on treatment Tests given once only
    NART
    Drug use questionnaire

Mood rating scale. This 16 item visual analogue mood rating scale was used to assess subjective feelings at each test time. Principal components analysis of this scale yields three mood factors, alertness, contentedness and calmness (Bond & Lader, 1974). A 17th scale (anchored by "very stoned" - "not at all stoned") was added as a single item.

*Prose recall* Participants listened to an audio-taped prose passage which they then recalled aloud immediately and then again after a delay filled by other tests. This task taps explicit memory. The four parallel versions used were from the Rivermead Behavioural Memory Test (Wilson, Cockburn & Baddlele, 1985) and scoring was standard (for each of 2] "idea units", 1 point is given for correct recall or exact synonym; half a point for partial recall or partial synonym).

*Word-stem completion task.* This task taps implicit memory and was administered post-drug on each test day. Participants were shown a series of 20 words presented one at a time and asked to rate these semantically (how much they liked each word on a five-point scale). They were then given a list of 32 word-stems to complete with "the first English word that came into their minds". Half of these stems could begin words previously presented; the other half were used to obtain base rates of completion. Two sets of words were used on each test occasion: half the subjects were presented one set and half the other set (cf. Curran & Gornstcin, 1993).

*Digit Symbol Substitution Test* (DSST). This sub-test from the Wechsler Adult Intelligence Scale (Wechsler, 1955) requires speeded recording of digits and symbols for 90 seconds.

*Digit cancellation.* This paper-and-pencil test requires visual selectivity at speed and taps focused attention. The participant is asked to delete a target number in rows of random numbers as carefully and quickly as possible. Forty instances of the target number are randomly interspersed with 400 numbers. Time to completion and errors of omission or commission are scored.

*Tapping rate.* This was used as a measure of motor sedation (Frith, 1967). Participants are required to press the space bar of a computer keyboard with two fingers of their preferred hand as quickly as possible for 60 seconds.

*Simple reaction time test.* Participants press the space bar of a computer as soon as they see a stimulus appear on the screen. Twenty-four trials with random inter-trial intervals were given and responses and reaction times were recorded automatically.

*Heroin craving.* The Tiffany Heroin Craving Questionnaire was administered post-drug on each test day. The participant has to rate each of 45 items on a seven-point scale from "strongly disagree to strongly agree". Scoring was standard to yield five components of heroin craving: (1) desire to use (2) intention and plan to use (3) anticipation of positive outcome (4) relief from withdrawal and dysphoria and (5) lack of control over use.

*Guess on treatment.* At the end of each test day, participants were asked to indicate on a form whether they thought they had received (i) an extra dose of methadone (ii) an inert placebo or (iii) were unsure what they had received.

*Demographic information.* This included a full drug history and details of current use of psychotropics.
Statistical analyses
Repeated measures analysis of variance was employed with drug (methadone versus placebo) and test time (pre versus post-drug) as within subjects factors and treatment order (methadone or placebo first) as a between subjects factor. Pearson correlation’s were use to correlate scores on the five HCQ craving factors and to assess relationships between daily dose of methadone and variables showing significant treatment differences.

Table 2. Means (and standard deviations) on mood rating scale, pre- and post-treatments

<table>
<thead>
<tr>
<th></th>
<th>Pre-</th>
<th>Post-</th>
<th>Pre-</th>
<th>Post-</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alert-</td>
<td>39.17(16.64)</td>
<td>42.30(14.85)</td>
<td>40.90 (14.99)</td>
<td>34.73 (11.68)</td>
</tr>
<tr>
<td>Drowsy</td>
<td>40.27(17.91)</td>
<td>37.59(14.44)</td>
<td>43.46 (14.65)</td>
<td>31.80 (13.96)</td>
</tr>
<tr>
<td>Contented-</td>
<td>40.27(17.91)</td>
<td>37.59(14.44)</td>
<td>43.46 (14.65)</td>
<td>31.80 (13.96)</td>
</tr>
<tr>
<td>Discontented</td>
<td>36.11(23.33)</td>
<td>29.47 (16.28)</td>
<td>37.17 (19.99)</td>
<td>29.64 (18.22)</td>
</tr>
<tr>
<td>Calm-anxious</td>
<td>36.11(23.33)</td>
<td>29.47 (16.28)</td>
<td>37.17 (19.99)</td>
<td>29.64 (18.22)</td>
</tr>
<tr>
<td>Stoned</td>
<td>78.78 (16.85)</td>
<td>71.72 (18.27)</td>
<td>72.12 (16.21)</td>
<td>73.62 (23.80)</td>
</tr>
</tbody>
</table>

Table 3. Means (and standard deviations) of performance pre-and post-drug on cognitive and psychomotor tests

<table>
<thead>
<tr>
<th></th>
<th>Methadone</th>
<th>Post-</th>
<th>Placebo</th>
<th>Post-</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simple reaction time (msecs)</td>
<td>317.2 (45.5)</td>
<td>311.8(44.4)</td>
<td>305.7 (60.3)</td>
<td>315.7 (77.1)</td>
</tr>
<tr>
<td>Tapping speed (N taps)</td>
<td>355.9 (36.5)</td>
<td>344.4 (51.7)</td>
<td>356.1 (41.6)</td>
<td>351.9 (70.7)</td>
</tr>
<tr>
<td>DSST (N substitutions)</td>
<td>51.8 (10.4)</td>
<td>54.1 (10.4)</td>
<td>52.1 (11.9)</td>
<td>51.3 (10.6)</td>
</tr>
<tr>
<td>Digit cancellation (secs)</td>
<td>73.8 (17.9)</td>
<td>71.3 (21.6)</td>
<td>68.1 (27.3)</td>
<td>66.9 (27.7)</td>
</tr>
<tr>
<td>Prose recall immediate</td>
<td>10.5 (3.0)</td>
<td>7.0 (2.8)</td>
<td>7.9 (2.1)</td>
<td>7.2 (3.2)</td>
</tr>
<tr>
<td>Prose recall delayed</td>
<td>6.7 (3.0)</td>
<td>6.3 (2.6)</td>
<td>6.7 (2.8)</td>
<td>6.3 (2.9)</td>
</tr>
</tbody>
</table>

Results
Demographic and drug use information
The 18 participants had a mean age of 37.5 (± 7.9) years, 14 were male, most (12) were unemployed, although five had unskilled jobs and one professional employment. In this, the sample was similar to most methadone patients (Department of Health, 1996). They were of slightly higher educational achievement than most patients (five had degrees, three had GCEs, two vocational qualifications and nine no qualifications). NART scores for the group gave an estimated IQ mean of 108 (± 11.95). The average daily prescribed methadone dose was 43.5 (± 16.2) ml, range 20-80 ml, and therefore the mean 33% increase in dose administered was 14.5 ml (range 6.7-26.6 ml). This fairly low methadone dose is in keeping with the policy of the service in which the study was based where the goal is abstinence from illicit opiate use and eventual total detoxification. All subjects had been using methadone for a minimum of 6 months, as stipulated in the inclusion criteria, and had been on the same dose for at least 4 weeks before participating in the study.
Participants' reported illicit drug use was fairly typical of this treatment population; 72% of participants reported using at least one illicit drug in the previous month; 67% of participants reported using heroin in the week prior to testing. All but two participants reported frequent use of cannabis; amphetamine use was less frequent than cannabis or heroin. History of opiate use ranged from 2 to 5 years. One of the sample reported that he did not always take his full prescribed methadone dose as he was trying to cut down independently. Four participants reported using extra methadone on top of their prescribed dose. Five participants were taking diazepam prescribed for their benzodiazepine dependence.

Urine screening and breathalyser
Urinalysis indicated that 50% of participants had taken illicit opiates, three were positive for amphetamines, two for cocaine and three for cannabis. Five participants who had not reported illicit
opiate use were positive for opiates, and two who had reported using were negative. Twenty-seven per cent of participants were negative for illicit drugs at both test screens, 17% were positive for the same drugs at each screen and 56% were positive for different drugs at each screen. Only one subject had detectable levels of breath alcohol and these were very low on both test days.

Table 4. Means (and standard deviations) of scores of the five heroin craving factors following treatments with methadone and placebo

<table>
<thead>
<tr>
<th>HCQ factor</th>
<th>Post-methadone</th>
<th>Post-placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticipation of positive outcome</td>
<td>39.06 (8.79)</td>
<td>32.78 (11.96)</td>
</tr>
<tr>
<td>Lack of control</td>
<td>36.80 (6.56)</td>
<td>33.67 (8.79)</td>
</tr>
<tr>
<td>Desire to use</td>
<td>23.67 (6.75)</td>
<td>18.50 (10.59)</td>
</tr>
<tr>
<td>Intention to use</td>
<td>30.72 (7.28)</td>
<td>27.06 (7.28)</td>
</tr>
<tr>
<td>Relief from withdrawal</td>
<td>36.56 (6.89)</td>
<td>30.56 (11.40)</td>
</tr>
<tr>
<td>Total craving</td>
<td>166.81(22.34)</td>
<td>142.57 (43.25)</td>
</tr>
</tbody>
</table>

Table 5. Correlation’s (and significance of correlation’s) between the five craving factors on the HCQ

<table>
<thead>
<tr>
<th>Anticipation of pos. outcome</th>
<th>Lack control</th>
<th>Desire</th>
<th>Intent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticipation of pos. outcome</td>
<td>0.50 (.002)</td>
<td>0.45</td>
<td>0.63</td>
</tr>
<tr>
<td>Lack control</td>
<td>0.53 (.001)</td>
<td>0.49</td>
<td>0.51</td>
</tr>
<tr>
<td>Desire</td>
<td>0.50 (.002)</td>
<td>0.48</td>
<td>0.49</td>
</tr>
<tr>
<td>Intent</td>
<td>0.86 (.0001)</td>
<td>0.48</td>
<td>0.49</td>
</tr>
</tbody>
</table>

Mood rating scale. Principal components analysis yielded three mood factors. There was a main effect of drug treatment on alertness (mood factor 1) and contentedness (mood factor 2) (Table 2). Participants were more alert following placebo and slightly more drowsy following additional methadone (F \(_{1,16} = 10.01\), p<0.01). They were also more contented following placebo than following methadone (F \(_{1,16} = 8.81\), p <0.01). No treatment differences emerged on mood factor 3 (calm-anxious) or on the single item "stoned".

Prose recall. There were no significant treatment effects (Table 3). Participants allocated to treatment order of methadone first had higher immediate recall scores pre-drug than those allocated to treatment order of placebo first (F \(_{1,15} = 4.7\), p<0.05). Word-stem completion showed no treatment or order effects. Simple reaction time tapping rate, DSST; digit cancellation. No significant treatment or treatment order effects emerged on any of these tasks.

Craving for heroin. Scores on the craving questionnaire were analysed as total score and as five factors (Table 4). Total craving was increased following methadone as compared with placebo (F \(_{1,16} = 5.64\), p < 0.03). Significant main effects of drug were found on two craving factors: anticipation of positive outcome (F \(_{1,16} = 5.35\), p <0.03) and relief from withdrawal or dysphoria (F \(_{1,16} = 5.01\),p<0.04). Scores on both were higher after methadone than after placebo, suggesting that an increase in methadone dosage increases craving for heroin. There was no significant difference found in either "lack of control" or "intention to use" factors. Desire to use heroin showed a marginally significant main effect of drug (p <0.06) with ratings again being higher post-methadone than post-placebo. Scores on desire to use showed a significant interaction of drug with treatment order (F \(_{1,16} = 6.2\), p<0.02). This reflected higher scores on the first compared with the second test day for participants given methadone first, whereas those given placebo first showed little change. For the methadone first group, "desire to use" scores were 24.8 ± 7.6 after methadone and 13.3 ± 6.1 after placebo. Corresponding figures for the placebo first group were 22.6 ± 6.0 and 23.7 ± 11.9. It can also be seen from Table 4 that the variance in craving scores was lower following methadone than following placebo. This is the case with each of the
five craving factors, though Levene's test for equality of variance had shown that ANOVA assumptions had not been violated for any factor except "lack of control". Correlations between the five craving factors are shown in Table 5. There were significant correlations between all five craving factors. "Anticipation of positive outcome" and "relief from withdrawal" correlated most highly of all the craving factors (r = 0.86), sharing 74% of the variance. "Intention" and "desire to use" also correlated fairly highly (r = 0.63), whereas all other factors inter-correlated at around 0.50.

**Correlation matrix:**

<table>
<thead>
<tr>
<th></th>
<th>Intention</th>
<th>Desire to use</th>
<th>Anticipation of positive outcome</th>
<th>Relief from withdrawal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intention</td>
<td>1</td>
<td>0.63</td>
<td>0.86</td>
<td>0.59</td>
</tr>
<tr>
<td>Desire to use</td>
<td>0.63</td>
<td>1</td>
<td>0.84</td>
<td>0.56</td>
</tr>
<tr>
<td>Anticipation of positive outcome</td>
<td>0.86</td>
<td>0.84</td>
<td>1</td>
<td>0.58</td>
</tr>
<tr>
<td>Relief from withdrawal</td>
<td>0.59</td>
<td>0.56</td>
<td>0.58</td>
<td>1</td>
</tr>
</tbody>
</table>

**Relationship between dose of methadone and treatment effects**

Correlations were carried out between daily dose of methadone and change in mood factor scores (methadone (post-pre-drug)) minus placebo post-pre-rug). These were positive but small and non-significant (for alertness changes, Pearson's r = 0.28; for contentedness changes, r = 0.17). Correlations were also carried out between daily dose and craving factor scores (methadone, minus placebo). These correlations were again small and non-significant (anticipation of positive outcome, r = 0.18; relief from withdrawal, r = 0.04; total HCQ score, r = 0.02).

**Guess on treatment.** There were a total of 36 treatment presentations (18 subjects attending two sessions). Participants' guess on treatment was at chance levels (correct in 39% of cases, incorrect in 36% of cases and in the remaining 25% of cases participants stated that they were unsure which treatment they had received). Participants therefore could not differentiate between methadone and placebo treatments. Thus double-blind procedures used, including the matching of placebo linctus with drug linctus, had been effective.

**Discussion**

Our main finding was that an increase in daily methadone dosage actually increased craving for heroin. This finding is perhaps more remarkable in that patients could not differentiate at all between whether they had been given extra methadone or matched placebo.

The two sub-scales of the craving questionnaire which showed significant differences were "anticipation of positive outcome from using heroin" and "relief from withdrawal or dysphoria". Respectively, they reflect what is often referred to as "positive" and "negative" craving. Dawe & Gray (1995) compared methadone with clonidine in terms of both "pleasant effect" (positive craving) and "alleviation of unpleasant feeling or mood" (negative craving) in detoxifying opiate addicts. Their study had no placebo control and no significant difference between the two groups of eight subjects emerged in craving, however positive craving was elevated in the methadone group. Had a larger sample been used, this increased craving may have reached significance as found in the present study.

The increase in total craving score showed virtually no relationship with patients' prescribed daily dose of methadone, with a correlation of only 0.02 between these two variables. As daily dose is proportional to the extra dose of methadone administered, increased craving was thus unrelated to the absolute size of extra dose given. It is also notable that these two factors of the HCQ which increased after methadone (anticipation of positive outcome; relief from withdrawal) were highly inter-correlated, sharing 74% of the variance. This may imply that the positive effects of heroin necessarily go hand in hand with relief from withdrawal. It also calls into question the degree to which these two craving factors are independent.

Treatment differences on the factor "desire to use heroin" just failed to reach significance, but again the trend was in the same direction of more desire to use following extra methadone than placebo. Scores on this factor showed a significant interaction of drug with treatment order. For participants given methadone first, desire to use was higher following active drug compared with placebo whereas those given placebo first showed little change. This implies a carry-over effect from the first to the second treatment. Given the 1 week "wash-out" period between the two treatments, this is unlikely to be a pharmacological carry-over. It may instead be a psychological effect, conceivably related to effects of
filling out the HCQ the first as opposed to the second time. Alternatively, the effect ma' be related to differences in participants' expectations on the two testing days. There was no effect of additional methadone on two craving factors: "lack of control" or "intention to use". Thus although extra methadone increase their positive and negative craving for heroin, it did not affect their ratings of control over using heroin. There are two possible interpretations of this differential effect on craving factors. One explanation could be that craving is operating at two separate levels, a conscious level controlling behaviour (use of heroin) and a non-conscious or automatic level concerning the desire for the positive effects of heroin. Extra methadone did not affect the participants' responses concerning conscious control, but at a non-conscious or automatic level it primed cravings for heroin. Further, these non-conscious cravings were primed by methadone even though participants were completely unaware of whether they had been given the drag or placebo. Tiffany's (1990) view is that craving is non-automatic (controlled) whereas drag use in chronic users has become automatised or non-conscious. However, it is possible that not all aspects of what is termed "craving" are equally controlled. A second explanation may be that patients may have suspected, despite our assurances of confidentiality, that information obtained in the study may be passed on to key-workers in the service. If this was the ease, they may have deliberately biased their answers to HCQ questions regarding intention to use heroin and control over use. However, this second explanation is at odds with the fact that two-thirds of the patients disclosed to us their use of heroin in the week prior to entering the study.

The findings of the present study are reminiscent of Hogson et al. (1979), who showed how a small dose of alcohol can prime craving for alcohol in abstinent drinkers. Also, Burton & Tiffany (1997) showed that alcohol can act as a primer for cigarettes and that drinking alcohol can lead to relapse in people giving up smoking. A priming hypothesis has thus been used previously to account for increased positive craving following an acute dose of drug in users. Priming has not been seen in terms of negative craving, although in our present study, positive and negative craving were so highly inter-correlated that any factor affecting one would be expected to affect the other. In suggesting that extra methadone may "prime" craving for opiates, one could argue that increased methadone dosage may theoretically increase relapse of methadone patients to illicit opiate use.

Many methadone substitution patients take additional opiates as well as methadone, and therefore they frequently self-administer an acute-on-chronic dosage of opiates. The findings of the present study would suggest that this form of drug-taking may cause significant fluctuations in craving which would contribute to the maintenance of illicit opiate use. Comment is also warranted on the finding that the variance in craving scores among our participants was very much higher after placebo than after methadone. Thus as well as increasing craving, methadone also reduced inter-individual differences in craving.

What other mechanism besides drug priming could account for our findings? Ball & Ross (1991) recommend that the minimum dose of methadone required to stop cravings for heroin is 50 mg, a dose higher than most of our participants were receiving. If our participants were receiving a dose too low to control heroin craving, then one would have expected the predicted, opposite pattern of results (i.e. reduced craving following methadone compared with placebo). Thus an explanation in terms of minimum daily dosage cannot accommodate our results of increased craving following increased methadone.

The effects of additional methadone on mood were also interesting. Patients felt more alert following placebo than following methadone. However, this subjective sedation following methadone was not found on objective measures: neither finger-tapping speed (a standard index of motor sedation) nor simple reaction times were affected by treatment. Often subjective and objective measures do not intercorrelate well. Our finding that participants were tolerant to the sedative effect of a third increase in their daily methadone dose on objective measures has important clinical implications in terms of establishing the appropriate dosage of methadone to prescribe. In order to avoid too high a dose of methadone-and thence the possibility of overdosing or of selling on part of the dose-many drug services use clinical judgement of sedation in patients. If an extra 33% has no apparent sedative effect, the validity of sedation as a clinical criterion is clearly limited. As Nutt (1996) suggests, a better approach to establishing dosage could be using neuro-imaging with PET to establish the proportion of brain opioid receptors occupied during methadone treatment and to relate this with levels of craving, dependence and treatment outcome.
The other mood factor showing significant treatment effects was contentedness. Patients were more contented after placebo than after methadone. This finding may be related to the craving effects of methadone in that patients would presumably be less contented when drug craving is increased.

The increased dose of methadone produced no cognitive or psychomotor impairments. Lack of effect on memory and focused attention was shown in the prose recall and cancellation tests, respectively. This is in accordance with Zaeny (1995) whose review concluded that single doses of methadone in chronic users (as opposed to normal controls) are devoid of cognitive effects. Lack of psychomotor effects accords with a study by Rothenberg et al (1977), who gave small doses (5 mg, 10 mg) of methadone and a placebo to 12 opioid dependent people and to 12 healthy volunteers. They found that the drug impaired reaction times only in healthy subjects.

The present study also found that additional methadone produced no psychomotor impairment using sensitive computer tests as well as traditional paper and pencil tests. This implies that participants are tolerant to the psychomotor effects of methadone and thus a 33% increase in dose is unlikely to impair driving skills. That patients in the present study were unable to discriminate an increased dose of methadone from placebo is similar to findings by Stitzer, Bigelow & Liebson (1984), who studied dose manipulations of methadone in two maintenance patients and found they did not detect increases in daily dose, although they could detect dose decreases of 50% or more.

In this client population research is difficult for practical reasons, including unreliability and un-co-operativeness. This study has shown that acute, placebo-controlled studies with this client group are feasible. Urinalysis was also used to check self-report measures, and there were discrepancies between the two sources of data. These discrepancies were not only in terms of positive screens for drugs not reported but also negative screens for drugs which were reported to have been taken. According to urine screens, 56% of participants had taken different drugs before the two test sessions. This is a limitation of the present study in that, even though a very effective placebo control was used, one cannot rule out the possibility of an interaction between additional methadone and use of illicit drugs. However, when the group is compared as a whole on placebo and methadone test occasions, the range of drugs taken on each occasion is broadly similar. We are currently carrying out a similar cross-over study in an inpatient detoxification unit where more control for additional drug use should be obtained. Further, by administering the HCQ pre- as well as post-drug, we hope to obtain increased power for detecting changes in craving from baseline levels on each test day.

Kreek's (1992) review of methadone maintenance treatment comments: "It is known that methadone prevents abstinence symptoms, prevents drug hunger or craving ... and prevents relapse to illicit use of opiates" (p. 205). Our findings add a note of caution to such a global claim. Extra methadone increased craving for heroin, and two-thirds of our participants disclosed their use of heroin in the week before entering the study. Drug-seeking behaviour has been reported in patients receiving 100 mg/day of methadone (Martin et al., 1973). Although methadone may reduce illicit use of opiates, it may also kindle the desire for heroin. In terms of craving, therefore, there may be real advantages of treatments aimed at eventual detoxification rather than those aimed at long-term methadone maintenance.

In summary, the present study used a double-blind, cross-over design to assess the effects of a 33% increase in daily dose of methadone compared with placebo in methadone substitution patients. Additional methadone did not produce any effects on cognitive or psychomotor performance. However, compared with placebo, the increased dose primed cravings for heroin and decreased both subjective arousal and contentedness.

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