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Use of hypnotic drugs among children, adolescents and young adults in Scandinavia

Running title: Hypnotic use among young Scandinavians

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Conflicts of Interest Statement

Anton Pottegård reports participation in research projects funded by Alcon, Almirall, Astellas, Astra-Zeneca, Boehringer-Ingelheim, Novo Nordisk, Servier and LEO Pharma, all with funds paid to the institution where he was employed (no personal fees) and with no relation to the work reported in this paper.

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Abstract

Background

Hypnotic use in children and adolescents is controversial.

Objective

To describe use of hypnotic drugs (melatonin, z-drugs and sedating antihistamines) among 5-24-year-old Scandinavians during 2012 to 2018.

Methods

Aggregate-level data was obtained from public data sources in Sweden, Norway and Denmark. We calculated annual prevalence (users/1000 inhabitants) stratified by age group, sex and country. Quantity of use (Defined Daily Dose (DDD)/user/day) was estimated for Norway and Denmark.

Results

Melatonin was the most commonly used hypnotic and its use increased markedly from 2012 to 2018, particularly among females and 15-24-year-old individuals. Sweden had the highest increase in use (6.5 to 25/1,000) compared to Norway (10 to 20/1,000) and Denmark (5.7 to 12/1,000).

The annual prevalence of sedating antihistamine use was also highest in Sweden, reaching 13/1,000 in 2018 in comparison to 7.5/1,000 in Norway and 2.5/1,000 in Denmark. Z-drug use decreased in all

countries towards 2018, dropping to 3.5/1,000 in Sweden, 4.4/1,000 in Norway and 1.7/1,000 in Denmark.

The quantity of hypnotic use in Norway and Denmark was 0.8-1.0 DDD/user/day for melatonin in 2018, as compared to 0.1-0.3 for z-drugs and antihistamines.

Conclusion

The use of melatonin and sedating antihistamines increased among young Scandinavians during 2012-2018, and the increase was twice as high in Sweden compared to Norway and Denmark. In addition, Sweden had the highest use of sedating antihistamines. The Scandinavian variation of hypnotic use could reflect differences in frequency of sleep problems between populations or variation of health care access or clinical practice between countries.

Significant outcomes

- Melatonin use is strongly increasing among young Scandinavians, particularly females and 15-24-year-olds
- Hypnotic use is markedly higher among Swedish 5-24-year-olds compared to Danish and Norwegian peers
- Males are twice as likely to use melatonin before the age of 15, whereas females are more likely to use z-drugs and sedating antihistamines after the age of 15 years
- Estimated quantity of use throughout a year indicates regular use of melatonin in Norway and Denmark and a more sporadic/short-term use of sedating antihistamines and z-drugs.

Limitations

- The analyses were based on filled prescriptions as proxies for hypnotic use
- Aggregate-level data does not allow for examinations of adherence or persistence
- Information on quantity of use was not available for Sweden

Key words (3-5)

Melatonin, utilization, hypnotics, Scandinavia, insomnia, sleep disorders

Introduction

Insomnia impairs quality of life (1, 2) and affects approximately one in four throughout childhood (3). A meta-analysis including more than one million people found that more than half of all adolescents (aged 14-17 years) had shorter sleep duration than recommended and that they reported more sleepiness than all other age groups (4). Sleep problems may occur comorbid to a specific medical condition or mental disorder, like Attention Deficit Hyperactivity Disorder (ADHD), which is often referred to as secondary insomnia (5). Neurotypical children may also suffer from sleep problems and in this case, behavioral interventions that focus on sleep routines are considered effective (6). Although recent studies show promising results of behavioral interventions for insomnia in clinical samples with psychiatric disorders (7, 8), the effect has been scarcely examined (6). Pharmacological treatment with hypnotics has therefore been common in young individuals with insomnia secondary to neurodevelopmental disabilities, even though randomized controlled studies on the evidence regarding efficacy and tolerability are few (9). In recent years, melatonin has been documented effective for sleep problems in children with neurodevelopmental disabilities (10, 11) and is now considered the safest treatment choice (9, 12). Conversely, only few studies have examined the effects of z-drugs for insomnia in children and adolescents (9). Some of these drugs (zolpidem, zaleplon and eszopiclone) have recently received a box warning by the Food and Drug Administration (13) due to reports about induced complex sleep behaviors that may lead to serious injuries including suicide (14).

Melatonin (Slenyto®) was approved by the European Medicines Agency (EMA) in 2018 for treatment of secondary insomnia in individuals aged 2-18 years with the specific neurodevelopmental disabilities autism spectrum disorder and Smith-Magenis syndrome (15). Melatonin is a natural hormone that has wide ranging effects (16-19), including a suspected role in pubertal onset (20). Accordingly, EMA specifically listed children and adolescents as being at risk for potential side effects of pubertal delay, particularly if exposed to long-term melatonin use (21). This raises some concern for the trends of melatonin utilization (22, 23), especially given that long-term consequences of pediatric melatonin use has not yet been examined according to recent meta-analyses (10-12). Furthermore, there is a need for studies looking at potential variation in hypnotic drug use across countries in relation to legislative approvals for use in children and adolescents.

Aims of the study

The aim of the study was to describe utilization patterns of hypnotics among Scandinavian children, adolescents, and young adults from 2012 to 2018.

Material and methods

We conducted a descriptive drug utilization study of the three Scandinavian nationwide unselected populations using publicly available data for the study period of January 1st 2012 - December 31st 2018. The study population consisted of all individuals aged 5-24 years in Sweden (2,372,337 in 2018), Norway (1,295,114 in 2018) and Denmark (1,397,324 in 2018) (www.nordicstatistics.org). Children under the age of 5 years were excluded due to negligible use of hypnotics. The upper age limit of 24 years was chosen in order to illustrate potential changes in hypnotic prescription patterns that could occur around age 18 years, due to different clinical and regulatory guidelines between children and adults.

Data sources

Data on drug use was retrieved from public authorities' websites: www.socialstyrelsen.se, www.norpd.no, www.medstat.dk (24) (see below). The datasources provide information on the number of individuals who filled a prescription for a given drug (or drug class) each year according to age and sex based on data from the national prescription registers (25). Corresponding annual population counts by sex and age was obtained from national census data (see below).

Drugs were categorized according to the WHO Anatomic Therapeutic Chemical (ATC) classification system (26). We examined the following hypnotic drug groups: 1) melatonin (N05CH01), 2) benzodiazepine-like drugs ('z-drugs' (N05CF*) including zopiclone N05CF01, zolpidem N05CF02, zaleplon N05CF03), and 3) sedating antihistamines (H_1 receptor antagonists (R06AD*) including alimemazine R06AD01, promethazine R06AD02, and promethazine combinations R06AD52) that are used as hypnotic drugs for children and adolescents. Benzodiazepine derivatives categorized in the ATC hypnotic group N05CD* were not included in the analyses due to very low use in the age range 5-24 years in all three countries, except for midazolam, which is mainly used as an antiepileptic or anasthetic in this age group. All drugs included in this study were obtainable via prescription only in the Scandinavian countries during the study period and hand out of free medication samples is not permitted.

The quantity of drugs dispensed was determined for Norway and Denmark by the unit Defined Daily Dose (DDD), which is 'the assumed average maintenance dose per day for a drug used for its main indication in adults' (26). DDD information was not available for Sweden (www.socialstyrelsen.se).

Data availability statement

The data that was used for this study is openly available in Zenondo.org at *xxx* (will be provided). The data was derived from the resources listed below.

Drug statistics data:

https://sdb.socialstyrelsen.se/if_lak/val.aspx (download date: 2020.06.15)

http://www.norpd.no/ (download date: 2020.12.06)

http://www.medstat.dk/ (download date: 2020.11.26)

Census data:

http://www.statistikdatabasen.scb.se (download date: 2020.06.12)

https://www.ssb.no/ (download date: 2020.06.15)

https://statistikbanken.dk (download date: 2020.06.12)

Statistical analyses

First, we calculated the total numbers and the prevalence of use (number of users per 1,000 individuals) for hypnotic drugs in 2012 and 2018 in the total Scandinavian population, by country and by drug. Second, we calculated the annual number of 5-24-year-olds per 1,000 individuals (annual prevalence, equivalent to one-year period prevalence), who filled at least one hypnotic prescription per year, stratified by drug group (melatonin, z-drugs, antihistamines, hydroxyzine) during 2012-2018. Third, the prevalence proportion of hypnotic users throughout the study period was illustrated for each drug group stratified by age group. Fourth, we calculated the annual prevalence proportion of hypnotic users in 2012 and 2018, by sex and age group (5-9, 10-14, 15-19, 20-24 years), specified by drug group (melatonin, z-drugs, antihistamines). The exact numbers and male/female prevalence ratios for 2012 and 2018 are presented in supplementary tables, as well as the relative change in use

over time, calculated by a 2018/2012 prevalence ratio (including 95% confidence intervals). Finally, the quantity of melatonin, z-drugs and antihistamines dispensed in 2012 and 2018 was determined for 5-24-year-olds in Norway and Denmark, stratified by sex and age group. This was calculated as the cumulated yearly amount of DDD per user per day. All statistical analyses were performed using STATA Release 16.0 (StataCorp, College Station, TX, USA) and R (27), including the tidyverse packages (28).

Ethics

The data is publicly accessible in the three countries and approval from any ethical committee or data protection agency is therefore not required.

Results

The annual prevalence of hypnotic use (users/per 1,000 individuals) is listed for the years 2012 and 2018 in **Table 1**. Melatonin was overall the most frequently used hypnotic drug in 2018, with Sweden representing the highest use (25/1,000) followed by Norway (20/1,000) and Denmark (12/1,000). The use of melatonin increased throughout the study period in all countries, and Sweden showed the steepest increase from 6.5/1,000 in 2012 to 25/1,000 in 2018. The slope of the ascending curve for melatonin use showed an additional rise in 2015 in Sweden, whereas it seemed to plateau between 2014-2016 in Norway. Z-drug use decreased slightly in all countries, reaching approximately 3.5/1,000 in Sweden, 4.4/1,000 Norway and 1.7/1,000 in Denmark in 2018. In Sweden, the decrease in z-drug use occurred around 2015, concurrent with the increase in use of melatonin. Antihistamines were the second most used drugs in all countries in 2018 and the use in Sweden was highest (13/1,000) compared to Norway (7.5/1,000) and Denmark (2.5/1,000). Annual prevalence proportions of hypnotic use in 5-24-year-olds are presented in **Figure 1**.

Figure 1 about here

The annual prevalence proportions of hypnotic use specified by drug group are illustrated in **Figure**

2, stratified by age groups. Individuals aged 15-19-years had the highest prevalence of melatonin use, followed by 10-14-year-olds in Sweden and Denmark, and 20-24-year-olds in Norway. Young adults (20-24 years), followed by 15-19-year-olds, had the highest use of z-drugs and antihistamines in all countries, but the use was very low in Denmark.

Figure 2 about here

Prevalence proportions of hypnotic use (per 1,000) in 2012 and 2018 are presented for melatonin, z-drugs and antihistamines in **Figure 3**, specified by sex and age groups.

Figure 3 about here

In 2012, melatonin was most frequently used among 15-19-year-olds in Norway (15/1,000) and Sweden (11/1,000) and among 10-14-year-olds in Denmark (7.7/1,000) (**Table S1**). In 2018, 15-19-year-olds were the most common users in all countries, but with wide national variation: 44/1,000 in Sweden, 28/1,000 in Norway and 17/1,000 in Denmark. The total male/female ratio was 1.0, but males were more likely to receive melatonin than females at age 5-14 years (Scandinavian male/female ratio 1.6-2.0), while the opposite was true from age 15 years onwards (male/female ratio 0.7-0.8) (**Table S1**). The relative increase in melatonin use from 2012-2018 was higher for females of all ages compared to males.

The relative change in melatonin use over time calculated by the 2018/2012 prevalence ratio was 3.8 in Sweden for all age groups, which was twice the relative change in Norway (1.9) and Denmark (2.1) (**Table S1**). The 15-24-year-olds had the highest increase in melatonin use compared to younger age groups in all countries, being most pronounced in Sweden with a 2018/2012 prevalence ratio of 4.0 for 15-19-year-olds and 5.4 for 20-24-year-olds.

Z-drugs were almost exclusively used for 15-24-year-olds in all countries and twice as often among females throughout the study period (**Table S2**). The 2018 prevalence proportion of z-drug use was comparable in Sweden (3.5/1,000) and Norway (4.4/1,000), and twice the level in Denmark (1.7/1,000). The relative decrease in z-drug use over time was similar for the three countries

(2018/2012 prevalence ratio 0.6-0.8).

Antihistamines were used by all age groups but at a lower level and with smaller sex differences for 5-14-year-olds compared to 15-24-year-olds. Females were more likely to use antihistamines at age 15-24 years than males, with male/female ratios at 0.5-0.6 across countries (**Table S3**). The Danish use of antihistamines was generally low compared to Sweden and Norway, but the relative increase in total use from 2012 to 2018 was twice as high (3.4) as in Sweden (1.8) and Norway (1.2). There was a marked difference in the prescribed antihistamine drugs between countries, with alimemazine being used frequently in Norway (7.1/1,000 users in 2018) but not at all in Denmark, and promethazine being used frequently in Sweden (8.8/1,000 users in 2018) but not at all in Norway (**Table 1**).

The quantity of dispensed melatonin, z-drugs and antihistamines in 2012 and 2018 was estimated for Norway and Denmark (**Table 2a-b**). The quantity of melatonin dispensed was equal in 2012 and 2018 with approximately 0.8 DDD/user/day for the Norwegian population and 1 DDD/user/day for the Danish population. This is equivalent to a daily dose of 2 mg (the recommended daily dose of Circadin for adults ≥ 55 years) (29). In both countries, males tended to receive slightly higher quantities of melatonin than females throughout the study period, but this tendency attenuated with increasing age. Children aged 5-14 years were dispensed with higher quantities of melatonin (1.1-1.3 DDD/user/day) indicative of daily use compared to adolescents and young adults (0.4-0.9 DDD/user/day).

The quantity of dispensed z-drugs was stable over time at approximately 0.1 DDD/user/day in Norway and Denmark for both sexes, suggesting sporadic use. A similar pattern was observed for antihistamines, where the amount of dispensed drugs was approximately 0.1 DDD/user/day in Norway and 0.3 DDD/user/day in Denmark. The quantity of antihistamines was also relatively stable within countries over time and equal between the sexes. In Norway, 5-14-year-olds had the highest amount of antihistamine use in 2018, whereas it was highest for 15-24-year-olds in Denmark.

Discussion

In this study, we found increasing overall use of hypnotics among children, adolescents and young adults throughout the study period and substantial differences in utilization patterns between the Scandinavian countries. Melatonin was the most frequently used hypnotic with an almost three-fold increased use in the total Scandinavian population from 2012 to 2018. Females and 15-24-year-olds

experienced the highest increase in melatonin use. Antihistamine use increased more modestly throughout the study period, and z-drug use decreased in all three countries. Sweden had the highest prevalence proportion of melatonin and antihistamine use in 2018 and the increase in melatonin use from 2012 onwards was twice as high as that in Norway and Sweden.

Although EMA did not formally approve of melatonin treatment for pediatric insomnia until 2018 (15), national clinical guidelines have for some years suggested melatonin use for sleep problems in children and adolescents with psychiatric disorders like ADHD and autism spectrum disorders (30-33). The quantity of melatonin dispensed in Denmark and Norway was equivalent to a daily dose of 2 mg, which was slightly lower than that reported for recurrent pediatric users in Norway (median daily dose 2.5-3.0 mg) (23). Still, it indicates regular use and long-term treatment, suggesting that melatonin is primarily used for sleep problems in patients with chronic neurodevelopmental conditions in accordance with clinical guideline recommendations (30, 31, 33). The growing use of melatonin observed in Scandinavia may therefore be related to increasing rates of childhood psychiatric disorders like ADHD, more frequent use in those diagnosed, or a combination there of. There are, to our knowledge, no studies that compare rates of ADHD and autism spectrum disorders between the Scandinavian countries. However, increasing use of psychotropics (34) and stimulants (35, 36) may be considered proxies for a rise in neurodevelopmental disorder diagnoses in the Scandinavian countries. A Nordic utilization study showed higher and continously increasing incidence rates in Sweden of centralstimulant and atomoxetine use for children and adolescents during 2008-2012 compared to Norway and Denmark (37). Hence, our findings of a Swedish predominance in melatonin use could be due to higher rates of young Swedish individuals with ADHD and comorbid sleep problems or higher treatment intensity compared to Norway and Denmark.

Our study shows that the previously observed increasing trends of melatonin use are ongoing (22, 38, 39). European children and adolescents generally experience increasing sleep problems related to social media and electronic device use (40-42) and overall poor mental health (43). A WHO survey of 11-15-year-olds showed that sleep problems increased markedly from 2002 to 2014 in Sweden (from 25% to 31%) and Denmark (from 20% to 26%), whereas it decreased slightly in Norway (from 19% to 17%) (44). The survey also provided information on psychosomatic symptoms (sadness, anxiety, back pain, sleep problems etc.) and found that Swedish 11-15-year-olds had the highest score of psychosomatic symptoms in 2002 (9.5) compared to Norway and Denmark (7.3 and 6.9, respectively) and experienced the highest increase towards 2018 (1.1 vs. 0.2 and 0.9, respectively) (45). Looking at 15-year-olds during 1985-2014, there was a doubling of psychosomatic complaints in Swedes

(reaching 57% for females and 30% for males), whereas the increase in Norway and Denmark was less steep (reaching 40% for females and 20% for males) (46). Higher levels of general sleep and emotional problems in Swedish adolescents could therefore contribute to a higher use of hypnotics.

Z-drug use declined throughout the study period in all countries, particularly in Sweden that had the highest use at the beginning of the study period. The Swedish decline occurred around 2015, following regulatory warnings regarding side effects of zolpidem in 2013-2014 (13) and awareness about the risk for misuse and withdrawal issues (47). It was, however, timed concurrent with a marked Swedish increase in melatonin and antihistamine use, suggesting a change in clinicians' treatment choices rather than reluctancy to prescribe hypnotic drugs. The quantity of z-drugs dispensed in Denmark and Norway was low, suggesting low dosage and/or sporadic use.

Sedating antihistamines were rarely prescribed in Denmark, whereas the use increased moderately in Sweden and slightly in Norway throughout the study period. Like for z-drugs, the quantity of antihistamines dispensed was low, suggesting sporadic use.

The 15-24-year-olds had the highest overall use of hypnotics, compared to individuals younger than 15 years. This is in line with a recent Danish population-based register study showing that the number of individuals diagnosed with regular sleep disorders increases with age (48). The 15-24-year-olds, however, also experienced the highest increase in use over time, especially of melatonin. Similar findings have been shown in studies describing patterns of use of antidepressants (49, 50) and central stimulants (35, 50). This could relate to more adolescents and young adults being referred to mental health clinics, which has been observed in Denmark (51), and subsequently assigned with clinical psychiatric diagnoses and pharmacologically treated for any comorbid sleep problems.

Melatonin use was twice as common for young boys compared to girls, while the opposite pattern was observed from age 15 years onwards. This may reflect that sleep disorders are more common in boys at a young age, and more common in girls at an older age (48). It could however also be due to variation in sex distribution and age at onset of any underlying psychiatric morbidity (52) that causes the insomnia. ADHD and autism spectrum disorders have an early onset and are more frequent in boys, which could contribute to the male preponderance in melatonin use before age 15 years. Depressive and anxiety disorders on the other hand, are more common in adolescent females (52) and insomnia in this subgroup is likely to be secondary to these disorders. We observed that adolescent females had a higher use of antihistamines and z-drugs than adolescent males. The effect of melatonin on sleep problems caused by depression and anxiety is rarely examined (12) and its clinical effect in

adults is limited (53). It is possible that insomnia caused by depression and anxiety is more treatment resistant leading to a higher use of second-line treatment choices, like antihistamines and z-drugs, in adolescent females.

The Swedish predominance and pronounced rise in hypnotic use compared to Norway and Denmark resembles that previously observed in Scandinavia regarding central stimulants (37) and antidepressants (54). The licensed indications for hypnotic use in children and adolescents are similar in the Scandinavian countries with two exceptions; Melatonin AGB was approved in Sweden in 2019 for individuals aged 6-17 years with ADHD (55), and promethazine has been approved for years in Sweden with the indication insomnia from age two years (Lergigan) (56) and five years (Prometazin Actavis) (57), respectively. This could contribute to higher melatonin use in Sweden, although we expect the contribution to be modest, given that clinical guidelines in all three countries have recommended melatonin use for this subgroup for some time (30-33). We suggest that the discrepancy observed could be based on variation in mental health care access. A comparison of 28 EU countries showed that Sweden had the highest accessibility of child and adolescent psychiatrists per 100,000 youths of all countries, and that it was more than twice that of Denmark (58). Our findings could therefore reflect that sleep problems are treated more intensely in Sweden due to a higher availability of mental health services. It is also possible that between-country variations in clinicians' treatment threshold is of importance. Finally, it is possible that the overall rise of pharmacological treatment of insomnia reflects reduced availability of non-pharmacological treatments like behavioral therapy that is a time-consuming health care procedure compared to standard medicine consultations.

Strengths and limitations

An important strength of our study is the use of three nationwide study populations with data sets that eliminate selection and recall bias. All drugs included in the study were obtainable via prescription only during the study period. Filled prescriptions are considered superior to medical record and questionnaire information (25) and are more indicative of use than prescriptions alone (59), but they are only a proxy for actual consumption. In addition, our data sources only allow us to report one-year period prevalence, i.e. the proportion of individuals treated at any point during a given year. This metric is different from the proportion of patients treated at the same time, a difference particularly proncounced for drugs such as melatonin that by some patients are used only shortly. Further, our

study does not include information regarding indications for hypnotic use, although a prescription was required in Scandinavia during the study period. This limitation is particularly important for antihistamine use, where insomnia is not the main indication (except for alimemazine in Norway), and there is a risk for overestimating hypnotic use. Due to the hierarchical ATC classification of data, we could only compare the use of individual drugs or complete drug groups. Drugs dispensed in hospital were not included in the databases and information on quantity of use was not available for Sweden.

Concluding remarks

The use of hypnotics - except from z-drugs - is increasing among Scandinavian children, adolescents and young adults, and Sweden displays a markedly higher use compared to Norway and Denmark. Melatonin is by far the most commonly used drug and there was an almost three-fold increase in use among young Scandinavians from 2012 to 2018. Melatonin seems to be dispensed regularly in this age group despite of warnings about potential interference with natural melatonin homeostasis and pubertal onset (12). Our study can not determine, whether the variation in Scandinavian rates of hypnotic use is rational, but the populations are considered comparable regarding culture, ethnicity and health care systems. Future studies should follow hypnotic utilization rates carefully and clarify the reasons for yet another Scandinavian discrepancy of psychotropic use in youths.

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Results tables – hypnotics

Table 1. Annual prevalence proportion of hypnotic use (users/per 1,000 individuals) in 2012 and 2018 by individual Scandinavian country (Sweden, Norway and Denmark) and in the total Scandinavian population

Year	Drug	ATC code	Sweden		Norway		Denmark		Total Scandinavian population	
			N	Users/ 1,000	N	Users/ 1,000	N	Users/ 1,000	N	Users/ 1,000
2012	Melatonin	N05CH01	14850	6.5	13068	10.3	7798	5.7	35716	7.3
	Z-drugs	N05CF	13935	6.1	6844	5.4	3652	2.7	24431	5.0
	Zopiclone	N05CF01	9606	4.2	5374	4.2	2519	1.8	17499	3.6
	Zolpidem	N05CF02	5550	2.4	1820	1.4	1235	0.9	8605	1.8
	Zaleplon	N05CF03	134	0.1	0	0.0	0	0.0	134	0.0
	Antihistamines	R06AD	16800	7.4	8069	6.4	1041	0.8	25910	5.3
	Alimemazin	R06AD01	8278	3.6	7574	6.0	0.0	0.0	15852	3.2
	Promethazin	R06AD02	8231	3.6	532	0.4	1041	0.8	9804	2.0
	Promethazin combinations	R06AD52	1909	0.8	0.0	0.0	0.0	0.0	1909	0.4
2018	Melatonin	N05CH01	59670	25.2	26013	20.0	16584	11.9	102267	20.2
	Z-drugs	N05CF	8308	3.5	5687	4.4	2432	1.7	16427	3.2
	Zopiclone	N05CF01	6508	2.7	4189	3.2	1669	1.2	12366	2.4
	Zolpidem	N05CF02	2310	1.0	1747	1.3	832	0.6	4889	1.0

Zaleplon	N05CF03	1	0.0	0	0.0	0.0	0.0	1	0.0
Antihistamines	R06AD	31736	13.4	9713	7.5	3553	2.5	45002	8.9
Alimemazin	R06AD01	11393	4.8	9251	7.1	0.0	0.0	20644	4.1
Promethazin	R06AD02	20820	8.8	518	0.4	3553	2.5	24891	4.9
Promethazin combinations	R06AD52	2563	1.1	0.0	0.0	0.0	0.0	2563	0.5

Table 2a. Quantity of hypnotic drugs dispensed per user per day in Norway by age group and sex in 2012 and 2018.

			Melatonin (N05CH01)			Z-drugs (N05CF*)			Antihistamines (phenotiazine derivates: R06AD*)		
Year	**Age groups (years)**	**Sex**	**Users (N)**	**DDD**	**DDD/user/day**	**Users (N)**	**DDD**	**DDD/user/day**	**Users (N)**	**DDD**	**DDD/user/day**
2012	**5-9**	All	1,415	568,701	1.10	6	255	0.12	1,011	51,911	0.14
		Male	977	397,868	1.11	6	135	0.06	574	32,102	0.15
		Female	438	170,832	1.07	(n<5)	(<1000)	-	437	19,808	0.12
	10-14	All	3,344	1,419,096	1.16	58	1,187	0.06	904	57,249	0.17
		Male	2,241	1,003,907	1.23	26	602	0.06	514	35,524	0.19
		Female	1,103	415,189	1.03	32	585	0.05	390	21,725	0.15
	15-19	All	4,785	1,184,949	0.68	1,507	48,432	0.09	2,382	84,517	0.10
		Male	2,244	633,449	0.77	583	19,380	0.09	831	32,117	0.11

		Female	2,541	551,500	0.59	924	29,052	0.09	1,551	52,400	0.09
	20-24	All	3,524	455,481	0.35	5,273	265,384	0.14	3,772	159,836	0.12
		Male	1,600	224,420	0.38	2,086	104,137	0.14	1,424	58,096	0.11
		Female	1,924	231,060	0.33	3,187	161,246	0.14	2,348	101,740	0.12
	5-24	All	13,068	3,628,227	0.76	6,844	315,258	0.13	8,069	353,513	0.12
		Male	7,062	2,259,645	0.88	2,701	124,255	0.13	3,343	157,840	0.13
		Female	6,006	1,368,582	0.62	4,143	190,883	0.13	4,726	195,673	0.11
2018	**5-9**	All	2,838	1,112,611	1.07	(n<5)	(<1000)	-	991	79,800	0.22
		Male	1,819	744,928	1.12	(n<5)	(<1000)	-	564	49,767	0.24
		Female	1,019	367,683	0.99	(n<5)	(<1000)	-	427	30,033	0.19
	10-14	All	6,285	2,545,222	1.11	39	1,580	0.11	1,046	66,494	0.17
		Male	3,866	1,668,392	1.18	22	757	0.09	564	41,703	0.20
		Female	2,419	876,830	0.99	17	824	0.13	482	24,792	0.14
	15-19	All	8,976	2,232,014	0.68	1,138	36,659	0.09	3,031	113,645	0.10
		Male	3,971	1,121,134	0.77	430	13,291	0.08	1,108	49,952	0.12
		Female	5,005	1,110,880	0.61	708	23,368	0.09	1,923	63,693	0.09
	20-24	All	7,914	1,306,348	0.45	4,510	209,887	0.13	4,645	188,071	0.11
		Male	3,452	609,253	0.48	1,740	81,153	0.13	1,676	63,859	0.10
		Female	4,462	697,095	0.43	2,770	128,733	0.13	2,969	124,212	0.11
	5-24	All	26,013	7,196,196	0.76	5,687	248,126	0.12	9,713	448,010	0.13
		Male	13,108	4,143,707	0.87	2,192	95,201	0.12	3,912	205,280	0.14
		Female	12,905	3,052,488	0.65	3,495	152,925	0.12	5,801	242,730	0.11

Abbreviations: DDD (Defined Daily Dose)

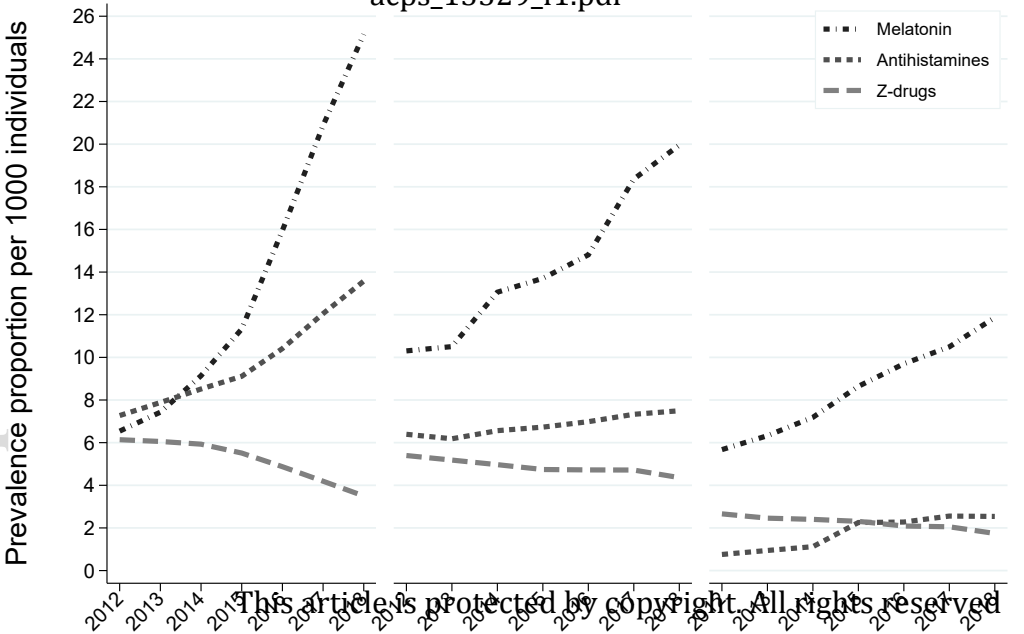
Table 2b. Quantity of hypnotic drugs dispensed per user per day in Denmark by age group and sex in 2012 and 2018.

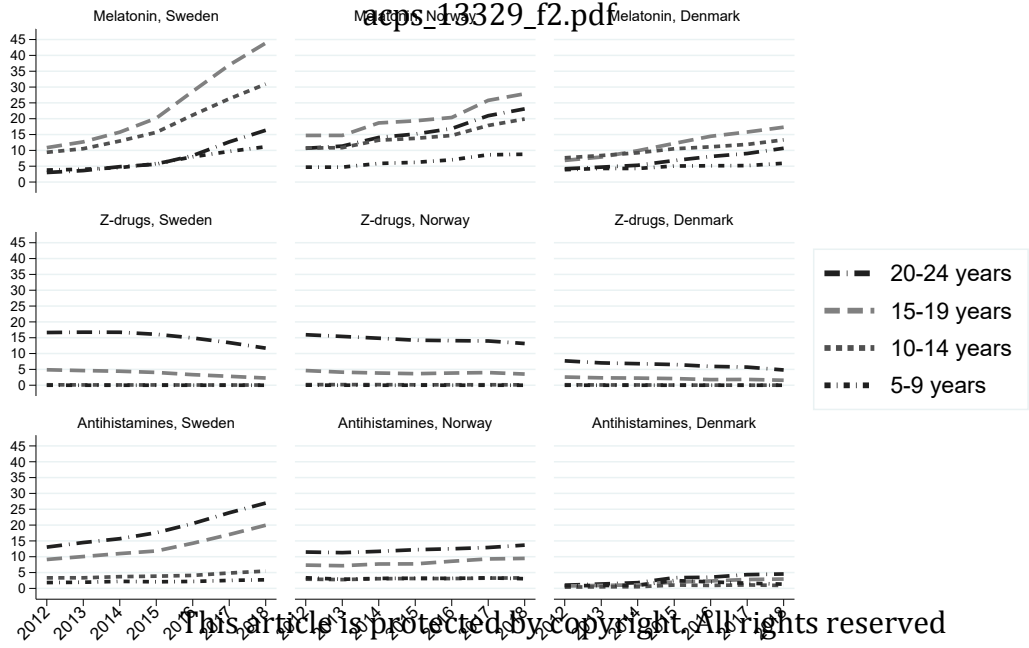
	Melatonin (N05CH01)	Z-drugs (N05CF*)	Antihistamines (phenotiazine derivates: R06AD*)

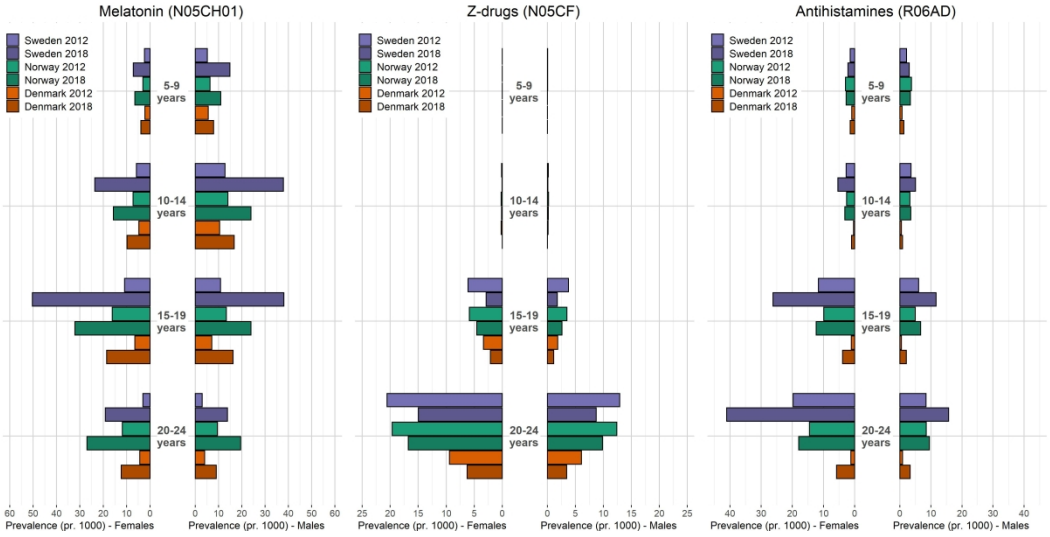
Year	Age groups (years)	Sex	Users (N)	DDD	DDD/user/day	Users (N)	DDD	DDD/user/day	Users (N)	DDD	DDD/user/day
2012	**5-9**	All	1,282	598,000	1.28	(n<5)	(<1000)	-	267	5,000	0.05
		Male	937	430,000	1.26	(n<5)	(<1000)	-	119	3,000	0.07
		Female	345	168,000	1.33	(n<5)	(<1000)	-	148	2,000	0.04
	10-14	All	2,599	1,122,000	1.18	49	1,000	0.06	140	13,000	0.25
		Male	1,820	809,000	1.22	16	(<1000)	-	81	6,000	0.20
		Female	779	311,000	1.09	33	(<1000)	-	59	7,000	0.32
	15-19	All	2,454	695,000	0.78	923	33,000	0.10	275	37,000	0.37
		Male	1,320	396,000	0.82	334	12,000	0.10	92	12,000	0.36
		Female	1,134	299,000	0.72	589	21,000	0.10	183	26,000	0.39
	20-24	All	1,463	245,000	0.46	2,680	132,000	0.13	359	47,000	0.36
		Male	714	125,000	0.48	1,074	56,000	0.14	157	23,000	0.40
		Female	749	121,000	0.44	1,606	75,000	0.13	202	25,000	0.34
	5-24	All	7,798	2,660,000	0.93	3,652	166,000	0.12	1,041	102,000	0.27
		Male	4,791	1,760,000	1.01	1,424	68,000	0.13	449	44,000	0.27
		Female	3,007	899,000	0.82	2,228	96,000	0.12	592	60,000	0.28
2018	**5-9**	All	1,915	875,000	1.25	(n<5)	(<1000)	-	435	14,000	0.09
		Male	1,312	606,000	1.26	(n<5)	(<1000)	-	216	7,000	0.09
		Female	603	270,000	1.23	(n<5)	(<1000)	-	219	8,000	0.10
	10-14	All	4,499	2,068,000	1.26	(n<5)	(<1000)	-	308	25,000	0.22
		Male	2,890	1,384,000	1.31	(n<5)	(<1000)	-	150	13,000	0.24
		Female	1,609	684,000	1.16	(n<5)	(<1000)	-	158	12,000	0.21
	15-19	All	5,997	1,952,000	0.89	547	22,000	0.11	1,026	138,000	0.37
		Male	2,873	1,006,000	0.96	192	7,000	0.10	371	49,000	0.36
		Female	3,124	946,000	0.83	355	13,000	0.10	655	89,000	0.37

	20-24	All	4,173	853,000	0.56	1,885	87,000	0.13	1,784	247,000	0.38
		Male	1,810	380,000	0.57	687	34,000	0.14	666	87,000	0.36
		Female	2,363	473,000	0.55	1,198	51,000	0.12	1,118	160,000	0.39
	5-24	All	16,584	5,748,000	0.95	2,432	109,000	0.12	3,553	424,000	0.33
		Male	8,885	3,376,000	1.04	879	41,000	0.13	1,403	156,000	0.30
		Female	7,699	2,373,000	0.84	1,553	64,000	0.11	2,150	269,000	0.34

Abbreviations: DDD (Defined Daily Dose)







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