Drug and Alcohol Dependence 181 (2017) 132–139

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcdep

Full length article

Constipation and other common symptoms reported by women and men in methadone and buprenorphine maintenance treatment

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ARTICLE INFO

Keywords:
Methadone
Buprenorphine
Symptoms
Sex
Gender
Somatic
Cardiac
PAC-SYM

ABSTRACT

Background: Opioid substitution treatment (OST) is often continued long-term and, therefore, opioid-associated symptoms are of interest. Symptoms associated with methadone maintenance treatment (MMT) in men are well described, but there are fewer reports concerning symptoms associated with buprenorphine maintenance treatment (BMT) and very few reports among women.

Method: Recipients of BMT (n = 113) and MMT (n = 184), non-opioid users (n = 105) and opioid users not receiving OST (n = 87) completed the Patient Assessment of Constipation (PAC-SYM) and a general symptom checklist. Multivariate analysis included other potential moderators of opioid-associated symptoms.

Findings: Opioid users reported a higher frequency and severity of symptoms than non-opioid users. Constipation, dry mouth, decreased appetite, sweating and fatigue were highly prevalent in the previous 30 days (51–80%). Nausea, itchy skin, trouble urinating, menstrual problems, lightheadedness, blurred vision, heart racing were also common (30–50%). Non-OST opioid users had significantly higher frequency and severity than OST recipients of nausea, vomiting, diarrhoea, decreased appetite, sweating and itchy skin. Sweating was significantly more common in MMT than BMT. Constipation scores were higher in women, otherwise most sex differences were small. Higher PAC-SYM scores were associated with vomiting (OR = 1.04) and sweating (OR = 1.06). Cannabis use was associated with vomiting (OR = 2.19). Constipation (OR = 1.07), insomnia (OR = 2.5) and depression (OR = 2.82) were associated with fatigue.

Conclusion: Men and women receiving OST report similarly high rates of somatic symptoms, though less than opioid users not receiving OST. There were few differences between BMT and MMT. Buprenorphine might be preferred where sweating is problematic. Several modifiable factors were identified.

1. Introduction

Methadone maintenance treatment (MMT) and buprenorphine maintenance treatment (BMT) are both commonly used as substitution treatments (OST) for opioid dependence. The effectiveness and cost effectiveness for both agents are well supported by randomised controlled trials (Mattick et al., 2009, 2014). The effectiveness of these two medications is similar, so treatment decisions may be influenced by actual or perceived side effects.

Extensive published literature describes symptom profiles in MMT. Less has been reported about symptom profiles in BMT. Of prospective studies comparing methadone to buprenorphine (Lofwall et al., 2005; Mattick et al., 2003; Pinto et al., 2010; Strain et al., 1994) the main reported treatment-emergent symptoms were constipation, sweating, nausea/vomiting, insomnia/somnolence, and sexual difficulties, in the order of prevalence of 8–20%, with little difference between methadone and buprenorphine.

There are numerous cross-sectional studies of symptom profiles in established MMT, and while the most common symptoms were similar to those indicated above for prospective studies, the reported prevalences were generally much higher, in the order 25–70% (Bloom and Butcher, 1970; Dyer and White, 1997; Kreek, 1973; Langrod et al.,

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http://dx.doi.org/10.1016/j.drugalcdep.2017.09.024
Received 3 May 2017; Received in revised form 19 September 2017; Accepted 23 September 2017
Available online 13 October 2017
0376-8716/

1981; Yaffe et al., 1973).

Where women have been included in these studies, their numbers have generally been small, and/or their symptoms not reported separately. In a study reporting help-seeking in methadone and buprenorphine maintenance patients, Winstock et al. (2008) also found almost half reported physical complaints using open ended questioning with no difference between the two treatment conditions, and no differences between men and women. However, Lofwall et al. (2005) reporting short-term methadone and buprenorphine treatment for opioid dependence, found buprenorphine treated subjects experienced higher symptom ratings than methadone treated subjects for constipation, heart racing, being often thirsty, dry mouth, ringing in the ears, blurred vision, skin rash, trouble swallowing, and dizziness/faintness. Women had higher reported prevalence of constipation and sexual problems than men, and there were several significant gender*time and gender*time*medication interactions suggestive of differences between men and women.

Given the limitations of the existing literature and the findings of Lofwall et al. (2005) we postulated that women's and men's symptom profiles in OST might differ, as might symptoms in BMT and MMT. Further, symptom profiles in OST may reflect factors other than the opioid pharmacotherapy itself. The studies cited above generally did not analyse other factors, including other drug use and physical and psychiatric comorbidities, which might contribute to symptoms.

Therefore, the intention of the present study was to gather information to better to inform OST choices – including whether to embark on and continue OST, the choice of MMT or BMT, dose, as well as the medical management of symptoms when they arise. The aims of the study were threefold: to provide robust cross-sectional data for frequency and severity of a range of symptoms in recipients of OST, comparing women and men and those receiving MMT and BMT; to compare and contrast these symptom profiles with those of opioid users not in treatment and non-opioid users; and to assess the impact of factors other than opioid treatment on key symptoms.

2. Methods

2.1. Study design

This was a cross sectional questionnaire survey of convenience samples of opioid users receiving MMT or BMT, and opioid users not receiving OST. As somatic symptoms known as common side effects in opioid users can also be found in non-opioid users for various reasons, and because the questionnaire contained items without a reference range, we also recruited a non-opioid using group as a representation of normality for the purposes of this study.

2.2. Study participants

2.2.1. MMT and BMT groups

In New South Wales (NSW), OST treatment is largely clinic-based, and OST clinic are the most feasible location for recruitment of OST recipients on a large scale for research purposes. Posters and leaflets inviting OST patients to participate in the study were placed in waiting areas at four OST clinics (three public and one private) in central and suburban Sydney, NSW. Inclusion criteria were being age 18 or over, and being enrolled in MMT or BMT for at least two months. Exclusion criteria were pregnancy, and psychiatric or cognitive impairment that might impair the participant's capacity to give consent or complete the questionnaire.

2.2.2. Opioid users not on OST

Posters and leaflets were also placed in waiting areas of four harm reduction facilities in Sydney that provide services including needle syringe programmes. These were considered the most feasible locations for recruitment of a group which may have little engagement with other health services. The inclusion criteria were regular use of illicit or pharmaceutical opioids, including methadone or buprenorphine, and being above age 18. Exclusion criteria were as for those recruited from OST clinics. Participants recruited from these sites who indicated being prescribed MMT or BMT and who received their treatment at least 10 times in the previous month were included in the applicable OST group.

2.2.3. Non-opioid using group

Posters and leaflets were placed in staff and public areas of the Royal Prince Alfred (RPA) Hospital inviting staff and public to participate. Staff, visitors, and students from the nearby university could also be reached by this method. Inclusion criteria were being "healthy" (by participants' own estimation) and being over 18 years of age. A convenience sample was considered sufficient for this group as the inclusion criteria were broad. Exclusion criteria were as for opioid users, plus current use of any opioids, as determined by questionnaire items about prescribed medications and last 30 days' substance use.

The questionnaire items for recent opioid use, current daily dose of methadone/buprenorphine, and for prescribed medications, were used to cross check eligibility for the appropriate opioid group.

2.3. Study questionnaire

The questionnaire consisted of a 27-item Symptoms Checklist, Patient Assessment of Constipation (PACSYM), Athens Insomnia Scale (AIS), the Hospital Anxiety and Depression Scale (HADS), an assessment of Recent Substance Use (last 30 days) and demographic and general health questions.

The Symptoms Checklist was developed by consultation among the principal investigators, based on comprehensive checklists used in previous studies (Dyer and White, 1997; Lofwall et al., 2005) and simplifying the English expression in some instances. We added items about urinary symptoms, also symptoms that might relate to cardiac arrhythmia based on the reported association of MMT with syncope and torsades de point (Fanoe et al., 2007). Each symptom was scored for five degrees of frequency (never/rarely/sometimes/often/always) and severity (nil/mild/moderate/bad/very bad).

PAC-SYM is a validated instrument for assessing constipation including opioid-induced constipation (Frank et al., 1999; Slappendel et al., 2006) consisting of 12 self-report items, scored on a five-point scale, from nil to very severe, in the previous 2 weeks. There is no cut-off point reported for caseness for this instrument. Athens Insomnia Scale is a validated instrument for assessing severity of insomnia (Soldatos et al., 2000, 2003). A score of 6 or more provided 93% sensitivity and 85% specificity for insomnia against ICD-10 criteria. The Hospital Anxiety and Depression Scale (HADS) is a screening tool for depression and anxiety, and measures each of these constructs independently (Hamilton, 1967; Snaith, 2003). For the present study, caseness of anxiety or depression on each of the subscales was defined as a score > / = 8.

PAC-SYM, AIS, HADS were chosen for their validation, ease of administration and brevity. The symptom checklist, while not validated, is a pragmatic instrument, derived from precedent in studies of OST, with the objects of being comprehensive and assessing both frequency and severity of symptoms.

To assess recent substance use, the questionnaire asked about the number of days in the previous 30 days where alcohol, opioids (heroin, methadone, buprenorphine, and other opioids) cannabis, benzodiazepines, amphetamines, cocaine and tobacco were used. For tobacco and alcohol, participants were asked to estimate their daily average use.

Demographics, substance use history, OST history and general health questions about sexual behaviour, employment status, partner status, acute housing problems, duration on pharmacotherapy, age of first injecting drug use and of first opioid use, major illnesses, current medications and tobacco smoking in packet years.

The study investigators supervised the administration of the