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Defining dosing pattern characteristics of successful tapers following methadone maintenance treatment: Results from a population-based retrospective cohort study

Bohdan Nosyk, PhD[1,2], **Huiying Sun, PhD**[3], **Elizabeth Evans, MA**[2], **David C. Marsh, MD, FRCPC**[4], **M. Douglas Anglin, PhD**[2], **Yih-Ing Hser, PhD**[2], and **Aslam H. Anis, PhD**[3,5]

[1]BC Centre for Excellence in HIV/AIDS, 613-1081 Burrard Street, Vancouver BC, V6Z 1Y6

[2]UCLA Integrated Substance Abuse Programs, Semel Institute for Neuroscience and Human Behavior, Department of Psychiatry and Biobehavioral Sciences, David Geffen School of Medicine, 1640 S. Sepulveda Blvd., 200, Los Angeles, CA, 90025, United States

[3]Centre for Health Evaluation & Outcome Sciences, 620B-1081 Burrard Street, Vancouver, BC, V6Z 1Y6, Canada

[4]Northern Ontario School of Medicine, 935 Ramsey Lake Rd, Sudbury, ON, P3E 2C6, Sudbury, Ontario, Canada

[5]School of Population and Public Health, University of British Columbia, 2206 East Mall, Vancouver, BC V6T 1Z3 Vancouver, British Columbia, Canada

Abstract

Aims—Identify dose tapering strategies associated with sustained success following methadone maintenance treatment (MMT).

Design—Population-based retrospective cohort study.

Setting—Linked administrative medication dispensation data from British Columbia, Canada.

Participants—From 25,545 completed MMT episodes, 14,602 of which initiated a taper, 4,183 individuals (accounting for 4,917 MMT episodes) from 1996–2006 met study inclusion criteria.

Measurements—The primary outcome was sustained successful taper, defined as a daily dose ≤5mg per day in the final week of the treatment episode and no treatment re-entry, opioid-related hospitalization, or mortality within 18 months following episode completion.

Findings—The overall rate of sustained success was 13% among episodes meeting inclusion criteria (646/4,917), 4.4% (646/14,602) among all episodes initiating a taper, and 2.5% (646/25,545) among all completed episodes in the dataset. The results of our multivariate logistic regression analyses suggested that longer tapers had substantially higher odds of success (12–52 weeks vs. <12 weeks: Odds ratio: 3.58; 95% confidence interval: 2.76 – 4.65); > 52 weeks vs. < 12 weeks: 6.68 (5.13 – 8.70)), regardless of how early in the treatment episode the taper was initiated, and a more gradual, stepped tapering schedule, with dose decreases scheduled in only 25–50% of the weeks of the taper, provided the highest odds of sustained success (vs. <25%: 1.61 (1.22–2.14)).

Contact Information for corresponding author: Bohdan Nosyk, PhD, 613-1081 Burrard Street, Vancouver, BC V6Z 1Y6, Telephone: 604-806-8649, Fax: 604-806-8778, bnosyk@cfenet.ubc.ca.

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Conclusions—The majority of patients attempting to taper from methadone maintenance treatment will not succeed. Success is enhanced by gradual dose reductions interspersed with periods of stabilization. These results can inform the development of a more refined guideline for future clinical practice.

INTRODUCTION

Opioid dependence is a chronic, recurrent disease[1] and long-term patient maintenance on pharmacotherapeutic agents has been recognized as a key component of effective treatment[2]. Methadone maintenance treatment (MMT) is the most common and effective treatment for opioid dependence[3,4,5] and has been shown to improve health-related quality of life and protect against mortality while clients are engaged in treatment[6,7].

A randomized trial found MMT to be more effective in retaining individuals in treatment, reducing illicit drug use, drug-related HIV risk behaviours and illegal activity than long-term detoxification[8]. Systematic reviews of methadone detoxification indicated that while withdrawal severity can be reduced, the majority of patients relapse to heroin use[9], though success is more likely with additional psychosocial care[10]. In fact, very few patients complete the process of tapering from MMT[11–15], and relapse is common among those who do reach a state of abstinence[16]. Despite widespread indications for long-term maintenance and largely negative results for detoxification, whether by patient or physician choice, methadone detoxification and dose tapering among maintained clients is commonly observed worldwide[17–19]. Individuals may choose to detoxify due to unrealistic expectations for recovery, pressure from family members or others, the social stigma associated with methadone, program-related factors, factors associated with financial or travel restrictions, and a desire to determine whether clients can cope without treatment[20]. Alternatively, physicians may choose to taper clients for disciplinary reasons, or in some jurisdictions, due to funding constraints or by standardized regulations on clinical practice.

Despite over 40 years of experience and millions of clients served worldwide, a number of important questions regarding methadone dose tapering strategies remain. Do the commonly recommended weekly taper guidelines, ranging from 5–10%[21–23], achieve optimal outcomes? Should a constant rate of tapering be maintained throughout the tapering process? Rather than considering only the rate of tapering, is the time from treatment episode initiation and the duration of the taper important?

The sparse evidence available provides little insight into effective dosing strategies or other predictors of success. A randomized trial of 63 MMT clients in rapid (10% of initial dose per week) versus gradual (3% of initial dose per week) methadone tapering found gradual tapering to be more effective[24]. Several other short-term and small-sampled studies identified the length of time in opioid replacement treatment, sustained abstinence from illicit drug use during treatment, vocational / financial stability, social stability (socialization with non-drug users) and strong motivation to detoxify as factors associated with successful tapering[25–27], though there was wide variation in outcome measurement across studies. A more recent study of 30 maintained clients found no successful methadone tapers, 20 clients stopped their tapers due to drug relapse or medical instability, and 10 remained in treatment over a maximum 41 months of follow-up[12].

Questions regarding clinical guidance for methadone tapering remain unanswered due in part to a lack of available longitudinal data and feasibility of long-term experimental studies. Population-level analysis of dosing dynamics during MMT episodes is facilitated in British Columbia (BC), Canada by a centralized medication dispensation database covering the entire province[18,28]. Methadone is recommended to be delivered with a maintenance-

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oriented philosophy in BC. Treatment is provided by specially-licensed physicians in office-based settings or specialized drug treatment centres, some offering additional psychosocial care. In most cases, medication is dispensed and consumed at community pharmacies under direct supervision. The general ineffectiveness of detoxification treatment is recognized[29], and penalization of patients who relapse into illicit opioid use as well as voluntary withdrawal is discouraged. BC Provincial guidelines for dose tapering recommend a gradual taper at no more than 5% of initial dose per week[21,30].

Our objective was to identify methadone dose tapering strategies associated with sustained success in terms of health and treatment outcomes following maintenance treatment. We conduct a population-level study of methadone clients in British Columbia, Canada to fulfill this objective.

METHODS

Patient Population

This study utilized data from the British Columbia PharmaNet database, which records all prescription medication dispensation in the entire province of British Columbia. The cohort was selected from all individuals receiving methadone maintenance treatment (MMT) over an 11-year period: January 1, 1996 to December 31, 2006. Methadone prescribed for opioid dependence was distinguished from prescriptions for pain indications by separate drug identification numbers in the dataset. Data fields available included a de-identified patient ID, date of birth, gender, drug identification number, the date of the prescription (*date*), the length of the prescription (number of days supplied, or *days*), medication dosage (*quantity)*, de-identified prescriber code and pharmacy code, as well as a geographical identifier, aggregated by local health area. Data on hospitalizations from the BC Ministry of Health Discharge Abstract Database (dates and most responsible diagnoses of hospitalizations) and Vital Statistics (dates and causes of death) was linked to this database throughout the period of study follow-up through Population Data BC[31]. The study was approved by the University of British Columbia/Providence Health Care Behavioural Research Ethics Board.

Measures

Episode definition—MMT episodes were the focal point of our analysis. These were constructed using the *service date* and *days supplied* fields; a treatment episode length was calculated as the difference between the last and first days of dispensed medication (episode length = $((\text{date}_{t1} + \text{days}_{t1}) - \text{date}_{t0})$, where t_0 is the date of episode initiation, t_1 is last date of service, and days_{t1} is the duration of the dispensation at time t_1) within a period of continuous retention in treatment, entailing no interruptions in prescribed doses lasting longer than 30 days. We considered all MMT episodes beginning after January 31st, 1996 to ensure consistency in our calculation of episode lengths and eliminate left-censored observations. We focused our analysis on completed treatment episodes, thus also excluding right-censored observations. Efforts were made to correct any misclassification in the dataset in regards to prescribed doses, lengths and dates of prescriptions. Less than 1% of identified errors could not be corrected.

Taper definition and study selection criteria—Consistent with prior research[18], periods of dose tapering were identified by examining changes in the mean daily dose per week ($\text{mean dose}: \sum_{i=1}^{J} \frac{quantity_i}{days_i} / J, J \leq 7$) over the course of each episode. The onset of the tapering period was defined as first instance, after the 12-week point, where the weekly dose decreased and remained at or below this lower level for at least four weeks ($\text{dose}_{t-i} < \text{dose}_t \leq \text{dose}_{t+i}$, $i = (1,\ldots,4)$). This method was chosen to eliminate the possibility of

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misclassification of taper initiation as a result of dose titration, vacation catch-up prescriptions, database errors or otherwise. Further, preliminary analysis indicated that many episodes with an observed initiated taper were either reversed or reverted to a stabilized dose. In such cases, in the absence of information of patient or physician intentions (ie. maintenance dose adjustment or intended taper) we selected completed episodes in which the mean dose was either decreasing over the final four weeks of the episode, or had decreased to ≤5mg per day during this period (included if (i) ((mean $dose_{t-3}$ – mean $dose_T$) / mean $dose_T$)<0; or (ii) mean $dose_t$ ≤5 mg, where t = (t−3, t−2, t−1, T) and T is the terminal week of treatment). The durations of tapers were therefore a minimum of 4 weeks.

Sustained successful taper definition—Given that an administrative data source was used, information regarding opioid use beyond the conclusion of treatment episodes was not available, resulting in potential outcome misclassification. We therefore constructed a multi-attribute proxy measure, defined as 'sustained success in tapering' using all available linked administrative data. As successful dose tapering is only the initial requirement towards the ultimate goal of indefinite opioid abstinence[32,33], this measure of sustained success featured four criteria: (i) methadone dose tapered to ≤ 5mg/day in the final week of treatment, and within 18 months of treatment: (ii) no treatment re-entry; (iii) no drug-related hospitalization; and (iv) no mortality. The 18 month reference period was chosen based on distributions of time to treatment re-entry, to capture the majority of re-entries following successful tapering while maintaining sufficient patient follow-up.

Explanatory variables—As dose control is ultimately at the discretion of the physician, we were specifically interested in how dosing practices influenced the odds of sustained taper success. To this end, individual plots of weekly dose tapering trajectories were visually inspected to inform construction of relevant covariates capturing dose changes during the tapering period. A set of five covariates were constructed: (i) the taper start week (number of weeks since treatment episode initiation, defined as: mean $dose_t$ < (mean $dose_{t-1}$, …, mean $dose_{t-4}$); mean $dose_t$ ≥ (mean $dose_{t+1}$, …, mean $dose_{t+4}$); t ≥ 12 weeks), (ii) the total duration of the taper, from the taper start week to the end of the treatment episode (in weeks), (iii) the median rate of dose change through the duration of the taper ($\text{taper change rate}=\text{median}[(\frac{mean\ dose_t - mean\ dose_{t-1}}{mean\ does_{t-1}})*100]$, t = (taper start week, …,episode end week)), (iv) the median rate of dose change during weeks in which the dose was decreasing through the duration of the taper (ie. taper change rate when ($mean\ does_t - mean\ does_{t-1}$) < 0), and (v) the percentage of weeks during which the dose was decreasing through the duration of the taper.

Other covariates, added to control for potential confounding, included the maximum mean dose per week (maximum dose) during the treatment episode, treatment adherence (the percentage of missed doses during the treatment episode: ($\text{adherence}=\frac{\sum_{i=1}^{T} days_i}{episode\ length}$), where T=max{episode length}), age, gender, episode count, calendar year of episode initiation, and individuals' Charlson Comorbidity Index (CCI) score[34], based on hospitalizations during the period 6 months prior to treatment episode initiation. Continuous variables were categorized taking into account observed distributions, and with the intention of maximizing clinical interpretability.

Data Analysis

Univariate analyses were conducted to identify variables for inclusion in multivariate models. Multivariate logistic regression analysis was used to identify independent factors

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associated with sustained success. As some individuals had repeated taper attempts, generalized linear mixed regression models, with logit link and binomial distribution, were also estimated to capture unmeasured individual-specific confounding. Due to the collinearity and conceptual overlap between dose taper dynamics variables (ii), (iii), and (iv – v), three separate multivariate regression models were estimated with covariates (i) and (ii), (i) and (iii), and (i), (iv) and (v), controlling for all other covariates. These sets of variables capture different aspects of the taper, and thus provide complementary evidence on appropriate means of tapering. The goodness of fit of these three model formulations were compared using Akaike's and Bayesian Information Criteria (AIC and BIC). All analysis was executed with SAS version 9.2.

RESULTS

From a total of 32,656 treatment episodes captured in the study, 25,545 were noncensored, from which 14,602 were identified as having initiated a taper at some point during the episode. Among these episodes, 4,917 were decreasing or had decreased below 5mg/day in the final four weeks of the episode, thus meeting study inclusion criteria, and ended prior to July 1, 2005, thus allowing 18 months follow-up to verify our definition of sustained success. These episodes were counted amongst 4,183 unique individuals.

From the study sample of 4,917 treatment episodes, 1,305 (27%) episodes were completed with a daily dose ≤ 5mg/day, however among episodes reaching this criteria, 659 were followed by at least one of the following events: treatment re-entry within 18 months (458 episodes, 35.1% of all completed tapers), opioid-related hospitalization (319 (24.4%)), mortality (29 (2.2%)). As such, 1305 − 659 = 646 episodes (13% of the study sample) were defined as sustained successful tapers.

Summary statistics stratified by treatment outcome were presented in Table 1. Individuals with treatment episodes resulting in a sustained successful taper were younger, more likely to be male, had lower CCI scores, better treatment adherence, lower maximum mean weekly doses, and longer taper durations.

Results of multivariate analyses on the odds of sustained success in the three models tested were presented in Table 2. Patient demographics and treatment adherence variables were included in each model, and their effects were largely consistent across model formulations. Individuals of age 25–34 and 35–49 had 27–40% lower odds of sustained success in tapering compared to individuals younger than 25. Females also had lower odds of sustained success, with the most conservative estimated odds ratio suggesting 19% lower odds of sustained success compared to males (model 3:Odds Ratio:0.81; 95% Confidence Interval: (0.67–0.99)). Individuals with higher levels of medical comorbidity also had lower odds of sustained success in tapering, however this effect was not statistically significant in model 2, when tapering dynamics were represented with the taper duration (0.83(0.68–1.00). Later subsequent treatment episodes had lower odds of sustained success, while episodes initiated in more recent calendar years, controlling for all other measured covariates, had higher odds of sustained success in tapering.

Treatment adherence was included in each of the model formulations, and was positively associated with higher odds of sustained success. Our results suggest that a 1% increase in adherence resulted in a minimum 1.9% increase in the odds of success (model 2: 1.02(1.00–1.03)).

Results of model 1 suggest that individuals reaching a maximum dose of between 60–100mg and more than 100mg had 44% and 60% lower odds of sustained success in tapering compared to those maintained on lower doses. Univariate results were similar to those

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obtained in the multivariate model. An early taper start week (before week 12) had higher unadjusted odds of sustained success; however the adjusted effect was not statistically significant. Finally, more aggressive tapers had lower odds of sustained success, as episodes with median percentage decreases greater than 4% were nearly 27% less likely to result in sustained success (0.73(0.61–0.88)) in comparison to less aggressive tapers.

Model 2 indicated that taper duration was strongly associated with sustained success. Episodes in which the taper lasted 12–52 weeks were 3.58 times more likely to result in sustained success than those lasting <12 weeks (3.58(2.76–4.65)), while tapers lasting longer than 52 weeks were 6.7 times more likely to result in sustained success (6.68(5.13–8.70)).

Model 3 provides a refinement of model 1 results, indicating that tapers with 25–50% of weeks where the dose was decreasing had the highest odds of success (1.61(1.22–2.14)). In weeks during which the mean dose was decreasing, a median percentage change < 5% had lower odds of success (0.53(0.41–0.71) than episodes in which the median percentage change was 5%–15%, while higher percentage changes in mean dose when the dose was decreasing did not have statistically significantly different odds of sustained success.

Of the three models tested, Model 2, with taper dynamics represented by the taper duration covariate, provided the highest AIC and BIC values, indicating greatest model fit and thus highest explanatory power. Each model formulation was tested using a generalized linear mixed regression model; however given the low number of repeated taper episodes, results using this type of model were identical to the pooled analysis presented.

DISCUSSION

We designed our analysis to inform the development of improved clinical practices for methadone dose tapering. Cumulatively, the results of our multivariate analyses suggest that longer tapers had substantially higher odds of success, regardless of how early in the treatment episode they were initiated, and a more gradual tapering schedule, with dose decreases scheduled in only 25–50% of the weeks in treatment, provided the highest odds of sustained success in tapering. These results provide a more refined and informative guideline for future practice. However these results, and methadone dosing guidelines in general, are intended to supplement physician decision making, rather than replace it. While patient and physician decision-making were not observed in the database and though such actions were discouraged in clinical guidelines, one might speculate that the more aggressive tapers were disciplinary in nature. Regardless of the reason for such tapers, it is clear that outcomes are substantially poorer in such cases. On the other hand, episodes with more gradual tapering, resulting in higher odds of success may be indicative of individualized care, with doses titrated and tapered according to individual needs in suppressing withdrawal symptoms; a practice which is widely recommended[2,20–22].

While we have characterized dose tapering strategies with higher odds of sustained success, the overall rate of success was just 13% among episodes selected for this analysis, 4.4% (646/14,602) among all episodes initiating a taper, and 2.5% (646/25,545) among all completed episodes in the dataset. These poor outcomes are consistent with the findings of prior analyses[9–15], and are observed despite the frequency with which tapers are observed in BC, contrary to clinical guideline recommendations. Further, longer duration of exposure in treatment is associated with improved post-treatment outcomes such as reduced opioid use, reduced criminal activity, improved social productivity and reduced risk of mortality[29, 35–38]. While our focus in this manuscript has been on the technical aspects of therapeutic tapering, there a number of reasons why methadone maintenance clients may wish to achieve a drug-free state in the process of recovery from drug use[32,33]. However, the

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high risks of drug relapse and adverse health outcomes need to be communicated to clients choosing to do so. In light of these risks, an informed consent process should be considered by regulatory bodies before initiating a tapering schedule.

The negative relationship between the maximum, or maintenance dose, as well as results of later subsequent taper treatment episodes and the probability of success need to be interpreted carefully. A recent Cochrane review of dosing in MMT programs concluded that clients receiving maintenance doses of 60mg–100mg per day were retained in treatment longer than those on lower doses[39], while a previous analysis of this dataset confirmed this result and found maintenance doses >100mg/day were associated with longer retention in treatment[28]. Clinical guidelines in British Columbia instruct physicians to use discretion, and work with patients to provide individualized care in identifying a suitable dose which eliminates withdrawal symptoms and drug craving. That said, physician decision-making was not observed, and often times methadone dose is determined by the policies of individual practices. In cases where doses were titrated to individuals' needs, those requiring higher daily doses could be considered to have higher addiction severity requiring a higher maintenance dose and, perhaps not surprisingly, had lower odds of successfully tapering. Though the relationship between the maintenance dose and a prior drug use severity is not observed and therefore not testable in our dataset, the notion that higher a priori drug use severity decreases the likelihood of successful transition to abstinence is supported in the available literature[40,41].

Strengths and Weaknesses

There are notable limitations that are important to consider when interpreting results of this study. First, the outcome we've constructed based on the data available to us is a proxy of sustained abstinence, and cannot capture those that revert to illicit opioid use without returning to treatment or experiencing the adverse health outcomes included in the outcome. What is being assessed is therefore more indicative of medical safety and patient stability following treatment rather than drug relapse. Further study is needed to confirm these results prospectively and potentially over longer timeframes. Second, due to the nature of the dataset, physician decision-making was not observed, which required us to classify stages of the methadone treatment episodes, particularly the point of initiation of a taper, according to observed changes in doses. This needs to be considered carefully in further research, and practical application. Third, any non-experimental study may be subject to residual and/or unmeasured confounding[42] - in our case, we could not observe whether clients were primarily users of heroin or prescribed opioids, addiction severity, treatment setting (office-based versus drug treatment centre) or availability of additional psychosocial care and other potential confounders. In a separate analysis, we used the random-effects frailty term from a prior analysis on the time to discontinuation of repeated methadone treatment episodes as an additional covariate in each model to determine the potential effects of individual-level unmeasured confounding. Results were similar to those presented, with only minor differences in the magnitude of effect sizes. However, we are careful not to interpret the tested relationships as causal, as these unobserved factors may confound or modify the effects of dose changes on sustained success. Finally, the results in the current study represent outcomes of practices in British Columbia, Canada where treatment is heavily subsidized, a maintenance-oriented philosophy persists, and office-based treatment is available. In other settings, barriers due to financial constraints or availability may impact clinical practice and compromise treatment outcome.

The advantages of using this dataset, however, were substantial: availability of a centralized drug dispensation database allowed for a population-level study of methadone dose tapering among maintained clients unparalleled in size. The large sample size and level of detail in methadone dosing allowed us to classify and compare dose tapering strategies, providing

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new insights into clinical practice. We are hopeful that this study will spur further research on tapering strategies for clients in opioid substitution treatment programs wishing to achieve a state of opioid abstinence.

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Table 1

Summary statistics

	Taper with sustained success^ (n = 646)	Unsuccessful taper (n = 4271)
CCI Score Mean (SD)	0.04 (0.43)	0.16 (0.93)
Episode No., Median (IQR)	1 (1, 2)	1 (1, 2)
Calendar Year, Median (IQR)	5 (4, 6)	5 (3, 7)
% Treatment adherence*, Median (IQR)	96.4 (91.8, 98.5)	94.7 (88.6, 97.5)
Taper start week, Median (IQR)	19 (13, 37)	22 (14, 38)
Female, No. (%)	184 (28)	1464 (34)
Age, No. (%) : < 25	162 (25)	728 (17)
25–34	217 (34)	1573 (37)
35–49	231 (36)	1737 (41)
≥ 50	36 (6)	233 (5)
Maximum dose, No. (%) **: < 60mg pd.	247 (38)	1040 (24)
60–100mg pd.	287 (44)	2114 (50)
> 100mg pd.	112 (17)	1117 (26)
Taper length, No. (%): <12 weeks	88 (14)	1829 (43)
12–52 weeks	238 (37)	1303 (31)
>52 weeks	320 (50)	1139 (27)
% change in dose, No. (%): < 1%***	327 (51)	1909 (45)
1%–4%	81 (13)	548 (13)
> 4%	238 (37)	1814 (42)
% change in dose when decreasing, No. (%): < 5%	65 (10)	695 (16)
5–10%	283 (44)	1567 (37)
10–15%	154 (24)	883 (21)
> 15%	144 (22)	1126 (26)
% weeks dose decreased: < 25%	79 (12)	665 (16)
25–50%	230 (36)	1094 (26)
50–75%	176 (27)	975 (23)
75–90%	75 (12)	397 (9)
> 90%	86 (13)	1140 (27)

^ Defined as an episode in which the daily dose in the final week is ≤5mg/day, and within 18 months of episode completion, the individual does not re-enter treatment, is not hospitalized for a drug-related cause, and does not suffer mortality.

* percentage of days received medication during treatment episode;

** Maximum mean weekly dose through duration of treatment episode;

*** median percentage change in mean weekly dose through duration of taper.

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Table 2

Results of multivariate regression analysis of sustained success in dose tapering

	Unadjusted Odds Ratios	Adjusted Odds Ratios	Adjusted Odds Ratios	Adjusted Odds Ratios
		Model 1	Model 2	Model 3
Covariate	**Odds Ratio (95% CI)**	**Odds Ratio (95% CI)**	**Odds Ratio (95% CI)**	**Odds Ratio (95% CI)**
Age : < 25	Ref	Ref	Ref	Ref
25–34	0.62 (0.50 – 0.77)	0.71 (0.56 – 0.89)	0.78 (0.61 – 0.98)	0.72 (0.57 – 0.91)
35–49	0.60 (0.48 – 0.74)	0.69 (0.55 – 0.87)	0.76 (0.60 – 0.96)	0.70 (0.55 – 0.89)
≥ 50	0.69 (0.47 – 1.03)	0.71 (0.47 – 1.06)	0.79 (0.52 – 1.21)	0.74 (0.49 – 1.12)
Gender: Male	Ref	Ref	Ref	Ref
Female	0.76 (0.64 – 0.92)	0.79 (0.65 – 0.95)	0.75 (0.61 – 0.91)	0.81 (0.67 – 0.99)
CCI Score	0.75 (0.62 – 0.91)	0.82 (0.67 – 0.99)	0.84 (0.69 – 1.03)	0.82 (0.67 – 1.00)
Episode No.	0.71 (0.64 – 0.78)	0.72 (0.65 – 0.80)	0.73 (0.65 – 0.81)	0.73 (0.66 – 0.81)
Calendar Year	1.03 (0.99 – 1.07)	1.08 (1.04 – 1.13)	1.09 (1.05 – 1.15)	1.07 (1.02 – 1.12)
Treatment adherence *	1.04 (1.03 – 1.05)	1.04 (1.02 – 1.05)	1.02 (1.00 – 1.03)	1.03 (1.03 – 1.05)
Maximum dose **: < 60mg pd.	Ref	Ref		Ref
60–100mg pd.	0.57 (0.48 – 0.69)	0.56 (0.46 – 0.67)	0.46 (0.37 – 0.56)	0.58 (0.48 – 0.71)
> 100mg pd.	0.42 (0.33 – 0.54)	0.39 (0.31 – 0.51)	0.31 (0.23 – 0.40)	0.43 (0.33 – 0.55)
Taper start week	1.28 (1.03 – 1.59)	1.01 (1.00 – 1.01)	1.00 (1.00 – 1.00)	1.00 (1.00 – 1.01)
Taper length: <12 weeks	Ref		Ref	
12–52 weeks	3.80 (2.94 – 4.90)		3.58 (2.76 – 4.65)	
>52 weeks	5.84 (4.56 – 7.48)		6.68 (5.13 – 8.70)	
% change in dose: < 1% ***	Ref	Ref		
1%–4%	0.86 (0.67 – 1.12)	0.77 (0.59 – 1.01)		
> 4%	0.77 (0.64 – 0.92)	0.73 (0.61 – 0.88)		
% change in dose when decreasing: < 5%	0.52 (0.40 – 0.69)			0.53 (0.40 – 0.71)
5–15%	Ref			Ref
15–35%	0.75 (0.60 – 0.93)			1.03 (0.82 – 1.31)
35–50%	0.70 (0.43 – 1.16)			1.42 (0.83 – 2.43)
> 50%	0.42 (0.18 – 0.97)			1.12 (0.47 – 2.67)
% weeks dose decreased: < 25%	Ref			Ref
25–50%	1.77 (1.35 – 2.33)			1.61 (1.22 – 2.14)
50–75%	1.52 (1.14 – 2.02)			1.29 (0.96 – 1.73)
75–90%	1.59 (1.13 – 2.23)			1.32 (0.92 – 1.87)
> 90%	0.63 (0.46 – 0.87)			0.56 (0.40 – 0.79)
AIC	--	3631.82	3485.36	3569.91
BIC	--	3714.14	3548.12	3684.65

Ref: Reference group; 95% CI: 95% Confidence interval; AIC: Akaike's Information Criterion; BIC: Bayes Information Criterion.

* percentage of days received medication during treatment episode;

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** Maximum mean weekly dose through duration of treatment episode;

*** median percentage change in mean weekly dose through duration of taper. Blank cells indicate the variable was not included in the specified multivariate regression model.