

TEN-YEAR RETROSPECTIVE STUDY OF DIAZEPAM CONSUMPTION IN INDONESIA

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ABSTRACT

Objective: This study aimed to evaluate annual consumption during 2004-2013 of diazepam, an essential medicine which is controlled under the 1971 Convention on Psychotropic Substances in Indonesia and to investigate factors influencing its use in health facilities.

Methods: This was a case study with quantitative and qualitative approaches. Annual consumption was calculated from the quantity of exports and imports. The use of diazepam was calculated from consumption deducted by 20% buffer stock. The consumption and use of diazepam were presented in kilogram and also in defined daily doses for statistical purposes (S-DDD). In-depth interviews were conducted to investigate factors that influence the use of diazepam. Triangulation was conducted to confirm the qualitative and quantitative findings.

Results: The annual average consumption in 2004-2006 was 530 kg. Furthermore, it decreased 38% during 2011-2013 to 329 kg. Calculated use of diazepam also decreased. The average consumption for the 10-year period of diazepam was 470 kg, and the calculated use was 376 kg (0.45 S-DDD). Considering the approximate need of diazepam to treat various health problems, its use should ideally be around 1-2 S-DDD. Therefore, the calculated use of diazepam was considered too low as confirmed by frequent stockouts. The interviews revealed that among the factors influencing its use was its limited production. There was an increased use of alprazolam, but it was unlikely to compensate for the diazepam stockouts.

Conclusion: Consumption and use of diazepam for medical purposes in Indonesian decreased over 10 years, and stockouts are often reported. The government should improve its availability and correct impediments for adequate production and supply of diazepam.

Keywords: Diazepam, Essential medicine, Consumption, Psychotropic medicine use.

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INTRODUCTION

Diazepam is an essential medicine of the benzodiazepine group which is listed on the 19th WHO Model List of Essential Medicines 2015 [1] and the Indonesian List of Essential Medicines 2015 [2]. Essential medicines must be available at anytime in appropriate dosage to be accessed by all people [3]. Access for essential medicine is affected by reliable health and supply systems, rational use of medicine, cost affordability, and sustainable financing [4].

The use of diazepam is under national and international control. Nationally, its use is regulated by Law No. 5/1997 on Psychotropics. While internationally, it is regulated by the Convention on Psychotropic Substances of 1971. These provisions aim to assure the availability of psychotropics for medical and scientific purposes while preventing their abuse [5]. Diazepam is used as an anxiolytic, antiepileptic, muscle relaxant, and in induction of anesthesia [6]. It is often abused with alcohol, opioids, and z-drugs [7,8], but even so, the availability for medical and scientific purposes should be fulfilled.

Annual global consumption of diazepam during the period of 2004-2006 decreased by 20% compared to 2011-2013 from 5.2 defined daily doses for statistical purposes (S-DDD) to 4.1 S-DDD per day 1000 population. S-DDD, a technical unit of measurement for statistical analysis purposes based on prescription dose. The largest decreases in consumption were observed in Asia (70%) and in America (44%). The average consumption in Asia during 2004-2006 was 2.56 S-DDD and decreased to 0.76 S-DDD in the period of 2011-2013. Africa and Oceania meanwhile experienced decreases of 70% and 11%, respectively [9].

Diazepam consumption in the ASEAN region with <1 S-DDD in 2011 was observed in Lao PDR (0.72 S-DDD), Malaysia (0.46 S-DDD), Cambodia (0.33 S-DDD), Vietnam (0.24 S-DDD), and the Philippines (0.04 S-DDD). The high consumption rates were observed in Thailand with 4.17 S-DDD and Singapore with 2.11 S-DDD [10]. No previous publication was available regarding the consumption of diazepam in Indonesia. Therefore, this study will reveal this situation and the trend of its consumption pattern in the last 10 years. The objective of the study was to evaluate the consumption of diazepam in Indonesia during the 10-year period of 2004-2013 and to investigate factors influencing its use in health facilities. Results of this study will be a strong basis for improving the quality of medical care.

METHODS

This was a case study with quantitative and qualitative approaches which was conducted between April and June 2016. The study was divided into two phases. The first phase was a quantitative review of diazepam consumption in Indonesia during 2004-2013 through the data published by International Narcotics Control Board (INCB) and the archive of the Directorate of Pharmaceutical Production and Distribution, Ministry of Health of Indonesia.

Annual consumption was calculated from the quantity of imported diazepam (kg) reduced by the quantity to be used for the manufacturing of exported diazepam products. The use of diazepam was calculated from consumption deducted by 20% buffer stock. The consumption and use were presented in a kilogram. The S-DDD was calculated from the amount of diazepam consumed or used in the country (in mg), divided by the DDD of diazepam (which is 10 mg based on its medical use as an anxiolytic), number of days in a year (365), and the country population in thousand unit.

$$S-DDD \text{ of diazepam} = \frac{\text{Amount of diazepam (mg)}}{10 \text{ mg} \times 365 \text{ days}} \times \text{population (in thousand unit)}$$

The second phase of the study was investigating factors influencing the use of diazepam. In-depth interviews were conducted with 14 key informants consisting of two informants from the Directorate of Pharmaceutical Production and Distribution, Ministry of Health, one informant from the National Agency for Drug and Food Control, one informant from the National Narcotics Board, one informant from the National Police Criminal Investigation Directorate, two informants from Kimia Farma Pharmaceutical Company, one informant from the Provincial Office of National Agency for Drug and Food Control in Yogyakarta, one informant from the Provincial Health Office of Yogyakarta, and five informants from Pharmaceutical Wholesalers. Interviews were followed by text messaging for completion of the information. Triangulation was applied to confirm the findings.

The proposal of the study has been approved by the Ethics Committee of Faculty of Medicine, Universitas Gadjah Mada (KE/FK/32/EC/2016) on April 6th 2016. Permission to conduct the study has been obtained from relevant institutions. All key informants signed written informed consents after receiving complete information regarding the objective and the procedure of the study.

RESULTS

Consumption and use of diazepam

The annual average consumption of diazepam in 2004-2006 was 530 kg, then was decreasing by 38% during 2011-2013 to 329 kg. The lowest consumption was in 2012 (263 kg) and the highest consumption was in 2008 (684 kg). In the period of 10 years (2004-2013), diazepam average consumption was 470 kg. Data on diazepam consumption and use within the period of 10 years are presented in Table 1.

Diazepam use was decreasing in the last 10 years. In 2013, its use was 0.37 S-DDD compared to the average of 0.45 S-DDD. Based on approximate need of diazepam to treat various indications (anxiolytic, antiepileptic, muscle relaxant, and anesthetic induction), the authors calculated that the use of diazepam should ideally be around 1-2 S-DDD. Therefore, the use of diazepam in Indonesia is considered too low. It means that many patients did not receive this medicine. This shortage was confirmed by frequent stockouts. From the interviews, informants stated that factors that influenced diazepam use included its limited availability in health facilities, and stockouts of generic diazepam, particularly. Below is the statement of a key informant from Provincial Office of Drug and Food Control.

"Shortages in 2014 could be overcome, but in 2015 the stockouts occurred more frequent than before. In addition, we do not know about the supplier. The problem is in its factory" (Informant from the Provincial Office of National Agency of Drug and Food Control).

Limited availability or even stockouts of medicine led to a reduction of its use in health facilities. Stockouts of generic diazepam also occurred in supplier level. This was a quote from one key informant at Provincial Office of National Agency of Drug and Food Control.

"As far as we know, there was no stock in wholesalers (because of no supply). It is difficult to get generic diazepam, I do not know why. Stockouts are getting frequent now. The only available diazepam is branded products" (Informant from the Provincial Office of National Agency of Drug and Food Control).

The difficulties of stocking generic diazepam were confirmed by five key informants from pharmaceutical wholesalers. They mentioned that only two pharmaceutical wholesalers provided generic diazepam and three did not provide generics. Stockouts of generic diazepam generally occurred in non-government wholesalers. Analysis of diazepam use in Yogyakarta through report from the system information of narcotics and psychotropic use (SIPNAP) during 2014-2016 revealed that the use of generic diazepam was between 8% and 17% of the overall use. Stockouts of generic diazepam at supplier level lead to low use of the medicine in public health facilities. However, while branded diazepam were available, the use of diazepam was considered too low.

Diazepam production

Import of diazepam quantity fluctuated during 2004-2013. It increased in 2010, but was always below one ton annually. Diazepam raw material was imported from India, Italy, China, and Denmark. Export of diazepam increased during 2010-2013, although it was <500 kg. Branded diazepam were exported to Cambodia, Hong kong, New Zealand, Singapore, Sri Lanka, and Taiwan. The data showed that the amounts of imported and exported diazepam increased, but the amount of diazepam used domestically tended to decrease.

The domestic use of diazepam was in generic and branded forms, while export was in the form of branded products. Branded diazepam production to fulfill export need was stated from a key informant from Kimia Farma Pharmaceutical Company.

"There are needs of this branded product, stockouts are in generic form, but the branded form is available. The product that exported was the branded, not the generic. They produce it for export purpose" (Informant from Kimia Farma Pharmaceutical Company).

Diazepam is used in primary and secondary health facilities, in public, and private health sectors. The use in public facilities is preferred in generic form, while private use in both generic and branded. Therefore, production of generic diazepam should be increased. From the data of diazepam use reported by health facilities to the Ministry of Health through SIPNAP, there were 42 products of single and combination diazepam in generic and branded products that had to be reported monthly. Of these products, there were four generic and the rest were branded. Unfortunately, separate data on the quantity of generic and branded diazepam used in health facilities were unavailable.

There are 17 pharmaceutical companies that produce diazepam, three government-owned and 14 private pharmaceutical companies. It is unknown whether the company tends to produce a more branded product

Table 1: Consumption and use of diazepam in Indonesia during 2004-2013

Year	Import (kg)	Export (kg)	Consumption (kg)	Use (kg)	Use (S-DDD)
2004	614	0	614	491.2	0.62
2005	380	0	380	304	0.38
2006	596	0	596	476.8	0.58
2007	455	0	455	364	0.44
2008	684	0	684	547.2	0.66
2009	NA	NA	NA	NA	NA
2010*	562.540	46.234	516.306	413.045	0.48
2011*	579.103	272.489	306.614	245.291	0.28
2012*	745.530	483	262.530	210.024	0.23
2013*	914.972	497.967	417.005	333.604	0.37
Average			470.162	376.129	0.45

Sources: INCB, 2005-2015; *Indonesia Ministry of Health, 2015; NA: Data not available, DDD diazepam as anxiolytics=10 mg, DDD: Defined daily doses, INCB: International Narcotics Control Board

than generic. According to two pharmacists from a pharmaceutical company and supervisory institution, they confirmed that generic diazepam was priced IDR 100, while branded diazepam was IDR 300. The two informants also expressed that even though the price is low, the administrative procedure is very tight due to regulatory control.

"The price of generic diazepam is IDR 100. However, the risk (administration and supervisory) is extraordinary, same as narcotics" (Informant from Kimia Farma Pharmaceutical Company).

At retailers, the highest price for 2 mg generic diazepam tablet in May 2016 was IDR 156/tablet, while the price for branded was between IDR 1500-2000/tablet.

Diazepam versus alprazolam use

The diazepam unavailability caused decreases in diazepam use and an increase in the use of other substances which have the same indication, such as alprazolam. Four informants stated that there was an increase in alprazolam prescriptions. Below are quotes from key informants:

"... many physicians prefer using alprazolam, considering its comforting effect on patients, alprazolam is more comfortable, but if the mechanism and addiction effect are taken into account, alprazolam is more dangerous when compared to diazepam, although they are both from the same benzodiazepine group" (Informant from National Narcotics Board).

"Trend of diazepam usage is declining, it had changed to alprazolam. I see that physician's prescription is shifting toward alprazolam. Diazepam is rarely prescribed. Maybe that is the reason why patients in need of psychiatric medicine are commonly prescribed with alprazolam maybe that is the beginning of the decline of diazepam usage. Medical world is dynamic, isn't it?" (Informant from Provincial Office of National Agency of Drug and Food Control).

Diazepam consumption decreased in 2010, and concurrently, alprazolam consumption increased. Differences in diazepam and alprazolam consumption are shown in Fig. 1.

The increase in alprazolam consumption indicated an increase in alprazolam use, although the total consumption amount of diazepam together with alprazolam was less than 1 S-DDD. It was unclear whether alprazolam use increased in public or private health-care facilities because alprazolam is not included in the National List of Essential Medicines and was not used at public primary health care level. It is possible that the increase occurs in private facilities or public referral health-care facilities. The increase in alprazolam use did not meet with diazepam demand because the two medicines have different places in medical treatment. Moreover, the total use of the two medicines was still less than 1 S-DDD.

DISCUSSION

Efforts to ensure diazepam availability for medical uses

Diazepam consumption in Indonesia was decreasing in the last 10 years and it was always below 1 S-DDD. Out of 164 countries that

reported to the INCB during 2011-2013, there were 37 countries that consumed diazepam higher than the global average where the highest consumption were Ghana (50.5 S-DDD), Yugoslavia (26.1 S-DDD), and Croatia (25.9 S-DDD). While 90 countries consumed diazepam less than 1 S-DDD per 1000 people per day and 22 countries consumed less than 0.1 S-DDD [10]. Diazepam consumption in Indonesia and several ASEAN countries were less than 1 S-DDD [11,12].

The Special Region of Yogyakarta is a province in the Republic of Indonesia, which uses the SIPNAP reporting system to provide the data of psychotropics use, including diazepam, monthly. From the SIPNAP data, it is known that there was 53% increase in diazepam use in health-care facilities in Yogyakarta between 2014 and 2016. Therefore, diazepam is needed in health-care facilities in Yogyakarta. However, diazepam was often unavailable in public health-care facilities. Yogyakarta is one of the Indonesian provinces which have the highest prevalence of mental disorders [13], hence the use of diazepam is needed more than other provinces. Diazepam is indicated for many treatments. The presence of 17 pharmaceutical industries in Indonesia which produce 42 branded and dosage forms showed that the demand for diazepam products is high.

Diazepam is used in almost every country. In the Republic of Macedonia, between 2003 and 2013, of all the patients requiring treatment with benzodiazepine, 59% were treated with 5 mg diazepam [14]. In Bosnia, diazepam was the most common psychotropic agent for outpatient uses between 2002 and 2008, followed by phenobarbital and carbamazepine [15]. In Latvia, between 2004 and 2007, diazepam was the most prescribed psychotropic (12 DDD/1000 people/day) compared to other psychotropic medicines such as bromazepam, alprazolam, oxazepam, nitrazepam, and clonazepam [16]. Data of outpatient prescriptions in general hospitals in Singapore between 2005 and 2013 showed high use of diazepam, alprazolam, and lorazepam [17]. The most common benzodiazepine used in outpatients from the Psychiatric Department in Academic Hospital in Karnataka, India, was clonazepam (47.86%), diazepam (21.05%), and lorazepam (18.95%) [18]. The most prescribed psychotropic in the Neurology Department of private hospital in Tamil Nadu, India, was phenytoin (92.10%), diazepam (36.84%), and sodium valproate (7.89%) [19]. Diazepam was the most commonly prescribed medicine for schizophrenia outpatients from the Psychiatric Department in the Owaisi Hospital and Research Center in Hyderabad, India (41.95%) and the least was aripiprazole (0.57%) [20]. Meanwhile, diazepam has the least frequency of potentially inappropriate medication use in the elderly population treated at Gondar University Hospital, Ethiopia [21]. Therefore, diazepam use should increase and not otherwise, as in Indonesia.

This study shows that one of the factors that affect diazepam use was limitation of availability. Frequent stockouts were reported, particularly of generic diazepam. Unavailability of diazepam caused obstacles in its use, especially in public health-care facilities, because public facilities mainly use the generic product. Although branded products were available, their use was low. Medicine use was influenced by four correlated factors: Health-care system, prescriber, dispenser, patients, and community [3]. From health-care system aspects, the obstacles were unreliable supplies, medicine shortage, expired medicine, and substandard, or fictitious products. Unreliable supplies clearly influenced use. Therefore, diazepam availability must be ensured by improving the supply system and increasing production to prevent stockouts.

Access to diazepam

Limitation of generic products availability leads to physicians prescribing branded products, although they are more costly than generic products. There were conspicuous price differences between generic diazepam products and branded ones. Data from Health Research and Development Agency of Indonesia in 2014 showed that there was a branded product of 5 mg diazepam which was 50 times more expensive compared to the generic product price [22].

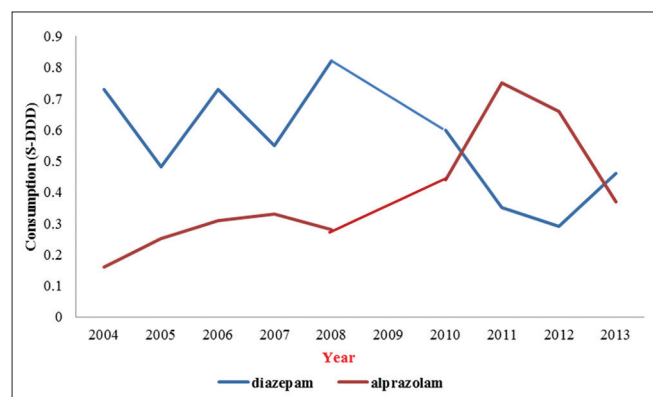


Fig. 1: Consumption of diazepam and alprazolam in Indonesia during the 10-year period of 2004-2013

Access to acquire essential medicine is influenced by price affordability [4], even though access to essential medicines is one of the human rights. Therefore, ensuring sustainable supply of diazepam is an obligation for the public and private health-care facilities [23]. For this reason, requantification of diazepam requirement is necessary to meet all domestic medical needs, and also to fulfill export demands. The estimation of diazepam requirements for domestic medical needs for various indications is ranging from 1 to 2 S-DDD, or approximately 900-1800 kg per year. By simulation, to meet domestic medical demands of 1 S-DDD and export of 500 kg, up to 1580 kg of raw material will need to be imported. In reality, the highest quantity of diazepam import in Indonesia in 2013 was only 915 kg. Countries with the highest production of diazepam are Italy, China, Switzerland, UK, India, Germany, and Denmark [10].

McBain, [24] in a study about the role of health system factors in 63 low-income countries and middle-to-low income countries in influencing accessibility to obtain psychotropics in health-care facilities found that the availability of psychotropics in 58 health-care facilities was 71%. The availability of psychotropics in low income and middle-to-low income countries was 70%, and in middle-to-high income countries was 82%. McBain also showed that the availability of psychotropics in a country was correlated with: (1) The presence of national laws, regulations, and policies about mental health which could increase psychotropics availability by 15%; (2) per capita income which had impact in budget allocation for mental health; (3) the presence of patient's family participation which could determine mental health policy and increase the availability of psychotropics by 16.5%; and (4) the presence of mental health assessment and treatment standard in primary health-care facilities, which could increase the availability of psychotropic by 17%. Consequently, to increase the access for psychotropic treatment, including diazepam, several requirements such as price affordability, medicine availability, and an adequate mental health system would need to be fulfilled.

According to Barbui [25] access to psychotropic medicines in countries with limited ability could be improved through medicine availability regulation, implementation of reliable supply system (provision, supply, and distribution), quality control of psychotropic medicines, and implementation of community-based mental health system. Availability could be improved through development of stricter pricing policy and encouragement of continuous payment system with affordable medicine prices. Padmanathan suggested the presence of a budget allocation policy by the government, particularly for essential psychotropic medicines [26].

Diazepam versus alprazolam

Shortage of diazepam availability could increase utilization of other medicines with the same indication, such as alprazolam. Concurrently, there was an increase in alprazolam use since 2010. However, it is unclear whether there was a shift of usage from diazepam to alprazolam; alprazolam is not an essential medicine and is not used in public primary health-care facilities. It is likely that alprazolam use increased in private or referral health-care facilities. Alprazolam is used medically as an anxiolytic, while diazepam could be used as an anxiolytic, antiepileptic, muscle relaxant, and anesthetic premedication. Although alprazolam was used to fulfill the shortage of diazepam as an anxiolytic, it could not replace diazepam for other indications.

Diazepam is a long-acting benzodiazepine. It has a half-life of 20-80 hrs, whereas alprazolam has a half-life of 12-15 hrs [6]. Therefore, the hangover effect of diazepam is longer. Ambarsari [27] conducted a study in 437 patients who were prescribed benzodiazepine in a pharmacy in Yogyakarta, Indonesia in 2016. The study showed that alprazolam was prescribed in 87.18% of all benzodiazepine prescriptions, whereas diazepam was only 0.91%. Increase in alprazolam prescriptions was also reported in Australia [28]. Apparently, this phenomenon of increasing alprazolam use was not correlated with diazepam in availability.

Some studies indicated that there was an increase in the use of benzodiazepine-related medicines, such as zopiclone, zolpidem, zaleplon, and eszopiclone. This group is commonly known as Z-drugs. They have a short-acting effect at the benzodiazepine receptor [6]. It was estimated that almost 95% of Danish Z-drugs users use it for 4 weeks, and more than 50% use it for 6 months [29]. The trend of zolpidem and zopiclone use in Denmark between 1997 and 2008 was increasing while benzodiazepine was decreasing [30]. In Canada, there was a change in benzodiazepine prescription practice, especially for the elderly patients. Benzodiazepine prescription was decreasing while Z-drugs use was increasing. Similar trends were also found in other international studies [31]. Z-drugs in branded dosage form are available in Indonesia, but the extent of its use in relation to diazepam is not known.

This study showed that the decrease in diazepam usage is correlated with an unreliable supply system. It will need improvements in production and supply system, to prevent a shortage of medicines. To prevent the shortage of essential medicines, requantification of domestic medical needs is needed. Inaccurate quantification will obviously result in an incorrect calculation of medical requirements, thereby limiting the amount of controlled substances available to the country [32].

CONCLUSION

Consumption and use of diazepam as an essential medicine were decreasing for the last 10 years. Diazepam availability was not maintained; as a result, there were numerous shortages in health-care facilities. Supply systems are important factors that determine the availability of medicine, which would affect health care quality. The government should meet the needs of diazepam by improving factors that affect its use, such as requantifying diazepam needs and ensuring its appropriate production and distribution.

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