INFLUENCING FACTORS ON METHADONE PHARMACOLOGY:
IMPACT ON PATIENT SATISFACTION WITH METHADONE
MAINTENANCE TREATMENT

by

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A thesis submitted in conformity with the requirements
for the degree of Doctor of Philosophy
Graduate Department of Pharmaceutical Sciences
University of Toronto

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Abstract:
The methadone maintenance treatment population suffers from high rates of comorbid psychiatric and substance use disorders. Despite a more than 40-year treatment history, not all patients are satisfied with methadone treatment and more than half of the patients complain of significant inter-dose withdrawal at least some of the time. The objectives of this research were to investigate the pharmacological response to methadone under the influence of comorbid major depressive disorder and smoking; and to identify factors other than physical withdrawal symptoms that can differentiate patients based on their complaints of dissatisfaction with treatment. In Study 1, seven depressed methadone maintenance patients experienced more opioid withdrawal symptomatology over a 24-hour methadone-dosing interval than 10 nondepressed methadone patients. Depression severity was significantly correlated with trough opioid withdrawal severity. This suggests that depression or depressive symptoms are related to reported opioid withdrawal. In Study 2, many factors other than physical opioid withdrawal symptoms were able to differentiate patients who were satisfied with treatment (holders, n=25), partially satisfied with treatment (partial holders, n=35), and not satisfied with treatment (nonholders, n=30). Results suggested that these patient satisfaction groups cluster differently depending on physical opioid withdrawal, mood, psychological distress, and
personality. Nonholders experienced more physical withdrawal symptoms, craving for opioids, and negative drug effects. Holders had less psychological distress and experienced less negative mood states than the other groups. Partial holders had less agreeable personalities compared to patients in the other groups. In Study 3, opioid and nicotine withdrawal symptoms and effects were measured in 40 methadone-maintained patients who were current smokers during trough and peak methadone effects, both pre- and post-nicotine administration. Cigarette smoking enhanced opioid withdrawal suppression during the peak methadone condition, methadone attenuated nicotine withdrawal, and methadone and nicotine shared many of the same main effects, suggesting that smoking and methadone effects may be inseparable dimensions. In summary, the results of these studies suggest that in addition to physical symptoms, mood related factors are important to opioid withdrawal perception and that the mood factors and drug interactions can impact on a patient’s perception of satisfaction with methadone treatment.
Acknowledgements

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<tr>
<td>Δmax</td>
<td>Maximum change from baseline score</td>
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<tr>
<td>[18F]</td>
<td>Radioactive Fluorine</td>
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<td>ARCI</td>
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<td>Asparagine</td>
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<td>Aspartate</td>
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<td>AUC</td>
<td>Area Under the plasma concentration vs. time Curve</td>
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<td>AUEC</td>
<td>Area Under the Effect vs. time Curve</td>
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<td>Benzedrine Group</td>
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<tr>
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</tr>
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<td>C&lt;sub&gt;24&lt;/sub&gt;</td>
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<td>cAMP</td>
<td>Cyclic Adenosine Monophosphate</td>
</tr>
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<td>CAMH</td>
<td>Centre for Addiction and Mental Health</td>
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<td>Cl/F</td>
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Section 1: INTRODUCTION

1.1 Statement of Problem

Methadone maintenance treatment (MMT) is the gold standard pharmacotherapy for the treatment of opioid dependence and has been used for this indication since the mid 1960’s.\textsuperscript{1,2} Opioid-dependent patients are a stigmatized group with significant social and health consequences.\textsuperscript{3,4} These patients have particularly high rates of concurrent psychiatric and drug use disorders.\textsuperscript{5,6} Despite proven efficacy, MMT is not equally effective for all patients: more than half of all patients report experiencing significant opioid withdrawal some of the time, despite attempted clinical dose optimization.\textsuperscript{7} In the literature, patients have been classified as ‘holders’ or ‘nonholders’ depending on their complaints of opioid withdrawal symptoms, with nonholders being patients who experience significant inter-dose opioid withdrawal frequently or all of the time.\textsuperscript{7} Factors that influence the pharmacology of methadone may have an impact on response to methadone treatment.

Currently available instruments for measuring opioid withdrawal were designed to assess symptoms during acute opioid detoxification and rely heavily on physical symptoms of withdrawal.\textsuperscript{8} In MMT, however; there may be other important aspects of opioid withdrawal (e.g., mood symptoms) that may impact the perception of opioid withdrawal. Characterizing MMT patients according to factors other than physical opioid withdrawal could be of clinical utility.
Mood has been related to perceived opioid withdrawal in methadone patients.\textsuperscript{9} Also, it is well known that these patients have high rates of comorbid major depressive disorder.\textsuperscript{10-12} Therefore, it is possible that depression could influence methadone pharmacodynamic responses, particularly in patients who complain of opioid withdrawal.

Another interesting observation in this population is that cigarette smoking is nearly universally prevalent in MMT patients.\textsuperscript{13-18} Greater methadone doses have been associated with increased cigarette smoking and increased nicotine dependence severity.\textsuperscript{14, 19-21} While, cigarette smoking and nicotine administration have been associated with increased methadone self-administration\textsuperscript{22, 23}; the pharmacodynamic influence of smoking/nicotine administration on perceived effects of methadone has not been well studied.

1.2 Overall Purpose of the Study, Objectives, and Hypothesis

1.2.1 Purpose:

To identify and evaluate factors that influence pharmacological responses to methadone in stabilized methadone maintenance treatment patients.
1.2.2 Objectives:

To investigate pharmacological responses of methadone in the context of concurrent major depressive disorder and during the concurrent administration of nicotine in two experimental trials in stabilized MMT patients.

To identify factors other than physical withdrawal symptoms that differentiate MMT patients based on their satisfaction with treatment and use these factors to modify an existing opioid withdrawal scale to better reflect the construct of opioid withdrawal in the context of opioid substitution therapy.

1.2.3 Overall Hypothesis

Methadone pharmacodynamic responses in methadone maintenance treatment patients are altered by many factors. Specifically, methadone pharmacokinetics, comorbid psychiatric states/symptoms, and drug interactions are likely to influence perceived opioid effects and opioid withdrawal symptoms; and have an impact on patient satisfaction with methadone treatment.
1.3 Specific Research Objectives and Hypotheses

1.3.1 Major Depressive Disorder and Patient Satisfaction in Relation to Methadone Pharmacokinetics and Pharmacodynamics in Stabilized Methadone Maintenance Patients (Study 1)

1.3.1.1 Specific Objectives

Primary: To investigate the influence of comorbid major depressive disorder on the relationship between methadone pharmacokinetics and pharmacodynamics in stabilized methadone maintenance treatment patients.

Secondary: To determine what impact patient satisfaction with methadone treatment has on these relationships in depressed MMT patients.

1.3.1.2 Specific Hypotheses

The relationship between methadone plasma concentrations and negative mood disturbance will be steeper in depressed methadone patients compared to those without comorbid depression, particularly in nonholders.
Pharmacodynamic responses to methadone will be different in depressed methadone maintenance patients compared to nondepressed patients, with depressed patients being more sensitive to negative effects.

1.3.2 Opioid Withdrawal Scale Modification and Characterization of Between Dose Opioid Withdrawal and Patient Satisfaction in Methadone Maintenance Treatment (Study 2)

1.3.2.1 Specific Objectives

Primary: To modify the Subjective Opioid Withdrawal Scale to include other measures that differentiate patients based on their satisfaction with methadone maintenance treatment.

Secondary: To characterize holder and nonholder populations through the examination of patient factors that may be related to the experience of opioid withdrawal symptoms in opioid substitution therapy.

1.3.2.2 Specific Hypotheses

Psychological factors will differentiate methadone maintenance treatment patients who self report as holders, partial holders and nonholders, as well as, or better than physical opioid withdrawal symptoms alone.
Modification of the Subjective Opioid Withdrawal Scale to include patient factors other than physical opioid withdrawal will result in a more sensitive instrument for measuring perceived opioid withdrawal in methadone maintenance treatment patients.

1.3.3 Methadone-Nicotine Interactions in Stabilized Methadone Maintenance Treatment Patients (Study 3)

1.3.3.1 Specific Objectives

Primary: To elucidate the pharmacodynamic interaction between smoking and methadone in MMT patients. Specifically, to determine how smoking alters acute methadone effects/methadone withdrawal effects and to determine how methadone alters acute smoking effects and withdrawal effects from smoking.

Secondary: To determine if the interaction between methadone and smoking is mediated by nicotine effects or behaviours related to cigarette smoking.

1.3.3.2 Specific Hypothesis

Methadone effects and nicotine (or smoking) effects interact with each other in different ways depending on the exposure to both drugs. Specifically, smoking can alter acute
methadone effects/methadone withdrawal effects and methadone can alter acute smoking effects and withdrawal effects from smoking.

1.4 Review of the Literature

1.4.1 Opioid Dependence

Opioid Dependence, like other substance use disorders is typically a long-lasting and relapsing condition that causes significant distress and disability. The illicit opioid using population is estimated to be approximately 290 to 430 per 100,000 of the adult population aged 15 to 64 in Canada, 60,000 to 90,000 persons. There are significant social and health consequences associated with opioid dependence. For example, in a study of 114 heroin users in Toronto, 52% were in temporary housing, 46% had no employment over the last year and a large percentage of their average monthly income came from social benefits and illegal activities. A large proportion of these users (62%) had used emergency services in the previous 12 months, half had overdosed on opioids in their lifetime, and many had tested positive for Hepatitis B (28%), Hepatitis C (56%) or HIV (7%).

Summary Point:
- Opioid dependence is a chronic relapsing condition with significant social and health consequences
1.4.2  Methadone and Methadone Maintenance Treatment

An important pharmacotherapy option for opioid dependence is substitution therapy with an opioid agonist. The rationale for substitution treatment is to replace the abused opioid with a long acting opioid preparation that will attenuate withdrawal symptoms, reduce the craving for opioids, avoid the risks associated with needle use and allow the individual to focus on lifestyle modifications to support recovery from opioid dependence. In Canada, methadone and buprenorphine are the only opioids available for this indication, with methadone as the mainstay of treatment.

Methadone is a synthetic opioid analgesic developed in Germany prior to World War II, in an attempt to develop an analgesic with minimal abuse liability. It was patented in 1941 but not used because German physicians did not know how to safely prescribe it. After the war researchers at the U.S. Public Health Hospital in Lexington, Kentucky found that it had effects similar to morphine but with a longer duration of action. Methadone has unique pharmacologic properties that makes it suitable for maintenance treatment. A single oral dose in a stabilized patient lasts between 24-36 hours without producing euphoria, sedation, or analgesia. This allows a patient to function normally, not be impaired when performing tasks, and to experience normal pain and emotional responses. Further, methadone relieves the persistent craving for opioids (one of the major causes of relapse) and in sufficient doses “blocks” the opioid effects of normal street doses of short-acting opioids (e.g. heroin). Tolerance to methadone develops and remains steady, hence patients can be maintained at the same dose for extended lengths
of time.\textsuperscript{26} Finally, methadone is a safe drug with minimal side effects.\textsuperscript{27-29} It is important to note that safety is a relative term in this case. A small oral dose (30 - 40 mg) produces respiratory depression that is sufficient to kill an opioid naïve adult, even lower doses can be fatal for children.\textsuperscript{30-33}

It wasn’t until the mid 1960s that Dole and Nyswander began treating heroin addicts in New York city with methadone maintenance treatment.\textsuperscript{1, 2} Now, in the United States over 150 000 opioid dependent individuals are enrolled in methadone maintenance programs. It is estimated that these services reach one in 10 to one in eight of the 12 to 15 million opioid dependent individuals in the United States.\textsuperscript{34}

Summary Points:

- Opioid substitution therapy helps stabilize opioid dependence individuals by minimizing opioid withdrawal and reducing craving, which allows a patient to focus on recovery.
- Methadone has unique pharmacology that enables it to be used as a once daily substitute.

1.4.2.1 The Canadian Experience

In Canada, methadone has been used since 1948 as an analgesic and since 1959 to treat opioid withdrawal symptoms.\textsuperscript{35} In 1963 Halliday and colleagues developed a ‘prolonged’ opioid withdrawal treatment program.\textsuperscript{35-37} This prolonged approach is
similar to the maintenance treatment of Dole and Nyswander\textsuperscript{1,2} though Halliday did not necessarily believe that ‘prolonged’ withdrawal treatment was synonymous with ‘maintenance’.\textsuperscript{36} Also, the approach of Halliday and colleagues set a maximum daily methadone dose of 40 mg.\textsuperscript{35,36} From 1968 to the early 1970s, there was an increase in the number of persons in methadone treatment. However, there were issues with misuse and abuse of methadone.\textsuperscript{38} To combat these issues, national health authorities prepared strict treatment guidelines for methadone maintenance.\textsuperscript{39} Following the implementation of these guidelines and regulations a sharp decrease in patients on MMT was noted.\textsuperscript{38} There was a slight increase in the number of MMT patients in Canada from the early 1980s to mid-1996.\textsuperscript{38,40} In 1996 methadone treatment was expanded in Ontario, resulting in an increase in the number of methadone patients in the province, from 975 in 1996 to more than 4000 in 1998.\textsuperscript{40} Currently in Canada there are between 25,000 and 30,000 patients in MMT\textsuperscript{24,41}, with half of the patients concentrated in Ontario and British Columbia.\textsuperscript{42}

Summary Point:

- Methadone has a long history in Canada for the treatment of pain and opioid withdrawal.

1.4.3 Methadone Pharmacodynamics

Methadone elicits its pharmacodynamic properties through binding to the \( \mu \), \( \delta \), and \( \kappa \) opioid receptors.\textsuperscript{43} The \( \mu \) opioid receptor is principally responsible for the typical opioid
pharmacological effects; its activation produces analgesia, respiratory depression, physical dependence, and tolerance.\textsuperscript{44, 45}

Methadone possesses a chiral carbon atom in its structure, see figure 1.1. This means that methadone exists as a racemate of two enantiomeric forms. These enantiomers have identical chemical compositions but differential spatial arrangements about the chiral carbon, with one enantiomer being the mirror image of the other. Racemic methadone consists of (R)- or levo- or (l)-methadone and (S)- or dextro- or (d)-methadone.

Figure 1.1: Methadone Chemical Structure

(R)-Methadone

(S)-Methadone

(R)-methadone is thought to account for most, if not all, of methadone’s opioid activity. In vitro binding studies have demonstrated that the IC\textsubscript{50} for (R)-methadone was 10 times lower than for (S)-methadone in whole rat brain homogenates.\textsuperscript{46} An approximate 10-fold difference in affinity has been found between the two enantiomers at the bovine \(\mu_1\) and \(\mu_2\) receptors. IC\textsubscript{50} values for the bovine \(\mu_1\) receptor, which mediates supraspinal analgesia, were 3.0 and 26.4 nmol/L for (R)- and (S)-methadone respectively. At the bovine \(\mu_2\)
receptor, which mediates spinal analgesia, the IC\textsubscript{50} values were 6.9 and 88 nmol/L for (R)- and (S)-methadone respectively.\textsuperscript{47} In human analgesia (R)-methadone is approximately 50 times as potent as (S)-methadone.\textsuperscript{48}

In a blinded study by Dole and Nyswander, stabilized methadone maintenance patients were switched from (R,S)-methadone to (S)-methadone.\textsuperscript{2,49} Initially, these patients were unaware of the switch because there was no difference in taste and immediate effects, however after 24 hours they began to experience symptoms of withdrawal and after three days they believed, without suggestion, that their medication was altered.\textsuperscript{2,49} Once this occurred, they were switched back to (R,S)-methadone and opioid withdrawal symptoms quickly resolved.\textsuperscript{2,49} In another study, in humans, both objective and subjective opioid effects were not detected after the administration of 15-90mg of (S)-methadone to non-tolerant, formerly opioid-dependent subjects.\textsuperscript{50} In the same study subcutaneous administration of 30-90 mg (S)-methadone failed to improve withdrawal symptomatology in opioid-dependent subjects abruptly withdrawn from morphine.\textsuperscript{50} In a study of healthy male volunteers the effects of 7.5 mg oral (S)-methadone on respiratory depression and pupil diameter were not significantly different from placebo. However, the oral administration of 7.5 mg (R)-methadone or 15 mg (R,S)-methadone caused sustained respiratory depression and miosis.\textsuperscript{51} (S)-methadone doses between 50 and 100 mg induced mild respiratory depression.\textsuperscript{51} High doses (650-1000 mg/day) of (S)-methadone to dependent patients induced opioid subjective effects, partially suppressed withdrawal and caused mild physical dependence.\textsuperscript{52} However, patients consistently denied experiencing subjective opioid effects.\textsuperscript{52} In another study, (R)- and (S)-methadone levels
were measured concurrently with mood states and opioid withdrawal symptoms over a 24-hour dosing interval in stabilized methadone maintenance patients. (S)-methadone was associated with negative mood states and opioid withdrawal in a manner opposite to (R)-methadone. Also, a greater (S)/(R)-methadone ratio was associated with negative mood states in patients on a methadone dose of greater than 100 mg/day.

Methadone is also a noncompetitive antagonist at the N-methyl-D-aspartate (NMDA) receptor. The $K_i$ values for methadone and dextromethorphan, an established NMDA receptor antagonist, are similar. NMDA receptor antagonism attenuates and reverses the development of tolerance to morphine without altering its analgesic properties. Both (R)- and (S)-methadone have similar affinities for the NMDA receptor, with $K_i$ values of 3.4 and 7.4 µmol/L, respectively. Methadone is also a strong inhibitor of serotonin and norepinephrine uptake. $K_i$ values for inhibition of serotonin are 0.014 and 0.992 µmol/L and for inhibition of norepinephrine are 0.702 and 12.7 µmol/L for (R)- and (S)-methadone respectively. It has been suggested that methadone’s antagonistic properties at the NMDA receptor and inhibitory action on serotonin and norepinephrine uptake may contribute to its antinociceptive properties.

**Summary Points:**

- Methadone effects are largely mediated by the µ-opioid receptor.
- Methadone is a chiral compound, with (R)-methadone accounting for the majority of methadone’s µ opioid effects
- (S)-methadone may be related to aversive effects of methadone.
1.4.4 Methadone Pharmacokinetics

1.4.4.1 Absorption and Distribution

Different oral formulations of methadone (tablet, liquid and disk) do not produce differences in Area Under the plasma concentration vs. time Curve (AUC), peak plasma concentrations, and trough plasma concentrations. The oral bioavailability of methadone tablets has been estimated between 70 and 80% for doses ranging from 10 to 60 mg. There is considerable inter-individual variation in these estimates (range 36-100%). As well, the oral bioavailability of methadone is different at treatment initiation compared to later on in treatment. In a study of six patients at the start of MMT, oral bioavailability fell from 95±9% at the start of treatment to 81±10% on day 25. This may be explained by auto-induction of methadone metabolism. \( T_{\text{max}} \) for methadone ranges from 2.5 to 4 hours after administration.

Methadone is a lipophillic drug with a volume of distribution greater than physiologic volumes. At steady-state the volume of distribution ranges from 1.4 to 6.7 L/kg. Methadone is highly bound to plasma proteins including albumin, lipoproteins and \( \alpha_1 \)-acid glycoprotein, with the latter accounting for the majority of the protein binding.
Summary Point:
- Methadone has high oral bioavailability, large volume of distribution, and is highly protein bound.

1.4.4.2 Metabolism and Elimination:

Methadone is extensively metabolized, mostly in the liver but intestinal Cytochrome P450 (CYP) 3A4 also likely plays a role. The main metabolite 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP) is the product of N-demethylation followed by spontaneous cycling (the product of the N-demethylation is unstable and hence ‘spontaneously’ forms a cyclic compound to increase its stability). More recent in vitro studies suggest that in addition to CYP3A4, CYP2B6 and CYP2C19 are involved in N-demethylation of methadone, with CYP2B6 playing the greatest role. In addition to methadone, 9 metabolites have been identified in urine and 3 metabolites have been identified in feces. Metabolites other than EDDP individually account for little of the metabolism of methadone. Mean plasma clearance rates range from 53 to 217 ml/min. There is considerable inter-individual variability in estimates of the plasma clearance rate. The elimination half-life of methadone also demonstrates considerable inter-individual variability. Reported estimates of methadone half-life range from 15 to 207 hours.

In a population pharmacokinetic study of 35 MMT patients the elimination half-life was significantly shorter at steady-state compared to treatment induction, with half-life
estimates of 48 hrs at steady-state compared to 128 hours at treatment induction. This was confirmed in another study of 12 subjects, half-life decreased from 55 hours at treatment induction to 22 hours on day 26. This again, may be accounted for by auto-induction of methadone metabolism resulting in an increased clearance rate.

When evaluating pharmacokinetic influences in MMT it is important to consider steady-state pharmacokinetics. As noted above, methadone pharmacokinetics are different under single-dose and steady-state conditions. Auto-induction of methadone metabolism leads to decreased estimates of half-life and oral bioavailability.

Summary Points:
- Methadone is metabolized by CYP3A4, CYP2B6 and CYP2C19.
- Methadone has a long elimination half-life.
- Methadone pharmacokinetics are altered at steady-state.
- There is considerable inter-individual variability in methadone pharmacokinetic parameters.

1.4.4.3 Influence of Enantiomers and Bound/Unbound Fractions

In a pharmacokinetic study evaluating the individual enantiomers, (R)-methadone was significantly different then (S)-methadone for a number of pharmacokinetic parameters. (R)-methadone values for $C_{\text{max}}$ and $T_{\text{max}}$ were 83% and 129% those of (S)-methadone, respectively. The ratio of (R)- to (S)-methadone at $T_{\text{max}}$ was significantly lower than at
the trough condition. A significant difference was detected at one hour after methadone administration and remained detectable until 4 hours after methadone administration. When accounting for protein binding, additional differences in pharmacokinetic parameters were apparent. Free (R)-methadone plasma concentrations at trough (pre- and post-dose) and peak were 170 to 175% those of free (S)-methadone. For free (R)-methadone, AUC, $C_{SS}$, and plasma clearance ($CL_u/F$) were 167%, 158%, and 59% of the values obtained for free (S)-methadone.

The significantly lower clearance of free (R)-methadone indicates that (R)-methadone has a lower intrinsic clearance. Further evidence of this is the significantly greater portions of (S)-EDDP and (R)-methadone found in urine compared to the corresponding enantiomers.

Methadone metabolism shows stereoselectivity; both CYP2B6 and CYP2C19 but not CYP3A4 have different preferences for (R)- and (S)-methadone N-demethylation. CYP2B6 demonstrates preference for metabolizing (S)-methadone and CYP2C19 demonstrates preference for metabolizing (R)-methadone.

Information about how methadone disposition changes over time is currently lacking. In one study, Mitchell et al. investigated pharmacokinetic fluctuation in five MMT patients with two separate 24-hour testing sessions separated by a minimum of one year. Average, dose-corrected (R)-methadone steady state levels changed between sessions, ranging from a 51% decrease to a 466% increase. These differences were not
consistently related to changes in methadone dose. (S)/(R)-methadone ratios increased 12% between sessions, suggesting different long term changes in the pharmacokinetics of each enantiomer.

Summary Points:
- There are differences in pharmacokinetics between methadone enantiomers.
- There is a greater exposure to free (R)-methadone and it is cleared more slowly.

1.4.5 Methadone Concentration-Effect Relationships

A number of studies have attempted to find a minimum plasma concentration for effective maintenance therapy. The results of these studies have been conflicting. In some studies a threshold concentration could not be determined. While other studies have reported a threshold for effective MMT ranging between 50 and 600 ng/mL. Most of these studies focused on trough plasma concentrations only; this may not be sufficient as demonstrated by the work of Dyer et al described below. Further, none of these studies examined the effects of chirality on the relationship between concentration and effect. Due to differences in pharmacokinetic and pharmacodynamic properties of (R)- and (S)-methadone, it may be useful to quantify both (R)- and (S)-methadone plasma concentrations when investigating the pharmacokinetics of methadone.
Dyer et al.\textsuperscript{92} investigated the relationship between methadone plasma concentration and effects in 18 methadone-stabilized patients where serial methadone blood concentration determinations were made over one 24-hour dosing interval. Results indicated that there was a significant inverse relationship between plasma methadone concentrations and withdrawal severity. Specifically, withdrawal severity was significantly correlated with the maximum hourly rate of decline in plasma concentration ($r = 0.67$) for all subjects.\textsuperscript{92} In a subsequent study Dyer et al. found a relationship between methadone plasma concentrations and total mood disturbance (an index of negative mood from the Profile of Mood States (POMS) scale): negative mood varied with the rate of decline in methadone plasma concentration.\textsuperscript{9}

In a study by Hiltunen et al. 50 methadone maintenance subjects were enrolled into two groups: satisfied and dissatisfied patients, dissatisfied patients felt their dose was too low.\textsuperscript{98} Well-being was rated using the Objective Opioid Withdrawal Scale (OOWS)\textsuperscript{99} and an augmented version of the Subjective Opioid Withdrawal Scale (SubOWS).\textsuperscript{99, 100} A correlation analysis between methadone plasma concentrations ((R)-, (S)-, and (R,S)-methadone) and total scores of positive opioid effects, SubOWS items and OOWS items was carried out for dissatisfied subjects only.\textsuperscript{98} For (R,S)-methadone, scores on the SubOWS items were significantly correlated to methadone plasma concentrations at 2 hours. For (R)-methadone, plasma concentrations were significantly correlated with SubOWS effects at 2 and 8 hours.\textsuperscript{98} Results suggest that relating (R)-methadone plasma levels to effects of methadone may be more useful than racemic methadone levels.
In a study by Eap et al.\textsuperscript{101}, trough (R)-, (S)-, and (R,S)-methadone plasma concentrations were measured in 180 methadone maintenance patients. The aim of this study was to determine whether (R)-methadone concentrations were related to therapeutic response (measured by opioid-free urine samples over a two month period prior to blood sampling). Patients were classified as responders if they had only opiate-free urine samples and non-responders if they had one or more opiate-positive urine samples. Thresholds from 100 to 500 ng/ml were tested for (R)- and (S)- methadone (in increments of 50 ng/ml), while thresholds from 100 to 1000 ng/ml were tested for (R,S)-methadone (in increments of 100 ng/ml).\textsuperscript{101} Sensitivity (responders above threshold concentration divided by all responders) and specificity (non-responders below threshold divided by all non-responders), as well as $\chi^2$ and p-values were calculated for all experimental thresholds. For (R)-methadone a significant $\chi^2$ value was reported for 200, 250 and 300 ng/ml, with the highest p-value at 250 ng/ml.\textsuperscript{101} For (R,S)-methadone a significant $\chi^2$ value was reported for 400 ng/ml). Significance was not reported for any of the tested (S)-methadone thresholds.\textsuperscript{101} At the (R)- methadone threshold of 250 ng/ml the specificity was 93%, therefore only 7% of the non-responders had (R)-methadone plasma concentrations above this threshold.\textsuperscript{101} At the (R,S)-methadone threshold of 400 ng/ml the specificity was 81%, therefore 19% of non-responders had plasma concentrations above the threshold.\textsuperscript{101} These results support the premise that (R)-methadone plasma concentrations may have greater predictive capabilities than racemic methadone levels.
Summary Points:

- No minimum effective trough methadone plasma concentration for withdrawal suppression has been identified.
- Withdrawal severity is proportional to rate of decline in plasma concentration.
- (R)-methadone may be more predictive of methadone opioid effects.

1.4.5.1 Pharmacokinetic-Pharmacodynamic Modelling

A major goal of clinical pharmacology is to understand dose-effect relationships in the therapeutic use of drugs. Pharmacodynamic models relate drug concentrations to drug effect. Simple models include the fixed effect model (where an observed effect is absent or present), the $E_{\text{max}}$ model (simplest model capable of describing drug effect over the whole range of possible concentrations), the linear model (drug effect is proportional to concentration), and the Sigmoid $E_{\text{max}}$ ($SE_{\text{max}}$) model (similar to the $E_{\text{max}}$ model, a more generalizable form, i.e. the $E_{\text{max}}$ model is the simplest form of the $SE_{\text{max}}$ model).

The $SE_{\text{max}}$ model is of particular utility in evaluating pharmacodynamic relationships mediated by receptors. The model is explained by the following equations (1 – when drug effect is to increase a measure and 2 – when drug effect is to decrease a measure)
1. \[ E = \frac{E_{\text{max}} \cdot C^N}{EC_{50}^N + C^N} \]

2. \[ E = E_{\text{max}} - \frac{E_{\text{max}} \cdot C^N}{EC_{50}^N + C^N} \]

Where, \( E \) is the drug effect, \( C \) is the plasma concentration, \( E_{\text{max}} \) is the maximum attainable effect, \( EC_{50} \) is the concentration that produces 50\% of the maximum effect and \( N \) is the sigmoidicity factor (slope factor). Assumptions using this approach for pharmacokinetic-pharmacodynamic modelling include: equilibrium between brain and plasma concentrations, no delay between changes in concentration and effect, tolerance to drug effects would have occurred previously and would be stable and that the drug effects are caused by the parent drug and not contributed to by an active metabolite.

Summary Point:
- \( SE_{\text{max}} \) model may be particularly suitable for investigating methadone PK-PD relationships.

1.4.5.2 Pharmacokinetic-Pharmacodynamic Modelling of Methadone

Pharmacokinetic-pharmacodynamic modelling has been utilized to investigate concentration-effect relationships for methadone. In two studies Inturrisi et al. related sedation and pain relief to methadone plasma concentrations in cancer and chronic pain patients after intravenous injection or infusion of methadone.\(^{79,103}\) They found large inter-individual variability in the Pharmacokinetic-Pharmacodynamic (PK-PD) relationships and suggested a clinical utility of PD-modelling for individualization and optimization of analgesic methadone use in chronic pain populations.\(^{79,103}\) Dyer et al.
used this model to link methadone concentrations to effects in methadone maintained patients.\textsuperscript{9, 92} But the model could not be applied to all subjects. Estimates of $EC_{50}$ and slope for pain relief were similar to those reported by Inturrisi et al.\textsuperscript{103} The Dyer studies suggest that the relationship between methadone and its effects in MMT patients is steep, indicating that small changes in methadone plasma concentrations could lead to robust differences in methadone effects.\textsuperscript{9, 92}

Summary Point:
- $SE_{\text{max}}$ model ably related analgesia, opioid withdrawal and sedation to methadone plasma concentrations

1.4.6 Opioid Withdrawal

Withdrawal from opioids (including methadone) is a characteristic syndrome consisting of any or all of the following symptoms: aching muscles and joints, insomnia, nausea, mood changes, tachycardia, lacrimation, stuffy nose, sweating, gooseflesh, loss of appetite, tremor, yawning, restlessness, fever, increased respiratory rate, increased blood pressure, weight loss, pupil dilation, irritability, and anxiety.\textsuperscript{104, 105} While not life-threatening, opioid withdrawal is associated with a very miserable phenotype; therefore an opioid-dependent individual suffering from opioid withdrawal may seek out opioids to alleviate the extreme discomfort. In the case of an opioid substitution therapy patient experiencing opioid withdrawal there is an increased risk of relapse and dissatisfaction with treatment.
Opioid withdrawal symptoms following abrupt cessation of opioid use may be qualitatively different from withdrawal symptoms routinely associated with substitution therapy (i.e. those that occur towards the end of the dosing interval). Also, inter-individual differences in opioid withdrawal perceptions and acceptance are also important to consider. As such, differences in the relative salience of physical and psychological symptoms of withdrawal may need to be accounted for at the individual patient level and may depend on the context of opioid use.

Summary Points:
- Opioid withdrawal can be extremely uncomfortable but not life threatening.
- Opioid withdrawal experienced in the context of abrupt opioid cessation or opioid substitution therapy may have clinically relevant differences.

1.4.7 Measuring Opioid Withdrawal

Opioid withdrawal is usually measured using three methods: self-report, clinician observation, and objective measurement. Self-report involves a patient’s own interpretation of withdrawal symptoms, as such it is a subjective measure, and can vary based on individual patient factors. Self-report is the most direct measure of withdrawal; however reliability may be reduced, as patients may not score items consistently. Clinician observation involves a trained observer rating various signs of withdrawal; as such it is considered more reliable than self-report. This method is indirect; therefore it
may lack sensitivity when quantifying lower levels of opioid withdrawal. Objective measurement of opioid withdrawal is accomplished by the measurement of physiological changes that are linked to opioid withdrawal. There are limited physiological markers for opioid withdrawal, e.g. heart rate, blood pressure, and pupil dilation. This type of measurement can be made very reliably; however physiological measures can be altered by other factors than opioid withdrawal. For example, heart rate can be altered by a patient’s activities prior to measurement, and hence, care should be taken in the interpretation of these objective measurements. These three methods for quantifying opioid withdrawal have been used alone or in combination.

Self-report may be of particular use when assessing opioid withdrawal in the context of opioid substitution therapy as this may provide a special case in which psychological modifiers of withdrawal are more important. Seventy years ago, Kolb and Himmelsbach importantly noted that some patients experiencing opioid withdrawal show many objective signs of withdrawal but complained little; while others may show no objective signs but present as restless, in pain, and nervous. This suggests that factors other than physical withdrawal may influence the perception of opioid withdrawal and consequently patient satisfaction with treatment.

To date, 16 opioid withdrawal scales have been published. These scales are strongly rooted in physical symptoms of withdrawal with many of the scales based upon the work of Kolb and Himmelsbach. Of the withdrawal scales, 13% had full validity and reliability testing, 19% had only reliability testing, 56% had only validity
testing and 38% had no form of reliability of validity testing (see table 1.1). Fifty percent were developed using patients in detoxification programs and 38% were developed based on a naloxone challenge during development and validation. The majority of scales (63%) are based on self-report. Of the available scales the best is the Subjective Opioid Withdrawal Scale (SubOWS), although it is based on self-report and consists of physical symptoms of withdrawal, it has full validity and reliability testing, and it is short and easily understood by patients. See table 1.1 for scale descriptions.

Summary Points:

- Self-report is the optimal method for measuring opioid withdrawal in the context of substitution therapy.
- Factors other than physical opioid withdrawal may relate to perceived satisfaction with treatment.
- SubOWS is the best available opioid withdrawal scale.
Table 1.1: Summary of published opioid withdrawal scales

<table>
<thead>
<tr>
<th>Scale</th>
<th>Acronym</th>
<th>Method of Quantification</th>
<th># of Items</th>
<th>Validity</th>
<th>Reliability</th>
<th>Patient Population</th>
<th>(development)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Himmelsbach Scale (1938)</td>
<td></td>
<td>- Clinician Observation</td>
<td>14</td>
<td>None</td>
<td>None</td>
<td>Opioid Addicts</td>
<td></td>
</tr>
<tr>
<td>Opiate Withdrawal Scale (long form) (1968)</td>
<td>OPWL</td>
<td>- Self Report</td>
<td>59</td>
<td>Yes</td>
<td>None</td>
<td>Opioid Addicts</td>
<td></td>
</tr>
<tr>
<td>Opiate Withdrawal Scale (short form) (1968)</td>
<td>OPW</td>
<td>- Self Report</td>
<td>29</td>
<td>Yes</td>
<td>None</td>
<td>Opioid Addicts</td>
<td></td>
</tr>
<tr>
<td>Strong Opioid Withdrawal Scale (1970)</td>
<td>SOW</td>
<td>- Self Report</td>
<td>80</td>
<td>Yes</td>
<td>None</td>
<td>Patients 10 days into Opioid Taper</td>
<td></td>
</tr>
<tr>
<td>Weak Opioid Withdrawal Scale (1970)</td>
<td>WOW</td>
<td>- Self Report</td>
<td>84</td>
<td>Yes</td>
<td>None</td>
<td>Detoxification patients</td>
<td></td>
</tr>
<tr>
<td>Wang (1974)</td>
<td></td>
<td>- Clinician Observation</td>
<td>10</td>
<td>Yes</td>
<td>None</td>
<td>Treatment seeking patients (confirm dependence)</td>
<td></td>
</tr>
<tr>
<td>Judson (1980)</td>
<td></td>
<td>- Clinician Observation</td>
<td>17</td>
<td>None</td>
<td>None</td>
<td>Treatment seeking patients (confirm dependence)</td>
<td></td>
</tr>
<tr>
<td>Subjective Opiate Withdrawal Scale (1987)</td>
<td>SOWS</td>
<td>- Self Report</td>
<td>16</td>
<td>Yes</td>
<td>Yes</td>
<td>Detoxification Patients</td>
<td></td>
</tr>
<tr>
<td>Objective Opiate Withdrawal Scale (1987)</td>
<td>OOWS</td>
<td>- Clinician Observation</td>
<td>13</td>
<td>Yes</td>
<td>Yes</td>
<td>Detoxification Patients</td>
<td></td>
</tr>
<tr>
<td>Opiate Withdrawal Scale (1987)</td>
<td>OWS</td>
<td>- Self Report</td>
<td>32</td>
<td>Yes</td>
<td>None</td>
<td>Detoxification Patients</td>
<td></td>
</tr>
<tr>
<td>Adjective Rating Scale (1988)</td>
<td>ARS</td>
<td>- Self Report</td>
<td>20/16</td>
<td>None</td>
<td>None</td>
<td>Detoxification Patients</td>
<td></td>
</tr>
<tr>
<td>Clinical Institute Narcotic Assessment (1988)</td>
<td>CINA</td>
<td>- Clinician Observation</td>
<td>13</td>
<td>None</td>
<td>Yes</td>
<td>Treatment seeking patients (confirm dependence)</td>
<td></td>
</tr>
<tr>
<td>Short Opiate Withdrawal Scale (1990)</td>
<td>SOWS</td>
<td>- Self Report</td>
<td>10</td>
<td>Yes</td>
<td>None</td>
<td>Detoxification Patients</td>
<td></td>
</tr>
<tr>
<td>Subjective Opiate Withdrawal Questionnaire (1991)</td>
<td>SOWQ</td>
<td>- Self Report</td>
<td>20</td>
<td>None</td>
<td>None</td>
<td>Detoxification Patients</td>
<td></td>
</tr>
<tr>
<td>Methadone Symptom Checklist (1997)</td>
<td>MSC</td>
<td>- Self Report</td>
<td>48(16)</td>
<td>None</td>
<td>None</td>
<td>Methadone Maintenance Treatment Patients</td>
<td></td>
</tr>
<tr>
<td>Clinical Opiate Withdrawal Scale (1998)</td>
<td>COWS</td>
<td>- Clinician Observation</td>
<td>11</td>
<td>None</td>
<td>None</td>
<td>Prior to Buprenorphine Induction</td>
<td></td>
</tr>
</tbody>
</table>

Table 1.1: Various opioid withdrawal scales: Overview of available opioid withdrawal scales, including description of the population of development, length, method of quantification, validity testing, and reliability testing. The SubOWS is the best available scale for measuring opioid withdrawal. It is has full validity and reliability testing and is a short self-report tool. It was developed in detoxification patients, and may lack sensitivity in describing psychological aspects of opioid withdrawal.
1.4.8 Patient Satisfaction with Methadone Maintenance Treatment: Holders, Nonholders, and Opioid Withdrawal

In MMT the term patient satisfaction can have multiple meanings. Often, client satisfaction with a treatment program relates to patient perception of the level of support they receive, the level of respect they receive, and if the program has the services the patient believes they need. Others in the field have related satisfaction to the methadone dose; Hiltunen et al. have previously labelled MMT patients as satisfied or dissatisfied (with dissatisfied patients reporting that they believed their methadone dose was too low). As mentioned previously, not all patients in MMT respond equally to treatment. Despite attempts at dosage optimization, clinically, as many as 53% of patients experience significant and unacceptable symptoms of inter-dose withdrawal at least some of the time and 34% of patients experience this frequently or all of the time. Dyer and White termed those who complained of withdrawal frequently or all the time as ‘nonholders’; and the rest of patients were termed ‘holders’. In this body of work, patient satisfaction with treatment is believed to be more than satisfaction with the methadone dose. Rather, it is a reflection of the level of opioid withdrawal that a patient experiences, how they perceive it, and how it impacts their quality of life.

In a subsequent study by Dyer et al, the impact of methadone pharmacokinetics on holder status was investigated in 18 patients. Of the 18 patients, nine experienced significant withdrawal towards the end of the dosing interval and these patients were termed nonholders, while the other nine patients did not experience significant withdrawal and
were termed holders. The mean trough plasma methadone concentrations were similar.
Peak plasma concentrations occurred at approximately three hours in both groups. Other pharmacokinetic factors compared were: dose, mean peak to trough plasma concentration ratio, and area under the concentration time curve (AUC); these were also not significantly different between groups. However, the maximum hourly rate of decline in methadone plasma concentration was significantly higher in the nonholder group compared to the holder group. Hence, Dyer et al. concluded that holders and nonholders differ in methadone pharmacokinetics: Not on usual pharmacokinetic parameters but rather on a relative rate of decline in plasma methadone levels in intervals from peak to trough. However, they were unable to exclude pharmacodynamic determinants as potential contributors to the difference between the groups.

In a similar study of 14 methadone-stabilized patients (seven holders and seven nonholders) the pharmacokinetics and pharmacodynamics of methadone and a slow release oral morphine product were compared in an open-label cross-over design. As in the previous study described above, there were no significant differences in $C_{\text{max}}$ or trough plasma concentrations between groups. For methadone patients who self-reported as nonholders, the number of self-reported opioid withdrawal symptoms prior to dosing was less when they received the sustained-release oral morphine product compared to methadone. This implies that for some nonholders, a switch to an alternate opioid can be clinically beneficial.
Hanna and colleagues examined the effect of time on methadone pharmacokinetics and pharmacodynamics in 6 nonholder methadone maintenance treatment patients. Pharmacokinetic and pharmacodynamic assessments were made serially over a 24-hour dosing interval on three occasions separated by 7-16 day intervals: during this time methadone doses remained stable. Overall, between-subject variability was greater than within-subject variability. As such, it was reported that nonholder methadone patients responded consistently to methadone and had stable plasma levels of methadone over the course of 1-2 months.

Summary Points:
- Patient satisfaction classifications may be related to opioid withdrawal complaints or the perception of having too low a dose of methadone.
- In this thesis, satisfaction is related to dose adequacy, perceived opioid withdrawal and impact of opioid withdrawal on quality of life.
- Patient ‘dissatisfaction’ or ‘nonholding’ can be related methadone pharmacokinetics.

1.4.9 Methadone, Mood and Major Depressive Disorder

In a study by Dyer et al., the relationship between mood states and patient satisfaction (holder status) in methadone maintenance patients was evaluated. They found that mood disturbance, as measured by the Profile of Mood States (POMS) scale, was associated with nonholder status. Specifically, in this population of non-psychiatric patients,
nonholders had significantly more mood disturbance than holders with maximum
differences during trough methadone conditions and minimum differences during peak
methadone conditions. Furthermore, they reported that negative mood varied with the
rate of decline in methadone plasma concentration. A steep concentration-effect
relationship was reported indicating that small changes in concentration could lead to
significant mood changes and because nonholders had a faster rate of decline in plasma
concentration, these mood changes could be exaggerated compared to holders.

These mood-related findings are important because opioid addiction is also associated
with high prevalence rates of psychiatric disorders. Regier et al. estimated the lifetime
prevalence of psychiatric disorders among those with an opioid use disorder to be 65%. More importantly, lifetime prevalence of depression in methadone maintenance patients
has been reported as high as 43%. However, current rates of depression in this
population vary greatly from study to study depending on the method used to identify
major depression. Studies that use stringent DSM-IIIR and DSM-IV criteria estimate a
prevalence of 19.4-23%. Concurrent depression is regularly associated with negative
impacts on the treatment outcomes of other diseases and illnesses. This is also the case
with MMT.

**Summary Points:**

- Nonholders have more mood disturbance than holders.
- There is a high prevalence of depression in MMT patients.
- Concurrent depression impacts negatively on MMT outcomes.
1.4.10 Major Depressive Disorder and the Opioid System

There is a body of evidence suggesting a neurobiological interaction between opioid pathways and major depressive disorder. 1.) Opioids have been implicated in the pathogenesis of depressive illness\textsuperscript{126} and 2.) Endogenous opioid peptides and receptors are abundant in regions associated with the regulation of mood and behaviour, such as the anterior cingulate, prefrontal cortex and amygdala.\textsuperscript{127-131}

1.4.10.1 Animal Studies

In an animal study, the influence of opioid agonists, antagonists, as well as the endogenous opioid system was investigated utilizing the learned helplessness animal model of depression.\textsuperscript{132} In this paradigm, animals are exposed to inescapable shocks and then re-exposed to the same shocks with a route of escape. Animals that do not escape from the second exposure have learned helplessness and constitute what is considered to be a valid model of depression.\textsuperscript{133-135} The administration of opioid agonists and endogenous opioid catabolism inhibitors to depressed animals resulted in a reversed escape deficit. The administration of an opioid antagonist resulted in an increased helplessness response.\textsuperscript{132, 136} Further work by this group, suggests that the δ-opioid receptor is involved in the effects produced by endogenous opioids (enkephalins) on learned helplessness.\textsuperscript{137} Specifically, a δ-opioid agonist was able to reverse the escape deficit, and a δ-opioid antagonist was able to inhibit the positive opioid effect.\textsuperscript{137} Broom et al. also implicated the δ-opioid system in depression, by demonstrating anti-depressant effects of δ-opioid agonists in the forced swim test; but they found no effects with a κ-
opioid agonist nor a μ-opioid, morphine. Filliol et al. developed knock-out mice for each μ-, δ-, and κ-opioid receptors and used them to investigate models of depression and anxiety. Kappa knock-out mice did not have an altered phenotype compared to wild-type mice, hence κ-opioid receptors may not have a role in the influence of depressive phenotypes. Mu and δ knock-out mice had opposing phenotypes, with δ knock-outs experiencing consistent depressive-like responses in the behavioural tasks. Naloxone-treated δ knock-out mice responded as wild-type mice suggesting that endogenous μ-opioid activity and hence μ-opioid receptors may be partly responsible for mood-related changes in δ knock-out mice.

Summary Points:

- Opioid agonists lead to anti-depressive effects, while antagonists increased depressive effects in animal models of depression.

1.4.10.2 Human Studies

It has been suggested that depressed patients may have a deficiency in endogenous opioid activity and that manic patients may have an excess of endogenous opioid activity. Clinical trials have indicated that opioid compounds have limited anti-depressant activity. Also, there is evidence that suggests that some of the effects of electroconvulsive therapy (ECT) (an effective treatment for refractory depression) may be mediated by opioid peptides. ECT resulted in increased plasma concentrations of β-endorphin. Zubieta et al. using Positron Emission Tomography (PET) showed that endogenous opioid receptor activation in the thalamus and dorsal anterior cingulate is involved in attenuation of pain-specific affective responses. In a human study, the
prolactin response (mediated by opioid receptor stimulation) was measured in depressed and control subjects following the administration of morphine. The prolactin response in the control group was normal, and significantly larger than that exhibited in the depressed group.\textsuperscript{149} This was replicated by two other investigators\textsuperscript{150, 151} and subsequently disputed by Zis et al. who used a longer sampling time in their study.\textsuperscript{152} In another human study depressed and control patients were randomized to receive either 6 mg hydromorphone p.o. or placebo. Depressed subjects, who received hydromorphone, experienced significantly attenuated negative opioid symptoms compared to the controls. This trend was even more pronounced in the severely depressed (Hamilton Depression Scale (HAMD) > 24) subgroup. As well, psychomotor function was improved in depressed patients compared to controls as measured by a Manual Tracking Test (MTT) (p<0.01).\textsuperscript{153} In an fMRI study, 21 MMT patients were studied and brain perfusion data was correlated with BDI scores. A significant inverse relationship was noted with BDI scores and prefrontal activation, suggesting that reduced fronto-limbic activity is associated with depressive symptoms in methadone maintenance treatment patients.\textsuperscript{154} Affect dysregulation is an important risk factor for addiction\textsuperscript{155} and could be an important factor in understanding the comorbidity between opioid dependence and depression.\textsuperscript{154}

Summary Points:

- Opioid agonists have anti-depressive activity in humans.
- Depressed patients may have altered responses to acute opioid administration.
1.4.11 Smoking and Methadone Maintenance Treatment

Smoking rates in alcohol and illicit drug using populations are greater than the general population. The prevalence of tobacco smoking in methadone maintenance treatment patients ranges from 85-98%.\textsuperscript{13-18} In long-term studies of opioid dependent populations, tobacco smoking is a significant predictor of morbidity and mortality.\textsuperscript{156, 157} Although MMT patients report a high level of interest in quitting smoking,\textsuperscript{16, 18, 19, 158-160} low levels of sustained smoking cessation are the norm.

In a study by Frosch et al. methadone patients were divided as non-smokers, tobacco-chippers, and heavy smokers. Methadone doses were higher in the heavy smokers group compared to the combination of the other two groups.\textsuperscript{161} Further, methadone has been shown to increase smoking rates, in a dose-dependent manner\textsuperscript{14, 20, 21}, and patients on higher methadone doses tend to have greater Fagerström Test for Nicotine Dependence (FTND) scores, a marker of nicotine dependence severity.\textsuperscript{159} Also, methadone administration led to dose-related increases in smoking satisfaction.\textsuperscript{14} Similarly, buprenorphine has been related to increased cigarette smoking rates after the start of treatment compared to pre-treatment.\textsuperscript{162, 163}

There is very little research on the influence of nicotine on methadone effects. Spiga et al. investigated the influence of nicotine (ad libitum smoking, 0-, 2-, and 4-mg nicotine gum) on methadone self-administration.\textsuperscript{23} Methadone self-administration was increased during ad libitum smoking and when 4-mg nicotine gum was available. The authors suggested
that nicotine may enhance the reinforcing effects of methadone or that nicotine may serve as a conditioned stimulus to methadone self-administration. In another study by Spiga et al. the influence of nicotine and methadone availability on self-administration was evaluated in methadone maintenance patients using a behavioural economics approach. Patients were willing to do more work to receive methadone when nicotine was available by cigarette puff than when cigarette puffs were not concurrently available. Methadone did not alter the level of work a patient was willing to do to receive nicotine through a cigarette puff; suggesting that methadone’s reinforcing properties are increased in the presence of nicotine while nicotine’s reinforcing properties are not altered by methadone.

Methadone patients report that they smoke more near the time of their methadone dose; they report experiencing more pleasing effects when the drugs are taken together and less methadone-induced sedation. Richter et al. monitored smoking patterns in methadone maintenance patients. They found that smoking rates are greatest relative to the time of methadone dosing administration, regardless of the time of waking. Results suggested that methadone may reduce variability in regular smoking patterns, and create a signature smoking pattern common to methadone patients who smoke. Methadone patients also believe that drug use increases their smoking rates but that smoking does not trigger them to use drugs. Despite this belief, smoking has been related to increased positive urine screens. Specifically, Stopshaw et al. conducted a smoking abstinence study in methadone maintenance treatment patients and showed that smoking abstinence led to significantly more opioid clean urine samples and Frosch et al. reported higher levels
of illicit drug use (cocaine or opioid positive urine samples) in smokers compared to tobacco-chippers or non-smokers.\textsuperscript{161}

**Summary Points:**

- Smoking is nearly universally prevalent in the MMT population.
- Methadone increases smoking and is associated with higher nicotine dependence scores.
- Methadone’s reinforcing properties increased when nicotine is available by cigarette.
- MMT patients may have a signature smoking pattern related to the timing of their methadone dose.

1.4.12 Smoking, Nicotine and the Opioid System

1.4.12.1 Animal Studies

Nicotine is known to affect the endogenous opioid system. Nicotine administration leads to increased levels of $\beta$-endorphin in rats.\textsuperscript{168} In an isolated perfused mouse brain preparation, direct administration of nicotine to the hypothalamus produced dose-related increases in $\beta$-endorphin levels.\textsuperscript{169} Similarly, after nicotine administration in the guinea pig and rat, plasma enkephalin levels were increased.\textsuperscript{170,171} After chronic nicotine administration in mice, little change in hypothalamic $\beta$-endorphin levels were found however upon termination of nicotine dosing, significant reductions in $\beta$-endorphin levels were
reported. In rat brain, nicotine also stimulated enkephalin release in nucleus accumbens (NAc) and amygdala.

Phosphorylation of cyclic adenosine monophosphate (cAMP) response element-binding proteins (CREB) has been associated with rewarding effects of nicotine. Environmental cues (e.g. conditioned place preference (CPP) chamber) previously paired with nicotine delivery can be an important part of the incentive to maintain smoking behaviour. In fact CREB phosphorylation is increased following exposure to environments with a prior association to rewarding effects associated with nicotine, increases are similar in magnitude to those seen with actual nicotine exposure. Naloxone administration 24 hours after the nicotine dose blocked conditional increases of phosphorylated CREB in the VTA and NAc. In chronic nicotine administration paradigms, naloxone increases Intra-Cranial Self Stimulation (ICSS) thresholds and causes a conditioned place aversion (CPA) in rats. Pre-treatment of rats with the μ-opioid receptor antagonist β-funaltrexamine abolished anxiolytic-like effects of nicotine on the elevated plus maze task. After chronic nicotine exposure, nicotine physical withdrawal could be precipitated by injections of opioid antagonists. Also, the nicotine abstinence syndrome precipitated with naloxone was reversible with subsequent morphine injection. Interestingly, neuropeptide F, which precipitates withdrawal in opioid-dependent rats, was able to precipitate nicotine abstinence syndrome. In a study of the cross-tolerance between morphine- and nicotine-induced CPP, it was found that both naloxone and mecamylamine (a nicotinic receptor antagonist) were able to reduce CPP of morphine and nicotine. As well, mecamylamine-precipitated nicotine withdrawal was attenuated with pre-injection of morphine. A potential explanation is
that chronic periodic nicotine administration leads to prolonged release of endogenous opioid peptides; and nicotine withdrawal results in decreased tone in opioid receptors.\textsuperscript{184}

In a knock-out study, rewarding effects of nicotine measured with a CPP test were noted in wild-type but not \textit{μ} knock-out mice.\textsuperscript{185} In another knock-out study, the role of the \textit{μ} opioid receptor in the development of tolerance to nicotine effects was examined. Chronic administration of nicotine induced tolerance to antinociceptive effects in both wild-type and \textit{μ} knock-out mice; but the knock-out mice developed tolerance more quickly.\textsuperscript{186} This suggests that release of endogenous opioids by stimulation of the nicotinic acetylcholine receptors may occur, and that the endogenous opioid system may be involved in nicotine pharmacodynamic effects, including tolerance to antinociceptive effects.

Summary Points:
- Nicotine administration leads to the release of endogenous opioids in brain regions related to reward.
- Opioid activity is required in order to experience the rewarding effects of nicotine.

1.4.12.2 Human Studies

In human studies, after 12-hour nicotine abstinence, smoking high nicotine content cigarettes increased plasma β-endorphin levels compared to baseline levels.\textsuperscript{187,188} Also,
the administration of naloxone was found to reduce the number of cigarettes smoked by dependent smokers as well as block the pleasurable response to smoking.\textsuperscript{189} This suggests that opioid peptides are released during smoking and may play a role in smoking maintenance.\textsuperscript{184} In an open-label pharmacogenetic study of transdermal nicotine versus nicotine nasal spray the role of the \textit{μ}-opioid receptor Asn40Asp variant was examined.\textsuperscript{190} Of 320 smokers of European ancestry, individuals carrying the Asp40 variant (heterozygous, Asn/Asp or homozygous Asp/Asp, N=82) were significantly more likely than those homozygous for the Asn allele (Asn/Asn, N= 238) to be abstinent after treatment.\textsuperscript{190} This difference was significant in the transdermal nicotine group, not the nicotine spray group. In the transdermal nicotine group, 52\% of the Asp carrier group vs. 33\% of the Asn group were abstinent at the end of the eight weeks of treatment (OR=2.4).\textsuperscript{190} Also, smokers with the Asp40 variant reported less withdrawal symptoms and less mood disturbance during the first two weeks of nicotine replacement therapy.\textsuperscript{190} A subsequent study by the same group showed that carrying the Asp40 variant was associated with reduced reinforcing values of nicotine (cigarette puffs) in women.\textsuperscript{191}

Summary Points:

- Smoking resulted in the release of endogenous opioids in humans.
- Opioid antagonists blocked the rewarding effects of smoking.
- Patients with a functional mutation at the \textit{μ}-opioid receptor were more likely to be abstinent from smoking at the end of a nicotine replacement therapy smoking cessation trial.
1.4.13 Nature of the Interaction Between Smoking and Methadone

There is currently no evidence to suggest that an interaction between methadone and nicotine would be pharmacokinetic in nature. The metabolic pathways that are induced by the polycyclic aromatic hydrocarbons in tobacco smoke (i.e., CYP1A1, CYP1A2, CYP2E1) or that metabolize nicotine (i.e., CYP2A6)\textsuperscript{192} are different than the enzymes involved in methadone metabolism or that are influenced by methadone (i.e., primarily CYP3A4).\textsuperscript{193}

Based on the evidence presented above a synergistic or additive pharmacodynamic interaction between nicotine and methadone is probable. MMT patients who smoke will, during the course of a day, experience agonist effects and withdrawal effects of both nicotine and methadone. Hence, interactions where agonist effects of one drug interact with agonist effects of the other, where abstinence effects of one drug interact with abstinence effects of the other, and where agonist effects of one drug interact with abstinence effects of the other are all possible. See figure 1.2 for a model describing potential interactions between methadone and nicotine.

Summary Points:

- There is no evidence to suggest that nicotine-methadone interactions would be pharmacokinetic in nature; pharmacodynamic interactions more likely.
- Interactions between methadone and nicotine are likely complex and variable over the course of the day.
Figure 1.2: Potential interactions between methadone and nicotine.

**Methadone Agonist Effects**

<table>
<thead>
<tr>
<th></th>
<th>Methadone (+)</th>
<th>Nicotine (+)</th>
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<tr>
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<td>Methadone (-)</td>
<td>Nicotine (+)</td>
<td>4</td>
<td>Methadone (-)</td>
<td>Nicotine (-)</td>
</tr>
</tbody>
</table>

Nicotine Agonist Effects

Methadone Withdrawal

Nicotine Withdrawal

Figure 1.2: Model representing potential interactions between methadone and nicotine. The (+) sign represents agonist effects present; the (-) sign represents withdrawal effects present. There can be additive/synergistic interactions (boxes 1 and 4), or mixed interactions with agonist effects of one drug interacting with withdrawal effects of the other (boxes 2 and 3). A methadone patient who is a smoker will experience different interactions at different points of the day depending on their smoking and methadone schedules. Patients are likely to start the day in box 4, then move between box 3 and 4 while they smoke prior to their methadone dose. After the methadone dose, patients will move between box 1 and 2 while they smoke until methadone effects begin to dissipate and they return to boxes 3 and 4.

1.5 **Restatement of Research Hypothesis**

1.5.1 **Overall Hypothesis**

Methadone pharmacodynamic responses in methadone maintenance treatment patients are altered by many factors. Specifically, methadone pharmacokinetics, comorbid psychiatric states/symptoms, and drug interactions are likely to influence perceived...
responses to methadone; including opioid effects, opioid withdrawal, and their impact on patient satisfaction with methadone treatment.

1.5.2 Specific Hypotheses

1.5.2.1 Major Depressive Disorder and Patient Satisfaction in Relation to Methadone Pharmacokinetics and Pharmacodynamics in Stabilized Methadone Maintenance Patients (Study 1)

Specific Hypotheses

The relationship between methadone plasma concentrations and negative mood disturbance will be steeper in depressed methadone patients compared to those without comorbid depression, particularly in nonholders.

Pharmacodynamic responses to methadone will be different in depressed methadone maintenance patients compared to nondepressed patients, with depressed patients being more sensitive to negative effects.
1.5.2.2 Opioid Withdrawal Scale Modification and Characterization of Between Dose Opioid Withdrawal and Patient Satisfaction in Methadone Maintenance Treatment (Study 2)

Specific Hypotheses

Psychological factors will differentiate methadone maintenance treatment patients who self report as holders, partial holders and nonholders, as well as, or better than physical opioid withdrawal symptoms alone.

Modification of the Subjective Opioid Withdrawal Scale to include patient factors other than physical opioid withdrawal will result in a more sensitive instrument for measuring perceived opioid withdrawal in methadone maintenance treatment patients.

1.5.2.3 Methadone-Nicotine Interactions in Stabilized Methadone Maintenance Treatment Patients (Study 3)

Specific Hypothesis

Methadone effects and nicotine (or smoking) effects interact with each other in different ways depending on the exposure to both drugs. Specifically, smoking can alter acute methadone effects/methadone withdrawal effects and methadone can alter acute smoking effects and withdrawal effects from smoking.
Section 2: METHODS AND MATERIALS

2.1 Major Depressive Disorder and Patient Satisfaction in Relation to Methadone Pharmacokinetics and Pharmacodynamics in Stabilized Methadone Maintenance Patients (Study 1)

2.1.1 Study Design

This was a non-interventional study of the relationship between steady state methadone pharmacokinetics and pharmacodynamics. The study procedure was the same for all subjects and consisted of one assessment day to determine eligibility and group assignment and one 25-hour study session over two consecutive days. Stabilized methadone patients were recruited based on depression status (with or without major depressive disorder) and patient satisfaction with treatment (holder/nonholder). On the first study day, subjects arrived one hour before they drank their regular dose of methadone and remained for 12 hours for blood sampling and to complete pharmacodynamic assessments. Subjects returned home at the end of the first study day and again on the second day arrived one hour before their methadone dose to complete the 24-hour testing cycle. Subjects were discharged after they had completed the last cycle and had taken their dose of methadone.
2.1.2 Subject Selection

Subjects were eligible for participation if they were able to provide informed consent (see appendix 1 for consent form), were 18 years or older, and were stabilized in treatment (i.e., enrolled in a methadone maintenance treatment program for at least the last 6 months and prescribed the same dose of methadone for at least the previous one month).

To be included in the depressed group, subjects had to be currently suffering a major depressive episode confirmed with the Structured Clinical Interview for DSM-IV criteria (SCID). Depressed subjects being treated with antidepressants were included if they continued to take their medication and had been on the same dose of the antidepressant for a sufficient period of time to arrive at a steady-state condition (ensuring that any pharmacokinetic interaction with methadone would have been stabilized).

The identification of holders and nonholders was made by self-report. Subjects were asked whether they thought that their daily methadone dosage was sufficient to maintain them for one full dosing interval (24 hours). Those who said yes were placed in the holder group; those who said no were placed in the nonholder group. If a subject was unsure he/she was asked to select the most appropriate group based on perceived withdrawal symptomatology over the past month.

All subjects were asked to abstain from caffeine and alcohol from 12 hours before the study day and for the duration of the study session. Subjects were asked to continue
taking any other regular medications. A SCID was conducted with all participants. Subjects suffering from other current psychiatric disorders (other than anxiety disorders) or other current substance use disorders (other than nicotine) were excluded from participation.

2.1.3 Sample Size Justification

For this preliminary study, a sample size of 20 subjects was proposed; 5 subjects in each of the 4 groups (depressed holders, nondepressed holders, depressed nonholders, nondepressed nonholders). In the Dyer et.al. study\textsuperscript{120} the mean Total Mood Disturbance score in holders (20±5, 25% coefficient of variation) was significantly lower than in nonholders (65±10, 15% coefficient of variation), estimated from the graphs. This study had a power of 80% for a 2-tailed test to detect a minimum difference of 20 points between depressed nonholders and nondepressed holders, assuming a 15% coefficient of variation in each group and an \( \alpha = 0.1 \) for this preliminary study, with 5 subjects in each group.

2.1.4 Subject Recruitment

Subjects were recruited from the Centre for Addiction and Mental Health (CAMH) and other methadone clinics in the Greater Toronto Area using posted flyers (see appendix 2 for recruitment flyer). Of the 226 individuals who responded to the advertisement, 174 were able to be contacted, 85 passed the brief telephone screen (see appendix 3 for the
telephone screen) and were willing to come for an assessment and 40 assessments were completed. A total of 22 subjects were eligible to participate following the assessment and were enrolled in the study, five did not complete the study. Of those who did not complete the study, three were not able to have an intravenous catheter stably inserted due to venous problems, one decided not to participate after enrolment, and one failed to report for the study session.

2.1.5 Assessment Day Procedures

All potential subjects who passed the brief screen attended an assessment session in order to determine study eligibility and group assignments as outlined in the subject selection section above. Subjects were asked to come to the CAMH clinical laboratory prior to taking their methadone dose so that patient satisfaction determination during the trough methadone condition could be assessed. All potential subjects then gave a urine sample for toxicology screening and were then given their methadone dose. Afterwards, potential subjects were asked a series of questions about demographics, general health, current medications, drug use history, drug treatment history, and methadone maintenance treatment history. At this point the SCID interviews were conducted. Subjects who were deemed ineligible were discharged at that point without completing the assessment. Finally, the 21-item Hamilton depression scale (HAMD)\textsuperscript{194} was given to assess the severity of depression.
2.1.6 Study Day Procedures

Subjects arrived at the CAMH clinical laboratory one hour prior to their regular methadone dosing time. At this point all subjects were asked to provide a urine sample for toxicology screening and to submit to an alcohol breathalyzer test. A 22-gauge intravenous catheter was inserted into a vein on the subjects’ forearm. Prior to methadone dosing a baseline blood sample was obtained for methadone concentration determination, vital signs were measured, a pupil diameter measurement was made, and subjects were asked to respond to computerized versions of the Addiction Research Center Inventory (ARCI)\textsuperscript{195-197} short-form, the POMS\textsuperscript{120}, the Subjective Opioid Withdrawal Scale (SubOWS)\textsuperscript{99}, the Digit-Symbol Substitution Task (DSST)\textsuperscript{198,199}, and the Manual Tracking Test (MTT)\textsuperscript{200}, for assessment descriptions see section 2.4. Following the baseline assessments, subjects consumed their regular methadone dose. Additional vital signs and blood samples were collected at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, and 24 hours after methadone dose administration. Blood samples were centrifuged, the serum was separated and stored at -80°C until analysis. The ARCI, POMS, SubOWS, DSST, and MTT were administered serially at 1, 2, 3, 4, 5, 6, 8, 10, 12, and 24 hours after methadone administration. After the 12\textsuperscript{th} hour cycle, the catheter was removed and subjects were excused for the evening. Subjects returned the following morning to complete the 24\textsuperscript{th} hour cycle; the final blood sample was obtained by venipuncture. A urine sample for toxicology screening and a breathalyzer measurement were again obtained. See table 2.1 for study scheduling chart. All subjects continued to take their regular prescribed daily dose of methadone. Subjects with take-home dose
privileges brought their regular dose with them, the rest received their regular daily dose at the CAMH pharmacy; study personnel observed all methadone dose administrations. Subjects were provided with a lounge to relax in between study cycles and were allowed to smoke cigarettes between study cycles when time permitted. All subjects were provided with a light breakfast, lunch and dinner.

Table 2.1: Study day schedule: Methadone/Depression study

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<tr>
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Table 2.1: Study schedule, subjects reported for two consecutive study days, on day one they went home following the 12th hour cycle. They returned the following day one hour prior to the regular time of their methadone administration.

2.1.7 Plasma Concentration Determination

Concentrations of (R)- and (S)-methadone were determined in plasma using an LCQ liquid chromatograph/mass spectrometer (LC/MS) with an electrospray interface (ESI) operating in the positive ionization mode (ThermoFisher, Mississauga ON). The methadone enantiomers were separated on an AGP Chiral 100 mm x 4.00 mm, 5 μm i.d. column (Chrom Tech Ltd., Apple Valley, MN). Optimal separation was achieved with a mobile phase comprised of a 10 mM ammonium acetate buffer with a pH adjusted to 5.5 and isopropanol in a ratio of 92:8 (v/v). One hundred microlitres of plasma was
combined with 100 μL of internal standard (deuterated methadone) solution consisting of 300 ng/mL deuterated methadone and 100 μL of 500nM sodium bicarbonate. The mixture was extracted with 750 μL hexane; 500 μL of which was dried off and the remaining residue was reconstituted with 100 μL of mobile phase. Twenty microlitres of this extract was injected into the LC/MS with a flow rate of 0.8 mL/min. The m/z monitored was 310 for methadone and 319 for deuterated methadone. Retention times for (R)- and (S)- methadone were 6.7 and 8.0 min respectively. Calibration curves over the range of 50 to 500 ng/ml were used to quantify each enantiomer. Intra-assay variability was 5% for both enantiomers and inter-assay variability was 6% for (R)-methadone and 10% for (S)-methadone. The limit of quantitation was 50 ng/mL. Quantitation of free enantiomers was made using the same instrumentation with an altered sample preparation. Serum samples were thawed and brought to room temperature. Immediately after thawing, 400 μL of serum was filtered through Centrifree Micropartition devices (Millipore, Billerica, MA) to separate free from protein-bound methadone. Samples were then centrifuged at 1500 x g to minimize effects of temperature and pH on ligand binding. Two hundred microlitres of protein-free filtrate was extracted twice with hexane (as above). After solvent evaporation, the residue was reconstituted with 60 μL of mobile phase and 20 μL were injected. Calibration curves over the range of 5-50 ng/mL were used to quantify each of the free enantiomers. Racemic methadone concentrations were calculated by adding the concentrations of the two enantiomers determined separately.
2.1.8 Ethical Considerations

This study was approved by the CAMH Research Ethics Board and all participants provided written informed consent prior to participating in the study. All data were kept strictly confidential. Subjects were identified by subject number and initials, not by name. The clinical research laboratory at CAMH is located near the Addiction Medicine Clinic at the 33 Russell Street site. For subjects currently experiencing depressive symptoms, we informed (when permitted) their treating physician of the diagnosis of depression in order that they could be followed-up and treated as necessary. Subjects who did not give their permission were offered information on resources and urged to discuss their feelings with their physician. Subjects were paid $150.00 Canadian for their time and participation upon completion of the study. Subjects deemed ineligible at the assessment were paid $25.00 Canadian. Subjects who arrived and were not able to complete the study because of venous problems (intravenous catheters) were paid $50.00 Canadian.

2.1.9 Data Analysis

The peak ($C_{\text{max}}$) and trough ($C_0$ and $C_{24}$) plasma concentrations as well as the time to peak plasma concentration were calculated from visual inspection of the data. Area Under the plasma concentration versus time Curve (AUC) from 0 to 24 hours was calculated by the linear trapezoidal rule. The average steady-state plasma concentration ($C_{ss}$) was calculated by dividing the AUC by the dosing interval. Average clearance
(Cl/F) was calculated by dividing the dose by the AUC. Peak/trough ratios were calculated by dividing $C_{\text{max}}$ by $C_{24}$. The maximum rate of decline in concentration from peak to trough was calculated by evaluating rates of decline in concentration at all sampling time points. These parameters were calculated for total and unbound (R,S)-, (R)-, and (S)-methadone plasma concentration levels.

Area under the Effect versus time Curve (AUEC) was calculated for all pharmacodynamic measures using the linear trapezoidal rule. The maximum change from baseline was also calculated for all measures. Composite scales were derived from ARCI subscales by summing positive drug effect subscales (euphoria, stimulation, abuse potential) together and negative drug effect subscales (sedation, dysphoria) together. A Cronbach’s alpha\textsuperscript{201} was conducted to confirm internal consistency when constructing the composite measures. Summary ARCI statistics and trough SubOWS scores were correlated with HAMD scores. The 24-hour SubOWS score was chosen for this correlation because this score was the most accurate measure of 24-hour post methadone withdrawal.

A Sigmoid $E_{\text{max}}$ model was used to relate plasma concentrations and effects of methadone. This was a stepwise procedure of four steps. Step 1: Plot the mean normalized data and determine initial estimates for fitting in step two. Step 2: Fitting the mean normalized data with initial estimates obtained in step one. In this step initial estimates for fitting in step three were obtained. Step 3: Fitting all data at once with
initial estimates obtained in step two. In this step initial estimates for fitting is step four were obtained. Step 4: Fit individual data with initial estimates obtained in step three.

Descriptive statistics were used to characterize the participants. An ANOVA was used with depression and holder status as the factors. No interactions were found. Hence, results are reported from independent samples t-tests in order to better illustrate differences between groups for pharmacokinetic, pharmacodynamic and modeling endpoints.

The primary outcome variable in this study was the total mood disturbance score. This was to be the primary focus of the pharmacodynamic modelling proposed. Secondary outcome variables were SubOWS, ARCI, MTT, DSST, and other POMS scale scores. Also, pharmacokinetic parameters were secondary outcome measures.

As mentioned previously, this study was powered to detect differences between patients distributed amongst four groups with five subjects in each group. However, because the sample size was insufficient for this, subjects were placed in two dichotomous groupings (depressed/nondepressed and holder/nonholder). Differences between depressed and nondepressed methadone maintenance patients on the pharmacodynamic measures and differences between holders and nonholders on pharmacokinetic and pharmacodynamic measures were secondary objectives.
2.2 Opioid Withdrawal Scale Modification and Characterization of Between Dose Opioid Withdrawal and Patient Satisfaction in Methadone Maintenance Treatment (Study 2)

2.2.1 Study Design

In this non-interventional study, perceived opioid withdrawal was investigated in stabilized methadone maintenance patients with varying degrees of satisfaction with treatment. Holder and nonholder methadone maintenance treatment patients were characterized using measures of physical opioid withdrawal, craving, pain, mood states, drug effects, pain, personality, quality of life, self-efficacy, and social support during the approximate trough methadone condition. In order to modify the SubOWS, candidates from the characterization measures were selected. Selection was based on the ability to distinguish between holders and nonholders.

2.2.2 Subject Selection

Subjects were eligible for participation if they were 18 years of age or older, were able to provide informed consent (see appendix 4 for consent form) and were stabilized in treatment (i.e., enrolled in a methadone maintenance program for 6 months or longer and prescribed the same dose for the previous one month or longer). Also all subjects were required to abstain from caffeine and alcohol from 12 hours before the study day until the study was completed.
After enrolment, subjects were divided into three patient satisfaction groups: Holders (none or little opioid withdrawal with no significant impact on quality of life), Partial Holders (mild to moderate opioid withdrawal with some impact on quality of life), and Nonholders (moderate to severe opioid withdrawal with significant impact on quality of life). Group assignment was accomplished with a guided self-report screening interview. The guided self-report process consisted of a series of questions with a focus on the impact of opioid withdrawal that a subject experienced and a classification guide, see appendix 5.

2.2.3 Sample Size Justification

Due to the nature of this study, there was no primary outcome measure. In general, with an alpha of 0.05 this study would have 80% power to detect an effect size of 0.60 on a two-tailed test with 43 subjects in each group using a dichotomous categorization (holders and nonholders). Therefore, a total sample size of 90 subjects was targeted.

2.2.4 Subject Recruitment

Subjects were recruited from the CAMH and other methadone clinics in the Greater Toronto Area with posted flyers (see appendix 6 for study flyer). Of the 205 individuals who responded to the advertisement, 183 were able to be contacted, 90 subjects passed the brief telephone screening (see appendix 7) and were eligible and willing to participate
in the study. All but one of the study participants completed the entire study day protocol. This one subject was not comfortable answering the questions and left after completing half of the study measures, partial data from this subject were included in this analysis.

2.2.5 Study Day Procedures

Subjects arrived at the CAMH clinical laboratory one hour prior to their regular methadone dosing time and were asked to provide a urine sample for toxicology screening and to submit to an alcohol breathalyzer test. Subjects were administered the Mini International Neuropsychiatric Interview (MINI)\textsuperscript{202} to screen for psychiatric disorders.

Subjects then completed a battery of subjective assessments (see below) divided into 2 blocks. Assessments that are subject to acute changes (block 1) were administered during the trough methadone condition and those that were more stable (block 2) were administered after a 30-minute break during which time subjects received their daily methadone dosage. Subjects with take-home dose privileges brought their regular dose with them, the rest received their regular daily dose at the CAMH pharmacy; study personnel observed all methadone dose ingestions. During the break subjects were provided with a lounge to relax in as well as a light meal. Questionnaires in each block were presented in a random order
For details about subjective assessments see section 2.4. Block one assessments consisted of the Subjective Opioid Withdrawal Scale (SubOWS)\textsuperscript{99}, Short Opioid Withdrawal Scale (ShOWS)\textsuperscript{107,108}, Addiction Research Center Inventory – Weak and Strong Opioid Withdrawal Scales (ARCI-WOW and ARCI-SOW)\textsuperscript{110}, Addiction Research Center Inventory (ARCI)\textsuperscript{195-197}, Profile of Mood States (POMS)\textsuperscript{120}, State-Trait Anxiety Inventory, state subscale (STAI-s)\textsuperscript{203}, Short-Form McGill Pain Questionnaire (SFMPQ)\textsuperscript{204-206}, and the Hopkins Symptom Checklist 90 (SCL-90)\textsuperscript{207,208}. Block two assessments consisted of the Neo Personality Index (NEO)\textsuperscript{209,210}, Obsessive Compulsive Drug Use Survey (OCDUS)\textsuperscript{211}, The Health Status Questionnaire (SF-36)\textsuperscript{212}, Drug-Taking Confidence Questionnaire (DTCQ)\textsuperscript{213}, Anxiety Sensitivity Index (ASI)\textsuperscript{214}, and the Multidimensional Scale of Perceived Social Support (MSPSS)\textsuperscript{215,216}.

2.2.6 Ethical Considerations

This study was approved by the CAMH Research Ethics Board, and all subjects provided written informed consent prior to participation. The clinical research laboratory at CAMH is located proximally to the Addiction Medicine Clinic and the Opioid Clinic where physicians and therapists were available. All data were kept strictly confidential and were identified by subject number and initials, not by name. Subjects received $30.00 Canadian for their time and participation.
2.2.7 Data Analysis

Descriptive statistics were used to characterize the sample. A multivariate analysis of variance (MANOVA) was conducted for each construct that was measured using multiple scales, i.e. opioid withdrawal (SubOWS, ShOWS, ARCI-WOW and ARCI-SOW) and anxiety (STAI-s, ASI) or for each scale comprised of multiple subscales (e.g. ARCI, POMS). Significant measures were reported using univariate ANOVAs and post-hoc tests. Discriminant function analyses were also preformed for each construct or scale that was comprised of multiple subscales. Measures that most highly correlated with significant discriminant functions from each analysis were selected for an overall combined discriminant function analysis to determine which measures were the best discriminators of the patient satisfaction groups. Measures that were selected by the discriminant function analysis would be used for SubOWS modification.

As mentioned in the sample size justification section; due to the nature of this study, there were no primary outcome variables.
2.3 Methadone-Nicotine Interactions in Stabilized Methadone Maintenance Treatment Patients (Study 3)

2.3.1 Study Design

This was a double-blind, randomized, within-subject, placebo-controlled trial to investigate methadone nicotine interactions in stabilized methadone maintenance treatment patients. Subjects attended the CAMH clinical laboratory for three identical study days, with the only exception being the method in which nicotine was administered on each day. On day one subjects received nicotine by their regular brand of cigarette; after this, subjects entered the randomized phase of the study and received 4-mg (2x2-mg) Nicorette® gum or matching placebo on days two and three.

2.3.2 Subject Selection

Subjects were eligible for participation if they were able to provide informed consent (see appendix 8 for consent form) 18 years or older, were stabilized in treatment (i.e., enrolled in a methadone maintenance treatment program for at least the last three months and prescribed the same dose of methadone for at least the previous two weeks), and had no plans to quit smoking or request a change of methadone dose during the course of the study.
All subjects were asked to abstain from caffeine, alcohol and smoking (and all nicotine products) from 12 hours before each study day and for the duration of each study session. Subjects were asked to continue taking any other regular medications. A Mini International Neuropsychiatric Interview (MINI)\textsuperscript{202} was conducted to screen out potential subjects with current psychiatric disorders and substance use disorders. Subjects were excluded if they suffered from concurrent psychiatric disorders (other than anxiety disorders) or other current substance use disorders. Subjects were also screened for their level of nicotine dependence with the Fagerstrom test for Nicotine Dependence\textsuperscript{217}, subjects were excluded if they scored less than six.

2.3.3 Sample Size Justification

In order to calculate an appropriate sample size, four subjects were piloted in a one-day study looking at the effects of cigarette smoking on methadone effects (similar to the design proposed here). These preliminary data indicated reductions in opioid withdrawal symptoms (SubOWS) following the first cigarette administration prior to methadone dosing (from 12 ± 3 to 9 ± 2), and increases in positive mood (POMS-rew) following the second cigarette administration during the time of peak methadone concentrations (from 24 ± 15 to 32 ±20). Based on this pilot data this study would have been able to detect a significant difference between conditions with a power of 80\% for a two-tailed test with alpha=0.05 with a total of 40 subjects.
2.3.4 Subject Recruitment

Subjects were recruited from CAMH and other methadone clinics in the Greater Toronto Area with posted flyers (see appendix 10 for study flyer). Of the 141 individuals responded to the advertisement, 122 were able to be contacted, 82 passed the brief telephone screen (see appendix 11 for the telephone screen) and were willing to come for an assessment, and 60 assessments were completed. A total of 53 subjects were eligible to participate following the assessment and were enrolled in the study, 13 did not complete the study. Of those who did not complete the study six failed to arrive for the first study day, four were unable to abstain from smoking, one was arrested after the first study day, one dropped out after the first study day, and one was released because of suspected hypertension.

2.3.5 Assessment Day Procedures

Potential research subjects were assessed for eligibility based on the following: smoking, drug-use and methadone treatment history; the MINI; the Fagerström test for nicotine dependence (FTND); and a urine sample for toxicology and pregnancy testing. The FTND is the most widely used tool to establish a patient’s level of nicotine dependence. Possible scores range from 0 to 11. A score of 6 or higher indicates a high level of nicotine dependence. In addition, subjects had their demographics recorded and completed the Nicotine and Other Substance Interaction Expectancies questionnaire (NOSIE). The NOSIE was constructed to measure patient perceptions of the effects of
smoking on other illicit drug use and vice versa. The scale consists of 4 factors: effect of drugs on smoking, effect of smoking on drug use, smoking to cope with drug urges, and difficulty of concomitantly quitting smoking and drugs. The 20 items are scored on a 5-point Likert Scale Ranging from never (1) to always (5). Subjects were also classified as holders, partial holders, and nonholders with the guided self-report screening process developed in Study 2.

2.3.6 Study Day Procedures

On study days, subjects arrived at the CAMH clinical laboratory one hour prior to their regular methadone dosing time. At this point all subjects were asked to provide a urine sample for toxicology screening and to submit to an alcohol breathalyzer test and carbon monoxide (CO) breath test. Subjects were required to score zero on the alcohol breath test and no greater than 10 ppm on the CO breath test in order to confirm 12 hours abstinence from smoking and alcohol use. Subjects had vital signs monitored and were asked to respond to the Addiction Research Center Inventory Cole-short form, Profile of Mood States, Subjective Opioid Withdrawal Scale, Questionnaire of Smoking Urges, Minnesota Nicotine Withdrawal Scale, and a Visual Analog Scale for smoking effects on 4 separate cycles. The first two cycles were pre- and post-nicotine administration during the trough methadone condition. The second two cycles were pre- and post-nicotine administration during the peak methadone effects condition. Nicotine administration on the first study day was by cigarette; subjects were allowed 10 minutes to smoke one of their regular brands of cigarette. Nicotine administration on the
subsequent days was the active and placebo gum; subjects were instructed to chew the gum for 30 minutes using the ‘chew-chew-park’ method (described in the product monograph); chewing the gum in this method requires an individual to chew the gum twice and then station the gum between the gums and the wall of the mouth for 30 seconds, this is repeated for 30 minutes. Subjects received their regular methadone dose following cycle two. Methadone administration was followed by a three-hour break (to reach approximate peak methadone effects), during which time smoking was prohibited. Blood samples were collected for methadone and nicotine plasma concentration determination during cycles two and four. See figure 2.1 for study design. Subjects were provided with a lounge to relax in during the break; as well, subjects received a light meal.

Figure 2.1: Methadone-nicotine interaction study design

![Figure 2.1: Methadone-nicotine interaction study design](image)

Figure 2.1: Methadone-nicotine interaction study design. Study procedures were identical between study days, with the exception of the nicotine administration type. Subjects completed identical study cycles pre and post nicotine administrations at both the trough (cycles 1 and 2) and approximate peak (cycles 3 and 4) methadone conditions. Subjects received either 10 minutes to smoke one of their regular brands of cigarette or chewed the gum (active or placebo) for 30 minutes using the recommended method. The three-hour break was to allow for approximate peak methadone effects.
2.3.7 Plasma Concentration Determination

Concentrations of methadone were determined in plasma using an LCQ liquid chromatograph/mass spectrometer (LC/MS) with an electrospray interface (ESI) operating in the positive ionization mode (ThermoFisher, Mississauga ON). Methadone was separated on a Kromasil C18 100 mm x 2.10 mm, 3.5 μm i.d. column (CSC, Montreal, QC). Optimal separation was achieved with a mobile phase comprised of acetonitrile and 0.1% formic acid in a ratio of 60:40 (v/v). Fifty microlitres of plasma was combined with 100 L of internal standard (deuterated methadone) solution consisting of 300 ng/mL deuterated methadone and 100 L of 500nM sodium bicarbonate. The mixture was extracted with 750 L hexane; 200 L of which was dried off and the remaining residue was reconstituted with 500 L of mobile phase. Ten microlitres of this extract was injected into the LC/MS with a flow rate of 0.2 mL/min. The m/z detected was 310 for methadone and 319 for deuterated methadone. The retention time for methadone was 2.6 min. Calibration curves over the range of 50 to 1500 ng/ml were used to quantify each enantiomer. Intra-assay variability was 5% inter-assay variability was 5-6%. The limit of quantitation was 50 ng/mL.

Concentrations of nicotine, cotinine and hydroxyl-cotinine were analyzed according to the method of Giesbrecht et al. This method was originally developed for measuring very low levels of nicotine metabolites in urine (for studying environmental exposure to smoking in non-smokers). However, the same method was used for determining nicotine and metabolite levels in serum with the following exceptions. A sample volume of 100
μL was used. Standard curves were constructed from 5-1500 ng/mL for each analyte. Retention times for hydroxycotinine, cotinine, and nicotine were 0.74 min, 1.0 min, and 2.4 min, respectively. The transitions monitored were: hydroxycotinine 193 to 80, deuterated hydroxycotinine 196 to 80, cotinine 177 to 80, deuterated cotinine 180 to 80, nicotine 163 to 84, and deuterated nicotine 167 to 84.

2.3.8 Ethical Considerations

This study was approved by the CAMH Research Ethics Board and received a letter of no objection from Health Canada Natural Health Products Directorate. Written informed consent was obtained from each participant of the study. All data were kept strictly confidential and was identified by subject number and initials, not by name. The CAMH clinical research laboratory is located proximally to the Addiction Medicine Clinic. Upon completion of the study, subjects received $225.00 Canadian for their time and participation. Subjects who dropped out prior to completion were paid on a prorated basis, at the rate of $50.00 per completed study day.

2.3.9 Data Analysis

Descriptive statistics were used to characterize participants. Pharmacodynamic data was analyzed with repeated measures ANOVAs with methadone status (two levels – pre/post), nicotine status (two levels – pre/post) and study day (three levels – cigarette day, nicotine gum day, and placebo gum day) as within-subject factors. Methadone
pharmacokinetic data was analyzed with repeated measures ANOVAs with methadone (two levels – pre/post) and study day (3 levels – cigarette day, nicotine gum day, and placebo gum day) as within-subject factors. Nicotine, cotinine, and hydroxy-cotinine pharmacokinetic data were analyzed with repeated measures ANOVAs with nicotine status (two levels – post first nicotine administration (cycle two)/post second nicotine administration (cycle four)) and day (three levels – cigarette day, nicotine gum day, and placebo gum day) as within-subject factors. Sex was used as a between-subjects factor in the ANOVAs. Order effects were analyzed using order of nicotine gum/placebo gum administration as a between-subjects factor in the ANOVAs. Holder status (holder/partial holder/nonholder) effects on results were tested as a between-subject factor in the ANOVAs.

The primary outcome measure of this study was the SubOWS score. Secondary outcome measures were scores on the ARCI, MNWS, POMS, QSU, and VAS (smoking effects) assessments tools. Methadone and nicotine plasma levels were also secondary outcome measures in this study.
2.4 Pharmacodynamic Measures

2.4.1 Objective Measures

Vital Signs: Heart rate, blood pressure, oxygen saturation, skin temperature and respiratory rate were taken using a Criticare (model number: 507EP) vital signs monitor.

Pupil Diameter: Pupil diameter was measured with a pupillometer. The pupillometer is a specialized camera that uses an infrared light source to acquire an image that is captured to a research computer and quantified. The pupillometer has been used in opioid research conducted in our laboratory.

2.4.2 Subjective Measures

Subjective Opioid Withdrawal Scale (SubOWS): The SubOWS is a 16-item symptom checklist for opioid withdrawal. Items comprise typical signs and symptoms of opioid withdrawal. Each item is scored on a 5-point scale from 0 (not at all) to 4 (extremely). A typical subject is able to complete this scale in one minute.

Short Opioid Withdrawal Scale (ShOWS): The ShOWS is 10-item symptom checklist for opioid withdrawal. Each item is scored on a 4-point scale from 0 (nil) to 3 (severe) and is used to rate opioid withdrawal over the previous 24-hour period. The ShOWS is a short form version of the Opiate Withdrawal Scale (OWS). A factor analysis was
completed and the OWS was shortened to 20 items. After removing confusing and redundant items the OWS was condensed to the 10-item ShOWS.\textsuperscript{108} A typical subject is able to complete this scale in less than one minute.

**Addiction Research Center Inventory - Weak and Strong Opioid Withdrawal Scale (ARCI-WOW and ARCI-SOW):** An opioid withdrawal scale was developed from the items of the ARCI.\textsuperscript{109} It was noted that this scale was accurate for when assessing strong opioid withdrawal symptoms but not necessarily reflective of weak, subjective opioid withdrawal symptoms. Hence, new scales were developed. The ARCI-WOW items were selected because they differentiated a group of no-withdrawal control subjects (opioid-dependent patients, one month after admission to an inpatient detoxification program) from subjects expected to be feeling weak opioid withdrawal (opioid-dependent patients, three days after admission to an inpatient detoxification program).\textsuperscript{110} The ARCI-SOW items were selected because they differentiated opioid addicts on the 10\textsuperscript{th} day of a taper from heroin or morphine from their own baseline.\textsuperscript{110} A typical subject is able to complete either of these measures in four to five minutes.

**Addiction Research Center Inventory (ARCI):** The ARCI scale was developed by the Addiction Research Center. It is the most commonly used scale for assessing the effects of different psychotropic drug classes. The full ARCI consists of 550 true/false statements.\textsuperscript{196} The Cole/short form of the ARCI was used; it is a combination of the 49-item ARCI short form\textsuperscript{197} and the 66-item ARCI-Cole\textsuperscript{195}. Because of overlap the Cole/short form version of the ARCI consists of 76 true/false questions that comprise 12
subscales (five from the short form and seven from the ARCI-Cole). The ARCI short form consists of five subscales assessing euphoria, sedation, dysphoria, and stimulation. Of the five subscales three were most useful for studying methadone. The Morphine Benzedrine Group (MBG) assesses morphine-like and stimulant effects. Its content reflects feelings of pleasantness, contentedness and happiness, as such it is commonly called the “euphoria” scale. The Pentobarbital Chlorpromazine Alcohol Group (PCAG) is sensitive to a variety of CNS depressant drugs. Its content reflects feelings of sedation and apathy. It is commonly called the “sedation” scale. The Lysergic Acid Diethylamide (LSD) scale’s (named after the hallucinogen) contents reflect feelings of dysphoria and sensory and somatic disturbance. It is commonly called the “dysphoria” scale.\textsuperscript{197} The ARCI-Cole was derived from ARCI List 116. A factor analysis was carried out by Cole et al. and three factors seemed most important, these were sedation, euphoria and dysphoria.\textsuperscript{195} These factors were broken down into somatic and psychic symptoms to comprise the following subscales: Sedation-Motor, Sedation-Mental, Unpleasantness-Physical, Unpleasantness-Dysphoria, Stimulation-Motor, and Stimulation-Euphoria. As well a composite scale for abuse potential was created with items that correlated significantly ($r=0.32$) with street value of the drug (based on assignment of monetary value by study subjects).\textsuperscript{195} A typical subject is able to complete this scale in five minutes.

**Profile of Mood States (POMS):** The POMS is an adjective checklist used for assessing drug-induced changes in mood. Subjects indicate how they feel using a five-point scale from “not at all” to “extremely”. The version used is comprised of 72-items
corresponding to 8 mood clusters and 2 derived mood clusters. These mood clusters include: anxiety/tension, depression, anger, fatigue, vigor, confusion, friendliness and elation. Derived measures are: arousal (sum of anxiety and vigor - sum of confusion and fatigue) and positive mood (elation – depression). A typical subject is able to complete this scale in four minutes.

Obsessive Compulsive Drug Use Survey (OCDUS): The OCDUS measures two factors of opioid craving over the previous one-week period: 1) thoughts about heroin and interference and 2) desire and control. The scale has 10 items framed around heroin. Subjects were asked to substitute the word heroin with methadone. A typical subject is able to complete this scale in less than one minute.

The Health Status Questionnaire (SF-36): The SF-36 is a quality of life measure suitable for self-administration. It has been shown to be valid in groups reporting different levels of ill-health. It assesses eight health concepts: physical functioning, role limitations due to physical health problems, social functioning, bodily pain, general mental health (psychological distress and psychological well-being), role limitations due to emotional problems, vitality (energy/fatigue), and general health perceptions. A typical subject is able to complete this scale in five minutes.

Drug-Taking Confidence Questionnaire (DTCQ): The DTCQ is a 50-item self-report questionnaire to assess situation specific coping self-efficacy for using a particular substance. The scale consists of eight subscales: Unpleasant emotions, physical
discomfort, pleasant emotions, testing personal control, urges/temptation to use, conflict with others, social pressure to use, and pleasant times with others. Items are graded on a 6-point scale ranging from not at all confident to very confident. Subjects were asked to respond to the items with opioids as the substance of interest. A typical subject is able to complete the DTCQ in four minutes.

State-Trait Anxiety Inventory (STAI): A 40-item self-report assessment that differentiates between state and trait anxiety. The STAI is comprised of two 20-item subscales one for state and one for trait anxiety. The subscale for state anxiety (STAI-s) was used. A typical subject is able to complete the STAI-s in two minutes.

Short-Form McGill Pain Questionnaire (SFMPQ): This instrument is designed to provide quantitative measures of clinical pain that are sensitive to change. It contains 15 descriptors (11 sensory, 4 affective) which are rated for intensity, as well as measures for current and average pain intensity. A typical subject is able to complete the SFMPQ in four minutes.

Anxiety Sensitivity Index (ASI): The ASI is a 16-item questionnaire in which participants indicate on a 5-point Likert scale (from very little to very much) the degree to which they fear anxiety symptoms. A typical subject is able to complete the ASI in two minutes.
Hopkins Symptom Checklist 90 (SCL-90): This is a 90-item self-report symptom inventory designed to reflect current psychological symptom patterns of psychiatric and medical patients. It is interpreted in terms of 9 primary symptom dimensions: somatization, obsessive-compulsive, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, and psychoticism. Normative data are available on non-patients and psychiatric outpatients. A typical subject is able to complete the SCL-90 in five minutes.

Neo Personality Index (NEO): This is a self-report instrument for measuring five major personality factors: neuroticism, extroversion, openness, agreeableness and conscientiousness; each containing six subfactors. There are 240 items and a subject can strongly agree, agree, be neutral, disagree, or strongly disagree. Normative data are available. The NEO has been extensively evaluated for reliability and validity in both normal and clinical populations. A typical subject is able to complete the NEO in 30 minutes.

Multidimensional Scale of Perceived Social Support (MSPSS): This is a short self-report measure where subjects indicate the extent of their agreement with a series of statements related to the social support they receive from family, friends and significant others. This scale provides a more direct measure of social support than just marital and employment status. A typical subject is able to complete the MSPSS in one minute.
Visual Analog Scales – Smoking (VAS): Visual analog scales are often used to assess momentary changes in effect. Twenty-six scales related to smoking were presented to subjects. Subjects select how much they agree or disagree with the statement by selecting where to intersect a 100-point line anchored by two opposing options. This scale has been used in previous studies in our laboratory. A typical subject is able to complete the 26 VAS in two minutes.

Questionnaire of Smoking Urges (QSU): The QSU is a 32-item scale consisting of four subscales: desire to smoke, anticipation of positive outcome, relief of withdrawal or negative affect, and intention to smoke. Also, the items of the QSU can be divided into two factors. Factor one is related to intention and desire to smoke for positive outcomes associated with smoking and Factor two is related to the relief of negative affect or withdrawal by smoking. Items of the QSU are scored on a 7-point Likert scale ranging from strongly disagree (1) to strongly agree (7). The QSU can be completed in three minutes by a typical subject.

Minnesota Nicotine Withdrawal Scale (MNWS): This is a brief, 8-item self-report instrument based on DSM-IV symptoms of nicotine withdrawal. Items are rated on a 5-point Likert scale. It has been shown to be sensitive to acute changes in smoking. A typical subject is able to complete the MNWS in one minute.

Digit Symbol Substitution Test (DSST): This is a computerized psychomotor test that requires subjects to replicate a template pattern on a blank numbered template. There are
10 different symbols, comprised of different combinations of blank and filled squares. These 10 symbols are randomly paired with the numbers 0-9. The subject is randomly given a number between 0 and 9 that is associated with a specific symbol from the legend. Replication is accomplished by clicking the appropriate squares in the blank template with a computer mouse. Subjects have 90 seconds to make as many substitutions as possible. The number of correct substitutions is used as a measure of psychomotor function.¹⁹⁸,¹⁹⁹

Manual Tracking Test (MTT): The MTT is a computerized test that requires the subject to navigate a virtual airplane over a set pathway that shifts across the screen using a computer mouse. Each assessment consists of three, 20-second trials. The mean percent time spent over the pathway is used as a measure of psychomotor function.²⁰⁰
Section 3: Results

3.1 Major Depressive Disorder and Patient Satisfaction in Relation to Methadone Pharmacokinetics and Pharmacodynamics in Stabilized Methadone Maintenance Patients (Study 1)

3.1.1 Study Participants

A total of 17 subjects completed the study protocol. There were no differences in baseline characteristics between subject groupings (depressed vs. nondepressed and holders vs. nonholders) with two exceptions. Depressed subjects were confirmed to be significantly more depressed than nondepressed subjects as evidenced by HAMD, POMS depression/dejection subscale and POMS total mood disturbance scores. As well, depressed subjects were significantly heavier; however, the dose relative to weight was not different between the depressed and nondepressed groups. While not significant, nonholders tended to have more negative mood disturbance and depression/dejection, though there was no difference between holders and nonholder for depression severity (HAMD). For a summary of patient characteristics see table 3.1. Urine screens were positive for benzodiazepines in 24% of cases, for cannabinoids in 18% of cases and for cocaine in 6% of cases; and there were no differences between subject groupings. All those with positive urine screens reported their last use as 3 or more days ago with the exception of one participant, who, after questioning reported using cannabis on the night prior to the study. None of the subjects had a positive urine screen for other opioids on
the study days. All but one subject were current tobacco smokers. The prevalence of anxiety disorders, according to DSM-IV criteria were: social phobia 12%, panic disorder 6%, obsessive compulsive disorder 6%, and post traumatic stress disorder 6%.

Again, there were no differences between subject groupings. Three of the 10 subjects in the control group had a history of major depression but were not suffering current symptomatology (HAMD <7). Two of the depressed subjects were currently taking antidepressants (one paroxetine and one sertraline). Removing patients currently taking antidepressants from the analysis did not affect study findings.
Table 3.1: Summary of patient characteristics. ns = not significant, HAMD = score on the 21-item Hamilton Depression Scale, POMS – Dep/Dej = score on Depression/Dejection subscale of the Profile Of Mood States scale at baseline, and POMS – TMD = score on the composite measure of Total Mood Disturbance derived from the Profile of Mood States at baseline. Scores are reported as: mean (SD).

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<th>Total</th>
<th>Nondepressed</th>
<th>Depressed</th>
<th>p</th>
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<th>Nonholder</th>
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<td>92%</td>
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<td>9.3 (10.5)</td>
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3.1.2 Pharmacodynamic Results

Depressed subjects experienced significantly more negative opioid effects, specifically dysphoric effects as measured with the LSD subscale of the ARCI. Both AUEC and maximum change from baseline (Δmax) scores were significantly higher in depressed subjects (AUEC: 14.1±32.3 vs. -31.0±46.7, p<0.04 and Δmax: 0.7±3.9 vs. -2.7±2.6, p<0.04 respectively). See figure 3.1. Depressed subjects did not score higher on any ARCI positive effects subscales (MBG, BG, amphetamine, mental stimulation, and abuse potential) compared to nondepressed subjects.

Depressed subjects experienced more opioid withdrawal symptoms compared to nondepressed subjects. This was observed in the higher scores for opioid withdrawal symptoms as measured by the Subjective Opioid Withdrawal Scale (SubOWS) (AUEC: 32.7±95.9 vs. -74.2±66.7, p<0.02). See figure 3.2a for comparison of SubOWS scores over the 24-hour dosing interval in depressed and nondepressed methadone maintenance treatment patients. Similarly, currently depressed patients tended to have higher SubOWS scores compared to patients who were not currently depressed but had a past history of major depressive disorder (n=3) (AUEC: 32.7±95.9 vs. -40.8±22.1, p=0.24). Nonholders did not score significantly higher on the SubOWS compared to holders, see figure 3.2b.
Figure 3.1: Depressed MMT patients experience more dysphoric opioid effects (LSD subscale). This was noted with both the a) AUEC and b) Δmax LSD summary scores. Error reported as SEM.
Figure 3.2: SubOWS scores over one 24-hour dosing interval in a) depressed vs. nondepressed and b) holder vs. nonholder methadone patients. Depressed patients had significantly more opioid withdrawal at all time points. There were no differences between holders and nonholders. Error reported as SEM.
Hamilton depression scores were significantly correlated with trough SubOWS scores ($r = 0.70$, $p<0.004$); see figure 3.3. There was a significant correlation between HAMD and the AUEC of a composite measure of negative ARCI subscales (LSD, PCAG, motor sedation, mental sedation, unpleasantness-physical, unpleasantness-dysphoria, $\alpha=0.85$) ($r = 0.50$, $p<0.05$).

Figure 3.3: Correlation: Trough opioid withdrawal and depression severity

Figure 3.3: Trough SubOWS scores were significantly correlated with HAMD scores.
There were no differences between groups in pupil diameter. Pupillary miosis was evident in all subjects, see figure 3.4.

Figure 3.4: Pupil diameter over the dosing interval

![Pupil Diameter (mm) vs. Time (hr)](image)

Figure 3.4: Pupil diameter vs. time. Pupil diameter decreased, with maximal miosis at 3 hours post methadone dose. Afterwards, pupil diameter rebounds to baseline levels. Error reported as SEM.

There were no differences detected in psychomotor function (both DSST and MTT) between groups.
3.1.3 Pharmacokinetic Results

There were no differences in pharmacokinetic parameters for methadone both as a racemate and as individual enantiomers (total and free levels) between depressed and nondepressed patients. The same was true for holders and nonholders with the exception of free (S)-methadone (see figure 3.5): Nonholders had significantly higher $C_{24}$, $C_{ss}$, $C_{max}$, and AUC compared to holders (see table 3.2 for a summary).

Figure 3.5: Free (S)-methadone levels over the day

Figure 3.5: Unbound (S)-methadone levels over one 24-hour dosing interval in holder and nonholder methadone maintenance treatment patients. Nonholder patients have greater exposure to unbound (S)-methadone over the entire dosing interval. This is demonstrated by the significantly higher $C_{max}$, $C_{ss}$, $C_{24}$ and AUC in nonholders compared to holders. Error reported as SEM.
Table 3.2: Free (S)-methadone pharmacokinetic parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Unit</th>
<th>Holder</th>
<th>Nonholder</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{24}$</td>
<td>ng/ml</td>
<td>2.7 (1.7)</td>
<td>6.1 (2.7)</td>
<td>0.008</td>
</tr>
<tr>
<td>$C_{ss}$</td>
<td>ng/ml</td>
<td>4.1 (2.5)</td>
<td>7.6 (4.0)</td>
<td>0.044</td>
</tr>
<tr>
<td>$C_{max}$</td>
<td>ng/ml</td>
<td>7.5 (4.2)</td>
<td>14.6 (7.1)</td>
<td>0.030</td>
</tr>
<tr>
<td>AUC</td>
<td>hr ng/ml</td>
<td>99.4 (60.6)</td>
<td>182.9 (94.8)</td>
<td>0.044</td>
</tr>
</tbody>
</table>

Table 3.2: Unbound (S)-methadone pharmacokinetic parameter estimates for holders and nonholders. $C_{24} =$ trough concentration at 24 hours, $C_{ss} =$ average Steady-State concentration, $C_{max} =$ peak concentration, and AUC = Area Under the plasma concentration vs. time Curve. Scores reported as mean (SD)

There were no differences between holders and nonholders in terms of maximum rates of decline in plasma methadone concentrations for total and unbound (R,S)-, (R)-, or (S)-methadone.

3.1.4 Concentration-Effect Relationship

The Sigmoid $E_{max}$ model did not fit enough of the data to justify the modelling. Furthermore, accounting for both protein binding and chirality did not lead to the production of better fitting models.
3.2 Opioid Withdrawal Scale Modification and Characterization of Between Dose Opioid Withdrawal and Patient Satisfaction in Methadone Maintenance Treatment (Study 2)

3.2.1 Study Participants

A total of 90 subjects; 25 holders, 35 partial holders, and 30 nonholders completed the study protocol. Partial holders had been enrolled in methadone maintenance treatment for significantly less time than the patients in the other two groups. Nonetheless, partial holders were in treatment for an average of more than four consecutive years and on their current dose for nearly eight months; a period of time assumed to be sufficient for the clinical optimization of the patients’ doses. Also a disproportionately greater number of males were enrolled in the partial holder group (24:11). See table 3.3 for a summary of patient characteristics. Urine screens were positive for cannabinoids in 32% of cases, for benzodiazepines in 21% of cases, for cocaine metabolite in 16% of cases, for opioids in 10% of cases, for cocaine in 6% of cases, and for amphetamine in 1% of cases. There were no differences amongst groups for positive urine samples. The majority (94%) of the participants were current smokers. The prevalence of psychiatric disorders, according to the MINI screening were: Agoraphobia (28%), major depressive disorder (20%), social phobia (16%), panic disorder (11%), bipolar disorder (11%), post traumatic stress disorder (10%), schizophrenia (psychotic disorder) (9%), generalized anxiety disorder (9%), dysthymia (6%), obsessive compulsive disorder (3%), and bulimia (3%). There were no differences amongst groups for psychiatric disorders with the exception of
agoraphobia being more prevalent in nonholders (holders 18%, partial holders 20%, and nonholders 47%, \( p=0.018 \)). Although rates of depression among the groups did not differ statistically, differences amongst the groups were noted (holders 4%, partial holders 25%, and nonholders 26%, \( p=0.064 \)).

Table 3.3: Patient characteristics from Study #2.

<table>
<thead>
<tr>
<th></th>
<th>Holder</th>
<th>Partial Holder</th>
<th>Nonholder</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>25</td>
<td>35</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Sex (F:M)</td>
<td>12:13</td>
<td>11:24</td>
<td>13:17</td>
<td>0.271</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>39.5 (8.3)</td>
<td>40.7 (8.5)</td>
<td>39.8 (8.3)</td>
<td>0.857</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>170.6 (10.2)</td>
<td>171.1 (7.9)</td>
<td>174.5 (9.7)</td>
<td>0.209</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>78.8 (24.3)</td>
<td>77.1 (25.8)</td>
<td>76.0 (14.7)</td>
<td>0.892</td>
</tr>
<tr>
<td>Time in Treatment (mo)</td>
<td>68.0 (49.5)</td>
<td>50.1 (4.7)</td>
<td>78.4 (47.6)</td>
<td>0.045</td>
</tr>
<tr>
<td>Time on Dose (mo)</td>
<td>8.3 (12.1)</td>
<td>7.8 (11.2)</td>
<td>7.9 (10.0)</td>
<td>0.984</td>
</tr>
<tr>
<td>Dose (mg/day)</td>
<td>73.0 (46.1)</td>
<td>80.8 (38.6)</td>
<td>99.5 (44.6)</td>
<td>0.062</td>
</tr>
</tbody>
</table>

Table 3.3: Study 2 patient demographics. Values reported as mean (SD). There are no differences between groups in demographics with the exception that partial holders were in treatment for significantly less time than the other groups and the ratio of men to women was greatest in the partial holder group.

3.2.2 Subjective Data

Study results suggest that patient satisfaction groups differed from each other in a dichotomous manner for some measures and over a continuum for other measures. When patient satisfaction suggested a dichotomous differentiation between groups three patterns emerged: 1) Nonholders were different from the other groups, 2) partial holders were different, and 3) holders were different.
3.2.2.1 Patient Satisfaction as a Dichotomy

3.2.2.1.1 Nonholders

Nonholders had more opioid withdrawal, pain, opioid craving, and unpleasant drug effects compared to holders and partial holders.

Opioid Withdrawal: Nonholders (NH) scored higher than partial holders (PH) and holders (H) on the SubOWS (NH: 22.0±8.8 vs. PH: 12.2±8.2 vs. H: 9.3±10.0, p<0.001), the ShOWS (NH: 13.2±5.6 vs. PH: 8.4±4.6 vs. H: 7.0±4.3, p<0.001), the ARCI-WOW (NH: 59.1±15.1 vs. PH: 47.6±17.2 vs. H: 42.9±14.9, p=0.001), and the ARCI-SOW (NH: 24.0±7.8 vs. PH: 16.8±8.9 vs. H: 15.4±8.2, p<0.001). Post-hoc tests showed that the difference between groups was driven by nonholders vs. holders/partial holders. See figure 3.6.

Pain: There were significant differences amongst patient satisfaction groups for current pain (NH: 1.9±1.2 vs. PH: 1.3±1.0 vs. H: 1.20±0.9, p=0.015) and past month average pain intensity (NH: 6.7±2.3 vs. PH: 5.0±2.7 vs. H: 5.0±2.7, p=0.013), according to the short form of the McGill Pain Questionnaire. Post hoc tests showed that the difference amongst groups was driven by nonholders vs. holders/partial holders. See figure 3.7.
Craving: Past week craving, measured by the Obsessive Compulsive Drug Use Survey (OCDUS) tended to be different amongst patient satisfaction groups. This was evident for the OCDUS total score (NH: 11.4±8.8 vs. PH: 6.4±6.6 vs. H: 6.5±6.2, p=0.016), the thoughts and interference subscale (NH: 6.9±5.6 vs. PH: 4.0±4.7 vs. H: 3.8±3.6, p=0.023), and the desire and control subscale (NH: 4.5±3.6 vs. PH: 2.4±2.6 vs. H: 2.8±2.8, p=0.022). Post hoc tests showed that the differences amongst groups were driven by the nonholders vs. partial holders. The difference between nonholders and holders approached significance (OCDUS total score, p=0.056; thoughts and interference, p=0.055; and desire and control, p=0.12). See figure 3.8.

Drug Effects: Many subscales of the ARCI tended to be different amongst groups: LSD (NH: 7.7±3.2 vs. PH: 5.4±3.4 vs. H: 5.2±2.9, p=0.005), Unpleasantness-Dysphoric (NH: 3.6±1.8 vs. PH: 2.4±2.1 vs. H: 1.8±1.8, p=0.002), Unpleasantness-Physical (NH: 4.0±2.5 vs. PH: 2.1±2.1 vs. H: 1.6±2.1, p<0.001), and Stimulation-Abuse Potential (NH: 3.6±2.9 vs. PH: 5.6±2.3 vs. H: 6.4±2.3, p<0.001). Post hoc tests showed that differences amongst groups were driven by nonholders vs. holders/partial holders. See figure 3.9.
Figure 3.6: Opioid withdrawal scores among groups, partial holders resemble holders.

a) Subjective Opioid Withdrawal Scale

b) Short Opioid Withdrawal Scale

c) ARCI - Weak Opioid Withdrawal

d) ARCI - Strong Opioid Withdrawal

Figure 3.6: Opioid withdrawal scores among groups. a) SubOWS, b) ShOWS, c) ARCI-WOW, and d) ARCI-SOW. Partial holders resemble holders and differences are driven by holders/partial holders vs. nonholders.
Figure 3.7: a) Average and b) Current pain among groups. Partial holders resemble holders and differences are driven by holders/partial holders vs. nonholders.
Figure 3.8: Opioid craving among groups, partial holders resemble holders.

(a) OCDUS - Thoughts and Interference

(b) OCDUS - Desire and Control

(c) OCDUS Total Score

Figure 3.8: Past week craving among groups. a) Thoughts about methadone and how these thoughts interfere with normal functioning, b) Desire for, and control over desire for methadone, and c) Total craving score. Partial holders resemble holders and differences are driven by partial holders vs. nonholders.
Figure 3.9: Drug effects (ARCI) among groups, partial holders resemble holders.

a) LSD Score

b) Unpleasantness - Dysphoria Score

c) Physical Score

d) Abuse Potential Score

Figure 3.9: Drug effects among groups.  a) LSD-dysphoria,  b) Unpleasantness-dysphoria,  c) Physical unpleasantness, and d) Abuse potential/drug liking. Partial holders resemble holders and differences are driven by holders/partial holders vs. nonholders.
3.2.2.1.2 Holders

Holders had less psychological distress and mood disturbance compared to partial holders and nonholders.

**Psychological Distress:** There were significant differences amongst groups on many subscales of the psychological distress Symptom Checklist-90: Obsessive-Compulsive (NH: 15.3±8.1 vs. PH: 12.3±7.3 vs. H: 6.6±5.1, p<0.001), Interpersonal Sensitivity (NH: 11.4±7.2 vs. PH: 9.5±6.7 vs. H: 5.4±6.5, p=0.007), Depression (NH: 21.1±11.5 vs. PH: 17.6±11.1 vs. H: 11.3±9.5, p=0.005), Anxiety (NH: 11.5±7.3 vs. PH: 9.3±6.9 vs. H: 5.3±5.8, p=0.004), Anger/Hostility (NH: 4.9±3.7 vs. PH: 5.5±4.9 vs. H: 1.6±1.5, p<0.001), Paranoid Ideation (NH: 6.9±4.2 vs. PH: 6.2±4.1 vs. H: 3.7±3.7, p=0.013), and Global Severity Index (NH: 1.3±0.7 vs. PH: 1.0±0.6 vs. H: 0.6±0.5, p=0.001). For the Obsessive-Compulsive, Anger/Hostility subscales and Global Severity Index, differences among groups were driven by nonholders/partial holders vs. holders, see figure 3.10. For the rest of the subscales the difference between groups was driven by nonholders vs. holders, with the difference between partial holders and holders approaching significance; Interpersonal Sensitivity (p=0.076), Depression (p=0.084), Anxiety (p=0.078), and Paranoid Ideation (0.059).

**Mood:** Profile Of Mood States subscales tended to be different amongst groups. Specifically, holders had lower scores on negative mood subscales (Tension/Anxiety (NH: 13.3±5.7 vs. PH: 11.2±6.4 vs. H: 7.2±5.2, p=0.001), Anger/Hostility (NH:
Figure 3.10: Psychological distress among groups, partial holders resemble nonholders. 

a) SCL-90 - Obsessive/Compulsive

b) SCL-90 - Anger/Hostility

c) SCL-90 - Global Severity Index

Figure 3.10: Psychological Distress among groups. a) obsessive/compulsive based psychological distress, b) Anger/hostility based psychological distress, and c) Global estimate of psychological distress. Partial holders resemble nonholders and differences driven by holders vs. partial holders/nonholders.
Figure 3.11: Mood states among groups, partial holders resemble nonholders.

- **POMS - Tension/Anxiety**
  - Holders: 7.2
  - Partial Holders: 11.2
  - Nonholders: 13.3

- **POMS - Anger/Hostility**
  - Holders: 5.1
  - Partial Holders: 11.2
  - Nonholders: 10.1

- **POMS - Confusion**
  - Holders: 5.2
  - Partial Holders: 8.0
  - Nonholders: 9.7

- **POMS - Depression/Dejection**
  - Holders: 7.9
  - Partial Holders: 17.2
  - Nonholders: 19.7

- **POMS - Positive Mood**
  - Holders: -1.5
  - Partial Holders: -11.6
  - Nonholders: -15.5

Figure 3.11: a) Tension/anxiety, b) Anger/hostility, c) Confusion, d) Depression/dejection, and e) Positive mood among groups. Partial holders resemble nonholders and differences are driven by holders vs. partial holders/nonholders.
10.1±6.4 vs. PH: 11.2±9.6 vs. H: 5.1±5.3, p=0.009), Depression/Dejection (NH: 19.7±13.7 vs. PH: 17.2±13.2 vs. H: 7.9±10.4, p=0.002), and Confusion (NH: 9.7±5.0 vs. PH: 8.0±4.2 vs. H: 5.2±3.9, p=0.001) and lower scores on Positive Mood composite subscale (NH: -15.5±15.0 vs. PH: -11.6±15.1 vs. H: -1.5±12.5, p=0.002). Post hoc tests confirmed that differences were driven by holders vs. nonholders/partial holders. See figure 3.11

**Personality:** On the Neuroticism factor (N-Factor) of the NEO personality inventory, there were significant differences amongst groups, (NH: 63.3±12.3 vs. PH: 60.9±10.0 vs. H: 54.0±8.8, p=0.006). Post hoc tests showed that differences were driven by holders vs. nonholders/partial holders. See figure 3.12. Sub-factors (anger/hostility, depression, self-consciousness, and vulnerability) of the N-Factor support these findings.

![Figure 3.12: Neuroticism among groups, partial holders resemble nonholders.](image)

Figure 3.12: NEO neuroticism factor scores among groups. Partial holders resemble nonholders and differences driven by holders vs. partial holders/nonholders.)
3.2.2.1.3 Partial Holders

Partial holders had less open and less agreeable personalities compared to holders and nonholders.

**Personality:** On the Openness factor (O-Factor) and Agreeableness factor (A-Factor) of the NEO personality inventory, there were significant differences amongst groups. O-Factor (NH: 53.7±10.0 vs. PH: 46.9±9.2 vs. H: 53.6±10.2, p=0.008) and A-Factor (NH: 44.2±8.6 vs. PH: 38.0±10.6 vs. H: 47.6±11.7, p=0.002). Post hoc tests confirmed that differences were driven by partial holders vs. holders and partial holders vs. nonholders, see figure 3.13. Sub-factors of the O-Factor and A-Factor were generally not significantly different between groups, differences were more attributable to the overall factor scores (for the O-Factor, the actions sub-factor was significant, for the A-Factor, the straightforwardness and altruism sub-factors were significant).

3.2.2.2 Patient Satisfaction as a Continuum

Scores on measures of pain, sedation, psychological distress, anxiety, and mood resembled a continuum with partial holders results falling in between nonholder and holders scores in a stepwise fashion.

**Pain:** There were significant differences amongst groups for subscales of the short form of the McGill Pain Questionnaire. Lower patient satisfaction groups showed higher
Figure 3.13: Openness and Agreeableness (personality) among groups, partial holders different than holders and nonholders.

Figure 3.13: NEO a) Openness and b) Agreeableness factor scores among groups. Partial holders act as their own group and differences are driven by partial holders vs. holders and partial holders vs. nonholders.
scores on the sensory (NH: 13.6±7.9 vs. PH: 11.1±7.0 vs. H: 8.2±7.3, p=0.027), affective (NH: 5.4±2.7 vs. PH: 3.9±2.5 vs. H: 2.6±2.7, p=0.001), and total pain (NH: 19.0±9.9 vs. PH: 15.0±8.8 vs. H: 10.8±9.4, p=0.006) subscales. Post hoc tests suggest that these differences were driven by nonholders vs. holders, with a stepwise increase in pain scores as patient satisfaction decreased. See figure 3.14.

**Drug Effects:** On the ARCI, the PCAG (NH: 10.0±4.1 vs. PH: 7.9±3.6 vs. H: 6.3±3.8, p=0.002), Sedation-Motor (NH: 5.3±3.2 vs. PH: 3.5±3.0 vs. H: 2.8±2.7, p=0.007), and Sedation-Mental (NH: 7.5±3.3 vs. PH: 5.7±3.1 vs. H: 4.6±3.0, p=0.004) subscales were significantly different amongst groups. Post hoc tests showed that differences among groups were driven by nonholders vs. holders, with a stepwise increase in sedation scores from holder to partial holder to nonholder. See figure 3.15.

**Psychological Distress:** According to the Symptom Checklist 90, Somatization (NH: 16.9±8.9 vs. PH: 13.2±8.3 vs. H: 9.0±7.4, p=0.003), Phobic Anxiety (NH: 6.9±6.2 vs. PH: 4.9±5.9 vs. H: 2.5±4.2, p=0.018), Psychoticism (NH: 9.2±6.8 vs. PH: 6.6±5.9 vs. H: 3.6±4.7, p=0.003), and Positive Symptom Distress Index (NH: 1.8±0.5 vs. PH: 1.7±0.4 vs. H: 1.4±0.4, p=0.024) were significantly different amongst groups and the differences were driven by nonholders vs. holders with a stepwise increase in psychological distress as patient satisfaction decreased. See figure 3.16.

**Anxiety:** Anxiety, as measured by the state subscale of the State-Trait Anxiety Index (STAIs) and Anxiety Sensitivity Index (ASI) was different amongst groups. Lower
patient satisfaction groups were associated with greater scores on the STAIx (NH: 52.3±10.3 vs. PH: 46.1±10.4 vs. H: 41.3±10.8, p=0.001). Differences were more strongly associated with negatively worded anxiety items (NH: 21.3±6.5 vs. PH: 17.7±6.1 vs. H: 14.6±5.0, p=0.001) than positively worded anxiety items (NH: 31.1±5.2 vs. PH: 28.3±6.0 vs. H: 26.7±7.3, p=0.035). ASI scores also tended to be greater in lower patient satisfaction groups (NH: 30.4±15.0 vs. PH: 25.0±11.0 vs. H: 22.3±8.2, p=0.052). Differences were driven by nonholders vs. holders, with a stepwise increase in reported anxiety as patient satisfaction decreased. See figure 3.17.

**Mood:** On the POMS groups differed on the Fatigue subscale (NH: 12.4±6.4 vs. PH: 9.4±5.8 vs. H: 6.8±5.3, p=0.003) and Arousal composite subscale (NH: -2.9±9.6 vs. PH: 1.4±7.6 vs. H: 3.1±8.5, p=0.028). Differences were driven by nonholders vs. holders with stepwise increases in fatigue and stepwise decreases in arousal as patient satisfaction decreased. See figure 3.18.

### 3.2.2.3 Other Measures

Multivariate ANOVAs were not significantly different nor did they approach significance among groups for measures of quality of life (SF-36), self-efficacy (DTCQ), and perceived social support (MSPSS). As such, there were no differences detected amongst groups for these measures.
3.2.3 Discriminant Function Analysis

According to the discriminant function analyses, the measures that were the best discriminators of patient satisfaction groups from each of the constructs or scales with multiple subscales were: The SubOWS score, SCL-90-Obsessive/Compulsive score, STAI-s (negative wording), NEO-Agreeableness score, NEO-Neuroticism score, and SFMPQ-Affective pain score. These measures were used in the final discriminant function analysis. The analysis yielded two significant functions (p<0.001 and p=0.004, respectively). On the first function SubOWS score had the strongest canonical correlation. This function accounted for 62% of the variance in the analysis. Only the NEO-Agreeableness score exhibited a strong canonical correlation with the second discriminant function; this function accounted for 38% of the variance in the analysis.

3.2.4 SubOWS Modification

Because, SubOWS scores were significantly (p<0.001) different between holders and nonholders and based on the results of the discriminant function analysis a decision was made that it would not be useful to go forward with the SubOWS modification.
Figure 3.14: Pain measures among groups, satisfaction resembles a continuum.

a) SFMPQ - Sensory Pain

b) SFMPQ - Affective Pain

c) SFMPQ - Total Pain

Figure 3.14: Scores for a) sensory, b) affective, and c) total pain among groups. Scores for partial holders fall between holders and nonholders, differences driven by holders vs. nonholders.
Figure 3.15: Drug effects (ARCI) among groups, satisfaction resembles a continuum.

Figure 3.15: Scores for ARCI drug effects; a) Sedation-PCAG, b) Motor sedation, and c) Mental sedation among groups. Scores for partial holders fall between holders and nonholders, differences driven by holders vs. nonholders.
Figure 3.16: Psychological distress among groups, satisfaction resembles a continuum.

Figure 3.16: Scores for psychological distress; a) Phobic-anxiety based distress, b) Psychoticism based distress, c) somatization based distress, and d) average distress severity among groups. Scores for partial holders fall between holders and nonholders, differences driven by holders vs. nonholders.
Figure 3.17: Anxiety measures among groups, satisfaction resembles a continuum.

Figure 3.17: Anxiety Scores; a) STAI-s negatively worded items, b) STAI-s positively worded items, c) Total STAI-s score, and d) Anxiety sensitivity index scores among groups. Scores for partial holders fall between holders and nonholders, differences driven by holders vs. nonholders.
Figure 3.18: Mood state scores; a) Fatigue and b) Arousal among groups. Scores for partial holders fall between holders and nonholders, differences driven by holders vs. nonholders.
3.3 Methadone-Nicotine Interactions in Stabilized Methadone Maintenance Treatment Patients (Study 3)

3.3.1 Study Participants

A total of 40 subjects completed the 3-day study protocol. Patients were stabilized in methadone treatment and were heavy smokers, see table 1 for a summary of patient characteristics. Urine screens suggested recent use of cannabinoids in 45% of cases, of cocaine in 8% of cases, of oxycodone in 8% of cases, of morphine in 8% of cases, of codeine in 8% of cases, of heroin in 5% of cases, and of benzodiazepines in 3% of cases. Recent use of cannabis did not influence study results. The prevalence of potential anxiety disorders in our population, according to MINI screening interview were:

Agoraphobia 10%, social phobia 8%, panic disorder 5%, obsessive compulsive disorder 5%, and generalized anxiety disorder 5%.

Table 3.4: Patient characteristics from Study #3.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
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<td>N</td>
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</tr>
<tr>
<td>Sex</td>
<td>17F:23M</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>40.6 (8.3)</td>
</tr>
<tr>
<td>Methadone Dose (mg)</td>
<td>81.1 (38.4)</td>
</tr>
<tr>
<td>Time on Dose (mo)</td>
<td>11.0 (21.8)</td>
</tr>
<tr>
<td>Time in Treatment (mo)</td>
<td>73.4 (65.8)</td>
</tr>
<tr>
<td>Cigarettes per Day</td>
<td>20.5 (8.0)</td>
</tr>
<tr>
<td>Fagerström Test for Nicotine Dependence</td>
<td>7.3 (1.1)</td>
</tr>
<tr>
<td>Age First Smoked (yr)</td>
<td>12.6 (2.3)</td>
</tr>
<tr>
<td># of Serious Quit Attempts</td>
<td>1.3 (1.8)</td>
</tr>
<tr>
<td>Baseline Carbon Monoxide (ppm)</td>
<td>8.0 (2.4)</td>
</tr>
</tbody>
</table>

Table 3.4: Subjects were stabilized in their methadone treatment and heavy smokers
On the Nicotine and Other Substance Interaction Expectancies questionnaire (NOSIE) questionnaire subjects rated how they believed smoking and drug use interacted with each other on four domains. The mean scores on the four subscales were: “substance use increases smoking” (20.0±3.6, range 5-25), “smoking increases substance use” (6.1±2.5, range 3-15), “smoke to cope with substance use urges” (13.1±5.1, range 9-45), and “receptive to quitting smoking during drug treatment” (17.3±4.0, range 7-35). These results indicate that these patients believed that substance use increased their smoking habits but that smoking did not trigger them to using drugs. They also show that the participants did not believe that they smoked to cope with urges to use drugs and that patients did not necessarily think that quitting smoking and receiving treatment for another drug-use disorder were incompatible goals.

3.3.2 Pharmacodynamic Results

There was a main effect of methadone to decrease SubOWS scores (p<0.001) and a day*methadone interaction (p=0.031) associated with decreased opioid withdrawal on the cigarette day. There was a significant effect of gender on SubOWS scores (p=0.025), with women having greater SubOWS scores, particularly during the trough methadone condition. See figure 3.19 for opioid withdrawal scores across days and cycles, between sexes.

There was a main effect of nicotine (p<0.001) and methadone (p=0.001) to decrease MNWS scores. Effects were driven by the scores on the cigarette day, as indicated by
day*nicotine (p=0.003) and day*methadone (p=0.004) interactions. There was a significant effect of gender on MNWS scores (p=0.036), with women having greater MNWS scores, particularly during the trough methadone condition. See figure 3.20 for nicotine withdrawal scores across days and cycles, between sexes.

There was a significant effect of day for POMS-friendliness (p=0.015), POMS-elation (p=0.017), VAS-pleasant feelings in mind (p=0.026), and VAS-pleasant bodily sensations (p=0.024). The effect of day was such that for all cycles, including the pre-nicotine administration cycles, patients rated these measures higher on the cigarette day. Also associated with the smoking day, there was an effect of day such that patients rated POMS-anger/hostility (p=0.018) lower on all cycles. See figure 3.21 for the effect of day on the discussed measures across days and cycles.

Methadone and nicotine shared many of the same main effects. Methadone and nicotine increased ARCI-stimulation-euphoria (p=0.001 and p=0.025, for methadone and nicotine, respectively), ARCI-stimulation-abuse potential (p<0.001 and p<0.001), ARCI-BG (p<0.001 and p=0.005), and VAS-pleasant bodily sensations (p=0.002 and p=0.004) scores. Also, methadone and nicotine decreased VAS-irritability (p=0.003 and p=0.044), VAS-restlessness (p=0.001 and p=0.048), VAS-depression (p=0.008 and p=0.011), and POMS-anger/hostility (p=0.049 and p=0.035). Figures 3.22 (methadone and nicotine had main effects to increase scores) and 5 (methadone and nicotine had main effects to decrease scores) describe effects of methadone and nicotine on the cigarette day only for clarity.
Methadone and nicotine had main effects in the opposite direction for VAS-increased thinking speed (p<0.001 and p=0.026, methadone and nicotine, respectively), VAS-difficulty concentrating (p=0.025 and p=0.031), with nicotine increasing thinking speed, and decreasing difficulty concentrating scores. See figure 3.23 for scores on the cigarette smoking day.

There were main effects of nicotine and day associated with reduced QSU scores. This was evident for all QSU subscales and factors: desire to smoke (p<0.001 and p<0.001, for nicotine and study day (nicotine administration type), respectively), intention to smoke (p<0.001 and p<0.001), relief of withdrawal or negative effects (p<0.001 and p=0.004), anticipation of positive outcome (p<0.001 and p=0.001), Factor 1 (p<0.001 and p=0.001), and Factor 2 (p<0.001 and p=0.001). The nicotine effects were mediated by the cigarette day as indicated by the nicotine*day interactions (p<0.001 for all measures). There were no effects of methadone on QSU scores. See figure 3.24 for QSU scores on the cigarette day. Nicotine and day also had main effects on VAS-nicotine effects (p<0.001 and p=0.001), VAS-good nicotine effects (p<0.001 and p<0.001), VAS-cigarette craving (p<0.001 and p=0.008), and VAS-I feel high (p=0.027 and p=0.001). Again these effects were driven by the cigarette day as indicated by nicotine*day interactions (p<0.03 for all measures) and methadone had no effects on these measures. See figure 3.25 for scores on the cigarette day.
Methadone alone had main effects for a number of measures. It increased ARCI-MBG (p=0.001), ARCI-amphetamine (p=0.002), POMS-vigor (p<0.001), POMS-arousal (p=0.002), POMS-positive mood (p=0.004), and VAS-increased energy (p=0.001) scores and decreased ARCI-PCAG (p<0.001), ARCI-sedation-motor (p<0.001), ARCI-sedation-mental (p=0.004), ARCI-unpleasantness-dysphoria (p<0.001), POMS-tension/anxiety (p=0.013), POMS-depression/dejection (p=0.026), POMS-fatigue (p=0.026), POMS-total mood disturbance (p=0.004), VAS-nasuea (p<0.001), VAS-sick (p<0.001), VAS-frustrated (p=0.022), VAS-GI disturbances (p<0.001), VAS-headache (p=0.017), VAS-dizzy (p=0.002), and VAS-drowsy (p=0.043) scores. See table 3.5 for the values on these measures on the cigarette day (as an example of the effect size).

Including the order of nicotine gum (active first or placebo first) or holder status (holder/partial holder/nonholder) into the analysis did not influence study findings.
Figure 3.19: Subjective Opioid Withdrawal Scale (SubOWS) scores by cycle and by study day stratified by sex.

Women tended to have greater opioid withdrawal scores, particularly during the trough methadone condition. There was a main effect of methadone to decrease SubOWS scores. There was an interaction between study day and methadone, suggesting that opioid withdrawal reduction was enhanced on the cigarette-smoking day.
Figure 3.20 Minnesota Nicotine Withdrawal Scale (MNWS) scores by cycle and study day stratified by sex. Women tended to have higher MNWS scores, particularly during the trough methadone condition. There were main effects of both nicotine and methadone to reduce MNWS scores. Effects were driven by scores on the cigarette-smoking day.
Figure 3.21 Effect of Day

There was a significant effect of day to increase positive feelings: a) Friendliness, b) Elation, c) Pleasant feeling in mind, d) Increased thinking speed, e) Pleasant feeling in body, and to decrease negative feelings: f) Anger and hostility. On the cigarette day, this effect was prevalent at nearly every cycle, this is particularly interesting on the cycles before a cigarette was administered (1 and 3). As such, this may represent a non-pharmacological effect of cigarette smoking.
Figure 3.22: Methadone and Nicotine share main effects

Figure 3.22: Methadone and nicotine had main effects to increase: a) Euphoria, b) Drug liking, c) Stimulant effects, and d) Pleasant bodily sensations. Data is shown for the cigarette day only, to clearly demonstrate the effect of nicotine and methadone.
Figure 3.23: Methadone and nicotine both decreased: a) Irritability, b) Restlessness, c) Depression, and d) anger/hostility. Data from the cigarette day only, to more clearly demonstrate the effects of methadone and nicotine.
Methadone and nicotine have main effects in the opposite direction for a) Increased thinking speed and b) Difficulty concentrating. Methadone had a negative effect on thinking capabilities while nicotine had a positive effect on thinking. Data from the cigarette day only, to clearly illustrate effects of nicotine and methadone.
Figure 3.25: QSU scores on the cigarette day. Nicotine but not methadone decreased craving for cigarettes on all subscales and composite scales of the QSU. a) Anticipation of positive outcomes, b) relief of withdrawal and negative effects, c) intention to smoke, d) desire to smoke, e) Factor 1 (positive outcomes related), and f) factor 2 (relief of negative affect related).
Figure 3.26: VAS scores on the cigarette day

(a) VAS - I Feel a Nicotine Effect

(b) VAS - I Feel a Good Nicotine Effect

(c) VAS - I Crave a Cigarette

(d) VAS - I Feel High

Figure 3.26: Cigarette day data for a) Nicotine effects, b) Good nicotine effects, c) cigarette craving, and d) Feeling high. Like QSU scores, only nicotine and not methadone was able to increased nicotine effects and feelings of highness and decrease craving.
Table 3.5: Methadone Effects: Repeated Measures ANOVA

<table>
<thead>
<tr>
<th>Measure</th>
<th>Cycle 1</th>
<th>Cycle 2</th>
<th>Cycle 3</th>
<th>Cycle 4</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased by Methadone</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARCI-MBG</td>
<td>3.5 (3.1)</td>
<td>4.2 (3.3)</td>
<td>5.6 (4.3)</td>
<td>7.0 (5.3)</td>
<td>0.001</td>
</tr>
<tr>
<td>ARCI-Amphetamine</td>
<td>3.2 (2.1)</td>
<td>3.4 (2.7)</td>
<td>4.3 (2.7)</td>
<td>4.9 (3.0)</td>
<td>0.002</td>
</tr>
<tr>
<td>POMS-Vigor</td>
<td>6.6 (5.1)</td>
<td>7.4 (4.8)</td>
<td>9.8 (5.9)</td>
<td>9.4 (5.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>POMS-Arousal</td>
<td>0.8 (9.9)</td>
<td>1.2 (8.8)</td>
<td>3.8 (11.9)</td>
<td>4.1 (8.4)</td>
<td>0.002</td>
</tr>
<tr>
<td>POMS-Positive Mood</td>
<td>-5.5 (9.4)</td>
<td>-4.6 (9.9)</td>
<td>-1.2 (9.4)</td>
<td>0.0 (7.9)</td>
<td>0.004</td>
</tr>
<tr>
<td>VAS-Increased Energy</td>
<td>26.1 (20.8)</td>
<td>37.5 (26.9)</td>
<td>42.6 (26.8)</td>
<td>45.1 (26.9)</td>
<td>0.001</td>
</tr>
<tr>
<td>Decreased by Methadone</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARCI-PCAG</td>
<td>8.0 (3.8)</td>
<td>7.9 (4.0)</td>
<td>5.5 (3.6)</td>
<td>5.1 (3.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ARCI-Sedation Motor</td>
<td>3.3 (2.8)</td>
<td>4.1 (3.0)</td>
<td>1.9 (2.6)</td>
<td>2.3 (2.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ARCI-Sedation Mental</td>
<td>5.6 (3.3)</td>
<td>5.9 (3.5)</td>
<td>5.0 (3.1)</td>
<td>4.0 (3.1)</td>
<td>0.004</td>
</tr>
<tr>
<td>ARCI-Unpleasantness Dysphoria</td>
<td>2.9 (2.0)</td>
<td>2.5 (2.1)</td>
<td>1.6 (1.9)</td>
<td>1.6 (1.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>POMS-Tension/Anxiety</td>
<td>9.9 (5.6)</td>
<td>9.3 (5.8)</td>
<td>8.2 (5.2)</td>
<td>6.8 (4.3)</td>
<td>0.013</td>
</tr>
<tr>
<td>POMS-Depression/Dejection</td>
<td>10.8 (7.9)</td>
<td>10.7 (9.4)</td>
<td>8.8 (8.3)</td>
<td>7.5 (7.1)</td>
<td>0.026</td>
</tr>
<tr>
<td>POMS-Fatigue</td>
<td>9.3 (7.0)</td>
<td>8.7 (6.0)</td>
<td>7.6 (6.3)</td>
<td>6.8 (5.0)</td>
<td>0.026</td>
</tr>
<tr>
<td>POMS-Total Mood Disturbance</td>
<td>37.6 (27.2)</td>
<td>35.2 (30.2)</td>
<td>27.9 (26.4)</td>
<td>22.1 (21.4)</td>
<td>0.004</td>
</tr>
<tr>
<td>VAS-Nausea</td>
<td>29.9 (26.5)</td>
<td>35.4 (28.7)</td>
<td>16.4 (26.2)</td>
<td>16.7 (23.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>VAS-Sick</td>
<td>33.8 (28.4)</td>
<td>31.3 (28.9)</td>
<td>18.4 (25.4)</td>
<td>17.1 (22.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>VAS-Frustrated</td>
<td>53.8 (28.2)</td>
<td>46.5 (30.7)</td>
<td>42.7 (30.3)</td>
<td>33.5 (31.3)</td>
<td>0.022</td>
</tr>
<tr>
<td>VAS-GI Disturbances</td>
<td>33.9 (31.0)</td>
<td>31.5 (31.8)</td>
<td>14.8 (24.3)</td>
<td>13.7 (20.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>VAS-Headache</td>
<td>25.5 (31.4)</td>
<td>27.1 (30.7)</td>
<td>25.7 (33.9)</td>
<td>20.2 (29.6)</td>
<td>0.017</td>
</tr>
<tr>
<td>VAS-Dizzy</td>
<td>24.2 (24.3)</td>
<td>33.5 (29.3)</td>
<td>16.4 (22.4)</td>
<td>18.3 (25.4)</td>
<td>0.002</td>
</tr>
<tr>
<td>VAS-Drowsy</td>
<td>52.8 (25.2)</td>
<td>49.4 (27.2)</td>
<td>46.3 (28.9)</td>
<td>43.1 (39.4)</td>
<td>0.043</td>
</tr>
</tbody>
</table>

Table 3.5: Example results where methadone increased or decreased scores on the various measures. ARCI = Addiction Research Center Inventory, POMS = Profile of Mood States, VAS = Visual Analog Scales
3.3.3 Pharmacokinetic Results

Methadone plasma concentrations were not different among study days with average trough concentrations of 320.4±224.2 ng/mL, 331.5±204.4 ng/mL, and 316.9±220.7 ng/mL on the cigarette day (cig), nicotine gum day (nic), and placebo gum day (pla), respectively. See figure 3.26. Peak methadone concentrations ranged from 70 ng/mL to 1280 ng/mL across the study days.

Nicotine plasma concentrations were significantly greater on the cigarette smoking day compared to both the active and placebo gum days both at cycle two (cig: 18.5±21.6 ng/mL vs. nic: 11.3±26.3 ng/mL vs. pla: 9.1±21.9 ng/mL) and at cycle four (cig: 23.4±28.0 ng/mL vs. nic: 11.8±15.5 ng/mL vs. pla: 7.1±12.9 ng/mL), p<0.001, see figure 3.27. There was a main effect of nicotine (cycle) on cotinine and hydroxylcotinine concentration with lower plasma levels during cycle 4 compared to cycle 2 (p<0.001 p=0.001, respectively).

![Figure 3.27: Methadone plasma concentration by study day. Cycle 2 is pre-methadone and cycle 4 is post-methadone. There were no differences between study days in methadone levels. Methadone levels were significantly greater in the post-methadone dose condition.](image)
Figure 3.28: Nicotine levels

a) Nicotine Plasma Concentration (ng/mL)

- **Cigarette**
  - Cycle 2
  - Cycle 4

- **Nicotine Gum**
  - Cycle 2
  - Cycle 4

- **Placebo Gum**
  - Cycle 2
  - Cycle 4

b) Utilizing the placebo gum day nicotine levels, estimates for cycles 1 and 3 were derived for the cigarette and active nicotine gum days. This is not meant to represent true values but rather to illustrate the accumulation of nicotine on the cigarette day in comparison to the active gum day.

Figure 3.28: a) Nicotine plasma concentration by study day. Cycle 2 corresponds to the cycle following the first nicotine administration and cycle 4 corresponds to the cycle following the second nicotine administration. There was a main effect of day, such that nicotine levels were greatest on the cigarette day. b) Utilizing the placebo gum day nicotine levels, estimates for cycles 1 and 3 were derived for the cigarette and active nicotine gum days. This is not meant to represent true values but rather to illustrate the accumulation of nicotine on the cigarette day in comparison to the active gum day.
Section 4: GENERAL DISCUSSION, CONCLUSIONS, & RECOMMENDATIONS

4.1 Major Depressive Disorder and Patient Satisfaction in Relation to Methadone Pharmacokinetics and Pharmacodynamics in Stabilized Methadone Maintenance Patients (Study 1)

In Study 1 the influence of depression and satisfaction with methadone treatment on methadone pharmacology was systematically investigated over one dosing interval. Depressed methadone maintenance treatment patients experienced more opioid withdrawal symptoms and increased dysphoric effects compared to nondepressed methadone maintenance treatment patients. This is consistent with documented negative impacts of depressive disorder on the course of other diseases and illnesses. Also, current depression has been associated with poorer methadone maintenance treatment outcomes. Therefore, it is possible that the effect of depression on methadone maintenance treatment is to contribute to a decrease in patients’ satisfaction with treatment, as reported by an increase in the perceived level of opioid withdrawal experienced. The significant correlation between depression severity (HAMD scores) and trough methadone condition withdrawal symptoms (SubOWS) supports this concept. As well, trend results showing higher withdrawal scores in currently depressed participants compared to those who are currently not depressed but have a past history of major depressive disorder lends further support. Specifically, the negative impact of major depressive disorder on methadone pharmacodynamics appears to be related to current negative mood symptomatology. It is also possible that depressed methadone maintenance treatment patients are more sensitive to negative experiences in general.
This is supported by our findings that depressed methadone maintenance treatment patients had more dysphoric effects over the dosing interval compared to nondepressed methadone maintenance treatment patients and that depression severity (HAMD scores) and the AUEC of a composite scale of negative ARCI subscales were significantly correlated.

Overall, our results may suggest that treating depressive symptomatology in methadone maintenance treatment patients with concurrent major depressive disorder may lead to better patient satisfaction with methadone treatment. Effective treatment of depression is particularly important as current depression prevalence rates in this population are 20% or more, and past 6 months depression prevalence rates are more than 40%.\textsuperscript{10, 11, 225} Prevalence estimates of current depressive symptomatology based on Hamilton depression scores are even higher (50%).\textsuperscript{226} Also, in a recent study by Schreiber et al, depression severity was shown to decrease over time in methadone maintenance treatment.\textsuperscript{227} A more recent study by Galynker et al. supports this using \textsuperscript{18}F]fluorodeoxyglucose positron emission tomography; they show that aberrant mood processing in the left perigenual anterior cingulate cortex and mid-cingulate cortex is present in opioid-dependent patients who are long-term abstinent but is absent in methadone maintained patients, suggesting that methadone treatment may improve mood regulation in methadone maintenance populations.\textsuperscript{228} Interestingly, a specific region of the anterior cingulate cortex, the subgenual cingulate region, has been targeted in deep brain stimulation for treatment-resistant depression.\textsuperscript{229} Since depressed patients in our study were stabilized in methadone treatment for an average of more than 1.5 years, yet still suffering significant depressive symptomatology (even with two on antidepressants);
it is likely that they would benefit from aggressive treatment of depressive symptoms which may impact positively on treatment satisfaction.

While there was no difference in depression severity (HAMD) between holders and nonholders, there was a trend towards increased negative mood on the POMS measures of depression and mood disturbance in nonholders. Surprisingly, there was not a detectable difference between holders and nonholders using the SubOWS. Nor were there any detectable differences between holders and nonholders on other pharmacodynamic measures studied. The likely reason for lack of pharmacodynamic differences was the small sample size in the nonholder group. In terms of opioid withdrawal, other factors are possibly involved. It is likely that a patient’s perception of withdrawal is comprised of a combination of physical and psychological withdrawal symptoms. The psychological symptoms associated with opioid withdrawal could have increased salience during an opioid substitution therapy treatment (e.g. methadone maintenance treatment) because physical withdrawal is minimized in this context.

Alternatively the method of subject self-report as a means to identify patient satisfaction groups may have limited the ability to detect differences between the groups. Many subjects considered their situation to be more complicated than a dichotomous categorization of being ‘held’ for a full dosing interval or not. It is possible that a more graded identification system that accounts for the complexity of opioid withdrawal would make it easier for patients to identify their current state. This was employed in Study 2 with the help of a guided self report screening process; subjects found this system to be more intuitive.
Although there were no detectable differences in pharmacodynamic measures between holders and nonholders, there were differences in the pharmacokinetics of unbound (S)-methadone between holders and nonholders. It is interesting that nonholders had higher unbound (S)-methadone exposure (C$_{\text{max}}$, C$_{24}$, C$_{ss}$, and AUC) compared to holders. (R)-methadone is considered the active isomer of methadone,$^{2, 49-52, 230}$ while (S)-methadone has been associated with limited opioid activity.$^{48, 50, 51}$ Mitchell and colleagues showed that (S)-methadone was associated with negative mood states and withdrawal.$^{53}$ It is plausible that negative mood states associated with increased exposure to (S)-methadone relates to patient dissatisfaction. Mitchell and colleagues also suggested that patients with an unfavourable subjective effects profile (i.e. unacceptable negative mood states) who have had more exposure to (S)- vs. (R)-methadone, may benefit by a change in treatment strategy (e.g. to a different opioid substitution therapy or to (R)-methadone instead of (R,S)-methadone), if available.$^{53}$ Evidence from Study 1 supports this. Poor satisfaction with treatment is often assumed to be related to the elimination rate of methadone in the individual. If this is the case, dividing the daily methadone dose may be appropriate. If however, poor satisfaction is related to increased exposure to (S)-methadone then alternate treatment options should be explored.

Unfortunately, the pharmacodynamic modelling did not produce results that could be used for comparison with other studies. There are many potential explanations for this. Since, patients were on their methadone dosage to steady-state the range of methadone plasma concentrations was limited. It is also possible that pharmacodynamic responses vary little over the dosing interval, particularly with stabilized patients. These conditions of flat pharmacokinetic or pharmacodynamic profiles were prevalent in data from Study
1. Dyer and colleagues have also had difficulty fitting steady-state data into this model. It is interesting that accounting for both enantiomer and protein binding, alone or together did not lead to a better fitting model.

The limitations of this study include the dichotomous classification system between holders and nonholders. This may have limited a subject’s ability to properly self-identify with one of the two groups. It may be that the ability to detect and respond to opioid withdrawal is sufficiently complex to warrant expanding the grouping criteria. A more even split between the holder vs. nonholder groups may have resulted in an increased power to detect differences. The fact that two of the seven patients in the depressed group were being treated with antidepressants is also a limitation. However, all depressed patients were currently symptomatic and those on antidepressants were at a steady-state condition, limiting the impact of antidepressant use on study findings. It is also worth noting that this was a preliminary study ($\alpha=0.1$) that was powered to detect differences among patients grouped based on both depression and holder status: nondepressed holders, nondepressed nonholders, depressed holders, and depressed nonholders. These groupings were not possible because of sample size constraints. Because of this and difficulty with the primary outcome modelling endpoints interpretations of the findings of Study 1 are based on secondary study outcomes and dichotomous grouping of patients. Multiple comparisons were made in this study, increasing the risk of Type 1 errors. Despite these limitations, findings from Study 1 are in agreement with findings from Study 2.
4.2 Opioid Withdrawal Scale Modification and Characterization of Between Dose Opioid Withdrawal and Patient Satisfaction in Methadone Maintenance Treatment (Study 2)

In Study 2 methadone maintenance treatment patients were characterized with respect to patient satisfaction with treatment. Many factors were able to differentiate methadone patients who self-identified as holders, partial holders and nonholders. Specifically, partial holders resembled holders on measures of opioid withdrawal, craving, pain intensity, drug liking (ARCI abuse potential), dysphoria, and unpleasant drug feelings. On the other hand, partial holders resembled nonholders on measures of psychological distress (globally, and specifically on obsessive/compulsive and anger/hostility subscales), negative mood (increased tension/anxiety, anger/hostility, confusion, depression/dejection, and decreased positive mood), and neuroticism. These separable dimensions (physical withdrawal vs. negative emotionality or intolerance for negative affect) help to explain the difficulties patients experienced when self-reporting as holders or nonholders in Study 1. Partial holders would find this particularly difficult: Although they may report equivalently low levels of physical withdrawal as the holder group, they may also be experiencing psychological distress and negative mood symptoms and thus still be dissatisfied with treatment. Findings from the NEO also revealed that partial holders were less open and less agreeable in general than both holders and nonholders, making partial holders more likely to express dissatisfaction with treatment compared to the other groups.
Whereas opioid withdrawal scores can be used effectively to distinguish holders from nonholders, they appear to be of less value in detecting partial holders from holders. This suggests that although physical opioid withdrawal is an important factor in understanding patient satisfaction with methadone treatment, other factors are also important, e.g. mood and psychological measures.

These mood and psychological factors may be particularly important, as there is a high prevalence of psychiatric comorbidity in methadone maintenance patients. Mason et al. showed that methadone maintenance treatment patients had an average of 2.3 current diagnoses, excluding drug abuse/dependence. Most common were phobic disorders (45%), antisocial personality (37%), any depressive disorder (32%), generalized anxiety disorder (32%), and obsessive/compulsive disorder (20%). Further, comorbid diagnoses are regularly associated with poorer treatment outcomes. The prevalence of agoraphobia (assessed with the MINI) was greater in nonholders and that the prevalence of current depression in partial holders and nonholders tended to be greater than that in holders. Depression in particular has been associated with poor methadone treatment outcomes.

Because partial holders resembled holders with respect to opioid withdrawal symptomatology, craving and drug liking, it is not surprising that clinicians may be suspicious of their complaints of dissatisfaction with treatment. Partial holders appear to have a lower threshold for tolerating these symptoms or functioning despite them. Assessing psychological and mood factors when objective indices do not support breakthrough withdrawal symptoms could provide a mechanism for validating patient
complaints. The brief screening guide developed for this study could be of utility when treating challenging patients.

It is interesting that current and average pain intensity scores were higher in the nonholder group compared to both the partial holders and holders. Comorbid pain is prevalent in methadone treatment patients (37-61%)\textsuperscript{231-233} and has been associated with more psychiatric disturbance, poorer health, increased medication use, and an increased likelihood for patients to perceive themselves as under-treated.\textsuperscript{232} It is possible that pain symptoms are enhancing perceived opioid withdrawal and contributing to patient dissatisfaction.

Pain has often been characterized as a signal detection phenomenon,\textsuperscript{234} whereby the stimulus (signal) has some objective intensity (e.g., 2\textsuperscript{nd} degree burn) and the patient has a response bias (criterion for reporting the signal) that may be conservative (disinclined to report it; ‘stoic’) or liberal (inclined to report it; ‘histrionic’). The present findings indicate that signal strength and response bias may similarly each contribute to the extent of relief patients receive from methadone treatment. Future studies could benefit by incorporating procedures from the pain literature to better operationalize the objective and subjective aspects of opioid withdrawal.

Study 2 results suggest that for a number of measures (sensory/affective pain, sedative drug effects, anxiety, psychoticism, fatigue, and arousal) patient satisfaction follows a continuum. Intuitively, one would expect this pattern (where partial holders fall between nonholders and holders) for many measures. It is noteworthy, that physical opioid
withdrawal did not follow this, providing further support that patient satisfaction with treatment is complex.

Treating psychological distress and negative mood symptoms in dissatisfied methadone maintenance treatment patients could lead to improved treatment satisfaction. It is possible that treating these symptoms in partial holders could improve their satisfaction with treatment and retention. Nonholders however, may derive less benefit, as it seems that physical opioid withdrawal and craving may play a greater role in patient dissatisfaction for them, although the measurable constructs that suggested patient satisfaction followed a continuum suggest that nonholders could derive some benefit, particularly on those constructs.

Based on the discriminant function analysis, the SubOWS (physical opioid withdrawal) and the NEO-Agreeableness Factor (agreeable personality) were the most capable of predicting patient satisfaction group membership. These results provide empirical support for the characterization of sub-groups based on both subjective symptom severity and on the tendency to tolerate sub-optimal relief.

A limitation of this study was measuring the various factors only near the trough methadone condition. It is possible that interesting differences would have been detected during the peak methadone condition, when physical opioid withdrawal is minimal. Utilizing a non-validated screening tool to assign patient grouping was a limitation, however the results suggest that the screening tool supported groupings that were distinct on many measures. The patient population in this study was heterogeneous with reasonably high levels of comorbid psychiatric disorders and positive urine drug screens.
While there were few differences amongst the patient satisfaction groups on these measures, there were noted differences in rates of agoraphobia and depression. This may have had an impact on study results. The data analysis strategy for this study called for multiple multivariate analyses. While the sample size in this study was large, from the perspective of logistics and feasibility, it was not sufficiently large to make all of the multiple comparisons in one MANOVA. As such, data was reduced using groupings based on logical conceptual associations. There are inherent limitations to self-reported data; some patients may respond inconsistently. However, this study was primarily focused on patients’ perceptions and therefore self-report is an appropriate tool for these assessments.

4.3 Methadone-Nicotine Interactions in Stabilized Methadone Maintenance Treatment Patients (Study 3)

Study 3 was an investigation of interactions between methadone and nicotine during withdrawal and agonist effect conditions of each drug. It was found that mixed interactions, where agonist effects of one drug interacted with withdrawal effects of the other occurred, specifically, on the cigarette day, nicotine enhanced opioid withdrawal suppression (figure 4.1, box 3) and methadone attenuated nicotine withdrawal (figure 4.1 box 2). Methadone and nicotine shared many of the same main effects (figure 4.1, box 1), specifically to increase positive drug effects/feelings (e.g. ARCI-stimulation-euphoria, ARCI-stimulation-abuse potential (liking), and VAS-pleasant bodily sensations) and to decrease negative drug effects/feelings (e.g. VAS-restlessness, VAS-irritability, ARCI-
unpleasantness-physical, and POMS-anger/hostility). Also, methadone and nicotine had opposing main effects for thinking speed and difficulty concentrating (figure 4.1 box 1). A possible non-pharmacological effect of cigarette smoking was detected, with patients reporting increased positive feelings (e.g. POMS-friendliness, POMS- elation, and VAS-pleasant feeling in mind) and decreased negative feelings (POMS-anger/hostility) on the smoking day even prior to receiving a cigarette, non pharmacological effects of smoking could interact with agonist or withdrawal effects of methadone (figure 4.1 boxes 1 and 3). Together the results could help to explain the high smoking prevalence rates in methadone patients\textsuperscript{13-18} and may account for methadone patients reporting increased positive effects when they take both drugs together.\textsuperscript{164}

Figure 4.1: Potential interactions between methadone and nicotine

<table>
<thead>
<tr>
<th>Nicotine Agonist Effects</th>
<th>Methadone Agonist Effects</th>
<th>Nicotine Withdrawal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methadone (+) Nicotine (+)</td>
<td>1.</td>
<td></td>
</tr>
<tr>
<td>Methadone (-) Nicotine (+)</td>
<td>2.</td>
<td></td>
</tr>
<tr>
<td>Methadone (-) Nicotine (-)</td>
<td>3.</td>
<td></td>
</tr>
<tr>
<td>Methadone (-) Nicotine (-)</td>
<td>4.</td>
<td></td>
</tr>
</tbody>
</table>

Figure 4.1: Repeat of Figure 1.2: Model representing potential interactions between methadone and nicotine. The (+) sign represents agonist effects present; the (-) sign represents withdrawal effects present. There can be additive/synergistic interactions (boxes 1 and 4), or mixed interactions with agonist effects of one drug interacting with withdrawal effects of the other (boxes 2 and 3).
Mixed agonist effects/withdrawal effects interactions are of particular interest; with the potential for one drug to alleviate withdrawal associated with the other drug. Cigarette smoking was able to attenuate opioid withdrawal during the peak methadone condition. This supports the finding of Spiga et al. suggesting that methadone is a more effective reinforcer when tobacco smoke is concurrently available. Methadone attenuated nicotine withdrawal on the cigarette smoking day. Richter et al. reported that methadone patients who smoke, smoke the most frequently from the time of their methadone dose until four hours afterwards, regardless of the time of methadone administration; and that variability in smoking pattern is decreased in methadone patients who smoke compared to regular smokers. It is possible that methadone’s ability to attenuate nicotine withdrawal plays a role in reducing variability associated with smoking patterns and in the development of a characteristic smoking pattern in methadone maintenance treatment patients. It is also possible that for methadone patients, increased positive effects of methadone, mediated by cigarette smoking, leads to a greater drive to smoke than the drive associated with alleviating nicotine withdrawal, specifically at the peak methadone condition. It is interesting, that nicotine withdrawal but not tobacco craving, QSU scores and VAS-craving, was affected by methadone. Specifically, there was no effect of methadone on the QSU subscale related to the anticipation of positive outcomes from cigarette smoking. If the signature smoking pattern in methadone patients is related to increased positive effects, it is possible that methadone-maintained smokers would have a greater score on this subscale compared to regular smokers.

There was a significant effect of sex, such that women reported significantly more opioid withdrawal and nicotine withdrawal, particularly during the trough methadone condition.
Sex differences did not influence study findings related to opioid and nicotine withdrawal. This is not supported in the literature, although there are some animal studies that suggest sex differences: In rats, μ-opioid agonists have lower efficacy in females, in mice males develop greater physical dependence.\(^\text{235, 236}\)

There was no effect of holder status on study outcomes. This suggests that methadone-nicotinic interactions identified in Study 3 are present in all types of methadone maintenance treatment patient and that smoking may play an important role in stabilized methadone treatment regardless of satisfaction level with treatment.

It is possible that the non-pharmacological effects noted for cigarette smoking were related to an expectancy to smoke. The smoking day was not part of the blinding process, and as such subjects knew they would be smoking a cigarette directly after responding to the questions during the pre-nicotine cycles. In an fMRI study, expectancy has been associated with brain activation in anterior cingulate cortex, posterior cingulate cortex, dorsomedial prefrontal cortex, dorsolateral prefrontal cortex, medial orbital frontal cortex, anterior insula, superior temporal gyrus, ventral pallidum, and dorsomedial thalamus (areas associated with arousal, attention, and cognitive control) following the presentation of smoking cues; this was not seen when subjects did not expect to smoke, despite the fact that under both conditions self-reported craving scores were similar.\(^\text{237}\)

It was expected that behavioural effects of cigarette smoking would be detected by comparison with the nicotine gum day. However, there were no differences between the placebo gum day and active gum day. Further both placebo and active gums did not decrease cigarette craving. It has previously been reported, that both placebo nicotine
gum and 4-mg nicotine gum were able to decrease smoking craving equally, however, both were administered serially for four hours. There were no differences in nicotine levels between the active and placebo gum days, this could account for the lack of effect of nicotine gum.

NOSIE results suggested that study participants believe that drug use increased their smoking rate but that smoking didn’t alter their use of drugs. They also reported that they do not smoke to cope with urges to use drugs and that smoking cessation treatment and methadone maintenance treatment are not necessarily incompatible goals. These results are in agreement with the results of Stein et al. Results from Study 3 do support the concept that methadone use leads to increased smoking and could be related to an enhancement of positive effects when the two are combined, as discussed previously. It is interesting that subjects did not believe that smoking influenced their use of methadone. It is possible that this is more difficult to report because their use of methadone is very structured (same dose daily at roughly the same time). Results from Spiga et al. suggested that nicotine can influence methadone self-administration. Had these been an opioid abusing population different results may have been noted. Although patients did not believe that smoking helped to attenuate craving during opioid withdrawal the results of Study 3 do not support this. Specifically, nicotine/smoking effects seem to be minimizing urges for opioids as many of the main effects of methadone and nicotine were similar and because smoking enhanced opioid withdrawal suppression.
It is not surprising that patients believed that smoking cessation and methadone maintenance treatment were possible simultaneously, as there is a high level of interest in smoking cessation among methadone patients. In one study, methadone patients had lower nicotine dependence scores and had greater interest in smoking cessation compared to active opioid abusers. There is also evidence that methadone treatment is associated with positive changes in smoking behaviour. Methadone patients reported smoking fewer cigarettes per day, and choosing cigarette brands with lower nicotine content after starting methadone treatment. However, they may have compensated for decreased nicotine content by inhaling smoke more deeply or smoking more of the cigarette. These positive changes in methadone patients compared to active opioid abusers suggest that they may be more responsive to smoking cessation strategies. Because of the very high smoking rates and the fact that smoking is a major predictor or morbidity and mortality in methadone maintenance patients smoking cessation could lead to significant health improvements in this population. There have been trials to evaluate smoking cessation strategies for patients in opioid substitution therapy utilizing different behavioural and pharmacotherapeutic options. Results have shown negative results or modest success in smoking cessation rates. Recently, Mooney et al. noted that there continues to be a deficiency of evidenced-based smoking cessation treatment options in opioid-dependent individuals.

Tailoring smoking cessation strategies for methadone maintenance treatment may be beneficial based on Study 3’s findings. Certainly, both methadone and nicotine have similar main effects, this suggests that during times of peak methadone condition their influence on each other is greatest, this again supports patients’ self-report of using both
drugs to enhance methadone pleasing effects. In terms of nicotine replacement therapy (NRT), it would be important to account for this, and plan for maximal coverage during this timeframe. Identification of the interactions between methadone and nicotine is also important in the sense that they provide education targets, so that patients could be made aware of what to expect and so that they could prepare themselves and develop coping strategies. Because methadone attenuated nicotine withdrawal, it could be particularly detrimental to introduce methadone dosage reductions during smoking cessation/reduction attempts. Richter et al., suggest that nicotine directly affects not only the reinforcing effects of methadone but perhaps the therapeutic value of methadone and hence it is possible that nicotine could play an important part of the stabilization of methadone maintenance treatment. In fact a significant percentage of methadone clinic leaders believe that smoking in some way benefited a patient’s methadone treatment. Interactions reported here provide potential mechanisms through which nicotine could have these effects. Hence, it could be particularly difficult for methadone maintenance patients who smoke to quit smoking, as nicotine could be playing a role that is central to their methadone treatment outcomes. At the same time, if the interactions reported here are involved in the stabilization of methadone treatment for some patients, then it may be prudent to monitor methadone treatment outcomes during smoking cessation attempts.

The limitations of this study include the minimal effect of the nicotine gum. It was not possible to attribute interactions to nicotine derived from the nicotine gum as it did not differ from placebo with respect to the various subjective measures and plasma levels. As such, nicotine effects were driven by the cigarette-smoking day. Another limitation was the modest effect size compared to the variability in many nicotine effect measures.
It is important to note, that while modest, effects were consistent throughout the data. It is not surprising that nicotine effects were modest, considering that they were based on smoking one cigarette. Another limitation of this study was the difference in smoking or nicotine abstinence time prior to testing at the trough and peak methadone conditions. Patients were required to abstain from smoking for 12 hours before the testing cycles during the trough methadone condition and only for three hours before the testing cycles during the peak methadone condition. This suggests that patients may have experienced differential smoking abstinence effects during the pre-nicotine conditions. This was minimized because patients had only a minimal exposure to smoking or nicotine prior to the testing during the peak methadone effects condition and because QSU and other craving measures were similar both pre and post cigarette administration during the trough and peak methadone conditions. With a sample size of 40 subjects and three between-subjects factors (sex, holder status, and order of nicotine administration) it is possible that there was insufficient power to detect the impact of these factors.

4.4 Overall Discussion and Conclusions

Results from Study 1 suggest that nonholder methadone patients have increased exposure of (S)- vs. (R)-methadone. This supports the concept that differences between holder and nonholder methadone maintenance patients is related to pharmacokinetic differences and further supports the emerging concept that (S)-methadone may be responsible for the negative effects associated with methadone treatment. Findings have also shown that depressed methadone maintenance patients are more sensitive to negative opioid effects.
Specifically, they report increased levels of opioid withdrawal and dysphoria. These findings suggest that identification and treatment of depression in methadone maintenance populations could lead to improved satisfaction with methadone treatment.

Results from Study 2 suggest that patient satisfaction with methadone maintenance treatment is complex and that some patients do not fit into a dichotomous holder/nonholder grouping system. Partial holders resemble satisfied patients when assessing opioid withdrawal, craving, drug liking, and pain intensity while at the same time they resemble dissatisfied patients with increased psychological distress, negative mood and neuroticism. As suggested earlier, it is possible that treating psychological distress and negative mood in methadone maintenance patients could lead to improved satisfaction with treatment. The brief patient satisfaction screening guide developed for this study could facilitate this. Also, the brief screening guide could have research utility in studies evaluating methadone treatment outcomes. Overall, the results suggest that although physical opioid withdrawal symptoms are an important factor in assessing patient satisfaction with treatment, the ability or willingness to tolerate these symptoms are also important considerations in patients in methadone maintenance treatment.

Study 3 shows that interactions between agonist and withdrawal effects of methadone and nicotine occur, specifically by attenuating withdrawal states associated with each other and by increasing positive effect/feelings and decreasing negative effect/feelings. Not only nicotine effects but also behaviours associated with cigarette smoking appear to mediate these interactions. These interactions may constitute an important component of stabilized methadone maintenance treatment. Studying interactions between methadone
and nicotine/smoking can be of utility in advising smoking cessation strategies that are tailored to methadone maintenance treatment patients.

Findings from Study 1 did not support the idea that nonholders have faster maximum rates of decline in methadone plasma concentrations than holders, as suggested by Dyer et al. The finding that (S)-methadone exposure was greater in nonholders in Study 1 supports the concept that pharmacokinetics can explain the differences between holders and nonholders. At the same time, findings from Study 1 and particularly Study 2 suggest that depression, psychological distress and negative mood states are also important in explaining differences between holders and nonholders. In Study 1, there were no reported differences between holders and nonholders for any pharmacodynamic measures, including opioid withdrawal; however, there was a trend to greater depression/dejection and negative mood disturbance on the POMS. As discussed previously, this is likely a result of the small sample size in the nonholder group in Study 1. However, it supports the findings in Study 2 that suggest that negative mood states could have an impact on patient satisfaction and opioid withdrawal perception. Overall, it would seem that patient satisfaction with methadone maintenance treatment can be related to pharmacokinetic and pharmacodynamic differences between those satisfied and those dissatisfied with treatment. These factors could be acting separately or together depending on the individual thus making it difficult or challenging to treat dissatisfied patients.

A model to explain how the three studies presented above align with the overall hypothesis of this work is presented in figures 4.2 and 4.3. In figure 4.2a the overall
hypothesis is presented and figure 4.2b explains where the individual studies fit into the model. In figure 4.3 a revised model is presented; revisions to the model are based on study findings.

The co-occurrence of depression and smoking or nicotine dependence in methadone maintenance patients is not surprising based on the prevalence rates of both conditions alone in the population. Clinicians would likely have different opinions on how to best to treat a methadone patient who presents as depressed and interested in quitting smoking. In a study by Stein et al. the association between depression and success in smoking cessation efforts was studied.\textsuperscript{245} They found that depressed patients were less likely to set a quit date, however there were no differences in motivation to quit smoking.\textsuperscript{245} In another recent study, Wapf et al. examined barriers to smoking cessation in methadone and buprenorphine maintained individuals in Switzerland.\textsuperscript{246} Interestingly, they found that a diagnosis of depression was associated with readiness to quit smoking.\textsuperscript{246} Based on these findings, it would seem that initiating smoking cessation therapy in methadone maintenance treatment patients suffering from concurrent depression would be beneficial.

Variability in the acute response to psychoactive medications is well accepted. It is possible that variability in expectancy of drug effects contributes to this. There are well documented effects from placebo administration in the pharmacotherapy of depression; generally it is accepted that 50\% of depressed patients show placebo-associated improvements in antidepressant clinical trials.\textsuperscript{247} Placebo-associated improvements are more pronounced in the treatment of depression compared to other psychiatric disorders which may be linked to high levels of psychological distress and insight in depressed
patients. An fMRI study has shown that placebo treatment in depressed patients was associated with the activation of the limbic system, prefrontal cortex, and ventral striatum; regions that were activated with fluoxetine treatment. These activated regions are associated with anticipation and reward. Placebo response in depressed patients is not limited to antidepressant medications. In experimental studies of dextroamphetamine effects, placebo responses were greater in depressed patients compared to controls. Both Study #1 and Study #2 included depressed participants. It is possible that robust placebo responses seen in depressed participants in general may account for a component of the variability in responses seen in these studies. Study #3 was the only study that utilized a placebo control. Denicotinized cigarettes have been associated with smoking effects and a reduction in nicotine withdrawal and craving. Also, in methadone maintained patients, acute administration of active nicotine gum (4 mg every 30 minutes for 4 hours) or placebo was associated with equivalent decreases in craving for nicotine. In Study #3 the response to placebo and active nicotine gum were not different. However, there were differences noted compared to the cigarettes smoking day. Specifically, there was an expectancy effect associated with cigarette smoking that was noted on the cigarette day during the pre-cigarette administration conditions.

Methadone has had tremendous success and acceptance in the more than 40 years that it has been used. Nonetheless, new challenges for treatment have arisen. Patients are both younger and older than ever before. The younger patients, bring high rates of comorbid substance abuse, as well as the cognitive and emotional dynamics of youth and early adulthood into the clinics. Older patients are a great testament to the success of long term methadone treatment. However, at the same time, older methadone patients suffer
from the same ailments as other elderly individuals, adding to the challenge of treating elderly or geriatric patients in methadone treatment.\textsuperscript{5, 257, 258} As well, methadone patients have a high prevalence of depression and anxiety: Marion estimates that 60\% of the patients treated in his New York clinic have treatable depression or anxiety, a number that is much greater than seen previously.\textsuperscript{5} Regardless of whether this estimate is high, or whether the increased prevalence noted is due to better detection systems, findings from the studies presented here suggest the importance of treating these ailments. The prevalence of dissatisfaction with methadone treatment among patients ranges from more than one third to more than one half\textsuperscript{7}; this is clinically unacceptable; improving this through the treatment of mood and psychological factors and/or the switching of patients to an alternate opioid substitute (i.e. buprenorphine) as appropriate perhaps should be one of the next targets set for the improvement of MMT in the future.
Figure 4.2: a) Model representing the overall hypothesis proposed. Pharmacokinetics, comorbid psychiatric disorders and drug interaction were identified as factors influencing the relationship between methadone effects/withdrawal and patient satisfaction with treatment.

b) Emphasis (in red) of how Study #1 fits with the overall hypothesis. Study #1 examined the influence of pharmacokinetics and major depressive disorder on methadone effects and opioid withdrawal, their relationship with satisfaction with methadone treatment, as well as, satisfaction with treatment directly.
Figure 4.2: c) Emphasis (in red) of how Study #2 fits with the overall hypothesis. Study two was an investigation of opioid withdrawal, patient satisfaction and the relationship between them. d) Emphasis (in red) of how Study #2 fits with the overall hypothesis. Study #3 examined the influence of smoking on methadone effects and opioid withdrawal.
Opioid withdrawal is composed of more than physical opioid withdrawal symptoms. Study two has demonstrated that psychological factors have impact on perceived opioid withdrawal, with many mood, and psychological distress factors differentiating the opioid withdrawal based patient satisfaction groups. Patient factors seemed to have direct impact on satisfaction with treatment and perceived opioid withdrawal. Specifically, a number of personality related factors, neuroticism, agreeableness, and openness were able to differentiate patient satisfaction groups in different ways. It is unclear if these patient factors are impacting on how methadone effects are perceived. However, this is likely, hence its placement in the model with a dotted line.
4.5 Clinical Significance

To illustrate the clinical implications of these studies the following hypothetical case; which deals with the treatment of a challenging methadone maintenance treatment patient is presented. This case highlights some of the research results presented in this thesis, which could have clinical impact.

Case:

A 41-year-old methadone maintenance treatment patient comes for her first visit at your clinic. Her file indicates that she has been on methadone continuously for the last 8 years. She is on a dose of 100mg/day and has been on that dose for the last 2 years. She complains that her dose is not holding her. When asked to elaborate, she complains of a consistent lack of motivation, and an overall feeling of unpleasantness and uneasiness. Her file indicates that she has made this complaint (not holding) regularly throughout her methadone treatment. Blood samples were obtained for pharmacokinetic assessment of elimination rate of methadone, utilizing the ratio of methadone to EDDP (metabolite). Her results were in the expected range. Her file also notes that her previous physician had assessed her complaints of opioid withdrawal with a self-report measure known as the Subjective Opioid Withdrawal Scale (SubOWS) on a few occasions. When questioned about illicit opioid use, she denied using any. Her urine screens were negative for opioids but positive for cocaine (30% of the time). Based on the withdrawal and pharmacokinetic assessments her physician has concluded that her complaints are unfounded. She is a regular cigarette smoker, who smokes 25 cigarettes/day. She consistently takes her methadone dose between 9:00AM and 11:00AM every day.
Discussion:

It seems that her previous physician was willing to explore her complaints, with the opioid withdrawal and pharmacokinetic assessments. However, when the results showed low SubOWS scores and that her methadone/metabolite ratios were indicative of a normal methadone elimination rate, the physician decided the patient was not experiencing opioid withdrawal and perhaps was not being truthful. The lack of opioid in her urine screens affirmed for her previous physician that the methadone was effective.

Applied Lessons

We could try increasing her dose; however she is on a reasonably high dose already (100mg/day) and is not experiencing opioid withdrawal symptoms according to the SubOWS. We ordered a pharmacokinetic assessment of the patient, as we know that methadone/metabolite ratios are a poor estimate of elimination rate and that a fast elimination rate itself would not necessarily relate to a patient being a nonholder. We are specifically interested in exposure to unbound (S)-methadone relative to (R)-methadone. We know that increased exposure to (S)-methadone (determined with (S)-/(R)-methadone ratios) has been associated with aversive methadone effects, negative mood states, and has very recently been linked to dissatisfaction with methadone treatment. (S)-/(R)-methadone ratios were normal. We decide that the patient complaints are not related to pharmacokinetics of methadone. Fortunately, we are experienced with opioid withdrawal literature and assessment tools and know that the SubOWS used by the original physician, while a reliable scale, is strongly based on physical symptomatology and may not be sensitive to opioid withdrawal in the context of methadone maintenance because
we understand that perceived opioid withdrawal is likely a combination of physical withdrawal (what the SubOWS measures) and psychological withdrawal (factors that influence perceived withdrawal and treatment satisfaction). We decide to try our newly developed guided self-report screening process that was designed to help characterize methadone patients based on opioid withdrawal and treatment satisfaction. The patient is screened and classified as a partial holder. We know that partial holders appear to be similar to holders with respect to normal satisfaction signals (opioid withdrawal, craving, drug liking). This makes it difficult for any physician to explain treatment complaints in partial holders. We also know that partial holders have significant differences from holders in terms of negative mood and psychological distress. We note her complaints of negative mood and suggest that she be screened for various psychological disorders or symptoms and treated appropriately, as we know that treating symptoms of depression or other psychopathologies may lead to improved satisfaction with methadone treatment.

We note that she is a regular cigarette smoker and because we have heard of a recent report that there can be significant interactions between nicotine/smoking and methadone, including the possibility that methadone-nicotine interactions are part of stabilized methadone treatment for methadone patients who smoke. We then ask her if she has changed smoking habits lately. She informs us that she has been smoking a little more than one pack per day for at least the last 10 years and that she smokes most frequently in the morning with an increasing rate until between 11:00 AM and 1:00 PM. She estimates that she smokes about half of her daily total of cigarettes by two hours after ingesting her methadone dose. She indicates that she is interested in quitting smoking, or at least reducing her smoking. Her smoking schedule is not unusual for a methadone patient;
hence she may be smoking with great frequency in an attempt to alleviate opioid withdrawal until she takes her dose and then she smokes to maximize the effects of methadone. We can ask her if she has started to take any new medications that may be interacting with nicotine to minimize its effects, however, we do not expect that this is the case, as she has made regular complaints of not holding throughout her methadone treatment, she is not taking any new medications. To help guide her smoking cessation attempt, we inform her that from the time that she wakes up until a few hours after her methadone dose she is most vulnerable to interactions between methadone and nicotine. She should have a treatment schedule with maximum coverage of nicotine replacement therapy specifically during that time. It will also be important to regularly assess her methadone treatment progress and satisfaction as her smoking/nicotine intake reduces. With a loss of the usual methadone-nicotine interactions that influence her stabilized methadone treatment, adjustments may need to be made.

4.6 Recommendations

A study to examine the effect of treating depression or depressive symptoms in methadone maintenance treatment patients is a logical progression from results of the methadone/depression study (Study 1). Positive results from such a study would have profound treatment implications. Results also suggest that a more thorough examination of (S)-methadone pharmacokinetics and patient satisfaction with treatment should be undertaken. Confirmation of Study 1 findings with a larger sample size would be a good initial plan. If such confirmation occurs, it may be of benefit to investigate what
percentage of patient dissatisfaction with treatment is related to (S)-methadone exposure and how holder status (nonholder/partial holder) is associated.

It would be interesting to conduct a study with similar design to Study 2, except to investigate differences in patient factors during the peak methadone condition. It is possible that differences would have been detected during the peak methadone condition, when physical opioid withdrawal is truly at its minimum. As with the first study, results from Study 2 suggest that treating factors other than opioid withdrawal (negative mood and psychological distress factors) could lead to improved treatment satisfaction with methadone treatment. A treatment study to investigate if this is the case would be valuable. This sort of study could be coupled with a study investigating the treatment of depression on patient satisfaction (mentioned above). Results indicate that separating patients based on the guided self-report screening process was successful, further validation of this process as a screening tool would be of clinical utility. Nonetheless, it would still be useful to develop an opioid withdrawal scale tailored to suit the context of opioid substitution therapy. It would be important to develop a scale from first principles using established scale development techniques. Ideally, a novel opioid withdrawal scale would be multi-factored with physical opioid withdrawal symptoms making up only a portion of the overall scale score. A multi-factor opioid withdrawal/patient satisfaction scale would be helpful in better characterizing the partial holder group by helping to identify specific targets for treatment. As well, it would allow opioid withdrawal to be measured over a continuum rather than by category, as the screening process does.
The methadone-nicotine interaction study investigated the interaction with minimal nicotine exposure, one cigarette or 4mg of nicotine gum on two occasions each study day. It would be important to do a similar study with a greater exposure to nicotine. Smokers smoke to satiation, therefore studying methadone-nicotine interactions under satiated conditions would better approximate what is happening clinically. Specifically, one may expect to find more robust and more significant findings from such a study to confirm and extend results from Study 3. The study could follow methadone maintenance treatment patients from induction until they are stabilized, specifically monitoring smoking patterns as this could help to explain the high prevalence rates and to decide whether the prevalence rates are related to being opioid dependent or if methadone treatment is actually increasing smoking. Recent studies suggest that patients on methadone have a different smoking pattern than regular smokers, specifically they smoke most at the time of their methadone dose and the most important cigarette of the day for them is the one directly after the methadone dose, not the first in the morning as is the case with regular smokers. Following methadone patients as they start treatment could confirm these observations.

Buprenorphine offers avenues for further studies also. Since not holding in methadone treatment may be related to (S)-methadone exposure as suggested in Study 1, switching patients with unfavourable (S)/(R)-methadone ratios would be a logical step following the replication of study findings reported in this thesis and by Mitchell et al. Also, findings from Study 2 may not extend to buprenorphine maintenance therapy, a similar study to this could help to elucidate if mood and psychological factors are an important component in buprenorphine therapy. Dissatisfaction with buprenorphine treatment has
been reported at nearly comparable levels to those reported in methadone maintenance
treatment. Because buprenorphine is a partial agonist, it is not known if dissatisfation
with treatment is related to inability to treat very high levels of opioid dependence or if
other factors identified in this thesis could be playing a role.

4.7 Final Comment

Although methadone maintenance treatment has been around since the mid-1960’s with
documented effectiveness, not all patients are treated to satisfaction. Now more than four
decades have passed and new issues with methadone maintenance are being raised.
Results from this thesis suggest potential mechanisms to optimize and individualize
methadone maintenance treatment that with future study could become treatment
realities.
5.0 REFERENCES


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6.0 PUBLICATIONS

Refereed Papers


Under Internal Review


Abstracts


7. Sproule, B., Elkader, A. First exposures in prescription opioid abusers. 69th Annual scientific meeting of the College on Problems of Drug Dependence, Quebec City, Quebec. June 16-21, 2007. (Poster)


Appendix 1

Patient Informed Consent Form: Study 1
Study Name: “Influence of Major Depressive Disorder on the Pharmacokinetic Pharmacodynamic Relationships of Methadone’

Principal Investigator: Dr. B. Sproule
Co-investigators: Dr. B. Brands
Dr. E. Dunn
Dr. P. Selby
Study Coordinator: Alexander Elkader

This study will take place at the Centre for Addiction and Mental Health 33 Russell Street site under the supervision of Dr. B. Sproule. This project is part of the M.Sc. thesis of Alexander Elkader, under the supervision of Dr. B. Sproule. There will be 20 people taking part in this study.

You are being asked to participate in this study because you have been in methadone treatment for at least 6 months and on the same dosage for the past 2 months. We are interested in studying methadone effects and how the body handles methadone. Study participants will be classified into one of four groups for comparison purposes:

1. Patient doing well on methadone.
2. Patients experiencing withdrawal symptoms while on methadone.
3. Patients who are experiencing depressive symptoms and doing well on methadone.
4. Patients who are experiencing depressive symptoms and experiencing withdrawal symptoms while on methadone.
The study procedures are the same regardless of which group you are in. Please take the time to read this information sheet carefully and ask any questions that you may have before deciding whether you wish to participate in this study.

**Study Medications**

You will not be asked to take any medications other than your regular daily dose of methadone. You should continue to take any medications that you are currently prescribed.

**Purpose of the Study**

The purpose of this study is to get a better understanding of the relationship between the effects of methadone and how the amount of methadone in your blood changes over the course of a day. This may be important in explaining why some people still feel withdrawal symptoms while on methadone. In addition, we think that people with depression may experience methadone effects differently. This study is designed to help determine if this is true and how it might relate to methadone blood concentrations.

**Procedures**

This study will involve one assessment session that will take approximately 3 hours, one study session that will last 13 hours and one brief (1 hour) session the next morning.

At the assessment session you will be asked a number of questions to determine your eligibility for the study and to determine to which group you belong. You will also
be asked to provide a urine sample for toxicological screening. This will be used to
determine eligibility for the study only, and will not be disclosed to clinic staff. This
assessment will include questions about:

- demographics (e.g., your age, education, occupation)
- your past and present drug use
- current medications
- your treatment with methadone (we will confirm your current methadone
dosage and duration of time at this dose with your dispensing pharmacy)
- withdrawal symptoms over the previous 24 hours
- your previous treatments
- psychiatric symptoms and history (this will be a fairly long structured
  interview). If a diagnosis of current depression is made, your treating
  physician will be informed.

For the study session, you will be asked to arrive at CAMH, one hour before you
usually take your daily dose of methadone. If you have carry privileges you will be asked
to bring your dose for that day with you. Please note that you will also be required to
avoid alcohol, coffee and all sources of caffeine from 12 hours before the study session
until the testing is completed. A urine sample for toxicology screening and a breathalyzer
test will be administered when you arrive. Your meals will be provided during the study
session.

Over the course of the day you will be asked to provide urine and blood samples,
to complete a number of tasks and to answer a number of questions. The first set of
testing will be done before you take your methadone dose, then the testing will be spaced
out over the next 12 hours. You will then go home for the night and return the next morning for the final set of testing before you take your methadone dose again. A urine sample for toxicology screening and a breathalyzer test will be administered again at that time. You will be asked to:

- provide blood samples (2 teaspoonsful each) a total of 13 times (total amount is 130 mls of blood, which is less than half of a regular red cross donation). A catheter will be inserted with the first blood sample (when you arrive) and removed after the 12-hour blood sample. The 24-hour blood sample will be taken by venipuncture (with a regular needle).
- provide urine samples a total of 7 times over the course of the study session.
- have your vital signs monitored at the same times as the blood samples are taken (for example, your breathing rate and heart rate).

The following will each be repeated 11 times over the study session. You will:

- have your pupil size measured using a special camera.
- complete 2 computer tasks: one asks you to replicate box patterns on the screen, and the other has you track a computerized airplane over a moving road. (4 mins)
- complete a series of questions on the computer about how you are feeling. (20 mins)

After the final testing session the next morning, you will be finished the study and be able to take your next regular methadone dose.
Risks and Discomforts

There is little risk associated with this study. The main risk would be associated with the blood draws, although this is generally a safe procedure. Slight bruising, pain or inflammation is possible.

Benefits

There are no direct benefits to you for participating in this study. The findings of this study may be helpful in understanding the relationships between methadone dose, methadone concentrations in the blood and methadone effects. This could lead to the development of more effective dosing strategies for methadone.

Compensation

As payment for your participation you will receive $150.00 dollars at the end of the study.

Voluntary Participation

Your participation in this study is completely voluntary and you can withdraw from the study at any time and for any reason. If you decide to withdraw from the study, this will not affect your current or any future care at the Centre for Addiction and Mental Health in any way. The investigators may terminate your involvement in the study at any time. This could be due to medical reasons or for not following study procedures.
Confidentiality

Your identity will be kept strictly confidential to the full extent provided by the law. All information collected during the course of this study will be kept secure and confidential and will only be made available to the researchers in this study. The data will be identified by your initials and a code number only, and not by your name. Published reports and presentations at scientific meetings will refer to only a code number or grouped data, and not a name or initial.

If you are not a client of the CAMH methadone maintenance treatment program, you will be required to sign a Form 14 for your dispensing pharmacy, so that we can confirm your methadone dose. As well, you will be required to sign a Form 14 for your treating physician, if a diagnosis of depression is made. Your confidential information will not be discussed with anyone outside of the study personnel.

As part of continuing review of the research, your study records may be assessed on behalf of the Research Ethics Board and, if applicable, by Health Canada Therapeutics Products Programme. A person from the research ethics team may contact you (if your contact information is available) to ask you questions about the research study and your consent to participate. The person assessing your file or contacting you, must maintain your confidentiality to the extent permitted by law.
Informed Consent

I, ____________________________ have read (or had read to me) the information sheet for the study “Influence of Major Depressive Disorder on the Pharmacokinetic-Pharmacodynamic Relationship of Methadone”. The purpose of this research, the procedures and the risks associated with it have been fully explained to me. I have had the opportunity to ask questions and my questions have been answered to my satisfaction. I understand that I am able to withdraw from this study at any time and for any reason. I understand that my withdrawal from this study would in no way affect any current or future treatment at the CAMH. I voluntarily consent to participate in this research study.

I have been given a copy of this informed consent and patient information sheet to keep for my own records. If I have any further questions I understand that I can contact the Principal Investigator Dr. B. Sproule at (416) 535-8501 ex. 6501 or the Study Coordinator Alex Elkader at (416) 535-8501 ex. 6502. If I have any questions regarding my rights as a subject in this research, I may contact Dr. Padraig Darby at (416) 535-8501 ex. 6876.

Printed Name of Subject                 Signature of Subject               Date

Printed Name of Person                 Signature of Person               Date
Who Conducted Informed Consent Discussion

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Appendix 2

Advertisement Flyer: Study 1
Study Volunteers Needed

Are you in Methadone Maintenance Treatment?

We are looking for people who have been on methadone for at least 6 months to participate in a study of methadone effects and how the body handles methadone over one 24-hour period.

We would like to study people who have been on methadone who are:

- Doing well on methadone, and/or
- Feeling down or depressed, and/or
- Still experiencing withdrawal symptoms

If you are interested, please contact Alex for more information at,
(416) 535-8501 ex. 6502
Financial Compensation Available

CAMH provides other treatment options for mental illness or addiction. For more information call CAMH at 416-535-8501.

ALL QUERIES ARE STRICTLY CONFIDENTIAL
Appendix 3

Brief Telephone Screen: Study 1
Methadone PK-PD Study – Telephone Screen
Clinical Research Department, Centre for Addiction and Mental Health

Brief study explanation.

We are doing this study so that we can learn more about how methadone in your body relates to its effects. Should you meet study requirements, you would partake in a 24-hour study. You would arrive early in the morning (before you take your methadone dose) and answer some questionnaires, do some hand-eye coordination tests and give blood and urine samples. You would stay and repeat these tests and give blood and urine samples 11 times over the next 13 hours. On this day and your meals will be provided. Blood samples would be taken with the aid of an intravenous catheter; this means that you would receive only one poke for all the blood samples this day. You will come back the next day prior to your methadone dose and repeat all the tests one last time. At this point you would be finished the study and paid $150.00 dollars for your participation.

We are looking for participants who fit into 4 different groups: participants with and without current depression, and participants who do and do not experience withdrawal symptoms during the course of treatment.

How long have you been in the methadone program? ____________________________
How long have you been on the dose you are on? _________________________________
How many times a day do you take your methadone dose? ________________________
Do you feel that your methadone dose “holds” you?
i.e. do you feel withdrawal pains towards the end of the day) ______________________
Do you think that you are currently depressed? _________________________________
Have you ever been treated for depression? ________________________________
Other Psychiatric disorders? ________________________________________________
Do you use recreational drugs?
We will be doing a urine screen and a positive result for these drugs
would mean you cannot participate. __________________________________________
Where did you see the study advertisement? ________________________________
Study Name: “Modification of the Subjective Opioid Withdrawal Scale (SubOWS) for Measuring Opioid Withdrawal in the Context of Opioid Substitution Therapy”

Principal Investigator: Dr. B. Sproule
Co-investigators: Dr. B. Brands
Dr. M. Zack
Dr. R. Callaghan
Study Coordinator: Alexander Elkader

This study will take place at the Centre for Addiction and Mental Health 33 Russell Street site under the supervision of Dr. B. Sproule. This project is part of the Ph.D. thesis of Alexander Elkader, under the supervision of Dr. B. Sproule, and the faculty of Pharmacy at UofT. There will be 90 people taking part in this study.

You are being asked to participate in this study because you have been in methadone/buprenorphine treatment for at least 6 months and on the same dosage for the past 1 month. We are interested in studying opioid withdrawal symptoms and sensations in methadone/buprenorphine patients just before they take their daily dose.

Study participants will be classified into one of four groups for comparison purposes:

1. Complete Holders: Treatment is good, no withdrawal
2. Partial Holders: Satisfied with treatment, withdrawal is tolerable
3. Partial Nonholders: Not satisfied with treatment, withdrawal is not tolerable
4. Complete Nonholders: Treatment is bad, severe intense withdrawal

The study procedures are the same regardless of which group you are in. Please take the time to read this information sheet carefully and ask any questions that you may have before deciding whether you wish to participate in this study.
Study Medications

You will not be asked to take any medications other than your regular daily dose of methadone or buprenorphine. You should continue to take any medications that you are currently prescribed.

Purpose of the Study

The purpose of this study is to make changes to an available measurement tool of opioid withdrawal so that it is more appropriate for use in patients in opioid substitution therapy (methadone or buprenorphine). This may be especially important to help better understand patients who find that their treatment is not effective. This may be because currently available tools for measuring opioid withdrawal were designed to measure the features of withdrawal during acute detoxification rather than during opioid substitution therapy.

Procedures

• The study will involve one study session. On the study day you will be asked to arrive at the Russell St. site of CAMH one hour prior to the time you have your regular dose of opioid substitute (methadone or buprenorphine).
• To start with, you will be asked demographic questions, questions about you general and mental health, questions about your past use of drugs, and questions about your past drug treatments.
• You will be asked give a urine sample.
• You will be asked to respond to 9 questionnaires which will take approximately 30 to 45 minutes to complete.)
• After this you will receive your regular dose of methadone or buprenorphine. You will be dosed at the CAMH pharmacy or bring your regular dose with you.

• Then you will have a 30 minute break.

• After the break you will be have 5 more questionnaires to answer (which will take approximately 60 - 90 minutes to complete)

• Once you have completed these questionnaires you will be finished the study.

The questions you will be asked will be about opioid withdrawal, drug craving, your mood, how your dose makes you feel, your personality, anxiety, pain that you may be feeling and your quality of life.

Benefits

There are no direct benefits to you for participating in this study. The findings of this study may be helpful in understanding why some patients in treatment for opioid use do not do as well as others.

Compensation

As payment for your participation you will receive $30.00 dollars at the end of the study.

Voluntary Participation

Your participation in this study is completely voluntary and you can withdraw from the study at any time and for any reason. If you decide to withdraw from the study, this will not affect your current or any future care at the Centre for Addiction and Mental Health in any way. The investigators may terminate your involvement in the study at any time. This could be due to medical reasons or for not following study procedures.
Confidentiality

Your identity will be kept strictly confidential to the full extent provided by the law. All information collected during the course of this study will be kept secure and confidential and will only be made available to the researchers in this study. The data will be identified by your initials and a code number only, and not by your name. Published reports and presentations at scientific meetings will refer to only a code number or grouped data, and not a name or initial.

If you are not a client of the CAMH methadone maintenance treatment program, you will be required to sign a release of personal health information form for your dispensing pharmacy, so that we can confirm your methadone dose and duration at that dose. Your confidential information will not be discussed with anyone outside of the study personnel.

As part of continuing review of the research, your study records may be assessed on behalf of the Research Ethics Board and, if applicable, by Health Canada Therapeutics Products Programme. A person from the research ethics team may contact you (if your contact information is available) to ask you questions about the research study and your consent to participate. The person assessing your file or contacting you, must maintain your confidentiality to the extent permitted by law.
Informed Consent

I, ____________________________ have read (or had read to me) the information sheet for the study “Modification of the Subjective Opioid Withdrawal Scale (SubOWS) for Measuring Opioid Withdrawal in the Context of Opioid Substitution Therapy”. The purpose of this research, the procedures and the risks associated with it have been fully explained to me. I have had the opportunity to ask questions and my questions have been answered to my satisfaction. I understand that I am able to withdraw from this study at any time and for any reason. I understand that my withdrawal from this study would in no way affect any current or future treatment at the CAMH. I voluntarily consent to participate in this research study. I understand that signing this consent form does not waive my legal rights.

I have been given a copy of this informed consent and patient information sheet to keep for my own records. If I have any further questions I understand that I can contact the Principal Investigator Dr. B. Sproule at (416) 535-8501 ex. 6501 or the Study Coordinator Alex Elkader at (416) 535-8501 ex. 6502. If I have any questions regarding my rights as a subject in this research, I may contact Dr. Padraig Darby at (416) 535-8501 ex. 6876.

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Appendix 5

Patient Satisfaction Screening Guide used in Study 2
Patient Satisfaction With Methadone Maintenance Treatment

Brief Screening Guide

1. How long have you been on your current dose of methadone?
2. Do you find that this dose always holds you or do you sometimes experience symptoms of withdrawal during the day or evening, or just before your next scheduled dose?

If they experience withdrawal:

3. Would you say that your withdrawal symptoms are: tolerable, difficult to tolerate, or not tolerable.
4. If you had to classify the level of withdrawal that you experience would you rate it as: mild, moderate or severe?
5. Do you think that the withdrawal symptoms you experience affect your quality of life? Explain:

6. How many days a week do you experience withdrawal?

Classification Guide

- Establish that patient is on a clinically optimized dose.
- In cases where group assignment is difficult, rely on impact on quality of life and clinical judgment.

**Holder:** None or nearly no withdrawal. There is no impact on quality of life.

**Partial Holder:** Withdrawal is tolerable; mild in severity and infrequent (usually 3 or less days/week), there is minimal impact on quality of life.

**Nonholder:** Withdrawal is not tolerable/difficult to tolerate, severity is moderate to severe, frequency can vary from semi-frequent to very frequent. There is significant impact on the quality of life.
Appendix 6

Advertisement Flyer: Study 2
Study Volunteers Needed

Are you **Currently** being treated with **Methadone or Buprenorphine**?

We are looking for people who:
- Have been on the same dose for at least 1 month
- Who have been in treatment for at least the last 6 months
- Who are doing well in treatment
- Who are still experiencing withdrawal in treatment

To participate in a study to better understand why some people do better on these opioid substitutes than othersIf you are interested, please contact **Alex** for more information at, (416) 535-8501 ex. 6502

Financial Compensation Available
CAMH provides other treatment options for mental illness or addiction.
For more information call CAMH at 416-535-8501.

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Appendix 7

Brief Telephone Screen: Study 2
Opioid Withdrawal Scale Study – Telephone Screen
Clinical Research Department, Centre for Addiction and Mental Health

Brief study explanation.

We are conducting a study to understand why some people who take methadone or buprenorphine for opioid substitution therapy do better than others. This study involves filling out a series of questionnaires and providing a urine sample. The currently available tools for measuring opioid withdrawal may not be sensitive to the aspects of opioid withdrawal that are more unique to opioid substitution therapy. The results of the series of questionnaires will be used to develop a shorter series of questions with the purpose of identifying people who are more likely to have withdrawal symptoms while on opioid substitution therapy. This study will take approximately 3-4 hours to complete. At the end of the study you will be paid $30.00 for your participation.

How old are you?________________________________________________________
Are you taking methadone or buprenorphine? ______________________________
How long have you been in the program? _________________________________
What is your current dose? _____________________________________________
What time do you take your dose? _______________________________________
How long have you been on the dose you are on? ___________________________
Do you feel that your methadone dose “holds” you?
(i.e. do you feel withdrawal pains towards the end of the day) ________________
Do you use recreational drugs?
We will be doing a urine screen and a positive result for these drugs would mean you cannot participate. ________________________________
Where did you see the study advertisement? ______________________________
Carries? _____________________________________________________________
Appendix 8

Patient Informed Consent Form: Study 3
Study Name: Smoking in Methadone Maintenance Patients: Nicotine and Methadone Relationships.

Principal Investigator: Beth Sproule, PharmD
Co-investigators: Bruna Brands, Ph.D.
Peter Selby, MBBS
Graduate Student: Alex Elkader, Ph.D. Student

This study will take place at the Centre for Addiction and Mental Health 33 Russell Street site under the supervision of Dr. B. Sproule. This project is part of the Ph.D. thesis of Alex Elkader, under the supervision of Dr. B. Sproule. There will be 40 people taking part in this study. This study is funded by the Canadian Tobacco Control Research Initiative (CTCRI).

You are being asked to participate in this study because:

1. You have been in methadone treatment for at least 3 months.
2. You have been on the same methadone dosage for the past 2 weeks.
3. You are a current smoker.

Please take the time to read this information sheet carefully and ask any questions that you may have before deciding whether you wish to participate in this study.

Study Medications

During the course of this study you will be asked to smoke your usual brand of cigarettes, chew nicotine gum, and chew a placebo version of this nicotine gum on two occasions each (2 cigarettes, 4 pieces on nicotine gum, and 4 pieces of placebo gum). A placebo is an inactive substance that is made to look and taste like the real substance (does not
contain nicotine). You should continue to take any medications that you are currently prescribed. Please consult with the study coordinator prior to taking any other medications or natural health products for the duration of the study. The use of products designed to help you quit smoking are not permitted throughout the course of this study, including natural products. If you are a woman with the ability to have children, you will be required to use an approved method of birth control for the duration of the study. These methods include abstinence, oral contraceptives, and barrier devices; as well having a partner who has had a vasectomy or is on male contraceptives.

**Purpose of the Study**

There are very high rates of smoking in individuals on methadone maintenance treatment. The purpose of this study is to get information about how smoking and methadone can influence the effects of each other. This may be important in helping design stop smoking strategies for individuals on methadone maintenance treatment.

**Procedures**

If you agree to participate, you will first undergo an assessment to be sure you are eligible for the study and to collect general information about you. This will include questions about:

- demographics (e.g., your age, education, occupation)
- your past and present drug use
- current medications
- methadone dosage information (we will confirm your current methadone dosage and duration of time at this dose with your pharmacy)
- your smoking history
• your beliefs about how smoking and methadone interact
• your previous drug treatments
• psychiatric symptoms and history

Also, a urine sample (for a drug screen and pregnancy testing in women) will be collected.

The study itself will involve three (3) study days (5 hours each).

• For all of the study days, you will be asked to arrive at CAMH, 45 minutes before you usually take your daily dose of methadone. All study days will be the same, except for the type of nicotine you get.
• On the first study session you will be asked to smoke your regular brand of cigarette, and on the second and last study sessions you will be asked to chew nicotine gum or placebo gum in a random order. This means that you and the study personnel that you see will not know which of the two gums you have received.
• If you have carry privileges for your methadone you will be asked to bring your dose for that day with you. Otherwise, you will be escorted to the CAMH pharmacy for administration of your regular dose.
• You will be required to abstain from nicotine (smoking) from 12 hours before the study session until we ask you to use nicotine (smoke a cigarette, or chew nicotine/placebo gum). Before the study day starts, you will be asked to blow into a smokerlyzer. This measures the level of carbon monoxide (CO) in your breath as an indicator of recent smoking. A score of 10 ppm (parts per million) or greater will disqualify you for that study day and you will need to reschedule.
• Please note that you will also be required to avoid alcohol, coffee and all sources of caffeine from 12 hours before the study session until the testing is completed. Sources of caffeine include: tea and most non-clear sodas. If you have any questions regarding a specific beverage or food, please ask study personnel. At the start of each study day you will be asked to blow into a breathalyzer to confirm no recent alcohol consumption.

• When you arrive for the study day you will also be asked to give a urine sample for drug testing.

Each study session will take approximately 5 hours to complete, you will be asked to complete the same tests on 4 occasions:

1. When you arrive, prior to your methadone dose, and prior to your nicotine administrations (first smoke, or nicotine/placebo gum).

2. After you have your nicotine administration (before you have your methadone).

3. Three hours after your methadone dose, before you have a second nicotine administration (second smoke, or nicotine/placebo gum).

4. Three hours after methadone dose, after you have a second nicotine administration.

The tests you will be required to complete include the following computerized assessments:

1. Vital Signs measurement. We will record your vital signs (such as breathing and heart rate) at each cycle.

2. Measurement of drug effects. A number of questions will be asked about how you are feeling to estimate the drug effects of methadone and nicotine.
(time = 5 minutes).

3. Measurement of opioid withdrawal. A number of questions will be asked to assess the level of opioid withdrawal you are feeling (time = 1 minute).

4. Measurement of mood. A number of questions will be asked about how you are feeling, to estimate your current mood (time = 5 minutes).

5. Measurement of smoking urges and nicotine withdrawal. A number of questions will be asked about how much you want a cigarette and how much you feel that you need a cigarette (time = 5 minutes).

In addition, at each cycle you will be asked to blow into a smokerlyzer to measure carbon monoxide levels. At the first cycle each day we will ask you about your current level of desire to quit smoking.

At the 1st and the 4th cycles, you will give a blood sample by venipuncture. The blood samples will each be 10 ml (2 teaspoons). The blood samples will be tested for methadone, nicotine and cotinine (a breakdown product of nicotine) concentrations. As well on the first study day an extra blood sample will be taken to determine the genetics of the opioid receptor (specific to you). Often a gene can be responsible for various functions in your body. The opioid receptor is the product of a gene called OPRM1. You receive two copies of each gene (one from each of your parents). We will see what types of this gene you have, as it has been discovered that more than one type does exist, and these types lead to different effects. After completing the 4th testing cycle you will have finished the study day.
Risks and Discomforts

You will be required to stop smoking starting 12 hours before each study day and during the study sessions your smoking will be restricted as outlined in the study procedures. This may cause you some discomfort. The main physical risk would be associated with the blood draws, although this is a safe procedure, slight bruising, pain or inflammation is possible. Nicotine gum is usually well tolerated however it can cause the following side effects: headache, hiccups, upset stomach, mouth soreness, and throat soreness. Because the nicotine gum is a gum-based product, chewing it can cause fillings to loosen and aggravate other mouth, tooth, and jaw problems.

Benefits

There are no direct benefits to you for participating in this study. Findings of this study may be useful in the development of smoking cessation strategies specifically for methadone maintenance treatment patients.

Compensation

In consideration of your participation you will receive $225.00 at the end of the study. If you decide to drop out of the study, your compensation will be pro-rated.

Voluntary Participation

Your participation in this study is completely voluntary and you can withdraw from the study at any time and for any reason. If you decide to withdraw from the study, this will not affect your current or any future care at the Centre for Addiction and Mental Health.
in any way. The investigators may terminate your involvement in the study at any time. This could be due to medical reasons or for not following study procedures.

Confidentiality

Your identity will be kept strictly confidential to the full extent provided by the law. All information collected during the course of this study will be kept secure and confidential and will only be made available to the researchers in this study. The data will be identified by your initials and a code number only, and not by your name. Published reports and presentations at scientific meetings will refer to only a code number or grouped data, and not a name or initial.

As part of continuing review of the research, your study records may be assessed on behalf of the Research Ethics Board and, if applicable, by the Natural Health Products Directorate. A person from the research ethics team may contact you (if your contact information is available) to ask you questions about the research study and your consent to participate. The person assessing your file or contacting you, must maintain your confidentiality to the extent permitted by law.

A genetic measurement will be made from a blood sample you provide. We will use this sample only to see your genetic make up at the opioid receptor gene. We will not look at other genes than the one we have mentioned.
Informed Consent

I, ____________________________ have read (or had read to me) the information sheet for the study “Smoking in Methadone Maintenance Patients: Nicotine and Methadone Relationships”. The purpose of this research, the procedures and the risks associated with it have been fully explained to me. I have had the opportunity to ask questions and my questions have been answered to my satisfaction. I understand that I am able to withdraw from this study at any time and for any reason. I understand that my withdrawal from this study would in no way affect any current or future treatment at the CAMH. I voluntarily consent to participate in this research study.

I have been given a copy of this informed consent and patient information sheet to keep for my own records. If I have any further questions I understand that I can contact the Principal Investigator Dr. B. Sproule at (416) 535-8501 ex. 6501 or the Study Coordinator Alex Elkader at (416) 535-8501 ex. 6502. If I have any questions regarding my rights as a subject in this research, I may contact Dr. Padraig Darby at (416) 535-8501 ex. 6876.

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Time of Signing
Appendix 9

Advertisement Flyer: Study 3
Study Volunteers Needed

Are you a Smoker who is in Methadone Maintenance Treatment?

We are looking for people to participate in a study of the influence of nicotine on methadone effects.

We would like to study people who are:

- On methadone for at least 3 months
- On the same dose for at least 2 weeks
- Are current Smokers

If you are interested, please contact Alex for more information at,
(416) 535-8501 ex. 6502

Financial Compensation Available

CAMH provides other treatment options for mental illness or addiction.
For more information call CAMH at 416-535-8501.

ALL QUERIES ARE STRICTLY CONFIDENTIAL
Appendix 10

Brief Telephone Screen: Study 3
Brief study explanation.

We are conducting a study to gain a better understanding of how treatment with methadone is influenced by smoking and also how your smoking is influenced by your treatment with methadone. This is important, as smoking is very common among methadone patients and it has never been examined.

The study involves 3 study days, each for 4-5 hours. You will provide a urine sample each day, and 2 blood samples each day. On the first day, you will give one extra blood sample, for genetic testing. As well you will respond to a series of computerized questionnaires about how you are feeling each day. The study will involve abstaining from smoking for 12 hours before each study day. The first time you come in you will be asked to smoke 2 cigarettes (your regular brand), the next 2 times you come in, you will receive nicorette gum or placebo gum in a random order. At the end of the study you will receive $225.00 for your participation.

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