Global trends in the consumption of benzodiazepines and Z-drugs in 67 countries and regions from 2008-2018: a sales data analysis

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Abstract

Study objectives To investigate the trends in the consumption of benzodiazepines (BZDs) and Z-drugs at global, regional, and national levels from 2008 to 2018, across 67 countries and regions.

Methods This cross-sectional descriptive study investigated the consumption of BZDs and Z-drugs analysed by global pharmaceutical sales data from the IQVIA-Multinational Integrated Data Analysis System database between 2008 and 2018. Consumption was measured in defined daily dose per 1,000 inhabitants per day (DDD/TID). The global, regional, and national trends were estimated using linear mixed models. Additional analyses were conducted by grouping countries by income levels. The association between consumption and Gross Domestic Product (GDP) and the prevalence of different medical conditions was explored in univariable linear models.

Results BZD consumption decreased annually by -1.88% (95% CI: -2.27%, -1.48%), and Z-drugs increased by +3.28% (+2.55%, +4.01%). In 2008, the top ten countries for BZD and Z-drug consumption were all European, ranging from 63.69 to 128.24 DDD/TID. Very low levels were found in Russia, Kuwait, United Arab Emirates, Saudi Arabia, French West Africa, and the Philippines, with DDD/TID <1. The consumption in high-income countries was much higher than in middle-income countries. The results showed that increased consumption of BZDs and Z-drugs was statistically associated (P<0.05) with higher GDP and increased prevalence of anxiety, self-harm, neurological disorders, chronic respiratory diseases, cardiovascular diseases and cancers.

Conclusions

Distinct differences in consumption and trends of BZDs and Z-drugs were found across different countries and regions. Further exploration is needed to understand the association and safety of the use of BZDs and Z-drugs in patients with comorbidities.

Keywords: sedative-hypnotic drugs, benzodiazepines, Z-drugs, trend, prevalence

Graphical abstract

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❶ The study

Global pharmaceutical sales data (IQVIA-Multinational Integrated Data Analysis System database)

Benzodiazepines
Z-drugs

67 countries and regions

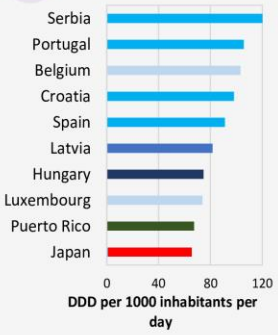
2008-2018

Aim:

- Investigate the consumption of benzodiazepines (BZDs) and Z-drugs and their global, regional and national trends.
- Explore the association between consumption of BZDs/Z-drugs and income level and the prevalence of different medical conditions.

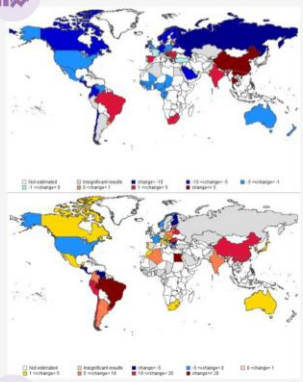
❷ Findings

Consumption



- The top ten countries for BZD and Z-drug consumption were mainly European in 2018.
- Very low levels were found in Russia, Kuwait, United Arab Emirates, Saudi Arabia, French West Africa, and the Philippines.

Trends



BZDs decreased annually by -1.88% (95% CI: -2.27%, -1.48%).

Z-drugs increased by +3.28% (+2.55%, +4.01%).

Increased consumption of BZDs and Z-drugs was statistically associated (P<0.05) with higher GDP and increased prevalence of anxiety, self-harm, neurological disorders, chronic respiratory diseases, cardiovascular diseases and cancers.

❸ Conclusions

Distinct differences in consumption and trends of BZDs and Z-drugs were found across different countries and regions. Further exploration is needed to understand the association and safety of the use of BZDs and Z-drugs in patients with comorbidities.

Statement of significance

To our knowledge, this study firstly provided a comprehensive picture of access to benzodiazepines and Z-drugs globally. We believe our results can provide evidence to support the imbalance between access and demand for the two drugs in countries with very low consumption; additionally, raise awareness to monitor countries with sustained high consumption and in patients with different comorbidities.

Introduction

Benzodiazepines (BZDs) are a class of prescription medications that sedate the patient by decreasing activity and facilitating falling asleep. Zolpidem, zopiclone, zaleplon and eszopiclone, commonly known as 'Z-drugs', were introduced into the market in the 1990s and are non-BZD agents that share a similar mode of action[1]. Both classes of medication are primarily indicated for the short-term management of insomnia, with BZDs being additionally used for anxiety[1]. Over the past decades, BZDs were one of the most widely prescribed classes of psychotropic medication in some developed countries across North America[2] and Europe[3–5], with prevalence for the use of BZDs ranging from 4% to 8%. Though BZDs are widely recognised as being effective, concerns regarding the misuse, addictive potential, withdrawal symptoms, and serious adverse effects have been highlighted for many years[6–8]. As an alternative to BZDs, Z-drugs were once considered to have a better safety profile than the BZDs [9]. However, a recent systematic review and meta-analysis reported that adverse events were similar with eszopiclone, zopiclone and zolpidem, compared with BZDs; in contrast, zaleplon seems to have a more benign profile[10]. Previous studies have shown decreasing trends in the consumption of BZDs in developed countries[2,11–16], along with increased consumption of Z-drugs in some countries[11,15,16]. Based on existing evidence, a consensus was found that the consumption of BZDs and Z-drugs increased with age[11,17,18], and is likely to be associated with the presence of chronic diseases[19–21]. Moreover, increased risks of some adverse outcomes, including cognitive decline[22,23], Alzheimer's disease[24] and injury[25,26] were found in older adults with a history of BZDs and Z-drugs use.

In recent years, mental disorders and sleep health have gained much attention, with increased awareness on the importance of adequate and optimal treatment of these disorders[27,28]. This has placed a huge burden on developing countries, where the lack of availability of psychotropic medicines is a pressing concern[29]. In 2018, the World Health Organisation (WHO) reported that the gap between the need for mental health treatment and its availability was substantial in non-high-income countries and regions[27]. However, the existing evidence is mainly from developed countries, and the latest information on the access and trend of BZDs and Z-drugs utilisation has not been well recognised worldwide. To our knowledge, there is no global surveillance study to investigate and compare country-level consumption of BZDs and Z-drugs.

To provide a comprehensive picture of global trends of BZDs and Z-drugs in different jurisdictions, this study aimed to describe the consumption of BZDs and Z-hypnotics in 67

countries and regions, across the decade from 2008-18. Additionally, we set out to capture any changes in consumption over time by geographical location, and explore relationships with income level, and the prevalence of different chronic mental and physical conditions.

Methods

Data sources

We used the global medication sales data of BZDs and Z-drugs from the IQVIA-Multinational Integrated Data Analysis System (MIDAS) database as a proxy for consumption of the medications by patients, which were available between January 2008 to December 2018. The MIDAS data provides international standardisation of sales value and volumes, which allows comparisons of national-level sales audits. Data sources differ by country, reflecting different distribution channels, including manufacturers, wholesalers, hospitals, and retail pharmacies. The average national coverage of MIDAS data has been reported as 88%[29–31]. For countries where the MIDAS database does not have 100% market coverage, adjustments were made by IQVIA to estimate the total sales volume based on knowledge of the market share of participating wholesalers and retail or hospital pharmacies (Table S1 in Online supplement) [32]. The MIDAS database has been validated against external data sources[33] and used to evaluate global consumption of various medications, including opioid analgesics, antibiotics, cardiovascular drugs, psychotropic drugs, biologic medicines and dementia drugs,[29–31,34–39].

Data on the sales of BZDs/Z-drugs were collected from 67 countries and regions in the IQVIA-MIDAS database, including two aggregate regions for which only aggregated data were available: Central America (Guatemala, Honduras, El Salvador, Nicaragua, Costa Rica, and Panama) and French West Africa (Benin, Burkina Faso, Cameroon, Chad, Republic of the Congo, Gabon, Guinea, Côte d'Ivoire, Mali, Nigeria, Senegal, and Togo). The included countries and regions were divided into the following continents or subcontinents: Africa, America (Latin America and The Caribbean), America (Northern), Asia (Central), Asia (Eastern), Asia (South-Eastern), Asia (Southern), Asia (Western), Europe (Eastern), Europe (Northern), Europe (Southern), Europe (Western), Oceania, based on their geographical regions as defined by the United Nations[40].

Benzodiazepines/Z-drugs and measurements

This study included BZDs with the WHO ATC codes N05BA, N05CD, and N03AE01. Z-drugs included N05CF. BZDs and Z-drugs were studied as one group and as separate classes. The list of BZDs/Z-drugs is available in Table S2 in Online supplement and the availability of these drugs in each country/region is presented in Table S3 in Online supplement.

Our main outcome measure was consumption of BZDs and Z-drugs, expressed as a defined daily dose (DDD) per thousand inhabitants per day (TID) (DDD/TID). The DDD is the assumed average maintenance dose per day for a drug used for its main indication and is available only for single-molecule products. Where the DDD of the product is not provided directly, DDD was converted from a standard unit (defined as a single tablet, capsule, or ampoule/vial or 5 mL oral suspension), strength or formulation, and the Anatomical Therapeutic Chemical Classification System/defined daily dose (ATC/DDD) system developed by the WHO Collaborating Centre (WHOCC) for Drug Statistics Methodology.[41] Products were excluded from analyses if their DDDs were not provided and strength or ATC/DDD were also not available. The details of excluded products are available in Table S3 in Online supplement.

Statistical analysis

The annual DDD/TID of a product in a country/region was calculated by [the sum of DDD of the product in the country/region ÷ (the sum of the mid-year population of the country/region /1000×365.25)] in the given year. The time trends of BZD and Z-drug consumption were evaluated at global, regional, and national levels across the study period. At the national level, the average annual change in DDD/TID - with 95% confidence intervals (CIs) - was estimated using a linear regression model, with DDD/TID as the dependent variable, and year as the independent variable. The global and regional trends were estimated using linear mixed models, controlling for within-country correlations and assuming autocorrelations between years. The trends were expressed as average annual changes. We further stratified the sales data based on country income levels (i.e., lower-middle income, upper-middle income, and high income) [42] to investigate how consumption trends of global BZDs and Z-drugs varied with country-level income. Stratified analyses were conducted for individual BZDs and Z-drugs.

Additional univariate analyses were conducted by including country/region-specific annual GDP per capita, rates of mental diseases, anxiety disorders, bipolar disorder, depressive disorders, self-harm, neurological disorders, Alzheimer's disease and other dementias, Parkinson's disease, headache disorders, chronic respiratory diseases (CRD), cardiovascular diseases (CVD), diabetes mellitus and cancers in the linear mixed model with random-effects to investigate their associations with global trend of BZDs/Z-drug consumption over the study period. The associations between these variables and BZDs/Z-drug consumption in 2018 were also estimated using univariate linear mixed models. The sources of annual

country and region-level data covering population, income, GDP, and rates of diseases were retrieved from publicly available sources detailed in Methods S1 in the Online supplement. The statistical significance level was set at $p<0.05$. All analyses were conducted using SAS version 9.4.

Results

BZD and Z-drug consumption from 2008 to 2018 among the 67 countries and regions were included, representing approximately 75% of the global population. The levels of BZD and Z-drug consumption varied greatly by continent and country, across the study period. In 2008, we found a highest level of DDD/TID in Southern Europe (70.59, 95% CI: 44.13, 97.04), followed by Western Europe (69.99, 95% CI: 32.13, 107.85), Northern Europe (45.73, 95% CI: 27.22, 64.24) and Northern America (42.95, 95% CI: 19.78, 66.11) (Table 1). The top ten countries in the BZD and Z-drug consumption were all from Europe in 2008, ranging from 63.69 to 128.24 DDD/TID. Consumption increased in countries from Southern Europe, including Serbia, Portugal, Croatia, and Spain, which occupied four of the top five positions for consumption in 2018 (Figure 1). These four countries also showed highest levels of consumption of BZDs (Figure S1 in Online supplement). Puerto Rico and Japan were the only two non-European countries among the top ten countries in 2018. In Asia, the consumption of BZDs and Z-drugs remained outstandingly high in Japan, with over 60 DDD/TID from 2008 to 2018 (Table 1 and Figure 1). The consumption rate remained lower than 10 DDD/TID throughout the study period in Africa and Asia (excluding Japan) (Table 1). In 2018, the consumption was at a very low level in six countries/regions, including Russia, Kuwait, United Arab Emirates, Saudi Arabia, French West Africa, and the Philippines, with the consumption lower than 1 DDD/TID (Table 1 and Figure 1). The consumption of BZDs was higher than Z-drugs in most continents and countries in 2018 (Table S4 in Online supplement). Exceptions were found in several Northern European countries, including Estonia, Ireland, Norway, and Sweden, with more consumption of Z-drugs than BZDs. Sweden (30.77 DDD/TID) and Norway (30.33 DDD/TID) were the top two countries in the consumption of Z-drugs in 2018 (Figure S2 in Online supplement).

The estimated average annual change of the consumption of BZDs and Z-drugs across the globe, was –0.14% (95% CI: -0.52%,0.25%, P = 0.489), from 29.99 (95% CI:22.08, 37.90) DDD/TID in 2008 to 29.24 (95% CI:21.95, 36.52) DDD/TID in 2018 (Table 1). Increasing trends with the statistically significant average annual change in DDD/TID ($P<0.05$) were observed in Latin America and The Caribbean, Eastern Asia, and Southern Europe. Consumption decreased over time in Northern America, Western Asia, Northern Europe, Western Europe, and Oceania ($P<0.05$). The estimated changes in consumption were not statistically significant in Africa, Southern-Eastern Asia, Southern-Asia, and Eastern Europe (Table 1,

Figure 2). BZD consumption decreased throughout the study period, with an average annual change of -1.88% (95% CI: -2.27%, -1.48%). Conversely, Z-drug consumption increased with an average annual change of 3.28% (95% CI: 2.55%, 4.01%). The trends in BZD and Z-drug consumption also varied at continent and country level (Figure 2, Table S4 in Online supplement). For example, among the eight countries in Eastern Europe, half showed increasing trends of BZD consumption and half, declining trends. When estimating the trends of individual drug consumption, alprazolam was the most consumed BZD, but with a decreased average annual change of -0.02 (95% CI: -0.04, -0.01) DDD/TID. The consumption of most BZDs decreased over the study period, except clobazam, clonazepam, estazolam and lormetazepam with an increasing trend, and chlordiazepoxide and flunitrazepam with non-significant trends. Among Z-drugs, eszopiclone consumption showed an increased trend (P=0.018). Zaleplon consumption decreased (P=0.017). Zolpidem was the top-selling Z-drug, with a non-significant trend in the consumption rate (Top 10 drugs with highest consumption: Figure 3, All drugs: Figure S3, Table S5 in Online supplement).

We stratified countries based on income levels and estimated BZD and Z-drug consumption and trends (Table 2). Whilst overall consumption decreased annually by -1.88% (95% CI: -2.27%, -1.48%) in high-income countries, there was an increase of 1.35% (95% CI: 0.42%, 2.28%) in upper-middle countries and of 1.19% (95% CI: 0.19%, 2.20%) in lower-middle-income countries. However, consumption in high-income countries was much higher than in middle-income countries across the decade, with around three-fold higher than upper-middle countries and 10-fold higher than lower-income countries. The consumption remained lower than 5 DDD/TID in lower-income countries. In additional univariate analyses, results showed increased yearly GDP per capita was associated with trend and increased consumption of the overall BZDs and Z-drugs (P<0.001) (Table S4 in Online supplement).

We further estimated the association between global BZD and Z-drug consumption and different disease conditions, in univariate analyses. The results showed mental diseases, depressive disorders, self-harm, bipolar disorder, neurological disorders, Alzheimer's disease, headache, cancer, CRDs, and CVDs were statistically significantly related trend of BZD and Z-drug consumption (P<0.05). Increased prevalence of anxiety, self-harm, neurological disorders, Alzheimer's disease, Parkinson's disease, headache, cancer, CVDs, diabetes, CRDs were statistically significantly associated with increased consumption of BZDs and Z-drugs in 2018 (Table S6 and Figure S4 in Online supplement).

Discussion

This study reports on the consumption of BZDs and Z-drugs using a database of medication sales data from 67 countries and regions from 2008 to 2018. We found no significant trend in the global consumption of overall BZDs and Z-drugs, with a -1.88% annual decreased consumption of BZDs and a 3.28% increased consumption of Z-drugs over the 11-year period. BZD and Z-drug consumption. Consumption was high in Europe and North America, with DDD/TID ranging from 42.95 to 70.59, but was very low in Africa and Asia, with DDD/TID lower than 10. The consumption of BZDs and Z-drugs in high-income countries was much higher than in middle-income countries, although a decreased trend in high-income countries and increased trend in middle-income countries were observed, over the period of study. The rates of consumption were associated with GDP, the prevalence of mental disorders, neurological disorders, CRDs, CVDs and cancers.

Our study found distinctive differences in the consumption of BZDs and Z-drugs among different regions and countries, which can be partially explained by country income levels. Consumption these medications in high-income countries (42.33 DDD/TID) was estimated to be around triple the consumption in upper-middle-income countries (15.98 DDD/TID) and ten times the consumption in lower-middle-income countries (4.06 DDD/TID) in 2018. For example, in Asia, consumption of BZDs and Z-drugs was much higher in high-income countries and regions, such as Japan and Taiwan, than in middle-income countries, such as the Philippines and Thailand. The WHO has recognised that the gap between the need for mental health treatment and its availability is large worldwide and is especially substantial in low-income and middle-income countries[27]. Future studies are required to identify and estimate whether middle and low-income counties with very low consumption are capable to provide sufficient access to BZDs and Z-drugs responding to their burden of related mental disorders.

In addition to low-income level, religion and geographic customs are possible barriers to the access to BZDs and Z-drugs. For example, Arab counties such as the United Arab Emirates, Saudi Arabia, and Kuwait, had the lowest consumption of BZDs and Z-drugs despite their high-income level. Similar results were found in the consumption of psychotropic medication in a previous study[29]. The study explained reliance upon religion probably can influence the awareness of mental illness in Arab countries. Some geographic customs can influence local clinical practice. For example, Chinese traditional medicines were reported to be commonly used as alternatives to BZDs and Z-drugs or as an additional therapy for the treatment of insomnia and anxiety in the Chinese population[43,44]. In addition, non-pharmacological

treatments, like massage and acupuncture, were considered as effective and safe for insomnia and anxiety in China and Thialand[45–47].

The safety profiles of BZDs and Z-drugs have been continually explored and reported for decades[8,48,49], which may affect their consumption in clinical practice over years. When estimating the global trends in BZDs and Z-drugs separately, we found a -1.88% annual decreased trend in BZD consumption and a 3.28% increased trend in Z-drugs. Similar trends were found in high-income countries, with -0.38 DDD/TID trend in BZDs and 0.10 DDD/TID change in Z-drug consumption. The declined trend of BZD use has been reported in previous research in some high-income countries, including the Canada[50], Australia[12,51], Belgium[52], France[14], Finland[13], Ireland[53] and Japan[18]. Also increased use of Z-drugs was found in the United States[54], Canada[50], Ireland[53] and Japan[18]. Z-drugs are generally considered safer than BZDs by physicians[55], which may explain the opposite trends in their consumption. However, adverse effects related to the use of Z-drugs have increasingly been reported in recent years, such as the risk of abuse[56] and residual effects on the day following intake[57,58]. In some high-income countries, decreased trends were found for both BZD and Z-drug consumption, including the US, Finland, Norway, Slovenia, France, and Switzerland. This can be explained – in part at least - by the increasing awareness of safety profiles associated with these medications[8,49]. However, in some countries with very high consumption of BZDs and Z-drugs, rates continuously increased throughout the study period, such as in Serbia, Croatia, Spain, Hungary, and Uruguay, with DDD/TID of 120.16, 98.23, 88.50, 74.74 and 62.37, respectively in 2018. A previous study has found an increased trend of BZDs in Spain from 2006 to 2015[59]. Previous studies also reported high prevalence of prescription and misuse of BZDs in Croatia, Serbia[60] and Spain[61]. The safety profiles and related misuse of BZDs and Z-drugs require constant attention and effective actions to improve their management in clinical practice. Moreover, there is a lack of existing evidence in addition to ours in countries and regions from Africa, Asia, Latin America and The Caribbean. Future studies are required to focus on the usage of BZDs and Z-drugs in these countries and regions, which can help improve policy evaluation and healthcare services for related mental disorders.

Our study additionally estimated the association between the consumption of BZDs and Z-drugs and the prevalence of some medical conditions. We found anxiety, self-harm, neurological disorders (including Alzheimer's disease, Parkinson's disease, and headache), cancer, CVDs, diabetes, and CRDs were likely positively correlated with BZD and Z-drug consumption. Previous evidence have demonstrated that patients with chronic medical conditions are more likely to have sleep disorders, anxiety or depression, which may explain

the concomitant demand of BZD and Z-drug treatment[62–64]. In the past few years, concerns have been increasingly raised about BZD and Z-drug exposure and the increased risk of the development and progression of some medical conditions, such as dementia[65], respiratory disease[66], and cancer[67]. For example, a large observational study in the UK found that BZDs and zopiclone may increase the risk of asthma exacerbation[66]. Previous systematic reviews found that BZDs use was associated with increased risks of dementia[65] and cancer[67]. Considering possible high demand of BZDs and Z-drugs, more explorations are needed to focus on the safety profile and management of their exposure in patients with different medical conditions.

Our study has contributed to a comprehensive understanding of the scale of the global gaps in access to BZDs and Z-drugs. The use of international pharmaceutical sales data enables a unique global comparison of trends in consumption of BZDs and Z-drugs over prolonged periods. It should be noted that clinical trials mostly do not provide long-term data. We provided consumption rates of BZDs and Z-drugs, particularly in middle-income countries, that can serve as a baseline to monitor future national, regional, and global public health policies. However, there were some limitations to this study. First, not all the countries in MIDAS database have both retail and hospital data. For example, MIDAS database only has retail data for United Arab Emirates, thus we may have underestimated rates of use; however, this should not affect the estimation of trends. Second, our data only reflects the country-level supply side of hypnotics. Pharmaceutical sales data do not translate directly to individual-level treatment. For this reason, we could not measure trends by age, gender, and indications or appropriateness of prescribing. In addition, some other factors that might impact the sales trends, including the licensing status of drugs, marketing efforts, policy support and guidelines were also unable to be estimated in our analysis. However, the main aim of this study is to describe the trend in a multi-national manner. Future studies may focus on individual-level use of BZDs and Z-drugs or identify the driving factors for the trend. Third, international studies of medicine utilisation usually present data in DDDs to allow comparisons between population groups. However, DDD is not a measure of therapeutic use; hence, our study cannot identify the prescribing indications and address the quality of prescribing. Last, as our study included data from 67 countries and regions, the findings are only applicable to these countries and regions. To provide a full picture, data from all other countries are needed to further our understanding of the use of hypnotics.

Conclusions

From 2008 to 2018, there was a decline in BZD consumption and an increased trend in Z-drug consumption, worldwide. Distinct disparities in consumption and trends were found across countries and regions, which can be partly explained by different country income levels. Efforts need to be made to improve the availability of BZDs and Z-drugs in countries with low consumption, particularly in middle- and low-income countries. Attention needs to be paid to the management of possible BZDs and Z-drugs related safety profiles in countries with high consumption. Moreover, further evidence is required to explore the association and safety of BZDs and Z-drugs exposure in people with different mental and physical conditions.

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Concept and design: Wong, Chui, Chan, Cheung, Ma.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Ma.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Ma, Wang, Qin, Ju.

Administrative, technical, or material support: Wong, Chui, Lau, Man.

Supervision: Wong, Chui.

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Figure Captions List

Figure 1. Rankings of benzodiazepines/z-hypnotics consumption for individual countries and regions in 2008 and 2018

Figure 2. Average annual change of DDD per 1,000 inhabitants per day in consumption of (A) benzodiazepines/Z-drugs, (B) benzodiazepines and (C) Z-drugs from 2008 to 2018

Figure 3. Globally observational trends of top 10 benzodiazepines/z-drugs individual drug consumption in DDD per 1,000 inhabitants per day, 2008-2018

Table 1. Global trends of benzodiazepines/z-drugs consumption in 67 countries and regions, 2008-2018

	DDD/TID in 2008 (95% CI)*	DDD/TID in 2018 (95% CI)*	Average annual change in DDD/TID (95% CI)	P value
Worldwide	**29.99 (22.08, 37.90)**	**29.24 (21.95, 36.52)**	**-0.08 (-0.17, 0.01)**	**0.065**
Africa	**4.05 (1.10, 7.00)**	**5.23 (1.19, 9.27)**	**0.11 (0.06, 0.16)**	**<0.001**
Algeria	4.88	5.39	0.03 (-0.04, 0.10)	0.379
Egypt	1.72	2.62	0.10 (0.08, 0.12)	<0.001
French West Africa[a]	0.53	0.22	-0.03 (-0.05, -0.02)	0.002
Morocco	3.68	4.10	0.03 (-0.03, 0.09)	0.318
South Africa	9.42	12.57	0.32 (0.29, 0.34)	<0.001
Tunisia	4.06	6.48	0.23 (-0.06, 0.51)	0.103
America (Latin America and The Caribbean)	**16.48 (4.03, 28.93)**	**20.18 (4.32, 36.05)**	**0.41 (0.25, 0.57)**	**<0.001**
Argentina	40.02	40.11	-0.01 (-0.43, 0.41)	0.947
Brazil	8.84	15.43	0.63 (0.54, 0.72)	<0.001
Central America[b]	2.91	1.91	-0.08 (-0.11, -0.05)	<0.001
Chile	12.72	16.06	0.24 (0.06, 0.43)	0.013
Colombia	1.13	1.56	0.02 (-0.02, 0.05)	0.296
Ecuador	2.39	5.81	0.40 (0.35, 0.45)	<0.001
Mexico	3.42	2.52	-0.09 (-0.10, -0.07)	<0.001
Peru	4.82	5.11	0.04 (-0.05, 0.13)	0.345
Puerto Rico	42.81	67.34	2.40 (1.76, 3.05)	<0.001
Uruguay	54.59	62.37	1.20 (0.68, 1.71)	<0.001
Venezuela	7.63	3.81	-0.24 (-0.47, -0.00)	0.046
America	**42.95 (19.78, 66.11)**	**33.00 (28.28, 37.71)**	**-0.99 (-1.29, -0.69)**	**<0.001**

(Northern)				
Canada	40.37	32.47	-0.78 (-1.13, -0.42)	<0.001
United States	45.53	33.52	-1.20 (-1.71, -0.69)	<0.001
Asia (Central)	-	-	-	-
Kazakhstan	-	1.81	-0.01 (-0.18, 0.16)	0.893
Asia (Eastern)	**24.88 (-13.46, 63.22)**	**27.22 (-11.61, 66.04)**	**0.15 (0.03, 0.27)**	**0.019**
China	0.5	1.34	0.09 (0.07, 0.11)	<0.001
Japan	62.82	65.69	0.05 (-0.49, 0.58)	0.849
Korea	8.19	12.20	0.35 (0.30, 0.41)	<0.001
Taiwan	28.01	29.63	0.10 (0.02, 0.19)	0.026
Asia (South-Eastern)	-	**2.80 (-20.36, 25.96)**	**0.10 (0.02, 0.17)**	**0.016**
Philippines	0.23	0.22	-0.00 (-0.00, 0.00)	0.378
Thailand	-	5.38	0.27 (0.17, 0.38)	<0.001
Asia (Southern)	**5.01 (-11.25, 21.27)**	**4.81 (-2.47, 12.08)**	-0.04 (-0.12, 0.05)	0.357
India	3.2	4.00	0.07 (0.04, 0.09)	<0.001
Pakistan	6.82	5.62	-0.14 (-0.28, 0.00)	0.055
Asia (Western)	**2.42 (-0.18, 5.01)**	**1.97 (-0.63, 4.58)**	**-0.07 (-0.13, -0.02)**	**0.008**
Jordan	4.96	1.69	-0.38 (-0.47, -0.28)	<0.001
Kuwait	0.49	0.66	0.01 (-0.04, 0.06)	0.744
Lebanon	6.62	7.39	-0.03 (-0.30, 0.23)	0.783
Saudi Arabia	0.21	0.10	-0.01 (-0.01, -0.01)	<0.001
Turkey	1.66	1.55	-0.02 (-0.03, -0.01)	0.003
United Arab Emirates	0.56	0.47	-0.01 (-0.02, 0.01)	0.275

Europe (Eastern)	**23.41 (6.50, 40.33)**	**26.34 (8.35, 44.32)**	0.36 (0.24, 0.47)	<0.001
Belarus	5.18	10.83	0.62 (0.54, 0.69)	<0.001
Bulgaria	10.18	10.13	0.04 (-0.05, 0.13)	0.366
Czech Republic	32.14	31.67	0.03 (-0.15, 0.22)	0.703
Hungary	68.63	74.74	0.98 (0.34, 1.62)	0.007
Poland	21.51	21.81	0.04 (-0.12, 0.20)	0.572
Romania	14.61	22.00	0.76 (0.63, 0.88)	<0.001
Russia	1.79	1.04	-0.14 (-0.21, -0.08)	<0.001
Slovakia	33.27	38.48	0.54 (0.41, 0.67)	<0.001
Europe (Northern)	**45.73 (27.22, 64.24)**	**36.84 (28.08, 45.59)**	**-0.76 (-1.15, -0.36)**	**<0.001**
Estonia	26.69	35.01	1.14 (0.82, 1.45)	<0.001
Finland	86.51	44.39	-4.28 (-4.41, -4.14)	<0.001
Ireland	53.36	41.70	-1.18 (-1.35, -1.00)	<0.001
Latvia	16.93	25.60	1.08 (0.79, 1.37)	<0.001
Lithuania	47.55	47.73	0.61 (-0.00, 1.22)	0.051
Norway	63.69	44.43	-2.00 (-2.18, -1.82)	<0.001
Sweden	50.97	40.79	-0.90 (-1.31, -0.49)	<0.001
United Kingdom	20.13	15.05	-0.51 (-0.84, -0.19)	0.006
Europe (Southern)	**70.59 (44.13, 97.04)**	**75.36 (49.29, 101.43)**	**0.70 (0.30, 1.10)**	**<0.001**
Bosnia and Herzegovina	-	49.43	2.98 (2.16, 3.81)	<0.001
Croatia	85.46	98.23	1.37 (1.13, 1.62)	<0.001
Greece	40.11	44.94	0.65 (0.14, 1.15)	0.018
Italy	72.96	71.03	-0.25 (-0.42, -0.09)	0.007
Portugal	108.99	105.63	-0.01 (-0.50, 0.48)	0.953
Serbia	-	120.16	5.29 (2.67, 7.91)	0.002

Slovenia	37.21	24.94	-1.27 (-1.41, -1.13)	<0.001
Spain	78.79	88.50	1.09 (0.88, 1.30)	<0.001
Europe (Western)	**69.99 (32.13, 107.85)**	**50.29 (23.67, 76.90)**	**-1.49 (-1.69, -1.29)**	**<0.001**
Austria	50.76	36.38	-1.61 (-1.83, -1.39)	<0.001
Belgium	128.24	103.30	-2.18 (-2.78, -1.57)	<0.001
France	74.88	62.04	-1.17 (-1.64, -0.70)	<0.001
Germany	18.75	13.36	-0.57 (-0.66, -0.48)	<0.001
Luxembourg	99.83	73.88	-2.57 (-2.85, -2.29)	<0.001
Netherlands	-	27.60	-0.58 (-0.67, -0.48)	<0.001
Switzerland	47.49	35.46	-1.21 (-1.36, -1.06)	<0.001
Oceania	**23.47 (12.49, 34.46)**	**20.72 (14.67, 26.77)**	**-0.44 (-0.66, -0.21)**	**<0.001**
Australia	24.7	20.05	-0.72 (-1.09, -0.35)	0.001
New Zealand	22.25	21.39	-0.15 (-0.31, 0.01)	0.056

DDD/TID = DDD per 1,000 inhabitants per day

* Worldwide and regional estimates with 95% CI were calculated by pooling the estimates from individual countries using a random-effects model.

[a] Data of French West Africa region were aggregated from Benin, Burkina Faso, Cameroon, Chad, Republic of the Congo, Gabon, Guinea, Côte d'Ivoire, Mali, Niger, Senegal, Togo. Niger and Chad.

[b] Data of Central America were aggregated from Guatemala, Honduras, El Salvador, Nicaragua, Costa Rica and Panama.

Table 2. Global trends of benzodiazepines/z-drugs consumption by income levels, 2008 - 2018

		DDD per 1,000 inhabitants per day (95% CI) [a]											Average annual change in DDD/TID
	Income[b]	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**	**2017**	**2018**	
Benzodiazepines or z-drugs	High income	46.16 (35.97, 56.36)	45.90 (35.90, 55.90)	46.17 (36.21, 56.14)	46.09 (36.38, 55.79)	45.57 (35.89, 55.24)	45.85 (36.14, 55.56)	45.62 (35.94, 55.31)	44.90 (35.38, 54.42)	44.40 (34.91, 53.88)	43.44 (34.13, 52.74)	42.33 (33.24, 51.42)	-0.20 (-0.22, -0.17)**
	Upper-middle income	7.70 (2.82, 12.57)	7.94 (2.88, 13.01)	7.68 (2.76, 12.60)	12.70 (3.71, 21.70)	13.71 (3.54, 23.88)	13.79 (3.90, 23.68)	13.94 (4.10, 23.78)	14.82 (4.06, 25.57)	14.96 (3.83, 26.08)	15.95 (2.98, 28.92)	15.98 (3.31, 28.66)	0.07 (0.05, 0.08)**
	Lower-middle income	3.51 (1.69, 5.34)	3.62 (1.77, 5.47)	3.55 (1.88, 5.22)	4.18 (1.94, 6.43)	4.07 (1.89, 6.24)	4.04 (1.93, 6.14)	3.95 (1.98, 5.92)	3.92 (2.06, 5.79)	4.02 (2.10, 5.94)	3.97 (2.13, 5.81)	4.06 (2.25, 5.87)	0.01 (0.01, 0.02)**
Benzodiazepines	High income	35.28 (26.32, 44.25)	34.76 (25.95, 43.57)	34.69 (25.88, 43.51)	34.39 (25.78, 42.99)	33.76 (25.11, 42.41)	33.78 (25.02, 42.55)	33.51 (24.67, 42.36)	32.93 (24.13, 41.74)	32.44 (23.63, 41.25)	31.70 (23.00, 40.39)	30.74 (22.19, 39.29)	-0.38 (-0.49, -0.28)**
	Upper-middle income	6.70 (2.06, 11.35)	6.80 (1.99, 11.62)	6.44 (1.78, 11.11)	11.25 (2.36, 20.14)	12.02 (2.04, 22.00)	11.99 (2.29, 21.69)	11.96 (2.36, 21.57)	12.69 (2.24, 23.14)	12.80 (2.05, 23.56)	13.67 (1.11, 26.23)	13.50 (1.43, 25.56)	0.16 (0.03, 0.29)*
	Lower-middle income	3.30 (1.49, 5.11)	3.39 (1.57, 5.21)	3.29 (1.67, 4.92)	3.90 (1.72, 6.08)	3.77 (1.69, 5.85)	3.72 (1.70, 5.73)	3.59 (1.72, 5.46)	3.55 (1.75, 5.35)	3.62 (1.71, 5.54)	3.55 (1.67, 5.42)	3.62 (1.70, 5.53)	0.02 (-0.03, 0.07)
Z-drugs	High income	11.50 (8.35, 14.66)	11.78 (8.66, 14.89)	12.14 (9.02, 15.25)	12.01 (8.98, 15.05)	12.13 (9.15, 15.10)	12.39 (9.44, 15.35)	12.44 (9.53, 15.34)	12.29 (9.49, 15.09)	12.28 (9.55, 15.01)	12.06 (9.48, 14.63)	11.91 (9.49, 14.33)	0.10 (0.04, 0.15)**

	Upper-middle income	1.00 (0.44, 1.55)	1.14 (0.54, 1.74)	1.23 (0.57, 1.90)	1.45 (0.80, 2.11)	1.69 (0.94, 2.44)	1.80 (0.95, 2.64)	1.98 (1.04, 2.91)	2.13 (1.10, 3.15)	2.15 (1.04, 3.26)	2.28 (1.09, 3.46)	2.49 (1.18, 3.80)	0.14 (0.11, 0.18)**
	Lower-middle income	0.21 (0.07, 0.36)	0.23 (0.07, 0.39)	0.26 (0.09, 0.42)	0.28 (0.12, 0.45)	0.30 (0.12, 0.48)	0.32 (0.13, 0.51)	0.36 (0.15, 0.57)	0.37 (0.15, 0.60)	0.39 (0.13, 0.66)	0.42 (0.10, 0.74)	0.44 (0.04, 0.85)	0.02 (0.01, 0.03)**

*P<0.05

**P < 0.001

[a] Estimates with 95% CI were calculated by pooling the estimates from individual countries using a random-effects model.

[b] Central America and French west Africa were not included, because the included countries are in different income levels.

Figure 1

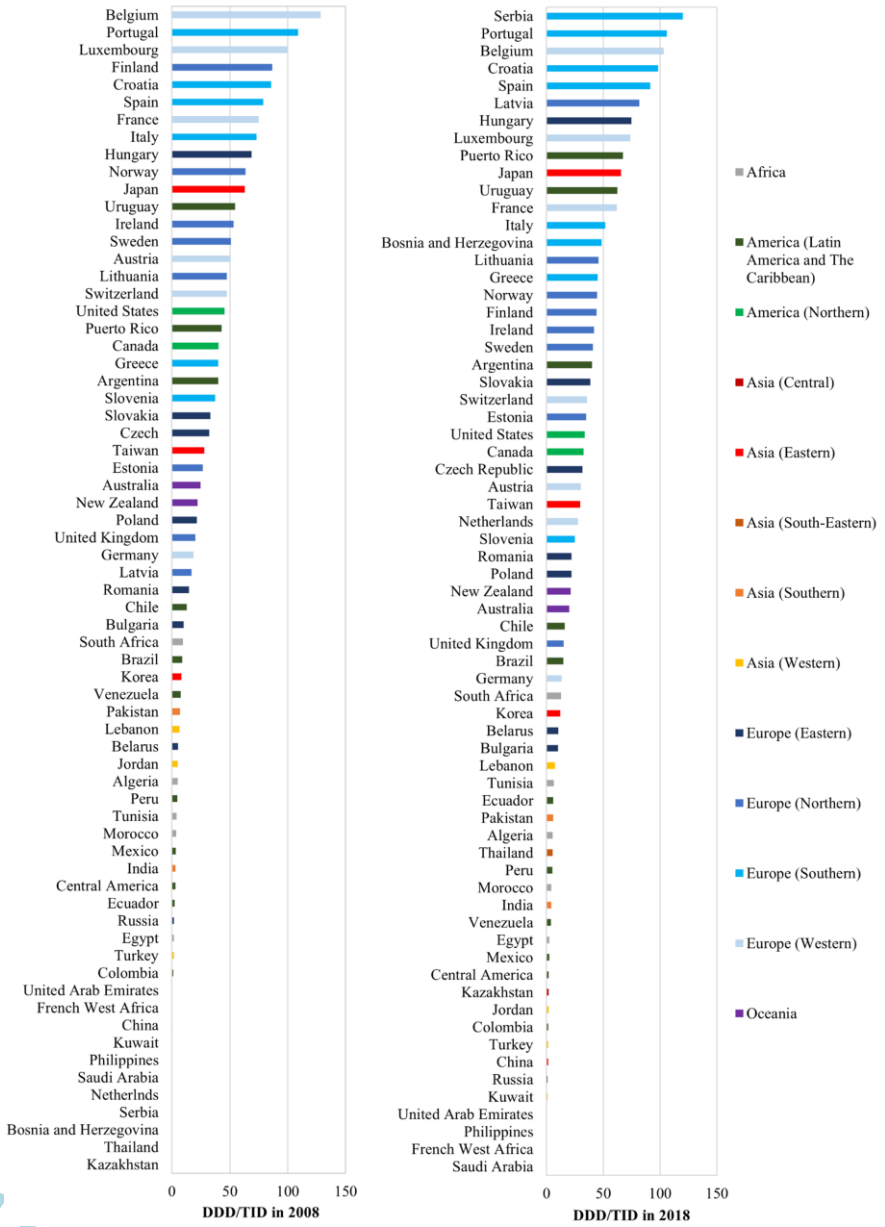
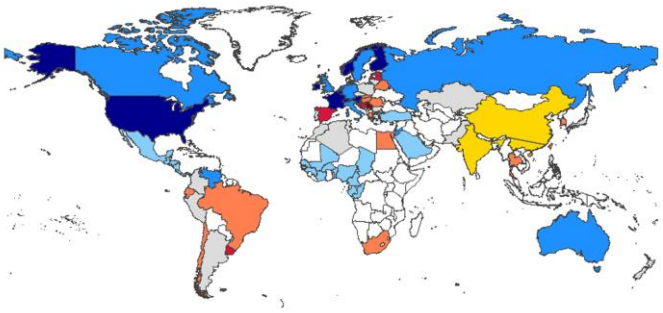
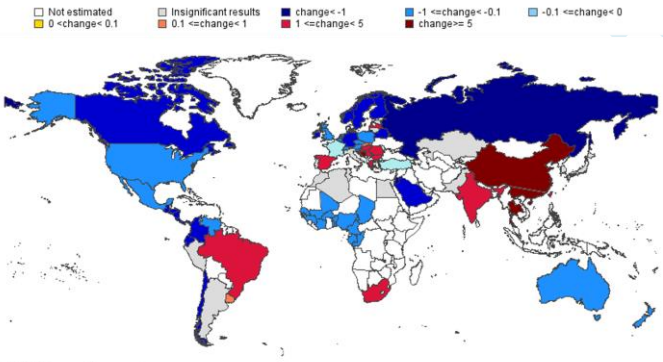


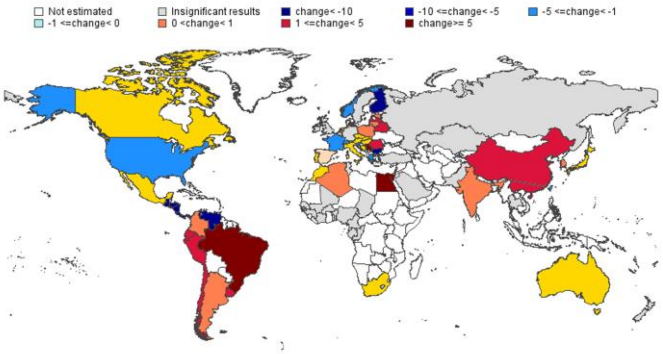
Figure 2



(A) Benzodiazepines/Z-drugs



(B) Benzodiazepines



(C) Z-drugs

Figure 3