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Treatment for latent tuberculosis infection (LTBI) during methadone maintenance therapy: Patients who receive methadone maintenance therapy are less likely to complete LTBI treatment and more likely to develop withdrawal symptoms if treated for LTBI with a rifapentine-containing regimen

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# Treatment for latent tuberculosis infection (LTBI) during methadone maintenance therapy: Patients who receive methadone maintenance therapy are less likely to complete LTBI treatment and more likely to develop withdrawal symptoms if treated for LTBI with a rifapentine-containing regimen

By

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B.S., University of Massachusetts Amherst, 2013

Thesis Committee Chair: David Kleinbaum, PhD

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**Abstract**

Treatment for latent tuberculosis infection (LTBI) during methadone maintenance therapy: Patients who receive methadone maintenance therapy are less likely to complete LTBI treatment and more likely to develop withdrawal symptoms if treated for LTBI with a rifapentine-containing regimen

By Deirdre Sheehan

Previous studies have shown that shorter regimens to treat latent tuberculosis infection (LTBI) have higher completion rates. Effectiveness of a 3-month weekly regimen of rifapentine plus isoniazid (3HP) is equal to that of standard 9-month daily isoniazid (9H) and 6-month daily isoniazid (6H) regimens, and treatment completion of 3HP is higher than that of 9H and of 6H (4, 25). Rifapentine belongs to the rifamycin drug class, which has been shown to interact with and decrease activity of methadone. Therefore, in patients concomitantly receiving methadone maintenance therapy and 3HP, methadone has the potential to hinder LTBI treatment completion rates. This analysis aims to determine (a) the effect of concomitant methadone maintenance therapy on the completion of a rifapentine-containing LTBI treatment regimen and (b) the effect of a rifapentine-containing treatment regimen on the development of withdrawal symptoms. The analysis used data from a clinical trial in which subjects were randomized to receive either 3HP or 9H. This analysis included 6242 subjects, 137 (2.19%) of whom were concomitantly receiving methadone maintenance therapy. Overall, 79% of subjects completed LTBI treatment, but completion rates were differential by treatment regimen and by methadone maintenance therapy. Among subjects not receiving methadone, 3HP was associated with significantly higher odds of treatment completion compared to 9H (OR=1.809, $p<0.001$), but subjects receiving 3HP during methadone maintenance therapy were significantly less likely to complete treatment than subjects receiving 3HP alone (OR=0.539, $p=0.026$). Among subjects concomitantly receiving methadone maintenance therapy, 38 of 137 (27.7%) developed methadone withdrawal, and 19 of these 38 (50%) were unable to complete LTBI treatment. The rifapentine-containing 3HP treatment regimen was associated with odds of developing withdrawal 5.6 times those of the 9H treatment regimen ($p<0.001$). In conclusion, clinicians should give careful consideration to prescribing rifapentine-containing regimens to treat LTBI in those who currently receive methadone maintenance therapy and should monitor patients for the appearance of early withdrawal symptoms during treatment to increase likelihood of treatment completion and to minimize risk of permanent discontinuation of the LTBI regimen due to development of withdrawal syndrome.

# Treatment for latent tuberculosis infection (LTBI) during methadone maintenance therapy: Patients who receive methadone maintenance therapy are less likely to complete LTBI treatment and more likely to develop withdrawal symptoms if treated for LTBI with a rifapentine-containing regimen

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# INTRODUCTION

## *Treatment for Latent Tuberculosis Infection*

Latent tuberculosis infection (LTBI) treatment is a major part of national strategies to reduce the burden of tuberculosis (TB) (1). In 2000, a joint statement was issued by the American Thoracic Society and the Centers for Disease Control and Prevention (CDC), recommending treatment of LTBI with 9 months of daily isoniazid (2). For more than 30 years, 6 to 12 month regimens of isoniazid had been common practice for treating LTBI in the US (2). However, the extended length of this treatment is problematic: while efficacious, the effectiveness is limited by patients' failure to complete treatment (3). In a study of LTBI patients in the US and Canada in 2002 who were prescribed either a 6-month or 9-month daily isoniazid regimen, fewer than half of those who started treatment for LTBI completed therapy; for those who were assigned a 9-month regimen, 42.9% did not complete even six months of isoniazid (3). A shorter regimen that was equally effective for preventing LTBI from progressing to TB disease was sought.

In 2011, results were published from a study that compared the effectiveness of a 3-month weekly regimen of rifapentine plus isoniazid to the standard 9-month daily regimen of isoniazid. This study found that the shorter rifapentine-containing regimen was as effective as the longer regimen in preventing TB disease and had a higher completion rate (4).

## *Methadone-rifampin drug interaction*

Rifapentine is a rifamycin derivative characterized by a long half-life and greater potency against *M. tuberculosis* than rifampin, which is also a rifamycin (4).

In 1976, when several patients being treated for pulmonary tuberculosis with rifampin at the Bellevue Chest Service Methadone Maintenance Program complained of withdrawal symptoms, the interaction between methadone and rifampin was detected (5). There were 86 patients in this methadone maintenance program being treated for TB: 21 of 30 (70%) patients treated with rifampin experienced withdrawal symptoms, while none of the 56 patients treated with anti-tuberculosis regimens not containing rifampin developed withdrawal symptoms (5). Fourteen of the 21 patients experienced mild withdrawal symptoms including abdominal cramps, rhinorrhea (runny nose), lacrimation (tearing), pilocarpal erection, yawning, irritability, and restlessness; the remaining seven patients experienced severe withdrawal symptoms including nausea, vomiting, anorexia, chills, joint pains, insomnia, tremulousness, and severe anxiety (6). Within two weeks of the start of the combined therapy—and for most of the severely affected patients, within six days –withdrawal symptoms appeared 6 to 8 hours after the combined methadone/rifampin therapy was administered and increased until 1 to 2 hours after the next methadone dose was given on the following day (6). In these patients, rifampin significantly lowered plasma levels of methadone, an effect that coincides with the appearance of withdrawal symptoms in patients that had been previously doing well on that dose of methadone (6).

Methadone is mainly metabolized in the liver, and the main step of its metabolism is N-demethylation by CYP3A4, an isoenzyme of cytochrome P450 (7). Rifampin is an inducer of CYP3A4, reducing plasma concentrations of methadone by 30 to 65%, and resulting in an onset of clinical effects within 6-8 hours following its administration (7). If on methadone maintenance therapy, a patient may begin to feel withdrawal symptoms

after the methadone has been metabolized and too little of the drug remains available for pharmacological activity (7). Rates of methadone metabolism vary as a result of differences in CYP3A4 activity between individuals, and the consequent variation in timing of withdrawal symptom onset stresses the importance of monitoring patients receiving both methadone and rifampin (7). Other metabolic inducers of CYP3A4 include alcohol, when chronically abused, and antiretrovirals (7).

In summary, the drug interaction between methadone and rifampin is well established. However, there is a lack of clinical data describing effects of the drug interaction between methadone and rifapentine in patients receiving these medications concomitantly.

*Importance of LTBI treatment completion for patients receiving methadone maintenance therapy*

In 2013, 142 of 9094 (1.6%) of those diagnosed with tuberculosis disease in the United States were injecting drug users and 633 (7.1%) were non-injecting drug users (8). Methadone maintenance has been an important treatment for many of these drug users: decades of randomized studies of methadone maintenance have consistently shown its effectiveness across cultures in the United States, Hong Kong, Sweden, and Thailand (9). At the same time, drug use has become a risk factor for TB, due to the overlap of factors associated with drug use and TB (10). Furthermore, the HIV epidemic has accelerated the spread of TB among drug users (10).

Methadone maintenance therapy for illicit drug users treats addiction in a way that minimizes withdrawal symptoms, making it more feasible for addicts to stop using illicit

drugs and helping prevent relapse. Nearly one million people in the US are addicted to heroin and other opioids such as oxycontin, dilaudid, and hydrocone (11). Intravenous, or injection, drug use is the third-most frequently reported risk factor for HIV infection in the US, and during the years 2004-2006, 40% of HIV diagnoses among injection drug users in the US were late diagnoses, meaning that AIDS was diagnosed less than one year after HIV diagnosis (12). According to the National HIV Behavioral Surveillance System, eight percent of new HIV infections in 2010 occurred among injection drug users (13).

HIV, in turn, is an important risk factor for the progression of LTBI to active TB disease. Among those latently infected with *M. tuberculosis*, the lifetime risk of progression to active TB disease is 5-10% in healthy adults, while the risk in HIV-infected individuals is up to 15% per year (14). A study of injection drug users enrolled in a methadone maintenance program concluded that while the incidence and prevalence of tuberculosis infection are similar in HIV-positive and HIV-negative persons, the risk of progressing to active TB is elevated for just the HIV-positive (15). Furthermore, authors found that active TB in the HIV-positive was most often from reactivation of LTBI rather than recent infection, encouraging the treatment of LTBI in an HIV-positive population of people (15).

The risk of HIV among injection drug users and the increased risk of TB disease in HIV-infected individuals illustrate the paramount importance of studying the ability of patients receiving methadone maintenance therapy to complete LTBI treatment.

*Factors associated with LTBI treatment completion*

A study of completion rates of LTBI treatment with isoniazid, where completion was defined as taking at least six months of isoniazid, found lower completion rates to be associated with homelessness, excessive alcohol use, and experiencing an adverse event during treatment (16). A cross-sectional survey of LTBI treatment and completion, which included people treated with one of four LTBI treatment regimens of varied lengths, reported that risk factors for treatment non-completion included being a resident in a congregate setting (i.e. nursing home, homeless shelter, jail, or prison), being an injection drug user, being older than 15, being an employee of a hospital or nursing home, and initiating the 9-month isoniazid treatment regimen as compared to the three shorter regimens (3). In patients treated for LTBI with isoniazid or rifamycin, completing treatment has been associated with age ≥35, Asian or black race compared to non-Hispanic whites, and being born outside the US (17). Females and non-smokers are associated with better adherence to LTBI treatment, a measure that is closely related to treatment completion (18).

*Factors associated with methadone withdrawal*

When cytochrome P450 enzymes are affected, methadone can be metabolized at a rate faster or slower than expected, and fast methadone metabolism can lead to symptoms of methadone withdrawal. Alcohol is broken down by two enzymes in the liver, one of which is a cytochrome P450 (19). Chronic alcohol abuse can increase cytochrome P450 activity up to ten-fold; when alcoholics are sober, this can result in much faster metabolic rates for other medications typically metabolized by cytochrome P450 enzymes (19). The presence of liver disease also affects cytochrome P450 activity, and the severity of liver

disease has a differential effect on the metabolic activity of cytochrome P450 enzymes (20). Cytochrome P450 content also differs significantly by age: P450 content is significantly lower in 40-49 year olds than in 20-29 year olds, and a further significant decrease is seen in those older than 70 (21).

It has been established that the 3-month, rifapentine-containing regimen has a higher completion rate than the 9-month, isoniazid-only regimen and is equally effective in preventing TB disease (4). This analysis seeks to investigate LTBI treatment completion rates in subjects receiving methadone maintenance therapy. If lower completion rates are detected in the population of people receiving methadone, then different strategies for LTBI treatment and monitoring in this group may be indicated, to increase likelihood of completion and to minimize risk of permanent discontinuation of the LTBI regimen.

## METHODS

### *Study design*

This analysis used data collected during Study 26 of the Tuberculosis Trials Consortium through the Centers for Disease Control and Prevention, Division of Tuberculosis Elimination, Clinical Research Branch. Study 26, *A Study of the Effectiveness and Tolerability of Weekly Rifapentine/Isoniazid for Three Months (3 RPT/INH) Versus Daily Isoniazid for Nine Months (9 INH) for the Treatment of Latent Tuberculosis Infection*, was a large international multi-site randomized clinical trial that evaluated the effectiveness of 3HP (a directly observed treatment of isoniazid and rifapentine given once per week for 12 weeks) compared to the most commonly used

treatment for LTBI, 9H (a self-administered treatment of isoniazid taken daily for nine months). This study was conducted during the years 2001-2013; results of the analysis from the cohort of subjects who completed treatment by 2011 (which excluded late-enrolling children less than 12 years old and HIV-positive subjects) are published in the *New England Journal of Medicine* (4).

The study enrolled high-risk tuberculin skin-test reactors, defined as being one of the following: (a) a close contact of a person with culture-confirmed tuberculosis within two years of enrollment and having a positive result on a tuberculin skin test, (b) a tuberculin skin test conversion to positive within two years of enrollment, (c) HIV-seropositive with either a positive tuberculin skin test or a close contact with culture-confirmed tuberculosis within two years, or (d) a positive tuberculin skin test result with fibrotic changes on chest radiography consistent with previous untreated tuberculosis. Definitions for a positive tuberculin skin test and conversion to a positive test were based on guidelines from the American Thoracic Society and the CDC (2). Exclusion criteria included confirmed or suspected tuberculosis, drug resistance in the source case, treatment with rifamycin or isoniazid within the previous two years, completion of an adequate course of treatment for active or latent tuberculosis if HIV-seronegative, sensitivity or intolerance to isoniazid or rifamycin, a serum aminotransferase aspartate five times the upper limit of the normal range, pregnancy or lactation, HIV therapy within 90 days after enrollment, or weight of less than 10.0kg.

Subjects were randomized to receive nine months of isoniazid (9H), which was self-administered daily, or three months of isoniazid plus rifapentine (3HP), which was given by directly observed therapy once per week.

Information concerning methadone maintenance therapy was collected from study participants, and verified by medical records if available, at enrollment and again at each monthly clinic visit. Subjects reported methadone dose and frequency, any change in methadone dose and frequency, and the reason for that change in treatment. Any symptoms of methadone withdrawal present for seven or more days in the previous month were also collected at baseline and at each subsequent visit during LTBI treatment. Narratives were written for each subject and were used to determine presence of methadone withdrawal: these narratives compiled information that includes, but is not limited to, medical history, methadone dose and frequency, symptoms of withdrawal, other adverse events, and reasons for discontinuation.

The study was approved by the institutional review boards at CDC and all study sites. Written informed consent was obtained from all study subjects.

Study 26 enrolled 8593 subjects, but some subjects were excluded from this specific analysis. First, 1058 (12.3%) participants under age 18 at enrollment were excluded, because minors are not typically offered methadone as long-term supportive therapy, and no minors were receiving methadone in the Study 26 population. Then, 264 (3.1%) participants who took no LTBI treatment doses, 25 of whom were already excluded based on age, were excluded because these subjects never started treatment and therefore were not at risk of developing drug-drug interactions. An additional 87 (1.0%) participants who became pregnant during study treatment were excluded, because these participants were required to discontinue LTBI treatment by study protocol, a reason unrelated to methadone therapy or LTBI treatment regimen. Finally, 967 (11.3%) participants who enrolled at sites where methadone was not available in the nearby vicinity as a long-term

supportive therapy were excluded, because participants at these sites were not 'at risk' for being on methadone during study treatment. Sites were contacted to determine if methadone was available as a long-term supportive therapy during the study period; some sites had closed at the time of this analysis, and for these sites a search of methadone clinics by zip code was conducted to determine availability. Subjects from sites in the US, Canada, Spain, and Hong Kong remained. A study population of 6242 was used for the analysis, of whom 137 (2.19%) were concomitantly receiving methadone maintenance therapy as a long-term intervention.

*Definitions*

For subjects randomized to 3HP, treatment completion was defined as taking at least 11 of 12 doses within 10-16 weeks. For subjects randomized to 9H, treatment completion was defined as taking at least 240 of 270 doses within 240-365 days.

Subjects were defined as having developed methadone withdrawal if (a) a clinician at the site indicated on one or more case report forms that the subject suffered from withdrawal, or (b) the subject experienced three or more of the following symptoms for seven or more days: nausea and vomiting, abdominal cramps, body aches, restlessness, irritability, dilated pupils, tremors, involuntary twitching, lacrimation, rhinorrhea, sneezing, yawning, excessive perspiration, goose flesh, or diarrhea.

Subjects who lived in the same household as another enrolled participant were defined as being part of a household cluster. Within household clusters, the first enrolled participant was randomized, and members of that household who enrolled subsequently received the same treatment regimen.

Subjects were asked at enrollment and at each study visit about use of concomitant medications. For this analysis, the number of concomitant medications during treatment was summed. Methadone was not counted toward the number of concomitant medications.

Information regarding subjects' history of alcohol use was collected during the baseline visit. Alcohol abuse was defined as answering yes to more than one question on the CAGE questionnaire, which is a widely used method of screening for alcohol abuse based on four questions.

Subjects were also asked at enrollment if they were current cigarette smokers, had ever used injection drugs, had been unemployed for over a year, had been homeless for over six months, or had been incarcerated for over one month.

*Statistical analysis*

Chi-square tests were conducted to determine significant associations between covariates. Where expected cell counts were less than five, Fisher exact tests were used. Median one-way analysis was used to test associations with median age. All tests used alpha of 0.05 and all tests were two-sided.

A logistic model was fit to evaluate the effect of two exposures—methadone maintenance therapy during LTBI treatment (yes or no) and LTBI treatment arm (3HP or 9H)—on the outcome, LTBI treatment completion (yes or no).

Covariates that were deemed relevant to the relationship between completion and the exposures, based on a review of the literature, were screened for potential interaction with exposures and confounding of the relationship between exposures and treatment

completion; any covariates that (a) had a significant interaction with either of the two exposures or (b) acted as confounders, as judged by a >10% change in odds ratio for completion, were included in the initial model. Interaction between the two exposures and between covariates and each exposure was assessed with backward elimination using Wald tests (alpha 0.05); all interaction terms between covariates and exposures were found to be statistically insignificant or biologically meaningless, and thus were dropped from the model. Collinearity within the model containing the two exposures, eleven remaining covariates, and an interaction term between exposures was assessed (22). Finally, confounding was assessed by comparing odds ratios derived from models that each controlled for one possible subset of the eleven covariates (23). The final model was a parsimonious model that adequately controlled for confounding while offering better precision than the model with all eleven covariates.

A second logistic model was fit to evaluate the effect of LTBI treatment arm (3HP or 9H) on the development of methadone withdrawal (yes or no), among those receiving methadone maintenance therapy. A similar modeling strategy to the strategy outlined for the treatment completion model was used to determine the best model for the relationship between LTBI treatment regimen and the development of methadone withdrawal.

## RESULTS

### *Subjects*

Baseline characteristics of subjects receiving methadone maintenance therapy and subjects not receiving methadone maintenance therapy are shown in Table 1. Subjects

were randomized to 3HP or 9H treatment for LTBI regardless of methadone maintenance therapy; 137 (2.19%) subjects were concomitantly receiving methadone.

At baseline, subjects receiving methadone maintenance therapy were more likely to have been born in the US/Canada ($p<0.001$) and less likely to have enrolled as part of a household cluster ($p<0.001$). As a group, these subjects were also older ($p<0.001$), male ($p=0.001$), black ($p<0.001$), had high prevalence of Hepatitis B or C ($p<0.001$) and other liver disease ($p=0.002$), and had high proportions of injection drug users ($p<0.001$), people with history of incarceration ($p<0.001$), current cigarette smokers ($p<0.001$), unemployed ($p<0.001$), and homeless ($p<0.001$) compared to subjects who were not receiving methadone maintenance therapy. Baseline characteristics of subjects stratified by LTBI treatment regimen and by methadone maintenance therapy can be seen in the Appendix (Table A).

*Treatment Completion*

Of the 6242 subjects in this analysis, 4917 (78.77%) completed LTBI treatment. Factors that had significant independent associations with treatment completion are presented in Table 2. In the univariate analysis, subjects randomized to the 3HP regimen had odds of completion 74.9% higher than subjects randomized to the 9H regimen ($p<0.001$) and enrollment in the US/Canada was also associated with higher likelihood of treatment completion ($p=0.001$). Factors that had significant independent associations with being less likely to complete treatment include birthplace in the US/Canada ($p<0.001$), Hepatitis B or C ($p=0.041$), history of alcohol abuse ($p<0.001$), history of alcohol use ($p=0.01$), history of injection drug use ($p=0.001$), history of incarceration ($p<0.001$), current cigarette smoking ($p<0.001$), unemployment ($p=0.008$), and

homelessness ($p<0.001$). Not all of these factors were included in the multivariate model, after following the modeling strategy described previously in Methods.

Results from the multivariate model, which assesses the relationship of the exposures (treatment regimen, methadone maintenance therapy, and an interaction between the two) with the outcome (LTBI treatment completion), controlling for unemployment and current smoking, are also presented in Table 2. There is no evidence that the model lacks fit for the data, with a Hosmer-Lemeshow statistic of 2.75 ($p=0.739$). Characteristics of subjects stratified by treatment completion can be found in Table B of the Appendix.

Adjusting for unemployment and current smoking, concomitantly receiving methadone maintenance therapy significantly lowers the odds of LTBI treatment completion for subjects being treated with the 3HP regimen (Table 3). Among subjects who were not receiving methadone, subjects randomized to 3HP were nearly twice as likely to complete treatment compared to those randomized to 9H ($p<0.001$). This echoes results published in 2011 from the main study, which found that treatment completion was higher for 3HP compared to 9H (4). However, among those randomized to 3HP, odds of completion were only half as high for subjects who were also receiving methadone compared to subjects who were not receiving methadone ($p=0.026$).

There was no significant difference in odds of completion between subjects receiving methadone who were randomized to 3HP and subjects receiving methadone who were randomized to 9H ($p=0.150$). Among those randomized to 9H, odds of completion were 73% higher for subjects receiving methadone than for other subjects, although this finding was also not significant ($p=0.067$). Nor was there a significant difference in odds

of completion between subjects receiving methadone who were randomized to 3HP and subjects not receiving methadone who were randomized to 9H (p=0.927).

*Development of methadone withdrawal*

Of 137 subjects who concomitantly received methadone maintenance therapy during LTBI treatment, 38 (27.7%) subjects developed methadone withdrawal (Table 4). While 11 of 73 (15.1%) subjects who were randomized to the 9H treatment arm developed withdrawal, 27 of 64 (42.2%) subjects who were randomized to the 3HP treatment arm developed withdrawal. Nineteen of 38 (50%) subjects who developed withdrawal symptoms were unable to complete treatment, compared to 17 of the 99 (17.2%) subjects who did not develop withdrawal symptoms (p<0.001).

Subjects receiving methadone maintenance therapy who were randomized to the 3HP treatment regimen were significantly more likely to develop withdrawal than those randomized to the 9H treatment arm (Table 5). In the univariate analysis, those randomized to 3HP had odds of withdrawal 4.1 times the odds of those randomized to 9H (p<0.001), and this increased to 5.6 times (p<0.001) after adjusting for concomitant medications and history of injection drug use.

Race, gender, and history of injection drug use were also independently associated with withdrawal. Blacks had odds of withdrawal only one-third those of whites (p=0.005). Females had odds of withdrawal 2.4 times as high as odds for males (p=0.029). Injection drug users had odds of withdrawal almost three times as high as those for subjects with no history of injection drug use (p=0.046). It was necessary to adjust for concomitant medications and history of injection drug use when estimating the

odds ratio for withdrawal in subjects receiving 3HP versus 9H, based on a confounding assessment that checked for a greater than 10% change in odds ratio estimate. There is no evidence that the multivariate model lacks fit for the data, with a Hosmer-Lemeshow statistic of 2.19 ($p=0.949$).

## DISCUSSION

For the vast majority of subjects—who were not receiving methadone maintenance therapy—3HP boasted higher completion rates than 9H. Results indicate that subjects treated for LTBI who were not also receiving methadone maintenance therapy had odds of completing LTBI treatment almost twice as high when treated with three months of a weekly rifapentine-containing regimen compared to nine months of daily isoniazid ($p<0.001$).

However, among the subjects who were treated with three months of rifapentine plus isoniazid, odds of completion were lowered by almost 50% if also receiving methadone maintenance therapy ($p=0.026$).

It appears that rifapentine, like rifampin, interacts with methadone in a way that results in the appearance of withdrawal symptoms when medications are given concomitantly, making it difficult for the patient to continue with the LTBI treatment regimen. Subjects receiving 3HP during methadone maintenance therapy had odds of developing withdrawal more than five times the odds for subjects receiving 9H during methadone maintenance therapy, after adjusting for other concomitant medications and history of injection drug use ($p<0.001$). Among subjects receiving methadone

maintenance therapy, only 50% of subjects who developed withdrawal went on to complete LTBI treatment, while 83% of subjects who did not develop withdrawal went on to complete LTBI treatment ($p<0.001$).

It is of note that the odds ratio comparing withdrawal among those receiving 3HP to those receiving 9H may underestimate the relative odds because the 3HP regimen is six months shorter than the 9H regimen. It is likely that some people who receive methadone maintenance therapy will experience withdrawal regardless of whether they are being treated for LTBI, and if it was possible to control for length of treatment, we may see relative odds of withdrawal even higher for the 3HP regimen compared to the 9H regimen.

In order to obtain an estimate of the effect of LTBI treatment regimen on development of methadone withdrawal, the model adjusted for concomitant medications and history of injection drug use because both of these factors were determined to be confounders of the true association between LTBI treatment regimen and methadone withdrawal. Inhibition or induction of CYP3A4 leads to a subsequent increase or decrease, respectively, of the amount of methadone in blood and tissues (7). Any medication that acted as an inhibitor or inducer of CYP3A4 may have decreased or increased the rate at which methadone was metabolized, thus affecting the development of withdrawal symptoms. In this context, it makes sense that the model adjusted for number of concomitant medications. In addition, it is possible that subjects taking many concomitant medications were sicker in general, predisposing them to the symptoms associated with withdrawal.

We can also extrapolate from this model that after adjusting for LTBI treatment regimen and concomitant medications, those with a history of injection drug use had odds of withdrawal more than three times odds for those with no history of injection drug use ($p=0.023$). This may imply that the development of withdrawal symptoms is related to the type of opioid abuse that preceded methadone maintenance therapy. For substances in general, the onset and course of withdrawal syndrome are related to the type of substance and the dose taken prior to cessation or reduction (24). Further research may be required to determine if withdrawal is more likely in people receiving methadone maintenance therapy to treat addiction to injection drugs, as opposed to addiction to drugs administered by some other route.

The primary goal of this analysis was to determine two relationships: (a) the relationship between LTBI treatment regimen, methadone maintenance therapy, and LTBI treatment completion, and (b) the relationship between LTBI treatment regimen and the development of methadone withdrawal. To do this, logistic regression models were fit to determine the most accurate and precise effect estimates for these relationships, while controlling for other factors that may confound the relationships. The goal of this analysis was not to fit predictive models that account for all factors which may influence treatment completion and the development of methadone withdrawal, hence why not all of the factors significant in the univariate analysis were included in the multivariate models. However, the significant univariate relationships seen in Tables 2 and 5 may inform future research or practice. For example, factors that independently decrease subjects' likelihood of completing treatment include Hepatitis B or C, history of alcohol abuse or use, history of injection drug use, history of incarceration, current

cigarette smoking, unemployment, and homelessness, so it may be helpful to note which LTBI patients have these characteristics and to more closely monitor them during the course of treatment.

*Limitations*

The primary objectives of this analysis were part of a secondary objective of the study for which this data was collected. The study did not specifically recruit subjects who were receiving methadone maintenance therapy. About 2.2% of study participants included in this analysis concomitantly received methadone during study treatment. The relatively small number of study participants who received methadone during study treatment may be a limitation of this analysis. However, this study has been the only clinical trial to date to collect detailed information about methadone maintenance therapy during LTBI treatment with rifapentine.

To assess the interaction between methadone and rifapentine was not the primary objective of the original study, and thus a related potential limitation is that some data regarding methadone maintenance therapy was collected retrospectively. Sites were contacted to determine dose and duration of subjects' methadone use where information on case report forms was inadequate. However, for most subjects, data concerning methadone maintenance therapy was reported in full during the study period.

The symptoms of methadone withdrawal can be general: symptoms like abdominal cramps, body aches, runny nose, nausea, and vomiting are non-specific to withdrawal and can be associated with seasonal influenza or rifapentine drug hypersensitivity reactions. Therefore, it is a possibility that methadone withdrawal could be misclassified. However,

the narratives written for each methadone withdrawal case were detailed, and included patient history, methadone use, changes in methadone dose, symptoms reported during treatment, notes written by study coordinators during patient evaluations, and a description of adverse events, in a chronological manner, in order to facilitate an accurate assessment of whether methadone withdrawal occurred. Therefore, even if misclassification occurred, it was minimized and was non-differential by LTBI treatment regimen.

Additionally, this analysis did not adjust for methadone dose or change in methadone dose, nor did it adjust for change in subjects' weight, which can influence the rate at which methadone is metabolized in the body. Further research may be needed to determine whether prophylactic increase in methadone dose helps to mitigate the appearance of withdrawal symptoms associated with rifapentine.

## CONCLUSION

Overall, 4917 of 6242 (79%) subjects completed LTBI treatment. However, completion rates were differential by LTBI treatment regimen and whether subjects were concomitantly receiving methadone maintenance therapy. Among subjects not receiving methadone, 3HP was associated with significantly higher odds of treatment completion compared to 9H (OR=1.809, $p<0.001$), but subjects receiving 3HP during methadone maintenance therapy were significantly less likely to complete treatment than subjects receiving 3HP alone (OR=0.539, $p=0.026$). Among subjects concomitantly receiving methadone maintenance therapy, 38 of 137 (27.7%) developed methadone withdrawal,

and 19 of these 38 (50%) were unable to complete LTBI treatment. The rifapentine-containing 3HP treatment regimen was associated with odds of developing withdrawal symptom 5.6 times those of the 9H treatment regimen ($p<0.001$). In conclusion, clinicians should give careful consideration to prescribing rifapentine-containing regimens to treat LTBI in those who currently receive methadone maintenance therapy. At least monthly monitoring of patients for the appearance of early withdrawal symptoms during treatment, and consideration of methadone dose adjustment if necessary, may increase likelihood of LTBI treatment completion due to prevention of development of withdrawal syndrome.

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## TABLES

**Table 1**. Baseline characteristics of subjects receiving methadone maintenance therapy and subjects not receiving methadone maintenance therapy

| Characteristic | Subjects receiving methadone (N=137) | Subjects not receiving methadone (N=6105) | p-value |
|---|---|---|---|
| **LTBI treatment**—no. (%) | | | |
| *3HP* | 64 (46.72) | 3199 (52.40) | 0.188 |
| *9H* | 73 (53.28) | 2906 (47.60) | |
| **Enrolled in US/Canada**—no. (%) | 131 (95.62) | 5849 (95.81) | 0.914 |
| **Birthplace in US/Canada**—no. (%) | 124 (90.51) | 2489 (40.77) | <0.001* |
| **Race**—no. (%) | | | |
| *White* | 53 (38.69) | 3465 (56.76) | ref |
| *Black* | 80 (58.39) | 1488 (24.37) | <0.001* |
| *Other* | 4 (2.92) | 1152 (18.87) | 0.002* |
| **Enrolled in cluster**—no. (%) | 3 (2.19) | 1698 (27.81) | <0.001* |
| **Male–** no. (%) | 95 (69.34) | 3380 (55.36) | 0.001* |
| **Age**, years—median (IQR) | 46 (41, 51) | 37 (28, 48) | <0.001* |
| **Completed high school**—no. (%) | 78 (56.93) | 3894 (63.78) | 0.178 |
| **Liver disease**—no. (%) | | | |
| *Hepatitis B or C* | 64 (46.72) † | 204 (3.34) ‡ | <0.001* |
| *Other chronic liver condition* | 5 (3.65) | 70 (1.15) | 0.002* |
| **LTBI Diagnosis**—no. (%) | | | |
| *Contact of infectious TB case* | 19 (13.87) § | 4103 (67.21) \|\| | ref |
| *Tuberculin skin test (TST) converter* | 101 (73.72) | 1655 (27.11) ¶ | <0.001* |
| *HIV positive (documented)* | 15 (10.95) | 182 (2.98) | <0.001* |
| *Fibrosis on chest X-ray* | 2 (1.46) | 165 (2.70) | 0.196 |
| **Concomitant medications**—no. (%) | | | |
| *≥5* | 30 (21.90) | 647 (10.60) | <0.001* |
| *1 to 4* | 47 (34.31) | 2315 (37.92) | 0.813 |
| **Alcohol**—no. (%) | | | |
| *History of abuse* | 16 (11.68) | 470 (7.70) | 0.065 |
| *History of use* | 64 (46.72) | 2797 (45.81) | 0.488 |
| **History of injection-drug use**—no. (%) | 102 (74.45) | 179 (2.93) | <0.001* |
| **History of incarceration**—no. (%) | 36 (26.28) | 353 (5.78) | <0.001* |
| **Current cigarette smoker**—no. (%) | 125 (91.24) | 1808 (29.62) | <0.001* |
| **Unemployment**—no. (%) | 71 (51.82) | 720 (11.79) | <0.001* |
| **Homelessness**—no. (%) | 24 (17.52) | 482 (7.90) | <0.001* |

* Significant at alpha=0.05

†3 (2.19%) have Hepatitis B only; 48 (35.04%) have Hepatitis C only; 13 (9.49%) have both

‡ 71 (1.16%) have Hepatitis B only; 120 (1.97%) have Hepatitis C only; 13 (0.21%) have both

§4 also TST converter; 6 also HIV-positive; 1 also TST converter and HIV -positive

|| 414 also TST converter; 27 also HIV-positive; 1 also TST converter and HIV-positive; 5 also had fibrosis on chest x-ray

¶ 9 also HIV-positive; 2 also had fibrosis on chest x-ray

**Table 2**. Univariate and multivariate analysis of factors associated with LTBI treatment completion

| Risk factor | Univariate analysis | | Multivariate analysis | |
|---|---|---|---|---|
| | Odds Ratio (95% CI) | p-value | Odds Ratio (95% CI) | p-value |
| **LTBI treatment:** 3HP vs. 9H † | 1.749 (1.546, 1.978) | <0.001* | 1.809 (1.596, 2.050) | <0.001* |
| **Methadone maintenance** vs. not † | 0.779 (0.528, 1.150) | 0.209 | 1.725 (0.963, 3.090) | 0.067 |
| **Enrolled in US/Canada** vs. outside US/Canada | 1.909 (1.318, 2.764) | 0.001* | | |
| **Birthplace in US/Canada** vs. outside US/Canada | 0.743 (0.658, 0.839) | <0.001* | | |
| **Race** | | | | |
| *Black* | 1.103 (0.953, 1.276) | 0.188 | | |
| *Other* | 1.264 (1.068, 1.496) | 0.006* | | |
| *White* | ref | | | |
| **Enrolled in cluster** vs. not enrolled in cluster | 1.145 (0.997, 1.316) | 0.056 | | |
| **Female** vs. male | 0.956 (0.846, 1.080) | 0.472 | | |
| **Age ≥35 years** vs. <35 years | 0.941 (0.831, 1.065) | 0.337 | | |
| **Did not complete** vs. completed high school | 0.905 (0.798, 1.026) | 0.119 | | |
| **Liver disease** | | | | |
| *Hepatitis B or C* | 0.747 (0.565, 0.988) | 0.041* | | |
| *Other liver disease* | 0.679 (0.409, 1.128) | 0.135 | | |
| *No liver disease* | ref | | | |
| **Alcohol** | | | | |
| *History of abuse* | 0.516 (0.416 0.639) | <0.001* | | |
| *History of use* | 0.801 (0.704, 0.911) | 0.01* | | |
| *No history of use* | ref | | | |
| **History of injection drug use** vs. no history | 0.614 (0.472, 0.799) | 0.001* | | |
| **History of incarceration** vs. no history | 0.572 (0.458, 0.716) | <0.001* | | |
| **Current cigarette smoker** vs. not current smoker | 0.752 (0.662, 0.855) | <0.001* | 0.768 (0.671, 0.879) | <0.001* |
| **Unemployment** vs. employment | 0.791 (0.665, 0.942) | 0.008* | 0.854 (0.711, 1.026) | 0.091 |
| **Homelessness** vs. no homelessness | 0.679 (0.553, 0.834) | <0.001* | | |

* Significant at alpha=0.05.

† The multivariate model includes a significant interaction term (p=0.0037) between LTBI treatment regimen and methadone maintenance therapy

**Table 3**. Odds ratios and 95% confidence intervals for LTBI treatment completion †

| | Odds Ratio (95% CI) | p-value |
|---|---|---|
| **Effect of 3HP among those not receiving methadone** | | |
| 3HP, no methadone maintenance therapy | 1.809 (1.597, 2.050) | <0.001* |
| 9H, no methadone maintenance therapy | ref | |
| **Effect of methadone among those randomized to 3HP** | | |
| 3HP, methadone maintenance therapy | 0.539 (0.312, 0.929) | 0.026* |
| 3HP, no methadone maintenance therapy | ref | |
| **Effect of 3HP among those receiving methadone** | | |
| 3HP, methadone maintenance therapy | 0.565 (0.260, 1.229) | 0.150 |
| 9H, methadone maintenance therapy | ref | |
| **Effect of methadone among those randomized to 9H** | | |
| 9H, methadone maintenance therapy | 1.725 (0.963, 3.091) | 0.067 |
| 9H, no methadone maintenance therapy | ref | |
| **Combined effect of 3HP and methadone** | | |
| 3HP, methadone maintenance therapy | 0.975 (0.566, 1.679) | 0.927 |
| 9H, no methadone maintenance therapy | ref | |

* Significant at alpha=0.05

† Adjusted for unemployment and current smoking

**Table 4**. Characteristics of 137 subjects receiving methadone maintenance therapy

| | **Methadone withdrawal (N=38)** | **No methadone withdrawal (N=99)** | **p-value** |
|---|---|---|---|
| **Total**—no. (%) † | 38 (27.74) | 99 (72.26) | - |
| **LTBI treatment regimen**—no. (%) | | | |
| *3HP* | 27 (71.05) | 37 (37.37) | <0.001* |
| *9H* | 11 (28.95) | 62 (62.63) | |
| **Race**—no. (%) | | | |
| *White* | 22 (57.89) | 31 (31.31) | ref |
| *Black* | 15 (39.47) | 65 (65.66) | 0.004* |
| *Other* | 1 (2.63) | 3 (3.03) | 0.641 |
| **Male**—no. (%) | 21 (55.26) | 74 (74.75) | 0.027* |
| **Age**, years—median (IQR) | 48 (41, 53) | 45 (41, 50) | 0.235 |
| **Liver disease**—no. (%) | | | |
| *Hepatitis B or C* | 19 (50.0) | 45 (45.45) | 0.921 |
| *Other* | 1 (2.63) | 4 (4.04) | 1.0 |
| **Concomitant medications**—no. (%) | | | |
| *≥5* | 9 (23.68) | 21 (21.21) | 0.613 |
| *1 to 4* | 14 (36.84) | 33 (33.33) | 0.580 |
| **Alcohol**—no. (%) | | | |
| *History of abuse* | 5 (13.16) | 11 (11.11) | 0.748 |
| *History of use* | 19 (50.0) | 45 (45.45) | 0.527 |
| **History of injection drug use**—no. (%) | 33 (86.84) | 69 (69.70) | 0.039* |

* Significant at alpha=0.05
† Row percent

**Table 5**. Univariate and multivariate analysis of factors associated with methadone withdrawal

| | **Univariate analysis** | | **Multivariate analysis** | |
|---|---|---|---|---|
| | Odds Ratio (95% CI) | p-value | Odds Ratio (95% CI) | p-value |
| **LTBI treatment regimen:** 3HP vs. 9H | 4.113 (1.828, 9.252) | <0.001* | 5.604 (2.304, 13.633) | <0.001* |
| **Race** | | | | |
| *Black* | 0.325 (0.149, 0.712) | 0.005* | | |
| *Other* | 0.470 (0.046, 4.819) | 0.525 | | |
| *White* | ref | | | |
| **Female** vs. male | 2.396 (1.094, 5.248) | 0.029* | | |
| **Age,** years | 1.021 (0.979, 1.065) | 0.329 | | |
| **Liver disease** | | | | |
| *Hepatitis B or C* | 1.126 (0.525, 2.413) | 0.760 | | |
| *Other* | 0.667 (0.070, 6.373) | 0.725 | | |
| *None* | ref | | | |
| **Concomitant medications** | | | | |
| *≥5* | 1.286 (0.485, 3.410) | 0.614 | 1.653 (0.547, 4.990) | 0.373 |
| *1 to 4* | 1.273 (0.541, 2.995) | 0.581 | 1.883 (0.718, 4.938) | 0.198 |
| *None* | ref | | ref | |
| **Alcohol** | | | | |
| *History of abuse* | 1.396 (0.413, 4.715) | 0.591 | | |
| *History of use* | 1.297 (0.579, 2.906) | 0.528 | | |
| *No history of use* | ref | | | |
| **History of injection drug use** vs. no history | 2.869 (1.021, 8.067) | 0.046* | 3.612 (1.191, 10.953) | 0.023* |

*Significant at alpha=0.05

# APPENDIX

**Table A**. Baseline characteristics of subjects by LTBI treatment arm and by methadone maintenance therapy

| | Randomized to 3HP (N=3263) | | Randomized to 9H (N=2979) | |
|---|---|---|---|---|
| | **Methadone maintenance** | **No methadone maintenance** | **Methadone maintenance** | **No methadone maintenance** |
| **Total—**no. (%) * | 64 (1.03) | 3199 (51.25) | 73 (1.17) | 2906 (46.56) |
| **Enrolled in US/Canada**—no. (%) | 60 (93.75) | 3046 (95.22) | 71 (97.26) | 2803 (96.46) |
| **Birthplace in US/Canada**—no. (%) | 57 (89.06) | 1299 (40.61) | 67 (91.78) | 1190 (40.95) |
| **Race—**no. (%) | | | | |
| *White* | 27 (42.19) | 1797 (56.17) | 26 (35.62) | 1668 (57.40) |
| *Black* | 33 (51.56) | 782 (24.45) | 47 (64.38) | 706 (24.29) |
| *Other* | 4 (6.25) | 620 (19.38) | 0 (0.0) | 532 (18.31) |
| **Subjects enrolled in cluster**—no. (%) | 3 (4.69) | 982 (30.70) | 0 (0.0) | 716 (24.64) |
| **Male sex**—no. (%) | 45 (70.31) | 1777 (55.55) | 50 (68.49) | 1603 (55.16) |
| **Age,** years—median (IQR) | 46 (39, 52) | 38 (28, 48) | 46 (42, 50) | 37 (28, 47) |
| **Completed high school**—no. (%) | 35 (54.69) | 2032 (63.52) | 43 (58.90) | 1862 (64.07) |
| **Liver disease—**no. (%) | | | | |
| *Hepatitis B or C* | 26 (40.63) | 103 (3.22) | 38 (52.05) | 101 (3.48) |
| *Other chronic liver condition* | 2 (3.13) | 39 (1.22) | 3 (4.11) | 31 (1.07) |
| **LTBI Diagnosis—**no. (%) | | | | |
| *Contact of infectious TB case* | 9 (14.06) | 2187 (68.37) | 10 (13.70) | 1916 (65.93) |
| *Tuberculin skin test (TST) converter* | 50 (78.13) | 829 (25.91) | 51 (69.86) | 826 (28.42) |
| *HIV positive (documented)* | 5 (7.81) | 104 (3.25) | 10 (13.70) | 78 (2.68) |
| *Fibrosis on chest X-ray* | 0 (0.0) | 79 (2.47) | 2 (2.74) | 86 (2.96) |
| **Concomitant medications—**no. (%) | | | | |
| *≥5* | 10 (15.63) | 282 (8.82) | 20 (27.40) | 365 (12.56) |
| *1 to 4* | 18 (28.13) | 1182 (36.95) | 29 (39.73) | 1133 (38.99) |
| **Alcohol**—no. (%) | | | | |
| *History of abuse* | 7 (10.94) | 269 (8.41) | 9 (12.33) | 201 (6.92) |
| *History of use* | 30 (46.88) | 1423 (44.48) | 34 (46.58) | 1374 (47.28) |
| **History of injection drug use**—no. (%) | 45 (70.31) | 104 (3.25) | 57 (78.08) | 75 (2.58) |
| **History of incarceration**—no. (%) | 14 (21.88) | 206 (6.44) | 22 (30.14) | 147 (5.06) |
| **Current cigarette smoker**—no. (%) | 59 (92.19) | 959 (29.98) | 66 (90.41) | 849 (29.22) |
| **Unemployment**—no. (%) | 31 (48.44) | 390 (12.19) | 40 (54.79) | 330 (11.36) |
| **Homelessness**—no. (%) | 7 (10.94) | 284 (8.88) | 17 (23.29) | 198 (6.81) |

* Row percent

**Table B**. Characteristics of subjects by LTBI treatment completion

| | **Completed LTBI treatment** | **Did not complete LTBI treatment** |
|---|---|---|
| **Total** | 4919 (78.80) | 1323 (21.20) |
| **LTBI Treatment—no. (%)** | | |
| *9H* | 2203 (44.79) | 776 (58.65) |
| *3HP* | 2716 (55.21) | 547 (41.35) |
| **Methadone maintenance treatment**—no. (%) | 102 (2.07) | 35 (2.65) |
| **Enrolled in US/Canada**—no. (%) | 4690 (95.34) | 1290 (97.51) |
| **Birthplace in US/Canada**—no. (%) | 1983 (40.31) | 630 (47.62) |
| **Race—**no. (%) | | |
| *White* | 2733 (55.56) | 785 (59.33) |
| *Black* | 1244 (25.29) | 324 (24.49) |
| *Other* | 942 (19.15) | 214 (16.18) |
| **Subjects enrolled in cluster**—no. (%) | 1368 (27.81) | 333 (25.17) |
| **Male**—no. (%) | 2750 (55.91) | 725 (54.80) |
| **Age**, years—median (IQR) | 37 (28, 48) | 38 (29, 48) |
| **Age ≥35 years**—no. (%) | 2910 (59.16) | 802 (60.62) |
| **Completed high school**—no. (%) | 3155 (64.14) | 817 (61.75) |
| **Liver disease**—no. (%) | | |
| *Hepatitis B or C* | 198 (4.03) | 70 (5.29) |
| *Other chronic liver condition* | 54 (1.10) | 21 (1.59) |
| **LTBI Diagnosis**—no. (%) | | |
| *Contact of infectious TB case* | 3190 (64.85) | 932 (70.45) |
| *Tuberculin skin test (TST) converter* | 1416 (28.79) | 340 (25.70) |
| *HIV positive (documented)* | 172 (3.50) | 25 (1.89) |
| *Fibrosis on chest X-ray* | 141 (2.87) | 26 (1.97) |
| **Concomitant medications**—no. (%) | | |
| *≥5* | 520 (10.57) | 157 (11.87) |
| *1 to 4* | 1853 (37.67) | 509 (38.47) |
| **Alcohol**—no. (%) | | |
| *History of abuse* | 337 (6.85) | 149 (11.26) |
| *History of use* | 2227 (45.27) | 634 (47.92) |
| **History of injection drug use**—no. (%) | 197 (4.00) | 84 (6.35) |
| **History of incarceration**—no. (%) | 268 (5.45) | 121 (9.15) |
| **Current cigarette smoker**—no. (%) | 1458 (29.64) | 475 (35.90) |
| **Unemployment**—no. (%) | 595 (12.10) | 196 (14.81) |
| **Homelessness**—no. (%) | 366 (7.44) | 140 (10.58) |