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LABORATORY MEASURES OF AGGRESSION IN METHADONE PATIENTS

Catherine M. Gayman, M.A.

Western Michigan University, 2012

Research suggests that current heroin users and individuals with a prior history of heroin dependence tend to be more aggressive than nonusers. No study has yet investigated whether opioid withdrawal affects aggressive responses on a laboratory task. The present study investigates whether mild opioid withdrawal affects aggression in six males and six females (N=12) undergoing methadone maintenance therapy. Aggressive behavior is measured using the Point Subtraction Aggression Paradigm (Cherek, 1981) computer task. Participants press buttons to earn money towards gift certificates. Money subtractions occur periodically and these are attributed to the behavior of a partner who is actually fictitious. Participants respond to protect their earnings or respond to protect their earnings while also subtracting money from the partner (the aggressive response option). Behavior on the PSAP is measured on two separate days; once prior to and once following the participant's daily methadone dose. There are no differences in rates of aggressive responding on the PSAP or in self-reports of mood across conditions. These data suggest that the opioid deprivation occurring 24-hrs following methadone administration in individuals undergoing MMT does not produce heightened aggression, at least on this task in these generally non-violent participants.

LABORATORY MEASURES OF AGGRESSION IN METHADONE PATIENTS

by

Catherine M. Gayman

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Catherine M. Gayman

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INTRODUCTION

Heroin addiction is associated with a variety of harmful and maladaptive behavior patterns. For example, heroin addiction has been linked to antisocial behaviors and social deviance (Fieldman, Woolfolk, & Allen, 1995), aggression (Gerra, Zaimovic, Moi, Bussandri, Bubici, Mossini, Raggi, & Brambilla, 2004; Gerra, Zaimovic, Raggi, Guisti, Delsignore, Bertacca, & Brambilla, 2001; Gerra, Zaimovic, Raggi, Moi, Branchi, Moroni, & Brambilla, 2007), anger and hostility (Steer & Schut, 1981), Antisocial Personality Disorder, and engaging in illegal and reckless behaviors (Darke, Hall, & Swift, 1994). A meta-analysis of 14 studies concluded that there is a strong positive association between heroin use and criminal activity (Bennett, Holloway, & Farrington, 2008). Heroin use is also strongly associated with violent and aggressive crimes. A study investigating violent offences determined that 81% of 160 heroin addicts interviewed had been the offender in a violent crime, and most of them had been involved in multiple violent incidents during their lives (Darke, Torok, Kaye, Ross, & McKetin, 2010). Heroin use and addiction is therefore a major public health and safety concern.

Four explanations have been offered as to why violence may occur in substance abusers, 1) violence occurs to obtain the drug of abuse, 2) violence occurs to resolve disputes related to the drug which cannot be resolved in a legal manner, 3) violent behavior may be related to some trait associated with drug abuse, or 4) drug effects may increase the probability of violent acts (Hoaken & Stewart, 2003). Some studies indicate that the relationship between aggressive responding and opioid use may be the result of personality factors (Gerra et al., 2001). Alternatively, some studies have shown that

acute administration of opioids directly increases aggression (Berman, Taylor & Marged, 1993; Spiga, Cherek, Roache & Cowan, 1990).

Laboratory Measures of Aggression

Most studies investigating the relationship between opioid use and aggression or violence are field studies and the data have been correlational (e.g., Fieldman, Woolfolk, & Allen, 1995; Steer and Schut, 1981). Thus, laboratory studies are needed to better assess the relationship between opioid use and aggression. Directly studying aggressive behavior in the laboratory is difficult, however, because aggressive responses occur only infrequently. As a result, many laboratory studies on aggression have used self-reports of aggression or aggressive tendencies, such as the Buss–Durkee hostility scale (Buss & Durkee, 1957), the Overt Aggression Scale (Yudofsky, Silver, Jackson, Endicott, & Williams, 1986), or the updated Buss–Perry Aggression Questionnaire (Buss & Perry, 1992).

Other researchers, however, have sought to develop more direct measures of aggressive behavior (Buss, 1961; Cherek, 1981; Taylor, 1967). In order to study aggressive behavior directly in the laboratory, it is necessary to develop an operational definition of aggression. That is, the behavior must be clearly defined, easily measurable, and observable. Most laboratory studies have operationally defined aggressive behavior as responding that results in the presentation of an aversive stimulus (e.g., electric shock or money loss) to another individual (Buss, 1961; Cherek, 1981; Taylor, 1967). Defining aggressive behavior in terms of its topography contrasts with typical response definitions in operant psychology that define behavior units in terms of the relationship between behavior and environmental variables. From an operant psychology perspective,

it is not sufficient to define aggression based solely upon response topography. A relationship must exist between an antecedent, a behavior, and a particular consequence for a behavior to be labeled as 'aggressive.' Cahoon (1972) lists several antecedent situations (e.g., aversive stimulation, discriminative stimuli associated with reinforcement, extinction, stimuli that signal the removal of positive reinforcers) and consequences (e.g., removal of aversive stimuli, presentation of positive reinforcers) that may maintain aggressive behaviors. Laboratory studies have shown that responses defined as aggressive do vary as a function of changes in antecedent and consequent variables, and therefore are functional units (Cherek, 1981; Cherek, Spiga, Bennett, & Grabowski, 1991). Aggression that is 'accidental' is distinguished from operant behavior maintained by particular consequences by its very low frequency of recurrence, as well as a low frequency of alternate aggressive behaviors in the individual's repertoire that result in the same consequence (Cahoon, 1972).

In laboratory aggression tasks, aggressive behavior is often provoked by delivering an aversive stimulus to the participant. For example, several laboratory tasks, including the 'teacher-learner' paradigm (Buss, 1961) and the Taylor Competitive Reaction Time Task (Taylor, 1967), ask participants to administer a painful shock to a confederate in order to study the frequency, intensity, and duration of shocks administered under various experimental conditions. Aggressive behavior in these studies is defined as responding that results in the delivery of a harmful or aversive stimulus (shock) to another individual. To provoke aggression in the Taylor Competitive Reaction Time task, the participant receives shocks that increase incrementally in intensity which are attributed to the behavior of the partner (confederate). Aggressive

responding is instigated in the 'teacher-learner' paradigm by asking participants to administer a shock contingent upon a wrong answer from the 'learner'.

Although the Buss and Taylor tasks have provided useful assessments of aggression (Buss, 1961; Taylor, 1967), they have some limitations. First, these tasks do not provide a nonaggressive response alternative. Including a nonaggressive option is important so that (a) responding on the nonaggressive option can serve as a control for any changes in responding on the aggressive option, and (b) the aggressive response option is not the only response option available to participants. Second, in these tasks measures of aggressive responding (i.e., magnitude or duration of shock delivery) can only vary across a limited range and therefore may not be sensitive to some experimental manipulations.

Another laboratory task developed to study aggression is the Point Subtraction Aggression Paradigm (PSAP; Cherek, 1981). This task includes a nonaggressive response alternative and it allows aggressive responding to vary across a wide range. During the PSAP, participants are provoked with presentations of money losses which are attributed to the behavior of a fictitious partner. Participants are presented with three choice options. One option produces money. The second option ostensibly subtracts money from a partner's earnings (the aggressive response) and initiates a temporary timeout from subtractions by the partner. The third option also initiates a temporary timeout from subtractions (the escape response). On this task, aggression is measured by the frequency of responding on the aggressive response option. Aggression on this task is therefore defined as responding to present an aversive stimulus (money loss) to another individual. Males (Cherek, Moeller, Schnapp, & Dougherty, 1997) and females (Cherek,

Lane, Dougherty, Moeller, & White, 2000) with violent criminal histories, individuals with Antisocial Personality Disorder (Moeller, Dougherty, Lane, Steinberg, & Cherek, 1998), and people with Borderline Personality Disorder with comorbid Intermittent Explosive Disorder (New, Hazlett, Newmark, Zhang, Triebwasser, & Meyerson, 2009) tend to show more aggressive responses than matched controls on the PSAP, thereby supporting the validity of the task as a measure of aggressive behavior. Although responding on the PSAP is typically assessed across multiple sessions (e.g., Cherek, 1981), the PSAP also can be an effective method of assessing individual differences in aggression when administered for only a single session (Golomb, Cortez-Perez, Jaworski, Mednick, & Dimsdale, 2007).

Because aggressive responses in laboratory aggression tasks occur following provocations, these tasks measure rates of reactive aggression. Reactive aggression is defined as a defensive response in retaliation for a provocation that was perceived as having hostile intent (Dodge & Coie, 1987). The PSAP, however, also allows an assessment of proactive aggression. Proactive aggression is defined as an aggressive response that occurs prior to any provocations (Dodge & Coie, 1987). Proactive aggression can be measured on the PSAP by recording the number of aggressive responses that occur prior to the first money subtraction per session. Reactive aggression can be measured by recording the number of aggressive responses that occur after money subtractions have been presented.

Opioids and Laboratory Measures of Aggression

The PSAP has been used to assess aggressive responding in substance abusers. Individuals who reported drug-use histories scored higher on the PSAP and on

psychometric measures of aggression than those without such histories (Allen, Moeller, Rhoades, Cherek, 1997). Studies have also shown that individuals who were previously addicted to heroin made more aggressive responses than control subjects on the PSAP task and scored higher on psychometric measures of aggression and irritability (Gerra et al., 2001; Gerra et al., 2004; Gerra et al., 2007). This was true whether participants were currently being treated with methadone or buprenorphine (Gerra et al., 2001; Gerra et al., 2007), or were abstinent without pharmacological treatment (Gerra et al., 2004). Individuals who were previously addicted to heroin also exhibited fewer monetary-reinforced responses when they were abstinent, compared to nonusers (Gerra et al., 2004) and when they were on methadone maintenance therapy (Gerra et al., 2001). The lower rate of responding on the monetary-reinforced option during abstinence or treatment may indicate either a decrease in motivational levels or decreased attention.

Two studies with humans have shown that the acute administration of opiates can increase levels of aggression in laboratory aggression tasks. Berman, Taylor and Marged (1993) showed that morphine increased the likelihood that an individual would deliver more intense and more frequent shocks to a confederate on the Taylor Aggression Task, whereas Spiga, Cherek, Roache and Cowan (1990) showed that codeine increased aggressive responses on a version of the PSAP that did not have an escape response. These findings are consistent with the results of several studies with rats that have also shown that acute opioid administration increases aggression (Haney, Mczek, 1989; Espert, Navarro, Salvador, & Simon, 1993).

Methadone

Methadone is a synthetic opioid agonist which binds to and activates opioid receptors (Ward, Hall, & Mattick, 2009). It is used as an opioid replacement in a treatment known as methadone maintenance therapy (MMT). This treatment involves replacing heroin use with methadone dispensed by a medical clinic. Methadone allows the patient to stop using heroin without experiencing sudden opioid withdrawal. Methadone is much safer than heroin because medical personnel ensure that the correct dose is taken each time, and the medication is guaranteed to be the same mixture and potency each time the person receives it. Methadone has the ability to reduce cravings for heroin, and to block feelings of euphoria if heroin is subsequently used (Ward, Hall, & Mattick, 2009). Methadone has an elimination half life of approximately 24-36 hrs (Ward, Hall, & Mattick, 2009), which is much longer than the 3-6 hr elimination half-life of heroin. Thus, unlike heroin, which must be injected every few hours to maintain steady blood levels, methadone is typically taken orally once per day. Absorption into the blood stream occurs at a slow rate with orally ingested methadone, and therefore does not produce the same intoxication and euphoria that results from heroin use. Methadone exerts dose-dependent effects. That is, higher doses are more effective than lower doses in reducing illicit opioid use (e.g., Donny, Walsh, Bigelow, Eissenberg, & Stitzer, 2002; Greenwald, 2002), reducing withdrawal symptoms and craving, and retaining patients in treatment (Veilleux, Colvin, Anderson, York, & Heinz, 2010). The typical methadone maintenance dose prescribed ranges from 50-150 mg per day (Veilleux et al., 2010).

A recent review of the pharmacological properties of methadone notes that onset of effect occurs within 30 min of administration, and the highest blood levels of

methadone occur within 2-4 hrs (Gordon, Hitchinson, La Vincente, Mitchell, Morrish, Newcombe, Somogyi, & White, 2009). Blood levels peak and then decrease from 4 hrs after administration until the next dose is given. The pharmacologic effect of methadone varies over the 24-hr dosing period, and is correlated with changes in blood concentrations of the drug. As blood concentrations decrease, withdrawal symptoms appear and become more severe. Severe withdrawal typically occurs 36-48 hrs after the last dose has been administered, and may last from 5 to 21 days.

Methadone maintenance has been shown to benefit individuals addicted to heroin by reducing many risky behaviors such as sharing needles, overdosing, and engaging in illegal behaviors (Ward, Hall & Mattick, 2009). Criminal behavior has been shown to decrease after methadone maintenance treatment (Simoens, Ludbrook, Matheson, & Bond, 2006), but it is unknown whether the decrease in criminal activity is a pharmacological effect of the drug, or if it is an effect of a change in lifestyle and living environment during treatment (Gossop, Marsden, Stewart, & Rolfe, 2000; Löbmann, & Verthein, 2009). No laboratory studies thus far have investigated the acute effects of methadone administration on aggressive behavior.

Opioid Withdrawal and Aggressive Behavior

It is important to study the effects of withdrawal from opioid drugs on aggression to determine whether aggressive responding is likely to increase during abstinence or when drug levels decrease. Several studies have investigated the effects of opioid deprivation on aggressive behavior. These studies have found that during withdrawal, participants show enhanced aggression and changes in mood. For example, participants in detoxification often display increased aggression and irritability, as shown by

subjective effects questionnaires and objective behavioral observations (e.g., Bickel, Stitzer, Liebson & Bigelow, 1988; Gerra, Zaimovic, Rustichelli, Fontanesi, Zambelli, Timpano, Bocchi, & Delsignore, 2000).

The effects of drug abstinence on aggression may be interpreted from an operant psychology perspective by assuming that drug deprivation functions as a motivational operation. A motivational operation is an event that alters the probability of certain behaviors by changing the reinforcing or punishing value of environmental stimuli (Michael, 1982). Drug deprivation may act as a motivational operation which affects the reinforcing potency of stimuli produced by acts of aggression. Alternatively, drug deprivation may make punishing events such as money loss more aversive.

No study has investigated the effects of opioid withdrawal on aggressive behavior using a laboratory aggression task. This may be because exposing individuals addicted to opioids to acute opioid withdrawal raises ethical concerns given the health risks and discomfort produced by withdrawal. During MMT, however, individuals regularly experience mild withdrawal prior to taking their daily methadone (see below). Thus, MMT may be a useful model for investigating the effects of opioid deprivation on aggression.

Methadone Withdrawal

Several studies suggest that mild to moderate levels of deprivation occur 24-hrs following methadone administration. For example, several studies have shown that blood levels of methadone peaked 2-3 hrs after administration, and decreased until the following dose was administered (Dyer, Foster, White, Somogyi, Menelaou, & Bochner, 1999; Hanna, Foster, Salter, Somogyi, White, & Bochner, 2005; Hiltunen, Beck,

Hjemdahl, Liljeberg, Almstrom, Brodin, Wachtenfeldt, & Borg, 1999). Objective physical signs of withdrawal and subjective participant ratings of withdrawal were lowest during peak blood levels, and increased as blood levels decreased. Dyer et al., (1999) reported that physiological effects of methadone, including pupil dilation, increased pain threshold, and subjective feelings, only lasted up to 8 hrs after administration.

Behavioral effects of methadone, including signs of withdrawal, are also affected by the passage of time since the last dose (Dyer et al., 1999; Hanna et al., 2005; Hiltunen et al., 1999;). For example Dyer et al., (2001) found significant changes in mood associated with the passage of time over the 24-hr dosing interval including increased anger, depression, tension, confusion, and fatigue, as measured by the Profile of Mood States (POMS) questionnaire. Furthermore, the presentation of a laboratory stressor (consisting of a 3000 Hz tone played at 90 dB for 10 min while the participant attempted to solve an unsolvable computer task) was shown to cause stronger cravings when administered just prior to dosing compared to just after the dose was given (Ilgen, Jain, Kim, & Trafton, 2008).

Several studies have found no withdrawal effects during methadone maintenance therapy. For example, McMillan and Gilmore-Thomas (1996) found no changes in self reported craving levels and Torrens, Castillo, San, del Mmoral, Gonzalez, and de la Torre (1998) found no changes in self-reports of physical withdrawal symptoms in individuals currently on MMT. However, these studies only collected self-reports (i.e., questionnaire data) rather than direct measures of behavior. More objective measures may provide a more accurate assessment of withdrawal.

Overall, the results of the studies described above suggest that at the end of the 24-hr dosing cycle, methadone maintenance patients may experience mild withdrawal and therefore may exhibit heightened aggression. To this author's knowledge, no field studies have reported increases in aggressive behavior in methadone patients near the end of the end of the 24-hr dosing cycle. Nonetheless, the possibility remains that participants on MMT experience heighted aggressive tendencies that go unreported. Investigating the effects of opioid withdrawal on aggressive behavior in patients undergoing methadone maintenance therapy may provide additional data on the effectiveness of a 24-hr dosing regimen in minimizing withdrawal symptoms.

Purpose

The present study investigated aggressive behavior in patients receiving methadone as part of opioid replacement therapy to determine if there were changes in aggressive behavior across opioid deprived and non-deprived states. Specifically, performance on a laboratory aggression task, the PSAP, was measured just prior to and just after patients received their daily methadone dose on separate days. Changes in responding on the aggressive, escape-maintained, and monetary-reinforced responses on the PSAP task were compared across the two time periods. Rates of responding prior to and following provocations on the PSAP were also analyzed to determine whether methadone deprivation selectively affected proactive or reactive aggression.

Because the findings from studies investigating the effects of methadone deprivation on mood have been mixed (e.g., Dyer et al., 2001; Hiltunen et al., 1999; McMillan & Gilmore-Thomas, 1996), in the present study changes in mood were also assessed using a self-report mood questionnaire, the Profile of Mood States (POMS;

McNair & Droppleman, 1971). Ratings of mood were measured prior to completing the PSAP after methadone administration (during drug satiation), and after 24-hr methadone deprivation. Mood ratings were also collected after completing the PSAP on both deprivation and satiation days to evaluate the effects of the task on mood, and any interaction between completing the task and deprivation condition.

METHODS

Participants

All methods were approved by the Human Subjects Internal Review Board at Western Michigan University. Twelve adults (six females and six males) ages 25 to 52 (average 36) years currently on methadone maintenance therapy with a history of opioid dependence participated. Participants were recruited by hanging flyers in lobbies of methadone maintenance clinics in Southwest Michigan. The flyers advertised a study on decision making and sought volunteers. Potential participants contacted experimenters by phone and were given a brief description of what participating involved. If the person was interested in participating, the experimenter scheduled an appointment to complete the informed consent process. After informed consent was obtained, participants filled out a brief subject information form. Participants were recruited into the study if they reported having no visual or auditory impairments that would prevent them from completing the computer task, reported not taking any psychiatric medications other than methadone, reported drinking fewer than 14 alcoholic drinks per week, and were able to read and understand the instructions. No participants were excluded from the study due to these criteria. Overall, 17 participants were recruited and completed the informed consent process and of these 12 completed the study. One participant reported being intoxicated after signing the informed consent document and failed to reschedule

sessions. One participant informed disclosed to the researchers after her second day of participation that she had taken her methadone dose prior to the session on both days, and her data were therefore excluded from the analysis. Three participants failed to complete the second day of participation. Of the twelve participants who completed the study, nine were Caucasian (75%), two were Hispanic (16.67%), and one was American Indian (8.33%). Length in methadone maintenance treatment ranged from 2 weeks to 9 yrs (M= 3.08, SD= 2.8). Drug use histories are shown in Table 1.

Table 1. Mean (with standard deviation in parentheses) years of drug use and percent of participants that reported using each drug.

Drug	Average	% of Participants
Prescription Narcotics (Including Opioids)	14.58 (±11.56) yrs	100% (12/12)
Heroin	5.38 (±5.32) yrs	67% (8/12)
Illicit Methadone	2.17 (±2.94) yrs	58.33% (7/12)
Morphine	5.2 (±6.11) yrs	58.33% (7/12)
Cocaine	8.85 (±9.45) yrs	83% (10/12)
Marijuana	12.7 (±9.8) yrs	92% (11/12)
Crack	4.63 (±9.32) yrs	50% (5/10)

Apparatus

Sessions were conducted in conference rooms in two methadone clinics. Curtains were used to create a 0.37 square meter cubicle. The cubicle contained a small table with a PC laptop computer, a chair, and a computer mouse. The laptop computer recorded and

controlled experimental sessions. Pink noise was generated and played through an individual speaker in each cubicle space. Pink noise varied between 20 Hz to 20,000 Hz.

Procedure

Individuals were asked to participate on three different days. On the first two days of participation, subjects came to a private room inside the clinic. Prior to the first session, subjects completed the POMS questionnaire. They also completed a recent drug use questionnaire to determine when the last dose of methadone was taken.

Participants completed three experimental (PSAP) sessions per day on the first two days (six sessions total). Each experimental session lasted 25 min, followed by a 5-min break. After completing all experimental sessions each day, participants completed a post-experiment questionnaire to evaluate the effectiveness of the social deception (whether they believed they were working with a partner), and completed the POMS questionnaire again. All participants believed they were paired with others each day and thus all data were included in the analysis.

On the third day of participation, participants were asked to complete the Buss-Perry aggression questionnaire which assessed lifetime aggressive tendencies (Buss & Perry, 1992). After participants completed this questionnaire, they were paid their completion bonus, and were partially debriefed. All earnings were paid in gift certificates to Meijer or Wal-Mart, depending on the preference of the participant. Full debriefing (i.e., information about the social deception) occurred when all participants had completed the study using a debriefing phone script (see Appendix). A diagram of the daily schedule for participants on each day of participation is shown in Tables 2-4. Note that not all participants began sessions at 9:00 am.

Table 2. Day 1 Daily Schedule Example

9:00 am	Check in & complete POMS
9:10 am	Task Instructions
9:15 am	PSAP Task Session 1
9:40 am	5 min Break
9:45 am	PSAP Task Session 2
10:10 am	5 min Break
10:15 am	PSAP Task Session 3
10:40 am	Deception Questionnaire and complete POMS
10:50 am	Payment in gift certificates and release

Table 3. Day 2 Daily Schedule Example

9:00 am	Check in & complete POMS
9:10 am	PSAP Task Session 1
9:35 am	5 min Break
9:40 am	PSAP Task Session 2
10:05 am	5 min Break
10:10 am	PSAP Task Session 3
10:35 am	Deception Questionnaire and complete POMS
10:45 am	Payment in gift certificates and release

Table 4. Day 3 Daily Schedule Example

9:00 am	Check in and complete Buss-Perry
9:05 am	Payment in gift certificates (including completion bonus) and debriefing
9:15 am	Release

Design

The experiment used a repeated-measures design. The PSAP task was administered the first time to half of the participants just prior to receiving their daily methadone dose (n=6). This was approximately 24-hrs after having received their last methadone administration, and was therefore a time at which the participant was expected to experience withdrawal. The task was administered the first time to the other participants approximately 30 min after receiving their methadone dose (n=6). Because peak effects of methadone occur 120 min after administration, we expected peak effect of methadone administration to occur during the last experimental session. The second day that participants completed the PSAP, those who completed it prior to receiving methadone took it after, and vice versa. This counterbalancing of methadone administration (before vs. after the PSAP) was designed to control for effects of repeated exposure to the PSAP task.

Point Subtraction Aggression Paradigm

The PSAP task required responding on a computer mouse to stimuli on the computer screen. A counter located at the top of the screen showed total earnings. At the start of the session, the counter was set to $0.00. The earnings counter never went into

the negative. At the start of each session, and in the absence of responding, the participant experienced a variable time schedule of money subtractions with intervals ranging from 6 s to 120 s. These subtractions were attributed to the behavior of the fictitious partner. The participant chose between three response options. The three options were designated on the computer screen with three letters; A, B, and C (left to right, approximately 50.8 mm in height). To choose an option, the participant had to move the mouse pointer over the letter and make a mouse click. Each response produced a brief flashing of the letter. Once a response was made on one of the buttons, the other letters disappeared until the response requirement was completed on the selected option. The first option, Button A (monetary-reinforced option), required that the participant emit 100 mouse clicks to earn money (15¢). Button B was the aggressive response option. The participant was told that if they made 10 mouse clicks on the B option then 15¢ would be subtracted from the counter of their partner. Completing the response requirement on option B also produced a timeout from the schedule of money subtractions for a variable time period averaging 125 s (participants were not told about this contingency). The third option, Button C, was an escape option. Ten mouse clicks on option C produced a timeout from the schedule of money subtractions for a variable time period averaging 125 s. One subtraction was required to occur before responses on button C or B initiated the provocation-free period. This ensured that the number of subtractions could be reduced but not completely avoided. Responses on Button B were considered aggressive, because the participant was told that this would result in monetary loss to another participant. In reality, the other participant was fictitious.

Instructions

At the start of each session, participants were given instructions about the computer task. The instructions read:

> Today, you will be able to earn money by working at the computer task. You will be participating with another person in this study. These other people will have similar computer tasks. These other people are located at another facility. Three buttons will appear on the screen labeled A, B and C. When each session starts, the letters A, B and C and a counter will appear on the computer screen. The counter will be at zero. Pushing the A button will cause the B and C letter to go off the screen. Pushing the A button approximately 100 times will cause the A letter to go off the screen, and add 15¢ to the counter. After about 1 s, the A, B and C letters will come back on the computer screen. At that time, you can continue to press button A or switch to button B or C. During the session the counter on your computer screen may become larger and 15¢ will be subtracted. After the 15¢ is subtracted, the counter will return to its normal size. This means that one of the other persons has subtracted 15¢ from your counter by pushing button B on his response panel. The money that this person subtracts from your counter is added to his counter. If you push button B on your response panel, the A and C letters will go off the screen. After you have pushed button B approximately 10 times, the letter B will go off the screen and 15¢ will be subtracted from the other person's counter. After about 1 s, the A, B and C letters will come back on the computer screen. You can continue to press button B and subtract additional money from the other person or switch to button A or C. If you

> subtract money from the other person, it will not be added to your counter. Remember, money subtracted from your counter by the other person is added to that person's counter. If you push button C on your response panel, the A and B letters will go off the screen. After you have pushed button C approximately 10 times, the letter C will go off the screen and your earnings displayed on the counter will be protected from subtractions initiated by the other person for some period. After about 1 s, the A, B and C letters will come back on the computer screen. You can continue to press button C or switch to button A or B.

The participant was then asked if he or she had any questions. If so, the relevant portion of the instructions was re-read to the participant. On the second day of participation the participant was asked if they remembered the instructions or wanted them to be re-read. All participants reported remembering the instructions and did not request another reading.

Earnings

Participants were paid $8 per hr to compensate them for time spent completing questionnaires, listening to the instructions, and being partially debriefed, which took approximately 1 hr total during the entire study. Participants also earned money during experimental sessions. Earnings during sessions varied as a function of performance, but averaged around $8-10 per hr. In the event that a participant's total earnings by the end of the study equaled less than a mean of $8.00 per hr of participation, the participant was compensated accordingly (i.e., paid an additional amount) so that the total earnings averaged $8 per hr that the subject participated. Seven participants required this additional payment. Participants were paid at the end of the last daily session the amount

earned during each of the three sessions that day. At the end of the study, participants who completed all scheduled sessions were also given a completion bonus of $10. Participants who quit the study early forfeited the completion bonus. All payments were made in the form of gift cards, which were rounded up to the nearest $5.

Data Analysis

Data were analyzed using non-parametric statistics, including the Wilcoxon Matched-Pairs Signed Rank and the Friedman test. To compensate for the increased potential for Type I error associated with multiple comparisons, the significance level was set at .01.

RESULTS

PSAP Responding

The primary dependent measures on the PSAP were aggressive, escape, and monetary-reinforced responses per session. Figure 1 shows mean responses summed across all three sessions on the PSAP on the three response options during the drug deprivation and drug satiation conditions. Rates of responding on all measures were similar across conditions. A Wilcoxon Matched-Pairs Signed Rank test showed no significant effect of deprivation condition on any of the three response options (mean monetary-reinforced responses pre versus post dose, $p=.64$; mean aggressive responses pre versus post dose, $p=.94$; mean escape responses pre versus post dose, $p=.78$). The same analysis showed no significant effect of deprivation condition on responses when only response rates from the last session of each day were compared (Session 3 monetary-reinforced responses pre versus post dose, $p=.05$; Session 3 aggressive

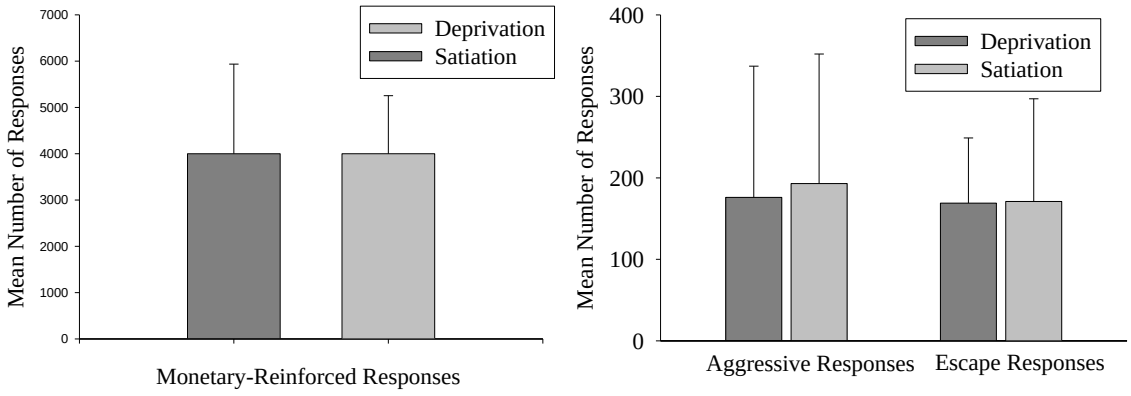

Figure 1. Mean and standard deviation of aggressive, escape, and monetary-reinforced responses on the PSAP compared on deprivation day and satiation day.

responses pre versus post dose, p=.62; Session 3 escape responses pre versus post dose, p=.82). Figure 2 shows monetary-reinforced, escape, and aggressive responses as a function of session across the 6 consecutive experimental sessions for participants exposed to both deprivation/satiation and satiation/deprivation condition sequences. A Friedman test revealed a significant increase in monetary-reinforced responses between the first session and the last session (p=.003), and a significant decrease in escape responses between the first session and the last session (p=.006). There were no significant changes in aggressive responding (p=.69).

An analysis of daily cumulative records of aggressive responses showed that all aggression that occurred was reactive aggression, as no participant made an aggressive response prior to a money loss provocation.

POMS

Overall, there were 6 missing values for Profile of Mood State (POMS) questionnaire data, out of 3,835. For these analyses, missing questionnaire data were handled as follows: The mean of the scores for that participant in that mood category was

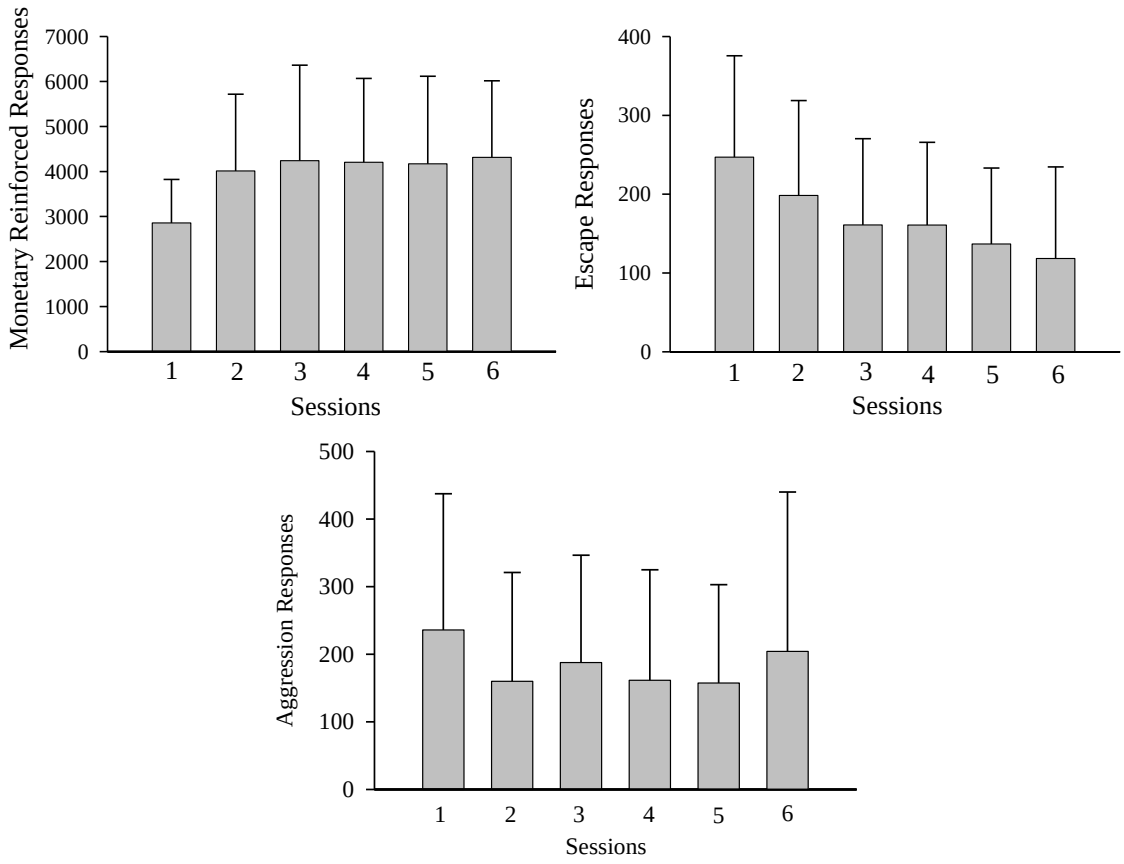

Figure 2. Mean and standard deviation of monetary-reinforced, escape, and aggressive responses on the PSAP across the 6 total sessions.

used to replace the missing value. Measures on the POMS questionnaire were compared across deprivation and satiation states prior to completing the PSAP to assess effects of deprivation on mood independent of task completion. Figure 3 shows deprivation day versus satiation day reports on the POMS when administered prior to the PSAP aggression task. Ratings on the POMS were also compared pre and post PSAP task on deprivation and satiation days to evaluate the effects of completing the task on mood under both conditions. Figures 4 and 5 show responses on the POMS questionnaire before and after the PSAP aggression task on both satiation and deprivation days,

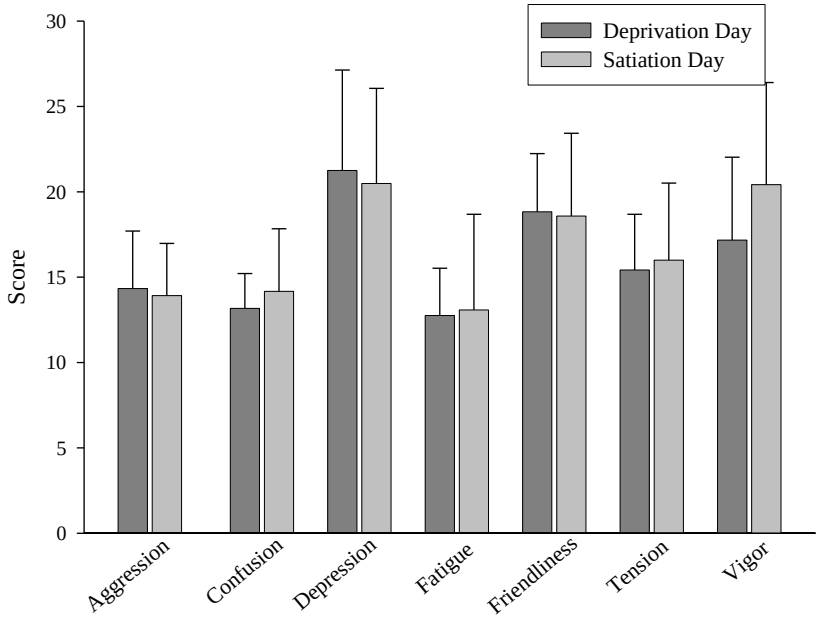

Figure 3. Mean and standard deviation of responses on the Profile of Mood States (POMS) taken prior to the Point Subtraction Aggression Paradigm (PSAP) task on deprivation day and satiation day.

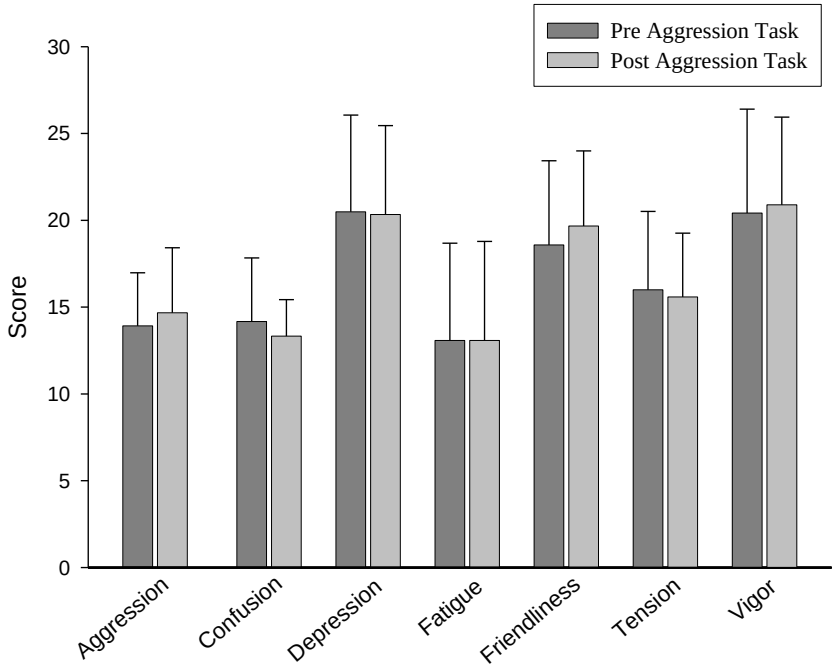

Figure 4. Mean and standard deviation of responses on the Profile of Mood States (POMS) taken on drug satiation day prior to and after completing the Point Subtraction Aggression Paradigm (PSAP) task.

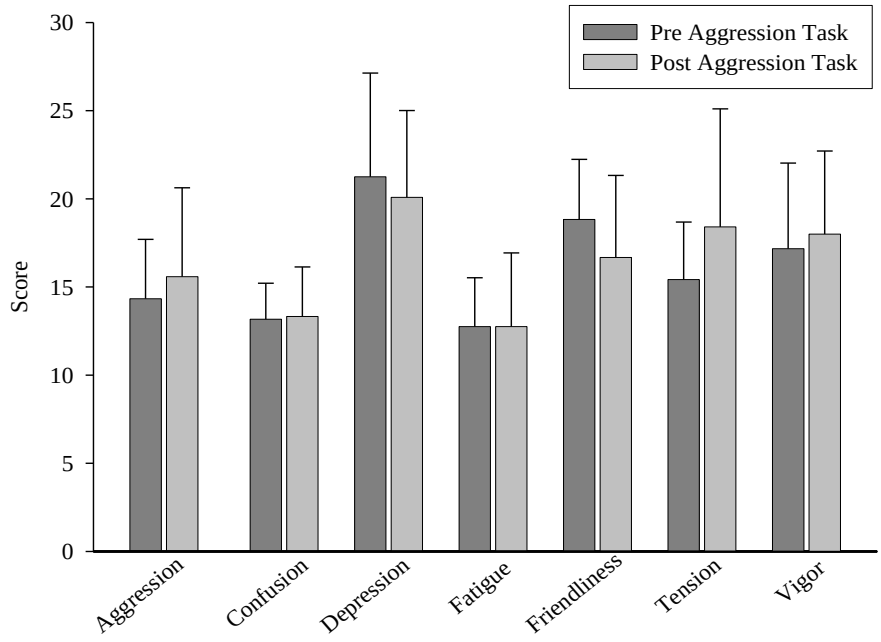

Figure 5. Mean and standard deviation of responses on the Profile of Mood States (POMS) taken on drug deprivation day prior to and after completing the Point Subtraction Aggression Paradigm (PSAP) task.

respectively. Mood on the POMS questionnaire was not affected by methadone condition or the PSAP task. A Friedman test revealed no significant differences between the composite mood scores when compared prior to and after the computer task on both deprivation and satiation day.

Correlations

Length in methadone maintenance treatment was not significantly correlated with aggressive responses on the PSAP (during either condition) or other psychometric measures of aggression. A Pearson correlation revealed no significant relationship between length in treatment and aggression on the PSAP, POMS, or Buss-Perry. The three aggression scores were not significantly correlated with each other: A Pearson correlation revealed no significant correlation between aggressive responses on the PSAP, reports of anger on the POMS, or trait aggression measured by the Buss-Perry.

Lastly, there were no significant gender differences on measures of aggression on the POMS, PSAP, or Buss-Perry.

DISCUSSION

The goal of the present study was to investigate the effects of mild opioid deprivation on aggressive responding during a laboratory choice task in patients currently undergoing opioid (methadone) replacement therapy. Specifically, performance on a laboratory aggression task, the Point Subtraction Aggression Paradigm (PSAP), was measured on two separate occasions, once just prior to and once just after patients received their daily methadone dose. Changes in responding on the aggressive, escape-maintained, and monetary-reinforced responses on the PSAP task were compared across the two time periods.

The study found that mild opioid deprivation associated with the 24-hr dosing interval used in methadone maintenance therapy was not associated with a statistically significant change in monetary-reinforced, aggressive, or escape responding on the PSAP. One possible reason for the similarity in behavior across deprivation and satiation conditions is that the deprivation experienced during MMT within the 24-hr dosing interval may not have been severe enough to influence levels of aggressive responding on the PSAP task, or self-reported anger, tension, or hostility. Several previous studies also have found no self-reported withdrawal effects during the typical daily methadone cycle (McMillan & Gilmore-Thomas, 1996; Torrens et al., 1998). Thus, these data may be interpreted as showing that the 24-hr dosing interval currently used in methadone maintenance therapy is adequate in preventing withdrawal severe enough to induce behavioral changes, at least on this task in this population.

Another possible explanation for the lack of effect of methadone deprivation on aggressive responding is that the participants in this study were generally non-violent and therefore unlikely to show much aggressive responding. Average aggressive responses on the PSAP were lower than those of methadone maintenance patients in previous studies (e.g., Gerra et al., 2001; Gerra et al., 2004; Gerra et al., 2007). The average aggressive responses made by the current participants across 3 sessions were 175.6 on deprivation day, and 193.4 on satiation day. These rates of aggressive responding are much lower than those made by participants in prior studies who were previously addicted to heroin and currently on methadone (Gerra et al., 2001; Gerra et al., 2007), buprenorphine (Gerra et al., 2007), or who had been abstinent from all opioid use for several years (Gerra et al., 2004), all of whom had mean rates of above 300 per 25 min session. In fact, aggressive responding of participants in the current study on the PSAP was similar to responding by the control subjects used in previous studies that were not previous opioid users (Gerra et al., 2001; Gerra et al., 2004; Gerra et al., 2007), which had average aggressive response rates of slightly over 100 per 25 min session. Approximately 20% of the participants in Gerra et al. (2007) had psychiatric symptoms of Antisocial Personality Disorder (ASPD). Individuals with this disorder tend to score higher on the PSAP than controls (Moeller et al., 1998; Moeller, Dougherty, Rustin, Swann, Allen, Shah, & Cherek, 1997). The present study did not directly assess whether participants had a history of ASPD (although no participants reported having any psychiatric diagnoses), making comparisons to the Gerra et al. (2007) study difficult. Nonetheless, it seems likely that the participants in the present study were less aggressive than the participants in the Gerra et al. (2007) study. Future research could compare

deprivation in individuals with or without ASPD to determine whether a history of aggressive responding contributes to heightened aggressive behavior under opioid withdrawal on the PSAP.

Exposure to the PSAP

Monetary-reinforced responses increased as a function of exposure to the task. This finding indicates that performance on the task improved with practice and participants learned to maximized the amount of money earned. Alternatively, escape responses decreased as a function of exposure to the task across the 6 sessions. The decrease in escape responding might have occurred because escape responding was inefficient in the first few sessions. In the first few sessions, participants pressed the escape option much more frequently than once per provocation. Recall that each escape response produced a variable-time 120s provocation-free period, and that one provocation was required before additional escape responses were effective. Thus, additional escape responses within that provocation-free period offered no additional protection from money losses. As participants gained additional exposure to the task, they emitted fewer escape responses, and allocated more responding to the monetary-reinforced option. Aggressive responding was not affected by exposure to the task and was similar across the 6 sessions. It is unclear why aggressive responding did not show the same decrease across sessions as escape responding.

Proactive aggression (aggressive responses prior to a money loss provocation) did not occur in any session for any participant during this experiment. All aggression was reactive aggression, in that it occurred after the first money-loss provocation of the session. This indicates that aggressive responses occurred in retaliation for the money

loss that was attributed to the fictitious partner. If drug deprivation acted as a motivating operation (MO) which made aggression reinforcers more potent, proactive aggression would be expected to increase. On the other hand, if drug deprivation made money-loss provocations from others more aversive, reactive aggression would be expected to increase, as individuals would be more likely to retaliate against opponents in order to avoid money losses (negative reinforcement). The lack of change in aggressive responding from satiation to deprivation states suggests that drug deprivation did not act as an MO to alter the potency of either aggression reinforcers or money loss.

Prior research has shown that opioid use tends to decrease cognitive-motor performance, and psychomotor speed (Mintzer & Stitzer, 2002; Specka, Finkbeiner, Lodemann, Leifert, Kluwig, & Gastpar, 2000). Despite this, there was no effect of methadone satiation or deprivation on monetary-reinforced responses. This may indicate that acute methadone administration does not affect motor responding, at least as assessed by mouse clicks on the PSAP task. One previous study using push buttons also found that monetary-reinforced responses on the PSAP were not affected by acute administration of an opioid (codeine) (Spiga, Cherek, Roache & Cowan, 1990).

POMS Findings

Mild methadone deprivation did not affect participant's self reported mood. This finding is consistent with two previous studies which also found no change in withdrawal symptoms or craving associated with the mild opioid withdrawal related to MMT (McMillan & Gilmore-Thomas,1996; Torrens et al., 1998). Contrary to this, several prior studies have found that the mild withdrawal associated with the 24-hr dosing interval of methadone maintenance therapy leads to higher tension, anger, and irritability on self-

report measures (Dyer et al., 2001) as well as objective and subjective signs of withdrawal (Hanna et al., 2005; Hiltunen et al., 1999). One possible explanation for the discrepant results is that in the above studies approximately half of the participants were non-holders, meaning that they complained of withdrawal symptoms and were unhappy with their current dosing level. This may have contributed to the fluctuations in mood and withdrawal symptoms that were observed during the methadone dosing interval. It is also possible that participants who showed no changes in mood, such as in the present study, may have had less violent histories. As described above, participants with violent histories tend to respond more aggressively on the PSAP and other measures of aggression (Moeller et al., 1998; Moeller et al., 1997). Unfortunately, it is impossible to determine definitively whether participants in prior studies were more aggressive overall because prior studies either did not take data on aggressive behavioral traits (e.g., Dyer et al., 2001), or they did not separate irritability/aggression from other negative withdrawal symptoms (e.g. Hiltunen et al., 1999). The average anger score on the POMS in the current study (14.96 on deprivation day, 14.30 on satiation day) is comparable to the lowest anger scores in methadone maintenance patients in prior research, but unlike previous research, anger scores in the present study did not increase as time from the last dose increased (Dyer et al., 2001). When the Dyer et al. scores were adjusted to account for the different Likert scale, the anger score on the POMS averaged approximately 14 two hours after methadone administration, and increased to an average of 18 twenty-two hrs later. The low anger scores in the current study support the hypothesis that the participants in the current study may have been a particularly nonaggressive sample.

Correlations

Aggression on the PSAP was not significantly correlated with aggression on the Buss-Perry or the POMS. Prior studies have correlated PSAP aggression scores with the Buss-Perry Aggression Questionnaire and also found no relationship between this psychometric measure and laboratory behavioral measure of aggression, although the lack of effect was attributed to small sample size (e.g., Dougherty, Bjork, Marsh, & Moeller, 1999; Lieving, Cherek, Lane, Tcheremissine, & Nouvion, 2008; Tcheremissine, Lane, Lieving, Rhoades, Nouvion, & Cherek, 2005). That the measures are not correlated may not be surprising, however, given that the Buss-Perry measures lifetime aggressive traits, whereas the POMS measures current mood state, and the PSAP measures the frequency with which an individual will actually make an aggressive response against others.

Length in methadone treatment also was not significantly correlated with aggression scores on the PSAP, POMS, or Buss-Perry. Prior research has found that individuals on methadone maintenance treatment show significant mood disturbance compared to healthy controls (Dyer et al., 2001). Based on this, one would assume that length on methadone maintenance therapy may be associated with increased aggression. It has been suggested that this increase in aggression may be a result of tolerance to the positive effect that opioids have on mood (White, 2004). Tolerance to opioids often causes a drug-opposite effect. For example, acute opioid administration causes increased pain threshold, pupil constriction, and decreased respiration (Dyer et al., 1999). With prolonged exposure to opioids, tolerance to these effects develops and individuals experience a drug-opposite effect where they chronically experience a lower pain

threshold, pupil dilation, and increased respiration. White (2004) proposed a compelling theory that the increase in positive mood experienced with acute administration of opioids may also be subject to the same drug-opposite effects with tolerance. This is supported by the increased mood disturbance seen in opioid users compared to healthy controls (Dyer et al., 2001). Contrary to this, the current study did not provide compelling evidence that length in treatment significantly affects mood or aggression.

Finally, gender was not correlated with aggression on any of the measures, indicating that being male or female did not make individuals more or less likely to behave aggressively on this task. Several meta-analyses of laboratory measures of aggression have shown that gender differences are inconsistent in the literature, but that generally males tend to display slightly more direct aggression (e.g., causing physical harm or name-calling), and that both males and females tend to display similar amounts of indirect aggression (e.g., spreading rumors or gossiping; Card, Stucky, Sawalani, & Little, 2008; Eagly & Steffen, 1986). Based on the inconsistency of gender differences in the previous literature it is not surprising that we did not see a significant difference in aggressive behavior between males and females in the current study.

Limitations

There were several limitations to the current study. One is that the withdrawal generated by 24-hr methadone deprivation was mild. MMT is designed to prevent the withdrawal that occurs while discontinuing heroin use. Although previous studies have shown that mood is influenced by the mild state of deprivation that occurs during MMT, this deprivation may not have been severe enough to affect behavior on an operant task. Moreover, this deprivation did not affect mood in the current study. Perhaps if

participants had abstained from methadone for a period longer than 24-hrs, this more severe deprivation would have had an effect on their behavior.

Another limitation of this study is the somewhat small sample size (N=12). As noted above, levels of aggressive responding in participants were generally low. It is possible that different effects may be seen in another population. Some studies have shown that drug effects differ in individuals with more aggressive histories (Bailly, & King, 2006; Cherek, Lane, Pietras, Sharon, & Steinberg, 2002)

Future Research

There are several potential directions for future studies to investigate the effects of opioid deprivation on aggression. First, as noted above, the PSAP could be used to determine whether the mild opioid deprivation associated with methadone maintenance has a greater effect on aggressive behavior in individuals with a more violent history. It may be possible to recruit participants with more violent histories by recruiting individuals with Antisocial Personality Disorder, or by using a self-report screener such as the Life History of Aggression assessment (Coccaro, Berman, & Kavoussi, 1997) to select individuals with violent pasts. Future studies could also investigate the effects of more severe opioid deprivation, which may be more likely to lead to a change in aggressive behavior. Although there may be serious ethical concerns with inducing opioid withdrawal for the sake of experimentation, it may be possible to study behavior in a population that is already experiencing withdrawal for the purposes of treatment. For example, it may be possible to measure aggressive behavior in individuals undergoing heroin detoxification, or in individuals initiating treatment of an opioid antagonist, such as buprenorphine. It is important to know whether these procedures may lead to an

increased probability of aggressive behavior. Lastly, it may be necessary to use an animal model to investigate the relationship between more severe opioid deprivation and aggression. Previous research on opioid withdrawal in animals has shown mixed results. One study in primates found no change in the aggressive behaviors of primates towards another primate following opioid deprivation (Fabre-Nys, Meller, & Keverne, 1982). Conversely, other studies have found that morphine withdrawal markedly increased aggression in rats (Felip, Rodríguez-Arias, Espejo, Miñarro, & Stinus, 2000; Tidey, & Miczek, 1992). Due to these conflicting results, future research is needed to investigate whether opioid withdrawal precipitates aggressive behavior.

Summary

In summary, the mild opioid deprivation associated with methadone maintenance therapy did not produce an increase in aggressive responding. This supports the clinical prescription of methadone as an opioid treatment. Specifically, it suggests that the 24-hr dosing period may not produce deprivation that is severe enough to induce potentially problematic aggressive behavior. Additional research needs to be completed to determine whether aggressive responding is likely to increase during more prolonged opioid abstinence.

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Appendix

HSIRB Signed Approval Letter

WESTERN MICHIGAN UNIVERSITY

Human Subjects Institutional Review Board

Date: February 24, 2011

To: Cynthia Pietras, Principal Investigator
Catherine Gayman, Student Investigator for thesis

From: Amy Naugle, Ph.D., Chair

Re: HSIRB Project Number 10-10-17

This letter will serve as confirmation that your research project titled "Decision Making in Methadone Patients" has been **approved** under the **full** category of review by the Human Subjects Institutional Review Board. The conditions and duration of this approval are specified in the Policies of Western Michigan University. You may now begin to implement the research as described in the application.

Please note that you may **only** conduct this research exactly in the form it was approved. You must seek specific board approval for any changes in this project. You must also seek reapproval if the project extends beyond the termination date noted below. In addition if there are any unanticipated adverse reactions or unanticipated events associated with the conduct of this research, you should immediately suspend the project and contact the Chair of the HSIRB for consultation.

The Board wishes you success in the pursuit of your research goals.

Approval Termination: October 26, 2011

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