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Prevalence of Heavy Alcohol Use among People Receiving Methadone Following Change to Methadose

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Abstract

Background—A recent switch in methadone formulation from methadone (1mg/mL) to Methadose (10mg/mL) in British Columbia (BC), Canada, was associated with increased reports of opioid withdrawal and increases in illicit opioid use. Impacts on other forms of drug use have not been assessed. Since alcohol use is common among people receiving Medication-Assisted Treatment (MAT), we assessed if switch was associated with increased prevalence of heavy alcohol use.

Methods—Drawing on data from two open prospective cohort studies of people who inject drugs in Vancouver, BC, generalized estimating equations (GEE) model examined relationship between methadone formulation change and heavy alcohol use, defined by National Institute for Alcohol Abuse and Alcoholism (NIAAA). A sub-analysis examined relationship with heavier drinking defined as at least eight drinks per day on average in last six months.

Results—Between June 2013 and May 2015, a total of 787 participants on methadone were eligible for the present analysis, of which 123 (15.6%) reported heavy drinking at least once in last six months. In an unadjusted GEE model, Methadose use was not significantly associated with an increased likelihood of heavy drinking [Odds Ratio (OR) = 1.03; 95% Confidence interval (CI) = 0.87-1.21]. Methadose use was not significantly associated with an increased likelihood of drinking at least eight drinks daily on average (OR = 1.09, 95% CI = 0.72-1.65).

Conclusions—Despite reported changes in opioid use patterns coinciding with the change, there appeared to be no effect of the methadone formulation change on heavy drinking in this setting.

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Keywords

alcohol; methadone maintenance treatment; heroin; longitudinal study; formulation; medication assisted treatment (MAT); opioid use disorder

Background

Poly-drug use continues to undermine medication-assisted treatment (MAT), impacting negatively on patients' health and treatment outcomes (Hartzler, Donovan, & Huang, 2010; Soyka, 2015; Young, Wood, Dong, Kerr, & Hayashi, 2016). Specifically, one common clinical challenge is concurrent alcohol and opioid use, with guidelines often recommending reducing methadone dosage if this occurs, given the risk of fatal overdose due to respiratory distress (Klimas, Wood, et al., 2016). While alcohol has also been shown to contribute to relapse into illicit drug use among poly-drug users (Staiger, Richardson, Long, Carr, & Marlatt, 2013), MAT has been shown to reduce problem drug use (Mattick, Breen, Kimber, & Davoli, 2009).

Research into excessive drinking by people in MAT began around 1965 when methadone started to be administered as an opioid use disorder therapy (Dole & Nyswander, 1965). The early work into alcohol and methadone interactions included research by Dr Kreek, from the Rockefeller University in New York City, a colleague of Drs. Dole and Nyswander, which indicated that there was not significant “acute” interaction between methadone and alcohol (Cushman, Kreek, & Gordis, 1978); however, there was significant liver impairment later (Beverley, Kreek, Wells, & Curtis, 1979; Hartman et al., 1983); and potential interactions of disulfiram with methadone were noted (Tong, Benowitz, & Kreek, 1980). Furthermore, in 1977, Dr Stimmel's team used a standardised screening for alcohol problems (self-administered alcoholism screening test - SAAST) in this population (Cohen, McKeever, Cohen, & Stimmel). Having found a high prevalence of problem drinking, they attempted behavioral treatment combined with Disulfiram (Antabuse), which was then the only approved medication for alcohol use disorders (Liebson, Tommasello, & Bigelow, 1978). A first clinical trial compared an abstinence therapy with controlled drinking plus behaviour modification in 1983 (Stimmel et al.), followed by a review of the existing evidence in 1987 (Bickel, Marion, & Lowinson). Unfortunately, effectiveness of those approaches could not be demonstrated. However, addiction science has much improved since then and the recent progress has brought more effective treatments and medications. Many of them can be delivered by generalists physicians in primary care-based agonist treatment, when available (Kaner et al., 2007). More recently, two main hypotheses were reviewed, the substitution and the relapse hypothesis (Soyka, 2015; Staiger et al., 2013). While some research indicated that patients entering methadone treatment may substitute one drug (alcohol) for another (heroin), longitudinal studies have not confirmed this substitution hypothesis and other research is inconclusive (Cullen, Kelly, Stanley, Langton, & Bury, 2005; Klimas, Wood, et al., 2016) (Kipnis, Herron, Perez, & Joseph, 2001). Alcohol's role in the relapse to other drug use, whilst in SUD treatment, has yet to be tested. Furthermore, while some patients may feel uneasy with the transition to Methadose, and subsequently drink excessively, or feel unsaturated with the Methadose dose and subsequently top up with opioids, a growing

body of research suggests a mediating role of alcohol in methadone treatment. Therefore, alcohol may fluctuate with changes in methadone treatment; however, the direction of this fluctuation is unclear.

In February 2014, the province of British Columbia (BC), Canada, changed regulations governing methadone maintenance therapy and replaced the previous methadone formulation with Methadose® (a more concentrated, pre-mixed solution) (Markwick, McNeil, Anderson, Small, & Kerr, 2016). It was changed in anticipation of benefits (e.g., faster administration, etc.) that would outweigh the perceived health risks (e.g., potential for overdose with stronger formulation). However, the health authorities' communication of risks involved in methadone formulation changes via leaflets led some to perceive that they would experience increased drug-related risks (e.g., skull and crossbones), and possibly led some patients to misinterpret the effect expected from Methadose (Markwick et al., 2016).

A province-wide survey of 405 patients receiving Methadose reported statistically-significant negative impacts of this change on substance-related outcomes of people receiving Methadose, which included “feeling more dope sick and worsening pain,” “topping up” with other drugs following the switch to Methadose (Greer et al., 2016). Reporting more intense feelings of dope sickness was associated with increases in Methadose dose increases in use of other opioids. Another qualitative study conducted with 34 patients from Vancouver's methadone maintenance treatment programme also indicated that the switch to Methadose triggered withdrawal symptoms (McNeil et al., 2015). While the main sources of information about new Methadose in the province-wide survey were methadone providers or pharmacists, the qualitative study from Vancouver's most disadvantaged area found peers and posters most informative. Furthermore, if a poster mentioned “stronger” methadone, this was viewed as increasing drug-related risks, as opposed to posters using descriptive text and common danger pictograms. In other words, and in agreement with previous literature, the latter approach may help persons on methadone treatment understand the change better and thereby avoid unforeseen escalated drug-seeking practices and ensuing harms (Kerr, Small, Hyshka, Maher, & Shannon, 2013; Miller, 2007). Cumulatively, these previous research findings called for further investigation of the fluctuation of substance use during transitions to new methadone formulations, especially whether patients top up or substitute with alcohol or with illicit drugs. However, the impact of methadone formulation changes on the use of alcohol by MAT patients has been understudied (Greer et al., 2016; McNeil et al., 2015). Therefore, we examined whether a switch from methadone to Methadose was associated with increased heavy alcohol use among MAT patients.

Methods

In British Columbia (BC), two institutions regulate methadone dispensation: BC Ministry of Health and College of Physicians and Surgeons of BC (CPSBC, 2014. Luce and Strike, 2011)(CPSBC, 2014; Luce & Strike, 2011). Other bodies involved in methadone regulation include BC PharmaCare and BC College of Pharmacists (British Columbia Ministry of Health, 2015). A pharmacist supervises daily consumption of methadone prescribed by a licensed family physician. Initially, methadone is administered every day, doses are

ascertained by the prescribing physician. With time, “stabilised” patients can take their methadone home if they comply with treatment. Typically, clinical stability is achieved at doses between 80 to 120 mg/day, which is similar to average doses in other countries (Mattick et al., 2009; Nosyk et al., 2012). Pharmaceutically, Methadose is methadone hydrochloride; each 1 mL of this red, cherry-flavoured liquid concentrate contains 10 mg of methadone, i.e., 10 times more concentrated than previous formulation.

Data were derived from two open, community-recruited prospective cohorts of people who use drugs in Vancouver, Canada: the Vancouver Injection Drug Users Study (VIDUS) and the AIDS Care Cohort to evaluate Exposure to Survival Services (ACCESS). As described previously, VIDUS enrols HIV-seronegative adults who inject drugs, and ACCES enrols HIV-seropositive adults who use illicit drugs (i.e., other than or in addition to cannabis) (Hayashi et al., 2016; Kerr et al., 2008; Strathdee et al., 1998; Wood et al., 2004). Both cohorts recruit potential participants through snowball sampling and street outreach. Bi-annual follow-up procedures include interviewer-administered, harmonized questionnaires covering demographic, behavioural and other characteristics. Participants receive a $40 CDN stipend at each interview. The University of British Columbia/Providence Healthcare Research Ethics Board approved both studies.

For the present analyses, we included participants who: (1) reported having ever injected drugs at the first interview completed during the study period; (2) completed at least one study visit during the study period and (3) reported enrollment in MAT (methadone or Methadose) in the past six months at each follow-up. Due to the timing of our bi-annual follow-up assessments, we restricted the study period to June 1, 2013 – May 31, 2015 (i.e., comparing the same number of follow-ups before (n=2) and after the introduction of Methadose (n=2)).

The primary explanatory variable was “On Methadose” in the past six months, as a dichotomous variable (Yes vs. No). All participants who completed interviews during the period prior to Methadose introduction were coded as “No” for this variable. The primary outcome was the National Institute on Alcohol Abuse and Alcoholism (NIAAA)-defined heavy alcohol use in the past six months, and was treated as a time-varying variable. NIAAA defined heavy alcohol use as an average of “>three drinks per occasion, or >seven drinks per week”, among females, and an average of “>four drinks per occasion, or >14 drinks per week”, among males (National Institute on Alcohol Abuse and alcoholism (NIAAA), 2010). The secondary outcome measure for sub-analysis was heavier alcohol use defined as daily drinking of eight or more drinks in past six months, given the body of literature suggesting that death rates seem to increase at over eight drinks of alcohol daily in general population (Doll, Peto, Hall, Wheatley, & Gray, 1994; Hart, Davey Smith, Hole, & Hawthorne, 1999). We used generalized estimating equation (GEE) to examine the bivariable association between the primary explanatory variable and the NIAAA-defined heavy alcohol use or the eight-drink heavier alcohol use. In a sub-analysis, we also used descriptive statistics to assess participants' satisfaction with the methadone dose via the following question “is the dose of methadone [or Methadose] you receive…? (about right, too low or too high.)” Analyses were performed using RStudio, version 0.99.892 (R Foundation for Statistical Computing, Vienna, Austria). All p-values were two-sided.

Results

A total of 787 MAT patients were included in this analysis (702/ 61.6% males) and 624 of them had more than one follow-up visit and were followed for a median of 17.06 (interquartile range [IQR] = 11.96-18.16) months (163 of them had one follow-up visit and were followed for a median of 13.54 (IQR = 5.92-17.91) months). The median age at baseline was 42 years (IQR = 36-48), and 123 (15.6%) reported NIAAA-defined heavy alcohol use at some point during study period. Before the formulation change, 92 (13.3%) persons reported NIAAA-defined heavy drinking and 87 (13.6%) did so after the change. In a crude GEE model, Methadose use was not significantly associated with an increased likelihood of NIAAA-defined heavy drinking [Odds Ratio (OR) = 1.03; 95% Confidence interval (CI) = 0.87-1.21] (Table 1). The association remained insignificant for heavier, eight-drink alcohol use. Table 2 lists perceived satisfaction with the medication dose, stratified by the NIAAA-defined heavy drinking status. Majority (73%) of the total 2184 observations felt their dose was about right with little differences between the groups on methadone or Methadose, except for a slightly larger proportion of Methadose participants who felt their dose was too low, compared to methadone participants (22.1% vs. 12.6%).

Discussion

In this study, the prevalence of heavy drinking did not appear to change after switching to Methadose, despite previous qualitative research suggesting negative impacts on health-related outcomes (McNeil et al., 2015). This finding held even when we accounted for heavier alcohol use. Satisfaction with the dose of medication was consistent across the sample.

Our findings should be interpreted in the context of previous literature on medication formulary changes (Bourgois, 2000; Fischer, 2000). While an “open” study found significant reductions in the number of positive illicit drug screens (20% reduction) after changing to a new version of R-methadone isoform, which is distinct from Methadose (Soyka & Zingg, 2009), previous studies from Vancouver reported opposite subjective effects – patients felt more craving and pain (Greer et al., 2016; McNeil et al., 2015). As a result, some of them used other drugs on top of their methadone, possibly to cope with the negative impacts of transition to Methadose (Greer et al., 2016). As found by the cited qualitative studies from Vancouver, peers were the main channels of communication about formulation change, although “descriptive language and universal hazard symbols” were effective too. This would seem to suggest that while the health authorities' posters informed patients of the upcoming change to new Methadose, they had little effect on the management of change and subjective experience because the information communicated among peer-networks was more important for patients. Furthermore, tolerance to change seems to be crucial to successful transitions to new medication formulations in opioid agonist treatment (Silver & Shaffer, 1996), although previous research has not confirmed a relationship between negative change experiencing and levels of the medication in plasma (Farr & Gwaltney, 1987; Gourevitch et al., 1999). In the light of previous reports on “change intolerance,” future studies should examine barriers and facilitators of successful transitions in opioid agonist treatment.

Binge alcohol use was an independent predictor of death among a community-recruited cohort of people who inject drugs (Johnson et al., 2015). While this aligns with previous literature, other work, which utilised a different measure of alcohol use than the recent analysis (binge use vs. NIAAA-defined heavy alcohol use), has suggested that MAT may also decrease the initiation of heavy drinking, further emphasizing the beneficial effects of opioid agonist treatment on the health of people with opioid use disorder (Klimas, Dong, et al., 2016; Klimas, Wood, et al., 2016).

This study has a few limitations. First, our findings may not be representative of local drug use. Second, these findings may not generalize to other settings. Third, self-reports may suffer from recall bias. However, we note they are widely accepted as a valid form of data collection from people who use drugs (Darke, 1998). Last, although we did not validate our outcome measures with objective measures, for example breath or urine ethyl glucuronide tests, these are not recommended as the gold standard without the complementary self-report methods, mainly due to short detection period (Aertgeerts, Buntinx, Ansoms, & Fevery, 2002; Wurst et al., 2011). Future research should examine why patients on Methadose report that dosage levels are too low compared with patients on methadone, as well as what the changes in treatment enrolment and retention are.

In conclusion, there appears to be no short-term effect of the methadone formulation change on heavy drinking in this setting. Various methadone formulations may have little short-term impact on heavy alcohol use. Long-term impact should be evaluated.

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Table 1

Heavy alcohol use before and after the methadone formulation change and unadjusted odds ratios among persons on methadone treatment (n = 2184 observations)

Characteristic	Yes n (%)	No n (%)	Odds Ratio (95% CI)	*p* - value
NIAAA-heavy alcohol use *	**244 (11.2) (15.6)**	**1940 (88.8)**	1.03 (0.87-1.21)	0.732
Methadone	127 (11.2)	1003 (88.7)		
Methadose	117 (11.1)	937 (88.9)		
8-drinks heavy alcohol use *	**44 (2.01)**	**2140 (97.9)**	1.09 (0.72-1.65)	0.084
Methadone	22 (1.9)	1108 (98.1)		
Methadose	22 (2.1)	1032 (97.9)		

*Both the NIAAA-defined heavy alcohol use and the heavy alcohol use adjusted to be >8 drinks per day on average, refer to six months prior to interview;

NIAAA = National Institute for Alcohol and Alcoholism

Table 2

Perceived dose of methadone/methadose stratified by NIAAA- heavy alcohol use before and after methadone formulation change (n = 2184 observations)

Comparison	Total (%) (*n* = 2184[†])	NIAAA-heavy drinking	
		No (%) 1876 (85.9)	Yes (%) 228 (10.4)
About right	**Total, N=1590**	**NO, N=1428**	**YES, N=162**
Methadone	860 (81.6)	767 (89.2)	93 (10.8)
Methadose	730 (64.6)	661 (90.5)	69 (9.5)
Too low	**Total, N=382**	**NO, N=326**	**YES, N=56**
Methadone	133 (12.6)	115 (86.5)	18 (13.5)
Methadose	249 (22.1)	211 (84.7)	38 (15.3)
Too high	**Total, N=132**	**NO, N=122**	**YES, N=10**
Methadone	70 (6.6)	67 (95.7)	3 (4.3)
Methadose	62 (5.5)	55 (88.7)	7 (11.3)

[†]The total N of missing observations was 80 (64 heavy drinking, 16 non-heavy drinking)