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

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.

Keywords

substitution, treatment, clients, -, 12, months, follow, up, after, alprazolam, related, harm, regulatory, among, rescheduling, opioid

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Running title: 12 month outcomes of alprazolam rescheduling among OST clients

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ALPRAZOLAM USE AND RELATED HARM AMONG OPIOID SUBSTITUTION TREATMENT CLIENTS - 12 MONTHS FOLLOW UP AFTER REGULATORY RESCHEDULING

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.

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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.

Keywords: alprazolam, opioid substitution treatment, prescription drug misuse, benzodiazepines

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, & 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, Giorlando, Nordfjaern, & Berk, 2012; Moylan et al., 2011). 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 (K. 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 (C. M. 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 0.5mg to 5mg diazepam.

Analysis

Analysis was conducted in SPSS version 21. Descriptive statistics were used to describe baseline characteristics of the cohort – current OST treatment, gender, age, employment, homelessness, education, and mental and physical health. Parametric tests (e.g. means, t-test) were used for normally-distributed data, and non-parametric tests (e.g. medians, Wilcoxon signed rank test) for skewed data. The characteristics of participants who were and were not followed up at 12 months were compared.

Linear mixed models were used to model changes in alprazolam and all benzodiazepine use over the three waves of data collection. A mixed model approach was selected to account for correlation between repeated measures, allow for both fixed and random effects, and impute missing data. The outcome variables for the four models were: (i) mean total mgs used in the last seven days and (ii) mean days of use in the last 28 for alprazolam; and (iii) total diazepam equivalent mgs used in the last seven days and (iv) mean days of use for all benzodiazepines. For each model, an autoregressive covariance structure was chosen with interview wave as the repeated measure and participants as the subject grouping. The intercept was included as a random effect and maximum likelihood estimation was used. Base models were calculated using only interview wave as a fixed predictive variable. Then other participant characteristics variables expected to influence benzodiazepine use were included in the model based on forward selection, with Akaike's Information Criterion (AIC) used to judge improved model fit. These were recruitment site, age, gender, cognition (MOCA score), physical health (PCS), depression, anxiety, and stress (using individual DASS subscale scores), and insomnia (ISI score). Base and best-fit model estimations at each interview wave are reported for each outcome variable.

Complete case analysis using descriptive statistics was used to explore the use of non-benzodiazepine drug classes including heroin, pharmaceutical opioids, amphetamines, cocaine, cannabis, alcohol, antidepressants and antipsychotics, as well as overdose reports, over the three waves of data. Data from those participants who were not interviewed at follow up one and two were not used for this sub-analysis as descriptive statistics cannot account for missing data.

Results

Baseline demographics

A flow diagram illustrating the number of participants at each wave is shown in Figure one. From an estimated pool of 750 OST clients across 3 clinics of which an estimated 285 or 38% (Deacon et al., 2014) would have used benzodiazepines (not necessarily alprazolam) in the last month, the total number of participants recruited was 57. Sixty one participants were screened for eligibility, with three of them not meeting eligibility criteria (no reported alprazolam use in the last 28 days). Of the 58 eligible participants, 57 completed the baseline interview, 48 (84%) completed the three month interview and 35 (61%) completed the 12-month interview. Of the 22 participants lost to follow-up, 10 remained clients of the OST clinic but either declined further interview (n=8) or were too unwell (n=2). Demographic, mental and physical health measures at baseline comparing the 35 participants followed up with the 22 participants lost to follow-up are presented in Table one.

<Insert Figure one here>

<Insert Table one here>

At baseline, 60% percent of participants were male and their mean age was 44 years. Thirty three percent had completed high school education, seven percent were currently employed and nine percent were homeless. Most (82%) were prescribed oral methadone, the remainder sublingual buprenorphine/naloxone. Participants reported a median of 15 years of regular benzodiazepine use (defined as the number of years since >one month without using benzodiazepines), ranging from one to 53 years. Twenty eight percent met the cut-off for normal cognitive functioning (MoCA >26/30). The only significant differences in baseline characteristics between participants followed up and not followed up at 12 months (Table one), was years of regular benzodiazepine use (24.5 years use compared to 8.5 for those followed up, $p=0.002$).

Changes in alprazolam and other benzodiazepine use

After alprazolam, the most frequently used benzodiazepines were, in order, diazepam, clonazepam, oxazepam, temazepam, nitrazepam and flunitrazepam. One person reported using zolpidem, a Z-hypnotic, at follow-up. As the effects of zolpidem are broadly similar to benzodiazepines, it was combined with benzodiazepines. Proportions of participants using diazepam (68%), clonazepam (37%), other benzodiazepines (19%), and any non-alprazolam benzodiazepines (77%) in the previous 28 days at baseline

did not change significantly at follow-up. However, alprazolam use did drop from 100% use at baseline to 36/28 (75%) use at three months and 20/45 (67%) use at 12 months follow-up.

<Insert table two here>

Table two presents the four linear mixed models for changes in volume and frequency of alprazolam and all benzodiazepine use over the three waves of data collection. The base model for Model one (total seven day alprazolam load) showed a significant ($p=0.007$) decrease at three months which was maintained ($p=0.001$) at 12 months post-rescheduling. After controlling for the covariates that improved model fit (PCS, depression, stress, ISI), time still remained a significant predictor of use. Alprazolam load decreased from a mean of 15.1 mg at baseline to 6.1 mg at 12 months follow-up ($p=0.001$). Similarly, days of alprazolam use in the previous 28 (Model two, Table two) significantly decreased at both three and 12 months, and nearly halved from 13.7 days at baseline to 7.1 days at 12 months follow-up (best-fit model controlled for physical component score, insomnia and anxiety; $p=0.001$).

There was no significant change in the seven day load of all benzodiazepines (diazepam equivalent) at three months (Model three: best-fit controlled for physical component score, insomnia and anxiety; $p=0.972$). However, at 12 months follow-up load had dropped from 225mg to 151mg ($p=0.028$). Days of use in the past 28 of all benzodiazepines did not reach significance after controlling for physical component score and insomnia (Model four; $p=0.065$).

A sensitivity analysis was carried out (results not presented) to assess the effect of the major non-benzodiazepine drug use classes (cannabis, alcohol, methamphetamine and heroin) on the four linear mixed models, but no significant effects on benzodiazepine use was seen.

Changes in other drug use

Data on non-benzodiazepine drug use among participants are presented in Table three. Considering the 35 participants who were followed up at both three and 12 months post-rescheduling, a majority of participants (60%) had used cannabis in the previous 28 days at baseline, followed by alcohol (51%), heroin (49%), amphetamines (34%), pharmaceutical opioids (20%) and cocaine (14%; table 3). One-third (31%) of participants used anti-depressants, and 14% anti-psychotics, mostly licit (prescribed) use. There were no

significant changes in proportions used over the three waves. Days of use in the last 28 (calculated only for those participants who used each drug at each time point) are also reported for the three waves. No significant changes in frequency of use were seen.

<Insert Table three here>

Changes in mental and physical health

Data on mental and physical health of participants are reported in Table four. At baseline, most (71%) fell below the cutoff for normal cognition. Most (71%) also fell below the Australian population norm for the physical (73%) and mental (91%) component scores of the SF36. Approximately half scored above the severe threshold for depression (54%), anxiety (69%), and stress (49%). Insomnia was also clinically significant in 51% of participants. There were no significant changes in mental or physical health between baseline and follow up two, except for a decrease in the proportion with clinically significant insomnia.

Three, zero and two participants reported overdose due to benzodiazepine use in the last 3 months at baseline, follow up 1 and follow up 2 respectively. Being a relatively low frequency event, with the sample size the study was not powered to detect a difference on this measure.

<insert table Four here>

Alprazolam availability and price

At baseline, most of the sample reported using only illicit alprazolam (n=45, 79%), defined as any source that was not a participant's own prescription (e.g. supplier, other person's prescribed medication). Three participants (five percent) reported using prescribed alprazolam only, and nine (16%) reported a combination of prescription and illicit sources. At 12 months follow-up, a similar proportion (n=20/28, 80%) reported using only illicit alprazolam, six participants (21%) reported prescribed use only, and two participants reported a combination of prescription and illicit sources. Seven participants (25%) had not used alprazolam in the previous three months.

The most common form of illicit alprazolam was 2mg tablets – the strongest dose formulation available in Australia. The cost of 'street' alprazolam doubled, rising from a mode of \$5 (20 out of 35 participants who reported a street price) per 2mg tab at baseline to \$10 (reported by 4/12) at three month follow up and \$10

(reported by 22/31) at 12 month follow-up. Too few people reported purchase of lower strength tablets to report meaningful estimates.

Conclusions

Using a longitudinal study design with within subject analyses, we were able to examine the effect of a change in the scheduling of alprazolam in a population of OST clients who report regular benzodiazepine use. To the authors knowledge this is the first prospectively conducted cohort study examining the impact of benzodiazepine up-scheduling. We found that alprazolam use reduced significantly in this population at three months follow up which was maintained at 12 months follow up but not eliminated. Total benzodiazepine consumption also reduced at 12 months compared to baseline. Furthermore, there was no evidence of substitution with other drug classes, with patterns of cannabis, alcohol, opioid, stimulant and other psychiatric medications (antidepressants, antipsychotic medications) remaining stable.

Following the change in scheduling the street price for 2mg alprazolam (the most commonly used strength amongst this cohort) increased, consistent with a reduction in its availability. Monitoring of street prices in larger surveillance studies such as the Illicit Drug Reporting System (Stafford & Burns, 2013) will further inform about the effect of this change on broader populations of people who use drugs.

Similarly, there were few observable changes in a range of self-reported health outcomes, suggesting that unintended harms (such as increased mental health or sleep problems) were not experienced by this group as a result of the scheduling change and associated reduction in total benzodiazepine use. Indeed, this study observed reductions in insomnia over time.

These findings are similar to a multicentre Australian cross-sectional study of the effects of a restriction in government subsidies for the capsule formulation of temazepam in 2002 (Breen, Degenhardt, Bruno, Roxburgh, & Jenkinson, 2004). This study also identified that few unintended harms were observed and there was some reduction in capsule prescription and injection, though many did continue to source and use this medication. However, injecting harms did continue to be observed until the product was removed from the market in 2004 (Degenhardt et al., 2008). It will be important to examine the longer-term outcomes of this scheduling change of alprazolam to determine if the medium-term benefits (reduced total benzodiazepine use) are maintained.

As alprazolam continues to be available, particularly from illicit sources for this cohort, it is unlikely that all of the concerns relating to alprazolam use will be addressed by this recent scheduling change. It is worth noting that a minority of participants continued to source alprazolam via prescription, despite the regulatory change restricting prescription to OST clients. We do not know if prescribing doctors were compliant with the regulations requiring them to seek authority prior to prescribing alprazolam to these participants, and there is limited capacity to monitor or enforce the regulatory changes. Nevertheless, reduced access appeared to follow the regulatory changes. Real-time prescription monitoring programs may provide another tool to enforce regulatory change, but given the majority of alprazolam use in this sample was illicit (not from people's own prescriptions) prescription monitoring may only have an indirect effect by reducing the volume of illicit alprazolam available.

Long-term effects on cognitive function have been well described with benzodiazepine use (Barker, Greenwood, Jackson, & Crowe, 2004). It is possible that with some continuing benzodiazepine and other drug use (and relatively high doses of diazepam equivalents at each time point) that we were not able to detect the changes in cognitive and general function. How best to achieve abstinence or even stable reduced doses of benzodiazepines remains an important and challenging clinical area in which further work is sorely needed, particularly for an OST population (Lintzeris & Nielsen, 2010). Given the high rates of benzodiazepine use among opioid dependent treatment populations internationally (Chen et al., 2011; Heikman, Sundström, Pelander, & Ojanperä, 2016; Meiler et al., 2005; Park, Bohnert, Austin, Saitz, & Pizer, 2014), cognitive effects of benzodiazepines remain an issue of significant public health concern

There are some important limitations in interpreting these data. Firstly, the small sample size may restrict power to detect both changes over time and predictors of change. Secondly, some recall bias amongst a cognitively impaired sample of OST clients who use benzodiazepines is possible, though with careful use of time-line follow back methods most participants were able to report their substance use in detail, and time-line follow back is a validated method of data collection amongst substance using populations (Hjorthøj, Hjorthøj, & Nordentoft, 2012; Sacks, Drake, Williams, Banks, & Herrell, 2003; Sobell & Sobell, 1992). Although self-report was not supplemented with objective measures such as urine drug screens, the latter would also have been restricted to indicating recent use only without indicating frequency or volume of use. Despite the small sample, clear changes were able to be observed. While small, this sample represents one of the highest risk populations at which regulatory changes were targeted. Another potential limitation is the

absence of a comparison group, and it is possible that some of the identified changes over time (such as reduced total benzodiazepine use) may represent maturation cohort effects of remaining in long term OST treatment – as suggested in previous OST studies (Brands et al., 2008). This study was restricted to OST clients only; results are not necessarily representative of drug using populations in general. The authors are aware of other cohorts (e.g. Illicit Drug Reporting System) monitoring changes among non-OST populations and look forward to the findings of these studies with interest. The last limitation is the follow-up rate of 61%. Those lost to follow-up did not differ from those followed up on most variables, but they did have significantly longer benzodiazepine use histories. This raises concerns about whether patterns of drug use in followed up participants was representative of the whole sample.

Strengths of the study include a prospective cohort design with a statistical analysis taking account of missing data, detailed measures of substance use and well validated measures that may capture a range of unintended harms from restriction of alprazolam. The population recruited are broadly representative of OST patients in NSW more generally being on standard OST doses, mostly being male and prescribed methadone, and representing an ageing OST cohort has had been identified in other data collection sources (Australian Institute of Health and Welfare, 2014).

Twelve months after the scheduling change we were able to detect significant reductions in both alprazolam use, and total benzodiazepine use amongst this high-risk population without observing unintended harms in terms of measures of sleep, mental health or non-benzodiazepine substance use. Examining the effects amongst other at risk populations, and over longer time periods is important further work.

Implications

Regulatory changes in pharmaceutical medications can impact upon the accessibility and patterns of use of medications. This study indicates that the regulatory change of rescheduling alprazolam from S4 to S8 was associated with reduced levels of alprazolam and total benzodiazepine use in a high-risk population of OST clients.

Conflict of interest

None.

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Table one. Participant demographics, physical and mental health at baseline, comparing those followed up and not followed up at 12 months

	A. Total sample, n=57	B. Followed up at 12 months, n=35	C .12 months not followed up, n=22	p (B v C)
Age, mean (SD)	44 (8.7)	44 (8.9)	44 (8.7)	0.959 ¹
Gender, n (%) male	34 (60%)	21 (60%)	13 (59%)	1.000 ²
Completed high school, n (%)	19 (33%)	15 (43%)	4 (18%)	0.083 ³
Employed at baseline, n (%)	4 (7%)	3 (9%)	1 (4%)	1.000 ³
Homeless at baseline, n (%)	5 (9%)	3 (9%)	2 (9%)	1.000 ³
Opioid substitution medication type methadone, n (%)	47 (82%)	28 (80%)	19 (86%)	0.725 ²
Years regular benzodiazepine use, median (range)	15.5 (1-53)	8.5 (1-40)	24.5 (3-53)	U=185, p=0.002 ⁴

¹ANOVA

²chi-square test

³Fischer's exact test

⁴Mann-Whitney test

Table two: Linear mixed model results for alprazolam and total benzodiazepine use over 3 time points.

Dependent variable	Model	Independent variables	Estimations		p
Model 1: Total 7 day alprazolam load mg	Base	Timepoint	Baseline 3 months 12 months	14.9 (10.8-19.0) 8.3 (3.9-12.6) 6.3 (1.5-11.2)	- 0.007 0.001
	Best fit	Timepoint + SF-36 physical component score ¹ + insomnia ² + stress ³	Baseline 3 months 12 months	15.1 (11.0-19.3) 8.7 (4.3-13.1) 6.1 (1.2-11.1)	- 0.009 0.001
Model 2: Alprazolam, days of use in last 28	Base	Timepoint	Baseline 3 months 12 months	14.1 (11.3-16.8) 8.6 (5.8-11.4) 7.9 (4.8-11.1)	- <0.001 0.001
	Best fit	Timepoint + site + SF-36 physical component score ¹ + insomnia ²	Baseline 3 months 12 months	13.7 (10.7-16.6) 8.5 (5.5-11.4) 7.1 (3.7-10.5)	- 0.001 0.001
Model 3: Total 7 day all benzodiazepine load, diazepam equivalent mg	Base	Timepoint	Baseline 3 months 12 months	222 (142-303) 212 (126-298) 157 (70-245)	- 0.857 0.044
	Best fit	Timepoint + SF-36 physical component score ¹ + insomnia ² + anxiety ³	Baseline 3 months 12 months	225 (144-306) 223 (136-310) 151 (63-239)	- 0.972 0.028
Model 4: All benzodiazepines, days of use in last 28	Base	Timepoint	Baseline 3 months 12 months	18.8 (15.9-21.8) 17.0 (13.8-20.1) 14.9 (11.4-18.5)	- 0.274 0.040
	Best fit	Timepoint + SF-36 physical component score ¹ + insomnia ²	Baseline 3 months 12 months	18.5 (15.5-21.4) 17.1 (13.9-20.2) 14.7 (11.1-18.3)	- 0.434 0.065

¹Measured using the SF-36v2 Health Survey

²Measured using the Insomnia Severity Index

³Measured using the short form version of the Depression Anxiety Stress Scales.

Table three: Changes in proportion and frequency of non-benzodiazepine substance use among 35 participants followed up at timepoints 2 and 3. Mean days of use is calculated using only those participants who used at each timepoint.

		Baseline (n=35)	Follow up 1 (n=35)	Follow up 2 (n=35)	p (McNemar)	
					<i>Baseline vs Follow up 2</i>	<i>Follow up 1 vs Follow up 2</i>
Heroin	% used	17 (49)	14 (41)	14 (40)	0.375	1.000
	Mean days of use (SD)	9 (8)	9 (7)	9 (8)	-	
Pharmaceutical opioids	% used	7 (20)	3 (9)	4 (11)	0.375	1.000
	Mean days of use (SD)	8 (10)	2 (2)	7 (9)	-	
Amphetamines	% used	12 (34)	11 (32)	11 (32)	1.000	1.000
	Mean days of use (SD)	6 (6)	6 (6)	4 (6)	-	
Cocaine	% used	5 (14)	4 (12)	0 (0)	0.063	0.125
	Mean days of use (SD)	4 (2)	4 (6)	4 (4)	-	
Cannabis	% used	21 (60)	18 (53)	21 (60)	1.000	0.625
	Mean days of use (SD)	17 (12)	17 (11)	19 (11)	-	
Alcohol	% used	18 (51)	16 (48)	18 (51)	1.000	1.000
	Mean days of use (SD)	13 (10)	12 (10)	10 (10)	-	
Antidepressants	% used	11 (31)	11 (32)	11 (31)	1.000	1.000
	Mean days of use (SD)	20 (12)	19 (12)	25 (8)	-	
Antipsychotics	% used	5 (14)	6 (18)	7 (21)	0.687	1.000
	Mean days of use (SD)	24 (7)	23 (7)	21 (13)	-	

Table four: Changes in mean scores and proportion scoring below normal range of physical and mental health markers among 35 participants followed up at waves 2 and 3.

		Baseline (n=35)	Follow up 1 (n=35)	Follow up 2 (n=35)	p (repeated measures ANOVA)
Cognitive impairment score¹	Mean (SD)	23.7 (3.3)	22.7 (3.5)	23.8 (3.6)	0.117
	<i>Proportion below cutoff for normal cognition (<26)</i>	71%	79%	60%	
Physical component score²	Mean (SD)	45.6 (9.5)	48.3 (10.1)	46.1 (10.5)	0.234
	<i>Proportion below population mean (<50.0)</i>	69%	56%	60%	
Mental component score²	Mean (SD)	32.0 (9.4)	34.2 (11.3)	34.6 (13.4)	0.434
	<i>Proportion below population mean (<50.0)</i>	91%	91%	83%	
Depression score³	Mean (SD)	11.6 (5.9)	10.3 (6.1)	9.7 (6.2)	0.291
	<i>Proportion above severe cutoff(≥11)</i>	54%	52%	51%	
Anxiety score³	Mean (SD)	8.9 (4.0)	8.7 (4.3)	7.3 (5.0)	0.200
	<i>Proportion above severe cutoff (≥8)</i>	69%	67%	43%	
Stress score³	Mean (SD)	11.5 (4.6)	12.3 (4.8)	10.1 (5.0)	0.108
	<i>Proportion above severe cutoff (≥13)</i>	49%	51%	37%	
Insomnia score⁴	Mean (SD)	14.9 (7.6)	15.3 (6.9)	11.8 (7.5)	<0.001
	<i>Proportion above clinically significant cutoff (≥15)</i>	51%	68%	37%	

¹Measured using the Montreal Cognitive Assessment; scores above 25/30 indicate normal cognition

²Measured using the SF-36v2 Health Survey; US population norms are 50.

³Measured using the short form version of the Depression Anxiety Stress Scales; Cut-off scores out of 21 for severe or very severe depression, anxiety and/or stress are 11+, 8+ and 13+ respectively.

⁴Measured using the Insomnia Severity Index; a score of 15 or above indicates clinically significant insomnia.