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The association between nicotine dependence and physical health among people receiving injectable diacetylmorphine or hydromorphone for the treatment of chronic opioid use disorder☆

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A B S T R A C T

Introduction: People with chronic opioid use disorder often present to treatment with individual and structural vulnerabilities and remain at risk of reporting adverse health outcomes. This risk is greatly compounded by tobacco smoking, which is highly prevalent among people with chronic opioid use disorder. Despite the known burden of tobacco smoking on health, the relationship between nicotine dependence and health has not been studied among those receiving injectable opioid agonist treatment. As such, the present study aims to explore the association between nicotine dependence and physical health among participants of the Study to Assess Longer-Term Opioid Medication Effectiveness (SALOME) at baseline and six-months.

Methods: SALOME was a double-blind phase III clinical trial testing the non-inferiority of injectable hydromorphone to injectable diacetylmorphine for chronic opioid use disorder. Participants reporting tobacco smoking were included in a linear regression analysis of physical health at baseline (before receiving treatment) and at six-months.

Results: At baseline, nicotine dependence score, lifetime history of emotional, physical, or sexual abuse and prior month safe injection site access were independently and significantly associated with physical health. At six-months nicotine dependence score was the only variable that maintained this significant and independent association with physical health.

Conclusions: Findings indicate that after six-months, the injectable treatment effectively brought equity to patients' physical health status, yet the association with nicotine dependence remained. Findings could inform whether the provision of treatment for nicotine dependence should be made a priority in settings where injectable opioid agonist treatment is delivered to achieve improvements in overall physical health in this population.

1. Background

Chronic opioid use disorder (OUD), particularly the injection of illicit street opioids, is known to exact a number of harms on the individual, including the risk of infectious disease such as human immunodeficiency virus (HIV) and hepatitis C (HCV), as well as the risk of fatal and non-fatal overdose, social disintegration, violence and incarceration (Roxburgh, Darke, Salmon, Dobbins, & Jauncey, 2017; van der Zanden, Dijkgraaf, Blanken, van Ree, & van den Brink, 2007). The burden of chronic opioid use disorder on communities includes death,

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public disorder, and health and criminal justice costs (Birnbaum et al., 2011).

Opioid agonist treatment (OAT) with long-acting oral opioids such as methadone is effective at managing cravings and symptoms of withdrawal, reducing the use of street opioids, and at attracting and retaining patients in treatment (Mattick, Breen, Kimber, & Davoli, 2009; Mattick, Breen, Kimber, & Davoli, 2014). However many individuals will not be retained in treatment long-term or will continue to inject illicit opioids even while engaged in oral treatment (Johnson et al., 2000; Mino, Page, Dumont, & Broers, 1998). Evidence from five randomized controlled trials (RCT) in Europe (Demaret et al., 2015; Haasen et al., 2007; March, Oviedo-Joekes, Perea-Milla, & Carrasco, 2006; Strang et al., 2010; van den Brink et al., 2003) and two in Canada (Oviedo-Joekes et al., 2009; Oviedo-Joekes et al., 2016) has demonstrated that for those that continue injecting despite access to available treatments, injectable opioid agonist treatment (iOAT), namely the provision of injectable diacetylmorphine (DAM; pharmaceutical grade heroin) or hydromorphone (HDM, a licensed opioid) under the supervision of registered nurses, offer safe, effective, and cost-effective treatments (Nosyk et al., 2012).

These clinical trials have recruited opioid users that have been injecting street opioids long-term, many of whom have had multiple prior treatment attempts and have not been effectively reached by the addiction treatment system for a number of years. While take home maintenance doses of DAM have been prescribed in the United Kingdom, iOAT is most commonly provided in clinics, self-administered under the supervision of nurses (Hartnoll et al., 1980). This direct observation is known to ensure patient safety, and daily contact with health care providers brings the opportunity to build relationships and offer comprehensive care. This approach has been effective at attracting and retaining patients in much needed, structured care at rates significantly higher than those in first-line treatments such as oral methadone (Ferri, Davoli, & Perucci, 2011). Studies of iOAT have further demonstrated broadly similar benefits with regards to reductions in street heroin use, and in secondary outcomes such as physical and mental health and social functioning (Strang et al., 2015).

Because of the profile of patients included in iOAT clinical trials (i.e. people that have been injecting illicit opioids for many years and continue doing so despite available treatments), participants had high rates of chronic conditions and infectious diseases (e.g. HIV, HCV, cardiovascular disease, cancer etc.) (Buster, Rook, van Brussel, van Ree, & van den Brink, 2002; Haasen et al., 2007; Oviedo-Joekes et al., 2015; van den Brink et al., 2003). At the time of recruitment, participants presented with a wide array of individual and structural vulnerabilities known to be associated with poor physical health including unstable housing conditions, high rates of physical, sexual, and emotional abuse, and the use of other substances (Oviedo-Joekes et al., 2015).

People with opioid use disorder (OUD) remain at a higher risk of reporting adverse health outcomes as compared to the general population (Schuckit, 2016). This risk is greatly compounded by tobacco smoking (Chisolm et al., 2013; Hurt et al., 1996). For example, a recent 15-year population based study found that smoking related conditions comprised 40% of all deaths among people with OUD. Further, those with opioid use disorder (OUD) had a significantly higher risk of mortality from all 19 tested smoking related conditions (i.e. cardiovascular, respiratory diseases and cancers) when compared to the general population (Callaghan, Gatley, Sykes, & Taylor, 2018). The observed relationship between tobacco smoking and health among people with OUD is particularly concerning given the high prevalence of smoking in this population. For example, prior studies of patients receiving treatment with oral methadone or buprenorphine in the United States and Europe have shown tobacco smoking rates to be significantly higher than in the general population, ranging between 80–100% (Nahvi, Richter, Li, Modali, & Arnsten, 2006; Pajusco et al., 2012; Richter, Gibson, Ahluwalia, & Schmelzle, 2001).

Despite the burden of tobacco smoking on the health of people with OUD the relationship between nicotine dependence and physical health has not been studied among iOAT patients, who have high daily treatment adherence, especially in the first year of treatment. This is of particular interest given iOAT patients present to treatment with several chronic health conditions, besides OUD and often face a number of vulnerabilities that have known implications for health. As such, iOAT patients present a population for whom targeted smoking cessation interventions may play a key role in supporting improvements in physical health. The present study aims to explore the association between nicotine dependence and physical health scores among participants of the Study to Assess Longer-Term Opioid Medication Effectiveness (SALOME) RCT at baseline and after six months receiving iOAT, accounting for other factors with known relationships to physical health in this population. These findings could, for the first time inform whether the provision of treatment for nicotine dependence should be made a priority in settings where iOAT is delivered to achieve improvements in overall physical health in this population.

2. Material and methods

2.1. Setting, participants, study design

SALOME was a double-blind phase III RCT involving 202 long-term street opioid injectors in Vancouver (Canada) not benefiting from available treatments. Full details regarding screening procedures and recruitment, participant profile, design, and main results are published elsewhere (Oviedo-Joekes et al., 2015; Oviedo-Joekes et al., 2015; Oviedo-Joekes et al., 2016). SALOME participants were randomly assigned to receive injectable diacetylmorphine (n = 102) or hydromorphone (n = 100) up to three times daily for six months under the supervision of registered nurses. Both HDM and DAM were provided under identical conditions at the Crosstown Clinic, with no differences in dose prescribed, or the provision of treatment services (i.e. all participants had access to the same set of comprehensive services). The SALOME trial demonstrated the non-inferiority of injectable HDM to injectable DAM, with no differences in primary (i.e. street opioid use) or secondary outcomes (e.g. dose, retention, adherence) tested at six months. Moreover, patients did not guess what drug they were receiving beyond what is expected by chance (i.e., the blinding was not broken). In addition, subgroup analyses have revealed no significant differences in treatment outcomes between HDM and DAM when comparing men and women, and Indigenous and non-Indigenous participants (Oviedo-Joekes et al., 2017 and Palis et al., 2017). Baseline and six-month data were collected through self-report questionnaires by a research team independent of the clinical team. Participants were asked whether they were current tobacco smokers. Participants responding “no” were excluded from the present analysis.

2.2. Study measures

2.2.1. Dependent variable

At both baseline and six months, physical health score was derived from the health domain of the Opiate Treatment Index (OTI). The OTI presents a comprehensive, standardized set of measures for six independent outcome domains: health, drug use, HIV risk taking, social functioning, criminality and psychological adjustment. The health domain is specifically designed with items reflecting areas within which opioid users tend to develop health problems (González-Saiz & García-Valderrama, 2012). It has been used extensively in studies of patients receiving OAT, and in assessing health in prior clinical trials of patients receiving diacetylmorphine (Haasen et al., 2007; March et al., 2006; Verthein, Haasen, & Reimer, 2011) since it was developed in 1992. A more recent review has demonstrated high internal consistency ($\alpha = 0.71$), and high correlation with the global assessment of functioning scale, (GAFS) which is part of the multiaxial system (Axis V) of the DSM-IV (González-Saiz & García-Valderrama, 2012).

The OTI measure of physical health is a 51-item scale of prior month health symptoms from 8 domains (i.e. general, injection-related problems, cardio/respiratory, genito-urinary, gynaecological (women only), musculo-skeletal, neurological, and gastro-intestinal) (Darke, Hall, Wodak, Heather, & Ward, 1992; Nahvi et al., 2006). In the present analysis the two questions on gynaecological symptoms (i.e. miscarriage or irregular period) were excluded so that men and women had the same number of response items and thus the same total possible physical health score. The score ranges from 0 to 49, with each reported present symptom contributing one point to the score, and thus a higher score indicates poorer physical health.

2.2.2. Independent variables

Domains of interest were (1) Nicotine dependence; (2) socio-demographics; (3) substance use and illegal activity; (4) history of addiction services access; and (5) health. The nicotine dependence score was derived from the Fagerstrom Nicotine Dependence Scale (FTND). The FTND is a validated instrument with six questions about tobacco smoking behaviors and patterns applicable only to those reporting current tobacco smoking (Heatherton, Kozlowski, Frecker, & Fagerstrom, 1991). The FTND has been used as a measure of nicotine dependence among opioid dependent patients in prior studies (Nahvi et al., 2006; Pajusco et al., 2012). The FTND score ranges from 0 to 10, with a higher score indicating a more severe level of dependence. Independent variables from each of the remaining four domains were collected using self-report validated questionnaires (Blacken, 1994) and questionnaires designed by our team and used extensively in our prior studies and analyses (Oviedo-Joekes et al., 2016; Oviedo-Joekes et al., 2017; Palis et al., 2017).

2.3. Statistical analyses

Characteristics of the sample are presented at baseline and at six months. Continuous variables are presented as means with standard deviations, or medians with the interquartile range where distributions are skewed. Categorical variables are presented as frequencies with percentages. Separate univariate linear regression analyses were carried out for each of the variables presented in Table 2 for the outcome of physical health score at baseline and at six-months. Coefficients and their standard errors are presented.

Separate multivariable linear regression models were built at baseline and at six-months. The influence of each observation that could potentially distort estimates of the regression coefficient of each predictor on physical health scores were assessed using dfbeta (Education UoCLAIoDRa, 2017). Three highly influential observations were identified at baseline and hence were excluded from the baseline univariate and multivariable linear regression models. All variables with a p-value < 0.2 in univariate analyses were eligible to enter the multivariable linear regression model. This more liberal criterion reduced the exclusion of potentially important independent variables of interest that may otherwise have been overlooked. Multivariable models were built using a forward selection approach, where eligible variables were entered into the model one at a time beginning with those with the most significant association with the outcome in univariate analyses. This approach allows for the determination of the contribution of each added variable to the model using the partial F test, whereby the sum of squared error (SSE) of the full and reduced models is compared (University TPS, 2017). Added variables were retained in the model when the SSE was significantly lower in the full model as compared to the reduced model. Gender, age, and Indigenous ancestry were forced in given prior knowledge of the importance of these variables to physical health in this sample (Oviedo-Joekes et al., 2010; Oviedo-Joekes et al., 2017; Palis et al., 2017). Interactions between age and gender and age and Indigenous ancestry were tested statistically at each time point. Where interactions were found to be significant, they were included in the final model. The model building approach was identical at six-months. Models were re-run with simultaneous entry of variables and backward elimination and yielded the same results.

An additional multiple linear regression analysis was conducted to connect data from the two time-points (baseline and six-months),

Table 1
Characteristics of tobacco smokers at baseline and at six months

	Baseline	Six-months
	N = 190 Mean (SD)/n (%)	N = 187 Mean (SD)/n (%)
Nicotine dependence		
Nicotine dependence score[a]	4.40 (2.44)	4.44 (2.35)
Socio-demographics		
Gender (men)[b]	132 (69.47)	131(70.05)
Age (years)	44.45 ± 9.62	44.30 ± 9.34
Indigenous ancestry[c]	57 (30.00)	58 (31.02)
Non stable housing (prior 3 years)[d]	133 (70.00)	128 (68.45)
Substance use and illegal activity		
Prior month heroin (injection) (days)	25.29 ± 8.13	4.05 ± 7.70
Prior month crack cocaine (smoked) (days)	11.07 ± 13.01	8.33 ± 11.55
Lifetime heroin injection (years)	15.47 ± 9.48	15.48 ± 9.41
Prior month illegal activity (days)[e]	13.88 ± 13.64	4.66 ± 9.36
History of addiction services access		
Prior month retention in opioid agonist treatment[f]	89 (46.84)	148 (79.14)
Prior month safe injection site access (days)	9.45 ± 13.77	2.38 ± 5.75
Months on methadone in life	36.00 [12.00, 72.00]	36.00 [14.00, 72.00]
Health		
Physical health score[g]	22.68 ± 11.72	20.21 ± 11.32
Lifetime abuse (physical, sexual, or emotional)	126 (67.74)	123 (66.13)
Hepatitis C diagnosis[h]	166 (87.40)	163 (87.17)
HIV diagnosis[i]	28 (14.74)	28 (14.97)

SD = standard deviation. Values are N (%); Plus–minus values are means ± SD. Square brackets indicate medians and their inter-quartile range (IQR). Table notes: Non-smokers were excluded from the present analyses. At baseline 190 participants reported nicotine use and at six-months 187 participants reported nicotine use. 182 participants were smokers at both time-points. Four participants reported quitting smoking between baseline and six-months. Four participants were lost to follow-up at six-months (including two that passed away). Five participants reporting no nicotine use at baseline reported nicotine use at six-months.

[a] FTND score ranges from 0 to 10, with a higher score indicating a more severe level of dependence.

[b] 3 participants self-identified as transgender women. These participants were included in the analysis as women.

[c] Indigenous ancestry refers self-reported First Nations, Inuit or Metis ancestry.

[d] Non-stable housing refers to single resident occupancy hotel rooms with restrictions or couch surfing.

[e] Prior month days of illegal activity refers to engagement in theft, drug dealing, or sex work.

[f] Retention is defined as receiving treatment at least 28 of the prior 30 days. At baseline this refers to retention in methadone maintenance treatment and at six-months refers to retention in injectable DAM or HDM.

[g] Health score is derived from the Opiate Treatment Index (OTI), a 51-item scale of prior month health symptoms from 8 domains, with a higher score indicating poorer health. The gynaecological items (n = 2) were excluded given this domain was not applicable to men and thus the score ranges from 0 to 49.

[h] Hepatitis C diagnosis is self-reported.

[i] HIV diagnosis is self-reported.

exploring the association between baseline nicotine dependence and physical health at six-months, adjusting for baseline physical health.

3. Results

Before randomization into the two opioid treatments (i.e. either injectable diacetylmorphine or injectable hydromorphone), 190 (94%) of the 202 SALOME participants reported tobacco smoking and thus completed the FTND on nicotine dependence. At six-months, four participants were lost to follow-up (including two deaths) and four participants reported quitting smoking. Five participants reported smoking at six-months that did not report smoking at baseline. A total of 182 participants were smokers at both time-points, making the baseline and six-months cohorts similar in terms of socio-demographics and lifetime variables (see Table 1). The baseline physical health score was 22.68 ± 11.72 (mean ± standard deviation) and at six-months was 20.21 ± 11.32 (mean ± standard deviation). At both baseline and six months participants reported an average nicotine dependence score of approximately 4.4 indicating moderate dependence (Heatherton et al., 1991).

Univariate linear regression coefficients and their standard errors demonstrate factors associated with the outcome of physical health score at baseline and at six-months (Table 2). While at baseline, a range of variables were significantly associated with physical health score below p-value = 0.05, most of these associations disappeared at six-months. The nicotine dependence score was the only variable significantly and independently associated with physical health score at both time-points.

The baseline multivariable linear regression model revealed factors independently and significantly associated with physical health score (Table 3). A significant interaction between age and gender was present, suggesting that the effect of gender on the mean physical health score depended on age. Nicotine dependence score, lifetime history of physical, emotional, or sexual abuse, and prior month safe injection site (SIS) access were significantly and independently associated with physical health score. For example, for each one-unit increase in nicotine dependence score, there was an increase of 0.90 (95% confidence interval (CI): 0.25, 1.56) in physical health score. The estimated mean physical health score among those with a lifetime history of physical, emotional, or sexual abuse was 4.27 (95% CI: 0.82, 7.71) units higher than those without a history of abuse. For each additional prior month day of access to safe injection services there was a decrease of 0.12 (95% CI: −0.24, −0.01) in physical health score (i.e. better health).

After six months of treatment, nicotine dependence score was the only variable that remained significantly associated with the outcome of physical health score, independent of adjustment for forced in variables age, gender, and Indigenous ancestry (Table 4). For a one-unit increase in nicotine dependence score, there was an increase of 1.26 (95% CI: 0.58–1.94) in physical health score, indicating significantly poorer physical health scores as nicotine dependence scores increase.

The analysis conducted to connect data from the two time-points (baseline and six-months) revealed that the relationship between

Table 2
Regression coefficients and standard errors from univariate linear regression analysis of physical health score

	Baseline (n = 187)		Six-months (n = 187)	
	Coefficient (SE)	p value	Coefficient (SE)	p value
Nicotine dependence				
Nicotine dependence score[a]	1.07 (0.34)	0.002	1.21 (0.34)	< 0.001
Socio-demographics				
Gender (men)[b]	−3.68 (1.86)	0.049	−1.07 (1.78)	0.549
Age (years)	−0.28 (0.09)	0.002	−0.11 (0.09)	0.200
Ethnicity (non-indigenous)[c]	−2.58 (1.87)	0.171	−1.05 (1.79)	0.560
Non-stable housing (prior 3 years)[d]	−1.82 (1.87)	0.332	0.73 (1.79)	0.685
Substance use and illegal activity				
Prior month heroin (injection)	−0.09 (0.10)	0.385	0.11 (0.10)	0.304
Prior month crack cocaine (smoked)	0.08 (0.07)	0.224	0.07 (0.07)	0.373
Lifetime years heroin injection[e]	−0.28 (0.09)	0.003	−0.17 (0.08)	0.059
Prior month days illegal activity[f]	0.13 (0.06)	0.039	0.12 (0.09)	0.187
History of addiction services access				
Retention[g]	1.96 (1.72)	0.255	−1.55 (2.04)	0.448
Prior month safe injection site access	−0.12 (0.06)	0.059	0.19 (0.14)	0.201
Months on methadone in life	−0.02 (0.01)	0.239	−0.01 (0.01)	0.858
Health				
Lifetime abuse (physical, sexual, or emotional)[h]	5.62 (1.79)	0.002	2.99 (1.74)	0.087
Hepatitis C diagnosis[i]	−0.36 (2.57)	0.888	−0.71 (2.48)	0.773
HIV diagnosis[j]	−0.49 (2.44)	0.841	−0.34 (2.33)	0.883

SE: standard error; HIV: human immunodeficiency virus. Values are coefficients and SEs from the univariate linear regression analyses of health score. Health score is derived from the Opiate Treatment Index (OTI), a 51-item scale of prior month health symptoms from 8 domains, with a higher score indicating poorer health. The gynaecological items (n = 2) were excluded given this domain was not applicable to men and thus the score ranges from 0 to 49. Three highly influential observations were identified at baseline and hence were excluded from the baseline univariate and multivariable linear regression models, reducing the baseline sample from 190 to 187.

[a] FTND score ranges from 0 to 10, with a higher score indicating a more severe level of dependence.

[b] 3 participants self-identified as transgender women. These participants were included in the analysis as women.

[c] Indigenous ancestry refers self-reported First Nations, Inuit or Metis ancestry.

[d] Non-stable housing refers to single resident occupancy hotel rooms with restrictions or couch surfing.

[e] Note: After adjusting for age lifetime years injecting does not remain significant (i.e. older participants have more years lifetime injection)

[f] Prior month days of illegal activity refers to engagement in theft, drug dealing, sex work, or other illegal activities.

[g] Retention is defined as receiving treatment at least 28 of the prior 30 days. At baseline this refers to retention in methadone maintenance treatment and at six-months refers to retention in injectable DAM or HDM.

[h] Lifetime abuse refers to any reported physical, sexual, or emotional abuse in life.

[i] Hepatitis C diagnosis is self-reported.

[j] HIV diagnosis is self-reported.

Table 3
Multivariable linear regression model of variables independently associated with physical health score at baseline

	Baseline		
	Coefficient (SE)	95% CI	p value
Nicotine dependence score	0.90 (0.33)	(0.25, 1.56)	0.007
Age (in years) by gender			
Men	−0.35 (0.10)	(−0.56, −0.14)	0.001
Women	0.08 (0.17)	(−0.26, 0.42)	0.686
Ethnicity			0.748
Non-indigenous	−0.59 (1.84)	(−4.34, 3.05)	
Indigenous	Reference	Reference	
Lifetime abuse (physical, sexual, or emtional)	4.27 (1.75)	(0.82, 7.71)	0.016
Prior month access to safe injection site (days)	−0.12 (0.06)	(−0.24, −0.01)	0.043

SE: standard error; CI: confidence interval. **Interpretation**: The final multivariable linear regression model was built with186 observations (n = 1 excluded due to missing value for lifetime history of abuse). The continuous outcome of health score is derived from the Opiate Treatment Index (OTI), a 51-item scale of prior month health symptoms from 8 domains, with a higher score indicating poorer health. The gynaecological items (n = 2) were excluded given this domain was not applicable to men and thus the score ranges from 0 to 49. Model coefficients and standard errors are presented for adjusted associations between each listed variable and the outcome of total health score. Coefficients represent the change in health score per one unit increase in the explanatory variable. For example, for each one-day increase in access to safe injection services, there is a 0.12 unit decrease in mean health score, adjusting for all other variables in the model. **Interaction term**: Interaction terms were tested after the entry of the main effects. As age increases among men, there is a significant improvement in health score (i.e. lower score), while among women this association is not significant. For example, at age 35, the mean health score for men is 25.62 (95% CI: 22.64, 28.61), for women the mean health score is 25.05 (95% CI: 21.37–28.74). At age 55, the mean health score for men is 18.26 (95% CI: 15.58, 20.95), and for women is 25.82(95% CI: 19.95–31.69).

Table 4
Multivariable linear regression model of variables independently associated with physical health score at six months

	Six months		
	Coefficient (SE)	95% CI	p value
Nicotine dependence score	1.26 (0.34)	(0.58, 1.94)	< 0.001
Age	−0.12 (0.09)	(−0.30, 0.06)	0.180
Gender			0.683
Women	0.74 (1.80)	(−2.82, 4.30)	
Men	Reference	Reference	
Ethnicity			0.746
Non-indigenous	−0.60 (1.84)	(−4.22, 3.02)	
Indigenous	Reference	Reference	

SE: standard error; CI: confidence interval. **Interpretation**: The continuous outcome of physical health score is derived from the Opiate Treatment Index (OTI), a 51-item scale of prior month health symptoms from 8 domains, with a higher score indicating poorer health. The gynaecological items (n = 2) were excluded given this domain was not applicable to men and thus the score ranges from 0 to 49. Coefficients represent the change in health score per one unit increase in the explanatory variable. For example, for each one-unit increase in smoking score, there is a 1.26 unit increase in health score on average, adjusting for all other variables in the model.

baseline nicotine dependence and physical health at six months followed with the direction of findings from the baseline and six-month models however was not significant after adjusting for baseline physical health (p = 0.08).

4. Discussion

The present study explored the association between nicotine dependence and physical health among people with OUD taking part in the SALOME RCT before and after six months receiving iOAT. Given the nature of long-term street opioid injection, participants presented to treatment with a number of vulnerabilities including histories of lifetime abuse, nearly daily heroin injection and frequent engagement in illegal activities. Despite this, nicotine dependence was the only variable that maintained a significant and independent association with the physical health outcome after six-months of iOAT engagement. This result is particularly noteworthy when giving consideration to other tested variables that have known associations with physical health in this population. This finding offers compelling evidence for the investment of resources into treatment for nicotine dependence among iOAT patients.

In order to understand the scope of the relationship between nicotine dependence and physical health it is important to give consideration to variables that were significantly and independently associated with physical health at baseline (before participants were enrolled in iOAT care). The differential impact of age on physical health scores by gender (as demonstrated by the significant interaction of age and gender) reinforces the importance of accounting for the diversity existing within genders based on various circumstances of the daily lives of men and women in the present study.

Before starting the RCT, those with histories of lifetime physical, emotional, or sexual abuse reported on average over 4 additional physical health symptoms compared to those that did not report such histories. The association between history of trauma and abuse and physical health is well documented (Norman et al., 2012; Scott et al., 2011). For example, studies have found that histories of abuse greatly increase the presence of risk factors for poor physical health such as smoking (Roberts, Fuemmeler, McClernon, & Beckham, 2008) and obesity (Fuemmeler, Dedert, McClernon, & Beckham, 2009; Williamson, Thompson, Anda, Dietz, & Felitti, 2002), and disease conditions such as osteoarthritis (Von Korff et al., 2009), heart disease, (Fuller-Thomson, Brennenstuhl, & Frank, 2010) and cancer (Fuller-Thomson & Brennenstuhl, 2009). In the present study, the lifetime physical, emotional, or sexual abuse variable remained in the baseline model despite consideration given to a range of socio-demographic, health, treatment history and drug use variables for inclusion in the model (it is noteworthy that the association between nicotine dependence and physical health score had a higher statistical significance than that of lifetime history of abuse and physical health score). This finding suggests that lifetime history of abuse plays a fundamental role in contributing to physical health status of participants in the present study (Cedar Project et al., 2008). Given this knowledge, treatment in the SALOME trial was delivered following the principles of trauma informed care (TIC). TIC includes the use of language that promotes recovery and empowerment, offers attention to boundaries among and between staff, patients, and visitors, and views punitive approaches, shaming techniques and intrusive monitoring as inappropriate (Covington, 2003; Covington, 2008). The association between lifetime abuse and physical health does not remain significant after six months of iOAT. We hypothesize that this is due to the provision of TIC services in iOAT care, which are known to provide a safe and trusting environment for patients to engage in care, and to have great implications for the maintenance of treatment and health benefits long-term.

Prior month access to supervised injection sites (SIS) was also independently and significantly associated with physical health score at baseline. SIS are known to be efficacious at attracting people whose treatment needs are not being met by existing available services, filling a critical gap (Potier, Laprevote, Dubois-Arber, Cottencin, & Rolland, 2014). There is a plethora of evidence supporting the role of SIS in improving health status among people who inject drugs (Degenhardt et al., 2010; Fischer, Rehm, Kim, & Robins, 2002). For example, studies

have found that SIS work to promote safer injection practices, reduce the frequency of overdose and fatal overdose, reduce the spread of infectious diseases, such as HIV and HCV (MacArthur et al., 2014; Semaan et al., 2011) and improve mental and physical health status through referral to primary health care services (Potier et al., 2014; Semaan et al., 2011). This association is particularly important, given it represents a stronger association with physical health than seen among any of the other tested treatment variables such as baseline retention in OAT. After six-months of iOAT engagement, SIS access does not remain significantly or independently associated with physical health score. This is intuitive, given the high six-month iOAT retention (approximately 80%) (Oviedo-Joekes et al., 2016) and the notion that daily iOAT care offers patients access to a stable medication in a safe environment, replacing the need for SIS access among people who inject street opioids.

After six-months of daily visits to receive iOAT, nicotine dependence score was the only variable that remained significantly and independently associated with physical health score. In our prior studies, we have demonstrated that after six months of treatment (in intention-to-treat analysis), baseline differences in health by participant characteristics (e.g. gender, Indigenous ancestry) no longer exist (Oviedo-Joekes et al., 2017; Palis et al., 2017). Findings of the present study are consistent with this finding, and suggest that the treatment has effectively brought equity to patients in terms of physical health status, and that despite these improvements, the association with nicotine dependence remains.

The persistent burden of nicotine dependence to physical health among iOAT patients found in the present study suggests the importance of the provision of services and supports for nicotine dependence in this population. Despite evidence of the great problems tobacco smoking places on physical health, and evidence that people with substance dependence are motivated to quit smoking (Richter et al., 2001) treatment for nicotine dependence is often overlooked among people receiving treatment for substance use disorder (Cookson et al., 2014; Okoli et al., 2010; Pajusco et al., 2012; Wapf et al., 2008). In cases where smoking cessation interventions have been offered to OAT patients, a number of barriers have been reported to the achievement of successful smoking cessation outcomes. One of the greatest challenges that has been noted in OAT settings is the maintenance of proper adherence to smoking cessation pharmacotherapy (Cooperman, Richter, Bernstein, Steinberg, & Williams, 2015). For example, patients are known to face difficulty in remembering to take the medication, managing side effects, communicating with physicians to obtain prescriptions, and following dosing instructions (Balmford, Borland, Hammond, & Cummings, 2011; Catz et al., 2011; de Dios, Anderson, Stanton, Audet, & Stein, 2012). Many of these barriers can be effectively overcome through daily contact between patients and health care providers, as is the standard in iOAT. This daily contact offers a prime setting for treatments for nicotine dependence to be offered. For example, iOAT nurses dispense medications to patients daily (e.g. antiretrovirals, HCV medication, etc.) and could additionally dispense nicotine replacement therapy (NRT) and pharmacological treatments and monitor patients for potential side effects. Physicians located onsite have pre-existing relationships with patients and could prescribe these medications, and work with patients on determining suited interventions and appropriate dosing.

Treatment for nicotine dependence offers an evidence based addition to iOAT service provision. A recent Cochrane Review of interventions for tobacco smoking cessation among people in treatment for substance use disorders found increases in tobacco abstinence when targeted smoking interventions were provided (Apollonio, Philipps, & Bero, 2016). Both pharmacotherapy interventions and combined pharmacotherapy and counseling were found to be effective. Research suggests that combination therapy and the use of multiple pharmacological agents may be necessary to encourage attempts at reducing or quitting smoking, and to sustain abstinence among people with severe dependence or with substance use disorders (Bornemann, Eissa, & Strayer, 2016; Hurt, Ebbert, Hays, & McFadden, 2009; Lamberg, 2004; Thurgood, McNeill, Clark-Carter, & Brose, 2016).

Following this evidence, interventions incorporating pharmacotherapy need to be increasingly integrated into clinical practice in order to reduce nicotine dependence among people in treatment for substance dependence (Apollonio et al., 2016). An existing barrier to such provision in British Columbia is that of pharmaceutical services coverage. The province's pharmaceutical services plan (PharmaCare) covers access to prescription smoking cessation medication or NRTs, but not both. In addition, only one smoking cessation attempt is covered per year (Government of British Columbia, 2018). This is contrary to evidence suggesting that people receiving treatment for substance dependence may require multiple quit attempts to achieve prolonged abstinence (Richter et al., 2001) and that longer treatment durations may be necessary for people receiving OAT with high dependency and longer smoking histories (Mendelsohn & Wodak Am, 2016; Okoli et al., 2010).

Further, it is important to recognize that among the many individual and structural vulnerabilities faced by people who inject street opioids, economic marginalization is predominant. Participants of the SALOME clinical trial reside in the Downtown Eastside of Vancouver, known to be the poorest postal code in Canada. As such, the cost of smoking cessation interventions may pose a barrier to their access. Current coverage is not sufficient, nor in line with existing evidence supporting a more intensive and specialized approach to treatment for nicotine dependence among long-term opioid users (Apollonio et al., 2016).

4.1. Limitations

The SALOME clinical trial offered participants six months of access to iOAT as well as access to ancillary services. However, during this RCT there was no protocol introduced to offer a smoking cessation intervention. Outside of the context of a rigid clinical trial, there is an opportunity to recommend the integration of additional services to meet the needs of our patient population, including interventions for smoking cessation.

In the present study, nicotine dependence was measured with the FTND. The FTND is a global measure of nicotine dependence and thus intends to assess overall dependence rather than any subcomponents or types of dependence. A natural limitation of this measure therefore is that it provides little insight into the nature or mechanisms of dependence. Nevertheless, the FTND remains a valid measure of nicotine dependence and has been shown to predict clinically important dependence criteria such as smoking heaviness and relapse (Alterman, Gariti, Cook, & Cnaan, 1999; Breslau & Johnson, 2000). Further, nicotine dependence as measured with the FTND provides a meaningful benchmark that could be compared to newer multidimensional measures in the prediction of clinically important outcomes (Piper et al., 2008). Future studies aiming to understand the nature of nicotine dependence among long-term street opioid injectors may consider the use of such multidimensional measures (Piper et al., 2004; Shiffman, Waters, & Hickcox, 2004) to complement more traditional measures such as the FTND. In addition, our study makes use of researcher collected self-report data and thus did not include clinical measures (e.g. HIV or HCV symptoms). Future studies might consider the relevance of such clinical measures to physical health in this population.

5. Conclusions

The present analysis has revealed that nicotine dependence has great implications for physical health among long-term street opioid injectors who had high iOAT retention during the six-month RCT. This evidence along with the known harms of tobacco smoking suggests an important need for nicotine dependence to be treated among patients engaged in iOAT. Given the high rates of daily adherence to iOAT,

treatment for nicotine dependence including NRT and pharmacotherapy should be increasingly integrated into iOAT care and delivered daily on site.

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