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Temporal associations between medication adherence for patients with schizophrenia and opioid dependence: A 17-year Canadian Cohort Study

Stefanie N. Rezansoff *, Akm Moniruzzaman, Julian M. Somers

Somers Research Group, Faculty of Health Sciences, Simon Fraser University, 8888 University Drive, Burnaby V5A 1S6, British Columbia, Canada

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ABSTRACT

The current study investigated whether a previously reported beneficial effect of methadone maintenance therapy (MMT) on antiretroviral adherence is also present in relation to antipsychotic treatment for schizophrenia. Administrative data were linked over a 17-year period for 1996 people who were dually diagnosed with schizophrenia and opioid dependence and, as an indicator of further marginalization, experienced at least one episode of correctional supervision in British Columbia. Adherence was estimated using the medication possession ratio (MPR ≥ 0.80), calculated in each 120-day period beginning with the first date of concurrent use of MMT and antipsychotic medication. Generalized Estimating Equations were used to estimate the association between independent and dependent variables. The probability of antipsychotic adherence doubled in periods that were preceded by a period of MMT adherence (AOR: *P*: 2.07; 95% CI: 1.90–2.26). Subgroup and sensitivity analyses yielded results similar to those derived through the primary analysis, examining: conviction history; length of follow-up; initiation of MMT prior to antipsychotic induction; excluding participants who died during the study period; and restricted to participants who received methadone exclusively as part of a MMT program. Despite a strong temporal association between MMT and antipsychotic adherence, overall MPRs for both prescriptions remained <0.50 throughout the study period. Antipsychotic adherence was more than twice as likely following periods of adherence to MMT among dually-diagnosed patients. Research is needed to identify the conditions responsible for MMT adherence, and to further clarify the relationship between opioid agonist treatment and antipsychotic pharmacotherapy in this vulnerable and under-studied population.

1. Introduction

Estimates of the co-occurrence of schizophrenia and opioid dependence vary considerably, with high prevalence rates reported among people who are socially marginalized, such as those who have contact with the criminal justice system (CJS) (Robertson et al., 2018). For example, a recent study involving 14,590 methadone (MMT) patients with any lifetime CJS contact reported that the prevalence of schizophrenia in the cohort was 15% (Russolillo et al., 2018), in contrast to the estimated general population prevalence of 0.48% (Simeone et al., 2015).

Approximately half of all people living with schizophrenia are diagnosed with a lifetime comorbid substance use disorder (Kerner, 2015), undermining treatment adherence (Murphy and Chand, 2012), exacerbating the progression of symptoms (Schmidt et al., 2011), and increasing the risk of justice system involvement (Rezansoff et al., 2013). Pharmacotherapies are foundational components of care for schizophrenia and opioid dependence, however little published evidence specifically addresses concurrent antipsychotic and opioid agonist treatment (OAT), (e.g., methadone), and the coordinated delivery of these medications has been described as obviously important yet uncommon in practice (DeLisi and Fleischhacker, 2017). The clinical significance of concurrent prescribing was underscored in a large study of mortality among OAT patients, (spanning 16 years) which found a 2.3 times increased risk of death among those receiving concurrent antipsychotic medications (many prescribed off-label) (Leece et al., 2015).

While highly cost-effective (Krebs et al., 2018), OAT is considered underused in general (Vestal, 2016), and in correctional settings in particular (Moore et al., 2018; Gilmer et al., 2004) where risk of fatal overdose is the leading cause of death following release from custody (Pizzicato et al., 2018). Existing studies suggest that patients with schizophrenia may have a biological basis for self-medication, and particularly for the use of opioids (Schmauss et al., 1987).

While not all patients living with schizophrenia necessarily derive equal benefit from the use of antipsychotics, these medications are considered essential to the management of the disorder (Harrow and Jobe, 2013). Nonetheless, consistent adherence is recognized as the

* Corresponding author at: Faculty of Health Sciences, Simon Fraser University, 8888 University Drive, Burnaby V5A 1S6, British Columbia, Canada.
E-mail addresses: stefanie_rezansoff@sfu.ca (S.N. Rezansoff), akm_moniruzzaman@sfu.ca (A. Moniruzzaman), jsomers@sfu.ca (J.M. Somers).

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'exception to the rule' (Eckman et al., 1992) in treated samples, with non-adherence rates averaging 50% and ranging from 20% - 95% (Gilmer et al., 2004; Sendt et al., 2015). Suboptimal adherence is described as taking medication <80% of the time for which it is prescribed (Velligan et al., 2009), and is associated with increased risk of relapse, hospitalization and suicide, (Novick et al., 2010; Ascher-Svanum et al., 2006), lower quality of life (El-Azzab and Abu-Salem, 2018) involvement with the criminal justice system (Rezansoff et al., 2017a), and greater overall public costs (Predmore et al., 2015).

A potentially useful parallel can be drawn to the treatment of infectious disease among OAT recipients: Integrated OAT has been shown to improve the pharmacological management of highly active antiretroviral therapy (HAART) for the treatment of comorbid HIV (Simeone et al., 2017). Greater treatment engagement and HAART refill adherence (Cocohoba et al., 2003) have also been reported, in addition to superior patient outcomes (Palepu et al., 2006) and reduced risk of HAART cessation (Reddon et al., 2014). A *causal* relationship between OAT and HAART refill adherence has been demonstrated (Nosyk et al., 2015). Integrated OAT has also been linked with improved pharmacological management of hepatitis C (Harris et al., 2010) and tuberculosis (Batki et al., 2002). The effectiveness of integrated OAT on infectious disease management may be at least partially attributable to the stabilizing effects of OAT and related improvements in social functioning, maintaining a routine, and encouraging greater investment in overall health (Bruce et al., 2012; Reddon et al., 2014).

The current study investigated whether a similar temporal association exists between OAT adherence and subsequent adherence to antipsychotic medication among patients receiving concurrent treatment for opioid dependence and schizophrenia. We selected patients with criminal justice contact, given prior evidence of relevant medication-related risks among offenders (Rezansoff et al., 2013), and examined comprehensive pharmacy data spanning a 17-year period. We hypothesized that antipsychotic adherence would be significantly more likely following periods of adherence to OAT. Due to the lack of prior research, we also sought to characterize this patient group, including the prevalence and average duration of conjoint treatment.

2. Methods

2.1. Data sources

The study was approved by the Research Ethics Board at Simon Fraser University. Analyses were conducted using data from the British Columbia Inter-Ministry Initiative (IMRI) which integrates linked, non-identifying, administrative data from the Ministries of Health (1990–2015) and Justice (1997–2015). Details of the IMRI that are not essential to the current study have been described elsewhere (Rezansoff et al., 2013).

The current analysis used data from the following program areas: community medical services (dates, costs and diagnostic codes (ICD-9)); hospital separations (dates, durations, and diagnoses); vital statistics (date of death); prescription fills; and correctional supervision (offence types, dates, probation, custody, remand, bail). Enrolment in the medical services system is compulsory for residents of British Columbia (BC) and is renewed annually.

Analyses of BC prescription data have been previously shown to accurately reflect medication adherence for most patients (Dahri et al., 2008), and have been used to assess antipsychotic adherence among people exposed to corrections (Rezansoff et al., 2017a). Methadone is prescribed by physicians holding an exemption from Health Canada and overwhelmingly dispensed via daily witnessed ingestion under the supervision of a pharmacist..[1] Unless delivered as part of a medication assisted treatment program, antipsychotic ingestion is not observed.

IMRI data cover all available time including periods of incarceration, and services preceding and following involvement with the justice system. Psychotropic medications (including opioid agonist treatment) are provided free of charge to citizens in financial need. A comprehensive list of drugs prescribed to patients in the study and their frequencies is presented in Supplementary Table 1.

2.2. Study design and participants

The study population consisted of all individuals exposed to correctional supervision under BC jurisdiction between January 1997 and March 2015. We included individuals diagnosed with schizophrenia (ICD-9 code 295) who were treated concurrently with antipsychotics between Jan 1998[2] and March 2015. Because comprehensive Justice data are only available for individuals 18 years of age or older, we excluded patients who had been prescribed MMT or antipsychotics before the age of 18. Our observation period started ($time_0$) when participants began using both medications concurrently[3] (anytime between January 1998 and March 2015) and ended ($time_1$) on March 31, 2015 or on the date of patient death.

2.3. Variables of interest

Expert guidelines define acceptable antipsychotic adherence as taking medications at least 80% of the time for which they are prescribed (Velligan et al., 2009). Adherence to MMT was our primary independent variable, operationalized using the medication possession ratio (MPR). MPR represents the percentage of time that an individual was prescribed medication (i.e., the number of days of medication supplied within a refill interval divided by the total number of days in the interval) and is the preferred measure of adherence using administrative data (Hess et al., 2006). In keeping with recent studies (e.g., Hardy et al., 2018) and the guidelines cited above, we set our adherence threshold at MPR ≥ 80%. We have used this threshold in previously published research (Rezansoff et al., 2017a, 2017b; Russolillo et al., 2018) (drawn from the same parent population included in the current study), showing that antipsychotic and methadone MPRs ≥0.80 are independently associated with significantly reduced risk of recidivism and mortality, respectively. Our primary dependent variable was antipsychotic adherence, operationalized using MPR ≥ 0.80.

2.4. Statistical analyses

Categorical and nominal variables (e.g., gender and education level) were presented using counts (n) and proportions (%). Continuous variables (e.g., age and MPR) were presented using means with standard deviation (SD) or/and median with interquartile range (IQR), as appropriate.

We employed a panel data design using 120-day cycles (Rezansoff et al., 2017a; Fazel et al., 2014), and followed patients for each cycle beginning with the date of first concurrent use of both medications until censoring (date of death or March 31, 2015). Analytic data were arranged longitudinally using one row per 120-day cycle. Generalized Estimating Equations (GEE) analysis was used to estimate the association between independent (MMT adherence) and dependent (antipsychotic adherence) variables. We selected a logistic model (logit distribution with log link) due to the binary nature of our dependent variable

[1] In select instances patients are permitted "carries", i.e., to take home doses of methadone for self-administration.

[2] January 1998 (rather than January 1997) was used to ensure all patients had at least a one-year pre-enrolment period for Justice encounters, which was used as a covariate in the analysis.

[3] For example, if a participant started AP treatment on January 30th, 1999 and MMT on March 15th, 2002: $time_0$ = March 15th, 2002 (date of MMT initiation); if another participant began MMT on April 30th, 2000 and AP treatment on May 15th, 2001, $time_0$ = May 15th, 2001 (date of AP initiation).

(antipsychotic & MPR ≥0.80 as 'yes' & < 0.80 as 'no'), and an exchangeable correlation structure to control for dependency over time. As an additional safeguard against heteroscedasticity and potential misspecification, we used the robust variance estimator to estimate standard errors for all parameters (White, 1980; Russolillo et al., 2017)

Our regression model controlled for several variables selected a priori as potential confounders. These included: age at enrolment; gender (men & women); ethnicity (White, Indigenous, Other & Unknown); formal education (<Gd. 10, Gd. 10/11, Gd. 12, vocational/university & unknown), # of 120-day intervals (continuous variable), convictions (yes vs. no), # of convictions in the one year pre-enrolment period (continuous variable), # of acute hospitalizations in the one-year pre-enrolment period (continuous variable) and length of hospital stay (days) in the one-year pre-enrolment period (continuous variable). Methadone MPR and other time varying covariates (length of stay and jail convictions) were analyzed as lagged variables (Zeger and Liang, 1986) to guard against reverse causality. For example, MMT MPR in the 1st cycle was used to predict the outcome (antipsychotic MPR) in the following (2nd) cycle.

We reported unadjusted and adjusted odds ratios along with 95% confidence intervals as our measure of effect size. We chose the conventional alpha level ($P \leq 0.05$) to report significance for the estimated parameters. All reported P values were two sided. GEE models met convergence criteria and the Hessian Matrix was positive. Goodness of fit statistics for the primary analysis (Quasi Likelihood under Independence Model Criterion) were as follows: the null model (only intercept): 46670.60; the reduced model (methadone MPR only): 45051.87; and the full multivariable model (all variables including MMT MPR): 44848.49 (a smaller value indicates better fit.) People with partially missing socio-demographic details were included in the analysis using unknown ethnicity and unknown education level as separate categories.

Sensitivity analyses were performed to compare results of the primary analysis when restricted to: (a) participants with histories of conviction ($n = 1801$), (excluding those who were detained or supervised without a finding of guilt); (b) individuals with >365 days of follow up ($n = 1896$); and (c) people who initiated MMT prior to antipsychotic treatment ($n = 905$). Further subgroup analyses were conducted and restricted to: (d) surviving participants ($n = 1835$); and (e) people who had received methadone exclusively as part of a methadone maintenance regimen ($n = 1850$), (excluding those who had ever been prescribed methadone for any other indication (e.g., pain management)).[4] IBM SPSS Statistics 24 and STATA 13 were used to conduct all analyses.

3. Results

3.1. Sample characteristics

Fig. 1 illustrates the flow of patients included in the current study. Over the 17-year period, 250,884 individuals were under BC provincial correctional supervision. Of these, 44,652 (17.8%) people filled at least one antipsychotic prescription; 16,375 (6.5%) filled at least one MMT prescription[5]; and 9474 (3.8%) filled at least one prescription for each medication. Among the latter, 2044 (21.6%) were diagnosed with co-occurring schizophrenia and opioid dependence. We excluded 48 individuals due to insufficient follow-up (<121 days). In total, 1996 people met the study inclusion criteria.

Descriptive characteristics are presented in Table 1. Participants were predominantly men (68.1%), with a mean age of 35.4 years at enrolment. The majority (73.5%) self-identified as White, and 13.2% as Indigenous. Fewer than half (41.5%) had completed grade 12 and/or vocational/postsecondary training. In the year prior to enrolment, participants were sentenced (mean: 1.2; SD: 2.9) and hospitalized (mean: 0.9; SD: 1.5) approximately once. In the first 120-day period of follow up, 8.6% of the sample ($n = 172$) received a custodial sentence, and cohort members were hospitalized for an average of 2.3 days (SD: 8.0).

3.2. Adherence

Medication possession ratios (MPRs) and related characteristics are reported in Table 2. The cohort accounted for a total of 12,678.3 person-years (mean follow-up duration, 6.4 years; range, 0.3–17 years). Antipsychotic adherence decayed over time. Mean antipsychotic MPR throughout the follow-up period was 0.40 (SD: 0.33). In the first 120 days of follow up, 588 people (29.5%) were considered adherent to antipsychotics. In the 2nd 120-day follow up, the number who were adherent dropped to 525 (26.3%). Throughout the entire follow up period, 366 individuals (18.3%) continuously met antipsychotic adherence criteria. Methadone adherence followed a similar pattern. The mean MPR for MMT over the entire follow-up period was 0.49 (SD:0.35). In the first cycle of follow up, 1022 people (51.2%) were adherent. In the subsequent cycle, 916 (45.9%) were adherent to MMT. Over the entire period, 562 people (28.2%) continuously met MMT adherence criteria. Order of initiation was balanced between the two medications: 54% of the sample were prescribed antipsychotics followed by MMT; 45.3% were first prescribed antipsychotics; and 0.7% were initiated on both drugs simultaneously (i.e., the same day). Peripheral to our objectives, it is nevertheless notable that many MMT patients were concurrently prescribed antipsychotic medications for conditions other than schizophrenia (78.4%).

3.3. Statistical analyses

Using adjusted odds ratios (AOR) we estimated the association between MMT adherence and subsequent antipsychotic compliance with a multivariable GEE model. The probability of antipsychotic adherence doubled in periods that were preceded by a period of MMT adherence (AOR: P: 2.07; 95% CI: 1.90–2.26).

All subgroup and sensitivity analyses yielded results very similar to those derived through the primary analysis, examining: people with histories of conviction ($n = 1801$; AOR: 2.04; CI: 1.87–2.24); those with greater than one year of follow-up ($n = 1896$; AOR: 2.07; CI:1.90–2.26); those who initiated MMT prior to antipsychotics ($n = 905$; AOR 2.17 & CI:1.93–2.44); excluding those who died during the study period ($n = 1835$; AOR: 2.09 & CI: 1.90–2.29); and restricted to participants who received methadone exclusively as part of a methadone maintenance treatment program ($n = 1850$; AOR: 2.16 & CI 1.96–2.37) (Table 3).

4. Discussion

Consistent with our hypothesis, a clear temporal relationship between MMT and antipsychotic adherence was observed, with antipsychotic adherence twice as likely in periods preceded by a period of MMT adherence. Our results are consistent with research reporting that adherence to OAT improves pharmacotherapy of comorbid non-psychiatric conditions (Simeone et al., 2017; Harris et al., 2010; Batki et al., 2002). On average, participants were prescribed both medications for nearly 6.5 years.

Treatment status was also evaluated: within the MMT treated group, nearly 60% of people had received an antipsychotic prescription, but <13% were receiving antipsychotics with a diagnosis of schizophrenia. To our knowledge, this is the first longitudinal population-level study conducted to investigate the association between OAT and antipsychotic medication adherence among patients receiving concurrent pharmacotherapies.

[4] 146 participants (7.3%) received methadone indicated for pain alongside MMT. Analysis was restricted to 1850 participants who only received MMT.

[5] Historically and during the period of our study, methadone maintenance therapy (MMT) comprised essential all OAT in British Columbia.

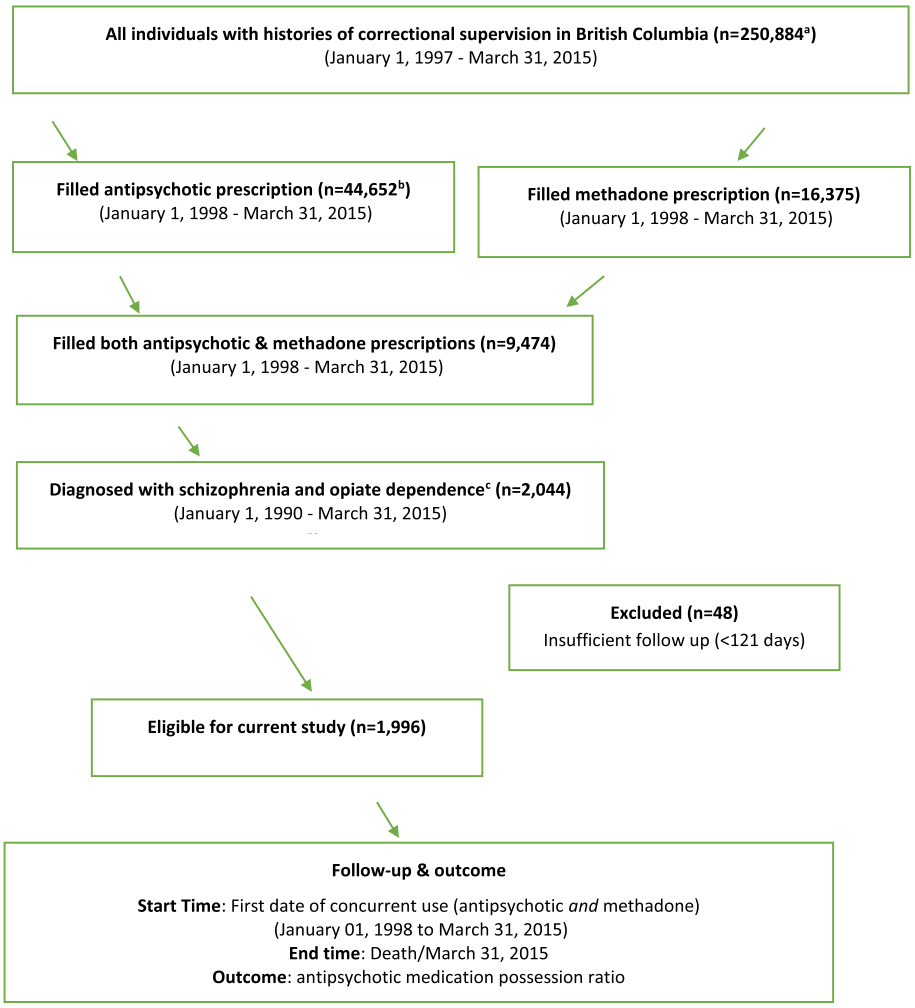

Fig. 1. Flow chart of participants under correctional supervision in British Columbia (1998–2015). [a] The study cohort included convicted offenders as well as individuals remanded to custody. [b] Antipsychotic and methadone recipients were mutually inclusive. [c] Receipt of methadone maintenance therapy was used to ascertain opiate dependence diagnosis.

It is important to note that some previous studies addressing the effect of OAT on HAART adherence were conducted using co-administration of prescribed medications (Binford et al., 2012; Hart et al., 2010). A recent case study describes the successful use of directly observed therapy integrating clozapine and MMT (Kinabalu et al., 2017). Antipsychotics were not co-administered or ingested under supervision in the current study, however our pattern of findings suggests that integration of antipsychotic and OAT protocols may be beneficial, particularly for patients in marginalized circumstances. The observed effects of MMT on concurrent pharmacotherapy may be due in part to the stabilizing effect of OAT, which can promote social functioning, the establishment of routine, and contribute to improved physical health (Bruce et al., 2012). Frequent contact with health care providers, as required under many regimens, can also facilitate the development of positive therapeutic relationships, and increase patients' motivation to attain improved health (Reddon et al., 2014). In the BC context, MMT is typically delivered in pharmacy settings with witnessed oral ingestion, with few integrated supports. Of specific relevance to the current study population, OAT has also been shown to decrease the risk of incarceration (Werb et al., 2008), which has multiple adverse health consequences including the disruption of pharmacotherapy (Palepu et al., 2004).

Integrated approaches to care are not the norm in British Columbia, where MMT is dispensed separately from other medications and at specific pharmacies, while antipsychotic ingestion is rarely witnessed. Our results suggest that delivery of MMT and antipsychotic prescriptions should be coordinated to allow witnessed ingestion of both medications.

Overall adherence to both medications was low. In the first 120-day follow up cycle following initiation of each prescription, only 51% of the sample were adherent to MMT, while merely 29% were adherent to antipsychotics. Adherence to both medications then decreased markedly over subsequent periods of observation. Our findings underscore the need to implement practices to improve overall adherence to these medications, particularly for people with concurrent prescriptions.

Previous research in the British Columbia justice population has demonstrated that antipsychotic and MMT adherence significantly reduce the risk of criminal recidivism (Rezansoff et al., 2017a; Russolillo et al., 2017), and that MMT adherence significantly reduces the risk of mortality, including overdose fatalities (Russolillo et al., 2018). However, we are not aware of any studies addressing the risk of overdose among people dually-diagnosed with schizophrenia and opioid dependence. This omission warrants further attention given the current opioid crisis, the low level of MMT adherence in our sample, and

Table 1
Sociodemographic characteristics of the study population, 1998–2015 ($n = 1996$).

Variable	Mean (SD)/n (%)
Age at enrolment[a]	
Mean (SD)	35.4 (9.4)
Median (IQR)	34.6 (28.1, 41.9)
Men, n (%)	1359 (68.1)
Ethnicity, n (%)	
White	1467 (73.5)
Indigenous	264 (13.2)
Other	167 (8.4)
Unknown	98 (4.9)
Education level, n (%)	
<Grade 10	310 (15.5)
Grade 10/11	654 (32.8)
Grade 12	586 (29.4)
Vocational/university	241 (12.1)
Unknown	205 (10.3)
Sentence in one-year pre-enrolment period, mean (SD)	1.2 (2.9)
Acute hospitalizations in one-year pre-enrolment period, mean (SD)	0.9 (1.5)
Jail sentence in 1st 120-day interval of follow-up period, n (%)	172 (8.6)
Length of stay in 1st 120-day interval of follow-up period, mean (SD)	2.3 (8.0)

SD: standard deviation; IQR: inter-quartile range.
[a] Age at enrolment based on the first date of concurrent use between January 1, 1998 - March 31, 2015.

Table 2
Medication possession ratio (MPR) related characteristics of the study population, 1998–2015 (n = 1996).

Variable	Mean (SD)/n (%)
Follow-up period, in years	
Mean (SD)	6.4 (3.9)
Median (IQR)	5.7 (3.1, 9.0)
Minimum, maximum	0.3, 17.0
Total follow up time (person years)	12,678.3
Number of days with AP in follow-up period	
Mean (SD)	894.5 (986.3)
Median (IQR)	549.0 (118.0, 1354.0)
Number of days with MMT in follow-up period	
Mean (SD)	1154.8 (1164.5)
Median (IQR)	771.5 (185.8, 1866.5)
AP MPR in entire follow-up period	
Mean (SD)	0.40 (0.33)
Median (IQR)	0.33 (0.07, 0.71)
AP MPR in pre-enrolment period[a]	
Mean (SD)	0.38 (0.31)
Median (IQR)	0.31 (0.08, 0.63)
AP adherence in entire follow-up period, n (%)	
<0.80	1630 (81.7)
≥0.80	366 (18.3)
AP adherence in 1st 120-day interval of follow-up period, n (%)	
<0.80	1408 (70.5)
≥0.80	588 (29.5)
AP adherence in 2nd 120-day interval of follow-up period, n (%)	
<0.80	1471 (73.7)
≥0.80	525 (26.3)
MMT MPR in entire follow-up period	
Mean (SD)	0.49 (0.35)
Median (IQR)	0.49 (0.13, 0.84)
MMT MPR in pre-enrolment period[b]	
Mean (SD)	0.58 (0.35)
Median (IQR)	0.63 (0.22, 0.93)
MMT adherence in entire follow-up period, n (%)	
<0.80	1434 (71.8)
≥0.80	562 (28.2)
MMT adherence in 1st 120-day interval of follow-up period, n (%)	
<0.80	974 (48.8)
≥0.80	1022 (51.2)
MMT adherence in 2nd 120-day interval of follow-up period, n (%)	
<0.80	1080 (54.1)
≥0.80	916 (45.9)
Order of prescription initiation, n (%)	
AP followed by MMT	1077 (54.0)
Simultaneous initiation	14 (0.7)
MMT followed by AP	905 (45.3)

SD: standard deviation; IQR: inter-quartile range; MPR: medication possession ratio; MMT: methadone maintenance treatment; AP: antipsychotic drug.
AP: antipsychotic drug; MMT: methadone maintenance treatment; IQR: inter-quartile range; MPR: medication possession ratio; SD: standard deviation.
[a] Restricted to participants who first initiated AP followed by MMT ($n = 1077$).
[b] Restricted to participants who first initiated MMT followed by AP (n = 905).

evidence suggesting that people experiencing psychosis may seek illicit opioids to self-medicate (DeLisi and Fleischhacker, 2017). Previous research has shown that opioid overdose is the leading cause of death among former inmates during the first two weeks after release and remains a leading cause of death up to 2 two years post-release (Binswanger et al., 2007). Close monitoring of MMT continuity following prison release may also significantly improve antipsychotic adherence among those treated concurrently for schizophrenia. This hypothesis warrants empirical investigation.

4.1. Implications

The current study demonstrates that OAT MPR was a valid predictor of antipsychotic MPR. It also supports its recommended use as a measure of antipsychotic adherence and substantiates previous research findings that it differentiates meaningful clinical and safety outcomes for people living with schizophrenia.

Our findings have practical implications for health care delivery in both the correctional context and the general patient population. Although the members of our cohort all had some lifetime exposure to correctional supervision (e.g., remand, pre-trial, community supervision, custody), we found no difference in effect size between our full cohort and a restricted sample excluding those with no histories of conviction.[6] Integrating receipt of MMT and antipsychotics may help ensure higher overall adherence to both medications, as well as the identification of common psychosocial needs in this patient group, such as job finding, housing, etc. Using a randomized trial design, Assertive Community Treatment has been shown to cause a large and statistically significant improvement in antipsychotic adherence among people (diagnosed with schizophrenia) with extensive homeless histories and concurrent substance dependence (Rezansoff et al., 2017b; White, 1980). Improvements to treatment and outcomes for people with complex concurrent disorders are clearly achievable via integrated psychosocial care.

Our study produced a few descriptive results that may be of note to clinicians and planners, warranting further investigation. The prevalence of schizophrenia among MMT recipients in our cohort (12.5%) was conservatively >20 times that reported in the general population (Simeone et al., 2015) and warrants further attention. Similarly, the rate of antipsychotic prescribing for conditions other than schizophrenia (i.e., off-label use) was approximately 70% (Rezansoff et al., 2017a). This exposes a number of important opportunities for research investigating the most common clinical presentations associated with these prescriptions, and whether their use suggests additional medical or psychosocial resources may be indicated. Accordingly, use of

[6] All participants ($n = 1996$) had experienced justice system supervision, but some of these ($n = 179$) were *not* convicted (i.e., detained on remand and released, or found not guilty.

Table 3
Subgroup/sensitivity analysis estimating the association between antipsychotic MPR[a] and methadone MPR, 1998–2015 (n = 1996).

Subgroup	Independent variable	Unadjusted odds ratio (95% CI[b])	Adjusted odds ratio (95% CI)[c]
History of conviction[d] ($n = 1801$)	MMT MPR (≥0.80)	**1.98 (1.81, 2.17)**	**2.04 (1.87, 2.24)**
≥ 366 days of follow-up[e] ($n = 1896$)	MMT MPR (≥0.80)	**1.99 (1.82, 2.17)**	**2.07 (1.90, 2.26)**
MMT followed by AP[f] ($n = 905$)	MMT MPR (≥0.80)	**2.24 (1.99, 2.52)**	**2.17 (1.93, 2.44)**
Surviving participants[g] ($n = 1835$)	MMT MPR (≥0.80)	**2.00 (1.82, 2.19)**	**2.09 (1.90, 2.29)**
MMT exclusively[h] ($n = 1850$)	MMT MPR (≥0.80)	**2.06 (1.88, 2.26)**	**2.16 (1.96, 2.37)**

AP: antipsychotic drug; MMT: methadone maintenance treatment; GEE: generalized estimating equations; MPR: medication possession ratio; CI: confidence interval.
P values for MMT MPR as highlighted by the bold emphases was <0.001 (for all sensitivity and subgroup analysis as well as unadjusted and adjusted GEE models).
[a] Both AP MPR (outcome) and MMT MPR (primary predictor) were dichotomized using the 0.80 threshold and analyzed as binary variables (≥0.80 as yes and <0.80 as no).
[b] 95% CIs and both un/adjusted odds ratios were estimated using Robust Standard Errors.
[c] Each multivariable GEE model controlled for age at enrolment; gender (men & women); ethnicity (White, Indigenous, Other & Unknown); education level (<Gd. 10, Gd. 10/11, Gd. 12, vocational/university & unknown); # of 120-day intervals (continuous variable); length of hospital stay in days (continuous variable); jail convictions (yes vs. no); # of acute hospitalization in one-year pre-enrolment period (continuous variable) and # of convictions in one-year pre-enrolment period (continuous variable).
[d] 195 participants (9.8%) had no history of conviction. These individuals were under the supervision of the BC Ministry of Justice due to remand or bail, and later found not guilty. Analysis was restricted to 1801 participants with a history of conviction.
[e] 100 participants (5.0%) had a follow-up of 121 to 365 days. Analysis was restricted to 1896 participants who had more than one year of follow-up (≥366 days).
[f] Analysis was restricted to 905 (45.3%) participants who first initiated MMT, followed by AP.
[g] 161 participants (8.1%) died during the study period (mean age at death was 43.3 years & range: 21.3–69.7 years). Analysis was restricted to surviving participants (n = 1835).
[h] 146 participants (7.3%) received methadone indicated for pain. Analysis was restricted to 1850 participants who only received MMT.

antipsychotic prescription as a proxy for diagnosed schizophrenia may seriously overestimate the prevalence of schizophrenia among opioid dependent patients.

4.2. Strengths & limitations

The study reveals a strong temporal relationship between MMT and antipsychotic adherence, and demonstrates that OAT MPR was a *valid predictor* of antipsychotic MPR. Nonetheless, our findings also present very low levels of overall medication adherence, despite few barriers involving cost or availability in the community. Strengths of the research include the use of comprehensive administrative records from a large and well-defined patient population diagnosed with co-occurring schizophrenia and opioid dependence, spanning a mean observation period of over 6 years of concurrent prescribing. Analysis was based on specific adherence measurements, a longitudinal design (MPR in 120-day cycles), and clear temporal ordering of primary exposure (MMT adherence) and outcome (antipsychotic adherence) variables. Observation periods included prescription histories preceding, during, and following correctional supervision, and represent the delivery of care in community settings.

Limitations of our study include our definition of adherence using the MPR, which (in the case of antipsychotics) was based on pharmacy refill records and may overestimate true adherence resulting in attenuated effect size. Without access to biomarkers or other direct measures, our results provide indirect and limited evidence that OAT may promote antipsychotic adherence. Our analysis of observational data precludes causal inference, and the temporal association reported in our findings is not evidence of a causal relationship.

Nevertheless, our primary hypothesis was informed by a previously demonstrated effect of OAT on medication adherence among marginalized patients treated for HIV (Simeone et al., 2017; Cocohoba et al., 2003; Reddon et al., 2014; Palepu et al., 2006; Nosyk et al., 2015). An experimental trial would enable more definitive investigation of the association between OAT and antipsychotic prescribing and practices that optimize co-prescribing. Although our regression model accounted for socio-demographic, health and justice-related variables, unmeasured confounding may have been present. Additional research is needed to clarify the structural and psychosocial conditions that promote adherence to OAT (e.g., housing stability, attenuation of symptoms, social support, etc. Finally, the Canadian context of universal health care and publicly funded psychiatric medication coverage may limit the generalizability of our results to other settings.

4.3. Conclusions

Among patients receiving medications for schizophrenia and opioid dependence, antipsychotic adherence was more than twice as likely in periods that were preceded by adherence to MMT. However, adherence to both medications was very low throughout the observation period. These findings suggest that antipsychotic and opioid agonist treatments prescribed as part of an integrated model of care and co-administered alongside access to additional resources (e.g., housing, employment) may increase antipsychotic adherence (Kinabalu et al., 2017). Additional research is needed to examine potential synergies between antipsychotic and opioid agonist treatments and the effectiveness of models of care that aim to promote recovery among people with concurrent schizophrenia and opioid dependence.

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Contributors

Stefanie N Rezansoff conceived and designed the study, conducted the literature search, and wrote the initial draft.

Akm Moniruzzaman conceived and designed the study and conducted statistical analyses.

Julian Somers conceived and designed the study.

All three authors conjointly revised the manuscript several times.

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Declaration of Competing Interest

The authors declare that they have no conflicts of interest.

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