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Research paper

Alprazolam use and related harm among opioid substitution treatment clients – 12 months follow up after regulatory rescheduling

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ABSTRACT

Background: Alprazolam, has been associated with disproportionate harms compared to other benzodiazepines, especially among people in opioid substitution treatment (OST). We examine the effect of the rescheduling of alprazolam in Australia, from Schedule 4 to Schedule 8 in February 2014 amongst a high-risk population of clients in OST.

Methods: OST participants who reported recent (last month) alprazolam use were recruited from three Sydney clinics. Participants ($n = 57$) were interviewed immediately prior to rescheduling and again three months and 12 months after rescheduling. We examined self-reported patterns of drug use, drug availability, mental and physical health. A linear mixed models approach was used to analyse changes in alprazolam and other benzodiazepine use.

Results: Mean days of alprazolam use in the past 28 days decreased from 13.7 to 7.1 days, and mean weekly alprazolam dose decreased from 15.1 mg to 6.1 mg at 12 months follow-up ($p = 0.001$). Total weekly benzodiazepine use also reduced from a mean of 222 mg diazepam equivalent to 157 mg ($p = 0.044$). Other substance use did not change significantly. Reported mode of cost price of street alprazolam doubled from $5 to $10 over the 12-month period.

Conclusion: Alprazolam rescheduling resulted in an overall reduction in alprazolam and total benzodiazepine use, without substitution with other drugs, in the short term. Unintended harms were not observed. Rescheduling appears to have been effective in reducing alprazolam use in this high-risk population.

Background

Benzodiazepine misuse among opioid-substitution treatment (OST) clients is both highly prevalent (Chen et al., 2011; Darke et al., 2010; Iguchi, Handelsman, Bickel, & Griffiths, 1993; Lavie, Fatseas, Denis, & Auriacombe, 2009; Nielsen, Dietze, Lee, Dunlop, & Taylor, 2007; Peles, Schreiber, & Adelson, 2010) and associated with a number of adverse outcomes (Ashton, 2005; Lintzeris & Nielsen, 2010). These include reduced likelihood of opioid abstinence (Kamal et al., 2007), early withdrawal from treatment (Meiler, Mino, Chatton, & Broers, 2005; Peles et al., 2010), increased use of other psychotropic drugs and greater levels of anxiety and depression (Lavie et al., 2009), participation in crime and injecting-related risks (Darke, Hall, Ross, & Wodak, 1992). Benzodiazepine misuse among OST clients presents a serious public health risk as these individuals are at increased risk for multiple drug overdoses (Chen et al., 2011). Internationally, benzodiazepines are commonly implicated in opioid-related mortality (Park, Saitz, Ganoczy, Ilgen, & Bohnert, 2015), with alprazolam the most commonly prescribed benzodiazepine in the US (IMS Institute for Healthcare Informatics, 2015) and most frequently implicated benzodiazepine in emergency department drug-related presentations (Substance Abuse and Mental Health Services Administration, 2013).

In the general population in Australia, benzodiazepine use has been gradually decreasing since 1992, with the exception of alprazolam where an 8-plus fold increase in alprazolam use was observed between 1992 and 2011 (Islam, Conigrave, Day, Nguyen,

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& Haber, 2014). Whilst not all OST clients experience harms or dependence on benzodiazepines (Lintzeris & Nielsen, 2010), approximately one third (38%) of clients at two public OST services in Sydney self-report benzodiazepine use in the past 28 days (Deacon et al., 2014).

Alprazolam has been thought to be associated with a disproportionate amount of harm compared to other benzodiazepines (Horyniak, Reddel, Quinn, & Dietze, 2012; Moylan et al., 2011; Moylan, Giorlando, Nordfjaern, & Berk, 2012). Alprazolam is considered a high potency benzodiazepine compared to other benzodiazepines (Truven Health Analytics). Due to its short elimination half-life and high potency it has been identified to be particularly problematic with respect to dependence liability and withdrawal seizures (Wolf & Griffiths, 1991). Among patients on methadone programs, alprazolam has been associated with aggression and problematic potentiation of both drugs (Jones, Nielsen, Bruno, Frei, & Lubman, 2011). There have been increased alprazolam detections reported with heroin-related overdoses (Rintoul, Dobbin, Nielsen, Degenhardt, & Drummer, 2013), an overrepresentation of alprazolam in overdose cases (Buykx, Loxley, Dietze, & Ritter, 2010) and an increased risk of overdose with alprazolam in general (Isbister, O'Regan, Sibbritt, & Whyte, 2004). Driving accidents and seizures are also associated with alprazolam use (Nielsen et al., 2008).

More stringent regulation is one public health approach in response to concerns about illicit or harmful use of medicines. A recent example is the rescheduling of hydrocodone, a commonly misused opioid analgesic in the US. Compared to the 36 months before rescheduling in October 2014, the number of hydrocodone prescriptions decreased by 22% and volume of dispensed hydrocodone product decreased by 16% in the following 12 months (Jones, Lurie, & Throckmorton, 2016). A modest (4.9%) increase in non-hydrocodone opioid analgesic prescriptions did not substantially offset the drop in hydrocodone. In response to concerns with alprazolam, increased restrictions around alprazolam supply were introduced in Australia on 1 February 2014, when this medication was re-categorised from Schedule 4 to Schedule 8. With this change came jurisdictional modifications in storage and prescribing requirements. For example, in NSW doctors must now obtain a specific authority from Pharmaceutical Services in the Ministry of Health to prescribe alprazolam for an extended period of time (>two months in New South Wales [NSW]) or prior to prescribing alprazolam to a drug dependent patient (this includes all OST patients as defined in the NSW Therapeutic Drugs & Poisons Act ("Poisons and Therapeutic Goods Act, 1966 [statute on the internet],")). Reduced availability is intended to reduce inappropriate use and harms. However, it is unclear as to whether such regulatory changes are effective in modifying access and use in those individuals at greatest risk of experiencing harms. Furthermore, restrictions in access to alprazolam could also be associated with unanticipated harms such as withdrawal syndromes in dependent individuals (presenting with seizures, panic attacks, anxiety, delirium) or increases in the use of other (and potentially more harmful) substances or routes of administration (e.g. injected opioids).

This study aimed to assess the intended and unintended consequences of rescheduling alprazolam, to examine the impact of regulatory policy changes in this high-risk population. Drug use and wellbeing were examined in alprazolam-using OST clients in the periods immediately before, three months and twelve months after the regulatory changes, using a prospective longitudinal cohort design.

Methods

Study design

The study used a longitudinal cohort design to examine a range of outcomes in a group of alprazolam using OST clients immediately before, three months and 12 months after the rescheduling of alprazolam on 1st February 2014. Participants were recruited from three public specialist OST clinics in Sydney: The Langton Centre, St George Drug and Alcohol Service (both services of Drug and Alcohol Services, South East Sydney Local Health District) and Rankin Court (Alcohol and Drug Service, St Vincent's Hospital), representing approximately 750 OST clients. Eligible participants were required to have been on OST (methadone or buprenorphine) at one of the study clinics for at least one month prior to being interviewed and to have self-reported use of alprazolam at least once in the past month. Exclusion criteria included severe mental health (e.g. acute psychosis, delirium) and/or severe cognitive deficits preventing informed consent, an impending custodial sentence or transfer to another service precluding participation in the follow-up interviews. Participants were required to attend three structured interviews (each approximately two hours in duration) with an independent researcher: one month before, three months and 12 months following the rescheduling. The study was advertised with fliers displayed in the clinics, as well as potentially eligible clients being referred by clinicians. Participants received a $40 supermarket voucher for reimbursement of time and effort at the conclusion of each interview.

Ethical approval was provided by the South Eastern Sydney Local Health District Human Research Ethics Committee (HREC/13/POWH/465) with site approval by St Vincent's Hospital Sydney Human Research Ethics Committee. It conforms to the provisions of the Declaration of Helsinki (as revised in Tokyo 2004).

Measures

Baseline demographic data was collected for all participants. Both pre- and post-rescheduling interviews explored participants' drug use including a 28-day recall of days of alcohol, illicit and pharmaceutical drug use, a detailed 7-day history of drug use (including amount used, source (illicit or licit/prescription) and cost (illicit or licit)) using time-line follow-back techniques, lifetime history of benzodiazepine and other sedative use and current OST treatment type. Participants were also asked if they had experienced any non-fatal overdoses in the last three months as a result of their benzodiazepine use. Cognition was measured with the Montreal Cognitive Assessment (MOCA) (Nasreddine et al., 2005), designed to distinguish participants with mild cognitive impairment (MOCA score less than 26/30) from those with normal cognition. Mental and physical health was measured with the SF-36v2 Health Survey (Ware & Sherbourne, 1992), a 36 item validated scale which measures general physical component scores (PCS) and mental health component scores (MCS). Normative scores based on US 1998 data are mean 50 and standard deviation 10. The short version (21 item) of the Depression Anxiety Stress Scales, or DASS, (Lovibond & Lovibond, 1995) was used to measure depression, anxiety and stress. Cut-off scores out of 21 for severe or very severe depression, anxiety and/or stress are 11+, 8+ and 13+ respectively. The Insomnia Severity Index, or ISI, (Bastien, Vallieres, & Morin, 2001) – a 7-item scale with a total score of 28, where a score of 15 or above indicates clinically significant insomnia – was used to assess sleep.

Benzodiazepine use was reported as (i) mean dose (mg) used in the last seven days and (ii) mean days of use in the last 28. Standard deviation (SD) was reported for each measure. Where different benzodiazepine types were combined, quantities consumed were converted into oral diazepam equivalent doses using available references (National Prescribing Service, 1999; Therapeutic Guidelines Limited, 2013). The alprazolam equivalent dose used was 0.5 mg to 5 mg diazepam.

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