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**Misuse of prescription medicines is as prevalent as the use of recreational drugs and novel psychoactive substances in Singapore: an unrecognised public health issue?**

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**Singapore Med J 2020, 1–14**  
<https://doi.org/10.11622/smedj.2020024>  
Published ahead of print: 17 March 2020

Online version can be found at  
<http://www.smj.org.sg/online-first>

## ABSTRACT

**Introduction:** Misuse of prescription medicines and the harms associated with such use are growing threats across the world. There is currently, however, limited data on the extent of prescription medicine misuse in Singapore and whether this is a current threat in the country.

**Methods:** An online survey, limited to 1,000 individuals (aged 21 years and over) who were residents in Singapore, was administered through a survey panel company in September 2015. The survey collected information on participant demographics, and their awareness, self-reported lifetime and past-year misuse of commonly available prescription medicines in Singapore as well as the use of a range of recreational drugs and novel psychoactive substances (NPS).

**Results:** Lifetime (6.7%) and past-year (4.8%) misuse of any prescription medicine was comparable to lifetime (6.0%) and past-year (3.0%) use of any recreational drugs/NPS. The top five prescription medicines for lifetime misuse were: diazepam (2.7%); codeine (2.3%); dhasedyl (promethazine, codeine and ephedrine; 1.6%); panadeine (paracetamol and codeine; 1.5%); and methylphenidate (1.2%). The top five drugs for past-year misuse were: diazepam (1.6%); codeine (0.9%); panadeine (0.7%); alprazolam (0.6%); baclofen (0.6%); and gabapentin (0.6%).

**Conclusion:** Misuse of prescription medicine in Singapore was common, with prevalence comparable to the use of recreational drugs/NPS. A common source for misused drugs was physicians. Further studies are required to determine whether this is more widespread in Singapore and establish the different forms of drug diversion, so that appropriate prevention strategies can be implemented.

*Keywords: benzodiazepines, drug abuse, GABAergics, opioids, prescription medicine misuse*

## INTRODUCTION

Prescription medicine misuse, often also described as non-medical use, is commonly defined as “the use of medications without a prescription (if required) or in a way other than their intended or prescribed indication, or the use of prescription medicines that are sold on the illicit market”.<sup>(1-3)</sup> This includes medications available on prescription only, as well as those available over the counter in both pharmacy and non-pharmacy locations for purchase without the need for a prescription. Some examples of this potentially harmful behaviour are: using medications at larger doses than intended/prescribed; more frequent dosing; prolonged duration of use; changing the route of administration; and/or intentional co-use with other medicines, recreational drugs and/or novel psychoactive substances (NPS).<sup>(4)</sup>

Prescription medicine misuse, especially that of prescription opioids, has been shown to be a major public healthcare issue in the United States, where over a quarter of drug overdose deaths were related to prescription opioids in 2016.<sup>(5-7)</sup> While the majority of focus on prescription medicine misuse has centred on the United States, more recent data from other developed regions, such as Australia and Europe, have shown that prescription medicine misuse is a more global problem.<sup>(8-13)</sup>

There is limited data to determine the prevalence and pattern of prescription medicine misuse in Asia, and the information that is available is largely qualitative or expert opinion based.<sup>(8)</sup> There is concern in this geographical region that, due to severe penalties – including the death penalty – for the possession and/or use of classical recreational drugs, there may be significant misuse of prescription medicines, given their availability and the lesser or no penalties associated with their misuse. In a recent survey of 102 practising emergency physicians in Singapore, 78 (76.5%) physicians were concerned about misuse of prescription drugs by their patients.<sup>(14)</sup> Following awareness of the local misuse of nimetazepam and buprenorphine, the Central Narcotics Bureau of Singapore controlled these drugs in 1992 and

2006, respectively, under the Singapore Misuse of Drugs Act and Intoxicating Substances Act.<sup>(15)</sup> It is currently estimated that 10% of adults experience chronic pain and this prevalence doubles to 19.7% in those aged above 65 years.<sup>(16)</sup> There have been concerns about increasing use of opioid analgesia in Singapore related to the potential for misuse and addiction; as a result, the Pain Association of Singapore convened a multidisciplinary expert panel in September 2011 to develop practical evidence-based recommendations on the use of opioids for the management of chronic non-cancer pain in Singapore.<sup>(17)</sup>

The lack of data to understand the extent and pattern of prescription medicine misuse in Asia means that appropriate public health interventions and services for misusers cannot be designed. This study aimed to undertake an anonymous survey of adults in Singapore to determine the prevalence of prescription medicine misuse, sources of medicines that were misused, and whether there was any association between prescription medication misuse and the use of classical recreational drugs/NPS.

## **METHODS**

An online survey was designed to collect the following information: (a) respondent demographics (e.g. age, self-ascribed ethnicity, gender, occupational status, current alcohol consumption and smoking status); (b) awareness and self-reported lifetime and past-year misuse (as defined earlier) of commonly available prescription medicines in Singapore (e.g. benzodiazepines, such as alprazolam [Xanax™], bromazepam [Lexotan™], clonazepam [Rivotril™], diazepam [Valium™], lorazepam [Ativan™], midazolam [Dormicum™] and nitrazepam [Mogadon™]; GABAergics [pertaining to or affecting the neurotransmitter gamma-aminobutyric acid], such as baclofen, gabapentin and pregabalin; opioids, such as codeine, dhasedyl [codeine, ephedrine and promethazine], panadeine [paracetamol and codeine], procodin [promethazine and codeine] and tramadol; stimulants, such as

methylphenidate [Ritalin™]; and Z-drugs, such as zolpidem [Stilnox™] and zopiclone [Imovane™]); and (c) awareness of and self-reported lifetime and past-year use of a range of recreational drugs/NPS (including cannabis/marijuana, cocaine, 3,4-methylenedioxymethamphetamine, ecstasy, gamma-hydroxybutyrate/gamma-butyrolactone, ketamine and mephedrone).

The online survey was administered through an online survey panel company. The survey utilised a probability-based quota sampling strategy from a preselected subpopulation of individuals who choose to participate in online surveys. Independent of this study, survey participants were recruited to be a part of the panel through email, e-newsletter campaigns, traditional banner placements and social media. Once individuals performed a double opt-in process to be a part of the panel, they regularly received email invitations to participate in surveys. For this survey, a random selection of individuals who self-reported living in Singapore were sent a generic email invitation to participate in the survey; if they decided to open the survey, they were informed of the content and goals of the particular study. Respondents had to confirm that they currently resided in Singapore at the beginning of the survey. If they answered no to this, the survey ended and they were excluded. Quota sampling was utilised to collect between 498–500 men, 498–500 women and 0–4 transgender respondents. Once the quota for men or women was filled, respondents who started the survey and reported being a part of the filled quota automatically exited the survey and were informed that they did not qualify for the study. Individuals were completely anonymous to the researchers. Participants were paid the standard survey panel compensation amount for completion of the survey.

Collation of responses from the surveys completed by the survey panel company was performed and data were entered into SAS version 9.4 (SAS Institute, Cary, North Carolina,

USA) for further analysis. Summary data were reported, along with mean  $\pm$  standard deviation and percentage values, where appropriate.

The study was approved by National Healthcare Group Domain Specific Review Board of Singapore (reference number 2014/00773) and approved for exemption by the Colorado Multiple Institutional Review Board on 1 September 2015 (submission ID APP001-2).

## RESULTS

Of the 1,000 individuals who completed the survey, 1 woman respondent was excluded due to anomalous data entered into the survey. Demographics of respondents who self-reported lifetime and past-year misuse of any prescription medicine is shown in Table I. Mean age was  $37.5 \pm 11.1$  (range 21–76) years, and 50.0% of respondents were men, 49.9% were women and 0.1% were transgender. Self-ascribed ethnicity in our survey was similar to that reported in the Singapore Census of Population 2010:<sup>(18)</sup> Chinese (present study vs. 2010 census: 82.6% vs. 74.1%), Malay (present study vs. 2010 census: 5.3% vs. 13.4%), Indian (present study vs. 2010 census: 8.2% vs. 9.2%) and others (present study vs. 2010 census: 3.1% vs. 3.3%). A majority of respondents (85.4%) were employed at the time of survey; 11.3% were unemployed and 3.3% were studying. 62.3% of respondents were current alcohol drinkers and 18.5% were current smokers; Singapore National Health Survey 2010 reported these figures as 46% and 16.3%, respectively.<sup>(19)</sup>

**Table I. Demographics of respondents who had heard of or misused prescription medicines.**

Variable	No. (%)		
	Full sample (n = 999)	Lifetime misuse (n = 67)	Past-year misuse (n = 48)
<b>Gender</b>			
Women	498 (49.9)	31 (46.3)	17 (35.4)
Men	500 (50.0)	36 (53.7)	31 (64.6)
Transgender	1 (0.1)	0 (0)	0 (0)
<b>Age (yr)*</b>	35 (16)	36 (11)	53 (12)

<b>Ethnicity</b>			
Chinese	825 (82.6)	54 (80.6)	40 (83.3)
Malay	53 (5.3)	2 (3.0)	1 (2.1)
Indian	82 (8.2)	9 (13.4)	7 (14.6)
Eurasian	8 (0.8)	1 (1.5)	0 (0)
Other	31 (3.1)	1 (1.5)	0 (0)

*\*Data presented as median (interquartile range).*

The percentage of respondents who had heard of each prescription medicine and the prevalence of lifetime and past-year misuse are shown in Table II, together with awareness and prevalence of self-reported lifetime and past-year use of recreational drugs/NPS. The self-reported prevalence of lifetime and past-year misuse of any prescription medicine was similar to the self-reported lifetime and past-year use of any recreational drugs/NPS. In addition, the self-reported prevalence of past-year misuse of the top three prescription medicines (diazepam, codeine and panadeine), cannabis and cocaine were all comparable.

**Table II. Awareness, lifetime and past-year misuse of prescription medicines and use of recreational drugs/NPS among survey respondents (n = 999).**

<b>Drug class</b>	<b>No. (%)</b>		
	<b>Heard of</b>	<b>Lifetime</b>	<b>Past-year</b>
<b>Any prescription medicine</b>	567 (56.8)	67 (6.7)	48 (4.8)
<b>Benzodiazepine</b>			
Alprazolam	183 (18.3)	9 (0.9)	6 (0.6)
Bromazepam	75 (7.5)	5 (0.5)	3 (0.3)
Clonazepam	88 (8.8)	4 (0.4)	2 (0.2)
Diazepam	249 (24.9)	27 (2.7)	16 (1.6)
Lorazepam	151 (15.1)	10 (1.0)	3 (0.3)
Midazolam	146 (14.6)	8 (0.8)	4 (0.4)
Nitrazepam	78 (7.8)	7 (0.7)	2 (0.2)
<b>GABAergic</b>			
Baclofen	103 (10.3)	7 (0.7)	6 (0.6)
Gabapentin	60 (6.0)	9 (0.9)	6 (0.6)
Pregabalin	41 (4.1)	2 (0.2)	1 (0.1)
<b>Opioid</b>			
Codeine	302 (30.2)	23 (2.3)	9 (0.9)
Dhasedyl	174 (17.4)	16 (1.6)	5 (0.5)
Panadeine	175 (17.5)	15 (1.5)	7 (0.7)
Procodin	125 (12.5)	4 (0.4)	3 (0.3)
Tramadol	136 (13.6)	11 (1.1)	5 (0.5)

<b>Stimulant</b>			
Methylphenidate	132 (13.2)	12 (1.2)	3 (0.3)
<b>Z-drug</b>			
Zolpidem	86 (8.6)	7 (0.7)	5 (0.5)
Zopiclone	67 (6.7)	4 (0.4)	3 (0.3)
<b>Recreational drug</b>			
Any recreational drugs/NPS	854 (85.5)	60 (6.0)	30 (3.0)
Cannabis	735 (73.6)	40 (4.0)	15 (1.5)
Cocaine	813 (81.4)	20 (2.0)	10 (1.0)
MDMA	765 (76.6)	16 (1.6)	5 (0.5)
GHB/GBL	103 (10.3)	5 (0.5)	2 (0.2)
Ketamine	669 (67.0)	11 (1.1)	3 (0.3)
Mephedrone	168 (16.8)	7 (0.7)	2 (0.2)

*GABAergics: pertaining to or affecting the neurotransmitter gamma-aminobutyric acid; GHB/GBL: gamma-hydroxybutyrate/gamma-butyrolactone; MDMA: 3,4-methylenedioxymethamphetamine; NPS: novel psychoactive substances*

Self-reported lifetime prescription drug misuse was cross-tabulated with lifetime recreational/NPS drug use (Table III). Over a third of respondents (n = 24, 35.8%) who had misused any prescription medicine in their lifetime also indicated that they had used recreational/NPS drugs in their lifetime. Among these 24 respondents, the most commonly reported misused prescription medicines were opioids (n = 16, 66.7% of those who had misused any prescription medicine and reported recreational drugs/NPS use) and benzodiazepines (n = 16, 66.7%).

**Table III. Cross-tabulation of lifetime prescription medicine misuse and lifetime recreational/NPS drug use.**

Prescription drug class misuse	Lifetime recreational drugs/NPS use	
	Yes	No
<b>Any prescription medicine</b>		
Yes	24	43
No	36	896
<b>Any benzodiazepine</b>		
Yes	16	22
No	44	917
<b>Any GABAergic</b>		
Yes	8	7
No	52	932
<b>Any opioid</b>		

Yes	16	27
No	44	912
<b>Stimulant (methylphenidate)</b>		
Yes	6	6
No	54	933
<b>Any Z-drug</b>		
Yes	7	4
No	53	935

*GABAergic: pertaining to or affecting the neurotransmitter gamma-aminobutyric acid; NPS: novel psychoactive substances*

Individuals reported sourcing prescription medicines for misuse from a variety of sources, with 12 of 67 (17.9%) respondents sourcing individual medicines from more than one source (Table IV). Overall, the most common sources of misused medicines were doctors, friends and family.

**Table IV. Source of supply of misused prescription medicines by drug class.**

Drug class	No. of respondents reporting lifetime misuse	Source of supply (no. [%])			
		Doctor	Internet	Family	Friend(s)
Benzodiazepine	38	26 (68.4)	12 (31.6)	10 (26.3)	15 (39.5)
GABAergic	15	7 (46.7)	4 (26.7)	9 (60.0)	1 (6.7)
Opioid	43	26 (60.5)	9 (20.9)	9 (20.9)	9 (20.9)
Stimulant (methylphenidate)	12	6 (50.0)	1 (8.3)	3 (25.0)	4 (33.3)
Z-drug	11	3 (27.3)	3 (27.3)	4 (36.4)	2 (18.2)

*GABAergic: pertaining to or affecting the neurotransmitter gamma-aminobutyric acid*

## DISCUSSION

To the best of our knowledge, this is the first population level survey to determine the demographics and prevalence of the misuse of prescription medicines in Singapore. Previous studies in the United States and Europe have demonstrated that opioid-containing medications and benzodiazepines are medicines of concern with respect to medication misuse.<sup>(10-12)</sup> The self-reported prevalence of lifetime and past-year misuse of any prescription medicine in our survey was comparable to the lifetime and past-year use of recreational drugs/NPS (lifetime

misuse vs. lifetime use: 6.7% vs. 6.0%; past-year misuse vs. past-year use: 4.8% vs. 3.0%). We postulated that, in Singapore, where any form of recreational drug use is illegal, prescription medicine misuse might be more common, as these drugs may be more easily obtained from a variety of sources. Prescription medicines also are not routinely tested during drug screening and may not carry the same or other penalties for possession and use when compared to recreational drugs. The most commonly misused medicines in our survey were diazepam and codeine. Interestingly, in a previous study of 100 benzodiazepine-dependent patients in Singapore, during 2003–2005, midazolam was reported as the benzodiazepine of choice for a majority of patients (69%); diazepam was only the drug of choice among 6% of patients, behind both nimetazepam (13%) and alprazolam (7%).<sup>(20)</sup>

Prescription opioids are commonly prescribed both in primary care as well as in the emergency department for pain relief; and, although opioids are not as widely prescribed for non-cancer pain in Singapore, recent studies have shown an increase in opioid use in the country.<sup>(17,21,22)</sup> Benzodiazepines are also commonly administered to patients with anxiety or sleep disorders. Studies are required to further characterise the misuse of these drugs in Singapore, including determining the demographics of misusers, doses misused, frequency of misuse and the association of misuse with chronic pain, to further understand the potential risk of opioid and benzodiazepine dependence among high-risk groups of individuals. This would enable the design of appropriate prevention and harm reduction measures. Preventing and reducing opioid misuse is particularly important, as opioid misuse has proven to be a significant healthcare burden in the United States, where according to the 2010 US Nationwide Emergency Department Sample dataset, prescription opioids (including methadone) were responsible for two-thirds of opioid overdose presentations to the emergency department, with estimated costs for both inpatient and emergency care charges being around USD 1.6 billion.<sup>(23)</sup>

Misuse of prescription medications could be associated with the use of recreational drugs/NPS. In our study, over a third of respondents who self-reported prescription medicine misuse in their lifetimes also reported recreational drugs/NPS use during their lifetime. Opioid and benzodiazepine misuse were frequently reported alongside recreational drugs/NPS use. While this time frame likely does not represent concomitant use, it could represent patterns of behaviour during a person's lifetime that would elevate risks of overdose and other morbidities.

Individuals who misuse prescription medicines often obtain them from a variety of sources, and the source may vary depending on the medicine that is misused. One study from the United States on entrants to addiction treatment programmes reported the three major sources for obtaining prescription opioids, as street-level drug dealers, from friends/relatives and 'doctor shopping'.<sup>(24)</sup> The sourcing for prescription opioids in Canada occurred via multiple routes and diversion: friends, family, street-level drug dealers, doctor-shopping, prescription fraud/forgery, thefts and robberies, and Internet purchases.<sup>(25)</sup> In our study, the most common source used to obtain misused benzodiazepines, opioids and methylphenidate was a doctor. In the previous survey of benzodiazepine-dependent individuals, 75% of respondents reported that they obtained benzodiazepine from their general practitioner and that the most common reason used to obtain was insomnia (72% of respondents).<sup>(20)</sup> Interestingly, 66% of these patients reported that the prescribing general practitioner asked about potential misuse and, where there were discussions about problematic use, this was most commonly initiated by the patient (62% of occasions). As previously noted in a survey in Singapore, over three-quarters of emergency medicine physicians were concerned that their patients may be misusing prescription medicines.<sup>(14)</sup> Further studies in Singapore should investigate whether medical prescribers were aware that the individual was misusing at the time of prescribing and/or whether they asked about potential misuse prior to prescribing. This would help target

education as well as interventions for improving prescribing habits and detection of potential misuse of prescription medicines.

This study was not without limitations. Our study was an online survey conducted via a survey panel company. As a result, the findings of our study cannot be generalised to statistical inference for the general population of Singapore. However, the results can be used to decipher general trends and patterns of misuse of prescription drugs, which would help guide further investigations. Lastly, information on drug use was based on self-reporting by respondents, which may be affected by recall bias. Since drug use and misuse is stigmatised in Singapore, there may also be a bias toward lower self-reported misuse.

In conclusion, prescription medicine misuse, especially that of benzodiazepines and opioid-containing drugs, appeared to be significant among the respondents who participated in our online survey in Singapore. Physicians are one of the common sources for drugs that are misused. Further work is required to determine whether this is a more widespread issue in Singapore and to study the different forms of drug diversion prevalent, so that appropriate and timely prevention strategies can be implemented to curb this emerging trend of prescription medicine misuse before it grows and into a major public healthcare emergency.

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