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Use of benzodiazepines and benzodiazepine-related drugs in the Nordic countries between 2000 and 2020

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Abstract

Use of benzodiazepines (BZ) and related drugs is subject to considerable debate due to problems with dependency and adverse events. We aimed to describe and compare their use across the Nordic countries. Data on the use of clonazepam, BZ-sedatives, BZ-hypnotics, and benzodiazepine-related drugs (BZRD) in adults (≥20 years) were obtained from nationwide registers in Denmark, Finland, Iceland, Norway, and Sweden, 2000–2020. Main measures were therapeutic intensity (TI:DDD/1000 inhabitants [inhab.]/day) and annual prevalence (users/1000 inhab./year). Overall, TI of BZ and related drugs decreased in all Nordic countries from 2004 to 2020. However, there were considerable differences between countries in TI. In 2020, the TI of BZ and related drugs ranged from 17 DDD/1000 inhab./day in Denmark to 93 DDD/1000 inhab./day in Iceland. BZRD accounted for 55–78% of BZ use in 2020, followed by BZ sedatives at 20–44%, BZ-hypnotics at <1–5%, and clonazepam at <1–2%. Annual prevalence of BZ use increased with age in all countries, and the highest annual prevalence was observed among people ≥80 years. Overall, the use of BZ and related drugs has decreased in all Nordic countries from 2004 to 2020, however, with considerable differences in their use between countries.

The highest prevalence was observed among the oldest age groups—despite warnings against their use in this population.

KEYWORDS
anxiolytics, benzodiazepines, drug utilization, hypnotics, pharmacoepidemiology, Z-drugs

1 | INTRODUCTION

The use of benzodiazepines (BZ) and benzodiazepine-related drugs (BZRD) has been, and still is, subject to extensive debate and attention from national health authorities. Both BZ and BZRD have been associated with a number of adverse effects such as dependency, sedation, cognitive impairment, increased risk of falls, fractures, other injuries, and road traffic accidents.[1–7]

Despite the associated risks, the use of BZ cannot be abandoned as they have a broad range of uses. BZ with long half-life (including clonazepam) are used in a wide range of medical conditions such as various psychiatric disorders, epilepsy, other types of seizures, alcohol-related withdrawal symptoms, as muscle relaxants, and as sedatives in connection to various medical procedures.[8] BZ with short half-life are primarily used as hypnotics, and BZRD have exclusively been developed for use as hypnotics.[8] Despite the broad range of indications for BZ use, a considerable proportion of their use is presumably due to use as anxiolytics or hypnotics with the potential to result in long-term treatment and an unfavourable benefit/risk ratio.[9]

Measures to reduce or control the use of BZ and related drugs have included general guidelines on their prescription, guidelines for their use in specific conditions (e.g., major depression, anxiety disorders, or insomnia), or condition-specific guidelines, emphasizing the use of non-pharmacological alternatives or alternative drugs (e.g., psychological approaches to insomnia or antidepressants for anxiety disorders). Similar drug prescribing recommendations (e.g., for analgesics) are often issued across countries, but not necessarily at the same time point.[10,11]

The overall impact of such initiatives is currently unknown as most prior studies of BZ or BZRD utilization in the Nordic countries are either outdated, have shorter follow-up periods, or have been restricted to specific subpopulations (e.g., the older population, long-term users, or concurrent use with opioids).[12–17] An updated description of BZ and BZRD utilization, including comparison between the Nordic countries, will provide basis for a discussion of both successful initiatives and the need for further initiatives to ensure the rational use of this drug class.

1.1 | Aims of the study

Our aim was (i) to describe the utilization of BZ and related drugs in Denmark, Finland, Iceland, Norway, and Sweden and (ii) to assess differences across age groups and changes over time.

2 | MATERIAL AND METHODS

We conducted a descriptive drug utilization study on the use of BZ and related drugs among adults (≥20 years) between 2000 and 2020 in the five Nordic countries (Denmark, Finland, Iceland, Norway, and Sweden). Only high-level aggregate data from publicly available sources were used and thus no informed consent or ethical approval was necessary.

2.1 | Data sources

We obtained data on the total amount sold of BZ and related drugs during the study period from the national prescription registers in each country. As data on the total amount sold are not available from the Swedish Prescribed Drug Register, we used Swedish wholesale statistics as a supplementary data source. To assess the number of individuals filling a prescription for a given drug, we obtained aggregate data from prescription registers in each country. As BZ and related drugs are only available on prescription in all study countries, all dispensing at community pharmacies is captured in these data sources, except for Finland where only reimbursed purchases are included in the Finnish Prescription Registry.

Data on the total amount sold were available for the entire study period (2000–2020) for Denmark,[18] Finland,[19] and Sweden, whereas it was available for Iceland from 2002[20] and for Norway from 2004.[21] Data on the number of users were available from 2000 in Denmark and Finland, whereas this first became available in Iceland from 2002, in Norway from 2004, and in Sweden from 2006.[22] See Appendix S1 for further details on the data sources.

From each register, we retrieved the total amount sold or the total number of users by year, age groups (as defined below), and WHO Anatomical Therapeutic Chemical classification system (ATC) codes.[23]

Additionally, information on recommendations, regulatory actions, and legislative changes regarding BZ or BZRD in each country was collected by the authors (Table 1).

2.2 | Benzodiazepines and related drugs

BZ and related drugs were divided into four groups (drug classes) with potentially different indications based on ATC codes[23]: (i) Clonazepam (ATC: N03AE01), which are used both in psychiatric conditions and in epilepsy; (ii) BZ with long (er) half-life (ATC: N05BA) which are used in a wide range of conditions, including anxiety; (iii) BZ with short (er) half-life (ATC: N05CD) which are used primarily as hypnotics; and (iv) BZRD (ATC: N05CF) which are used as hypnotics. BZ with long half-life will be referred to as "BZ sedatives" (BZS) and BZ with short half-life will be referred to as "BZ hypnotics" (BZH) to clarify this subgrouping. See Appendix S2 for individual ATC codes and drug names.

2.3 | Main measures

To assess the magnitude of, and development in, the use of BZ and related drugs, we calculated (i) therapeutic intensity as the number of WHO defined daily doses (DDD) used per 1000 inhabitants per day and (ii) annual prevalence as the total number of users per 1000 inhabitants. Calculations were based on data from prescription registers, wholesale statistics, and demographic information. We used population estimates from each country in the relevant year and age group from the national statistical institutes as the denominator for both measures. The total adult population (≥20 years) in the five Nordic countries was 21 million in 2020 (thereof 4.5 million in Denmark, 4.3 million in Finland, 0.3 million in Iceland, 4.1 million in Norway, and 7.9 million in Sweden).[24]

2.4 | Statistical analysis

Therapeutic intensity was calculated (i) for each country and for the five countries combined and (ii) for each drug class and for all four drug classes combined. We divided the amount of drug sold by the number of inhabitants and 365 days. The amount sold and the number of inhabitants was restricted to individuals aged ≥20 years, except for Sweden, where age-specific data were not available (however, use of, e.g., BZRD in those <20 years is limited[25]). To assess changes in therapeutic intensity, we calculated relative changes in DDD/1000 inhab./day from 2004 to 2020 $((TI_{2004} - TI_{2020})/TI_{2004})$. Data from 2004 were used in these calculations as this was the earliest year in the study period where register data were available from all five countries.

To assess which drug classes and specific drugs that were most commonly used in each country, we calculated their proportion of total national sales of all four drug classes, for example, DDD sold for N05BA01 (diazepam)/DDD sold of N03AE + N05BA + N05CD + N05CF * 100% in the years 2000/2010/2020. As there is a large number of ATC-codes (Appendix S2), we presented data on individual drugs for the drugs that comprised 90% of total sales in descending order.[26]

Annual prevalence was calculated for each drug class and country throughout the study period. The total number of users with prescription fills for a given drug class within a calendar year was divided by the number of inhabitants (≥20 years) in 1000s that year (yielding users per 1000 inhabitants). Annual prevalence was additionally calculated by sex and for predefined age groups (20–39, 40–59, 60–69, 70–79, and ≥80 years). Additionally, the ratio between annual prevalence for females and males was calculated.

All analyses were conducted using STATA IC, release 16.1 (StataCorp, College Station, TX, USA).

3 | RESULTS

Overall, the therapeutic intensity of BZ and related drugs in the Nordic countries decreased by 43% from 63.5 DDD/1000 inhab./day in 2004 to 36.0 DDD/1000 inhab./day in 2020 (Figure 1).

Although the therapeutic intensity of BZ and related drugs decreased in all countries from 2004 to 2020, there were considerable differences between countries in both the level of therapeutic intensity in 2020 and its change between 2004 and 2020 (Figure 1). The largest relative decrease in therapeutic intensity was by 74% in Denmark, followed by Finland (52%), Norway (27%), Sweden (27%), and Iceland (14%). In Denmark, the overall therapeutic intensity for BZ and related drugs decreased steadily from 2004 to 2020. In Finland and Norway, the overall therapeutic intensity of BZ and related drugs increased between 2004 and 2008/2010, whereafter it decreased continuously towards 2020. Therapeutic intensity was relatively stable in Sweden until 2015, after which a decrease was observed. In Iceland, the therapeutic intensity increased to a maximum of

TABLE 1 Timeline of specific recommendations or regulations in study countries

Country	Year	Action
Denmark	1980	First guideline on the prescription of drugs drug causing dependency (benzodiazepines, opioids, psychostimulants)
	2003	Ministerial initiatives on surveillance of benzodiazepine and benzodiazepine-related drugs
	2008	Guidelines on the prescription of drugs causing dependency – updated. Focus on benzodiazepines and driving
	2010	Guideline on anxiety disorders for general practitioners – treatment with benzodiazepines should be not first-line treatment and preferably for short-term treatment.
	2014	Guideline on treatment with antipsychotic drugs to individuals older than 18 years with psychotic disorders. Treatment with benzodiazepines for agitation should be of short duration. Combination of antipsychotics and benzodiazepines should be avoided due to increased risk of death.
	2017	Electronic prescriptions for addictive drugs preferred (benzodiazepines, opioids etc.)
	2018	Only electronic prescriptions allowed for addictive drugs
Finland	2007	Guideline for medicine use in the older people (Kapseli 35): long-term BZD use should be avoided
	2008	Current care - guideline for insomnia
	2010	Electronic prescriptions introduced
	2015	Current care - guideline for insomnia updated
	2017	All prescriptions electronic
	2018	Vältä viisaasti (Finnish variation of Choose Wisely®) - guideline on using benzodiazepines and other addictive drugs.
	2018	Advice for avoiding clonazepam prescribing by National Supervisory Authority for Welfare and Health (Valvira) and the Finnish Medicines Agency (Fimea)
	2019	Current care - guideline for anxiety
	2019	Vältä viisaasti (Finnish variation of Choose Wisely®) - guideline for the use of benzodiazepines in anxiety
	2020	Current care - guideline for insomnia updated
Iceland	2008	Clinical guidelines for indications and prescribing of hypnotics and sedatives
	2010	Icelandic Prescription Medicines Register includes drug dispensing within nursing homes
	2012	GPs get access to Icelandic Prescription Medicines Register a real-time electronic prescription database and patients get access to their prescription drug use
	2017	Sending prescriptions for addictive drugs to a pharmacy by telephone forbidden
	2020	Writing prescriptions for addictive drugs only allowed electronically
Norway	1990	Guide to the prescription of addictive drugs
	2001	Revised guide on addictive drugs. Prescribing and Justification, only in electronic format
	2003	Restriction in the prescription status from group B (addictive) to A (highly addictive) for flunitrazepam
	2014	Guide to the prescription of addictive drugs
	2021	The guide replaces the following guides: national professional guide for addictive drugs 2014 - requisition and professional soundness and national professional guide for the use of opioids for long-term non-cancer-related pain. The main lines of the professional recommendations for symptom-relieving treatment with benzodiazepines, benzodiazepine-like drugs and opioids are continued. The new guide is concise and more user-friendly than previous versions. The guide gives a reminder to treating physicians that there is room for quality improvements both in treatment choices and follow-up of patients with especially anxiety, sleep problems or long-term pain conditions that are not due to cancer.
Sweden	2004	National Indicators for Quality of Drug Therapy in Older Persons (National Board of Health and Welfare). Long-acting benzodiazepines should be avoided in persons aged ≥70 years.
	2006	Treatment recommendations for anxiety (Swedish Medical Products Agency). Benzodiazepines to be avoided in anxiety disorders (Swedish Medical Products Agency)

(Continues)

TABLE 1 (Continued)

Country	Year	Action
	2009–2010	National guidelines for treatment for depression and anxiety (National Board of Health and Welfare). Recommends benzodiazepines as last treatment option and should only be used as short-term treatment.
	2017	New national guidelines for treatment for depression and anxiety (National Board of Health and Welfare). Benzodiazepines should not be used to treat GAD, anxiety disorders, PTSD etc.
	2020	Flunitrazepam no longer available on the Swedish drug market

Abbreviations: GAD, generalized anxiety disorder; GP, general practitioner; PTSD, post-traumatic stress disorder.

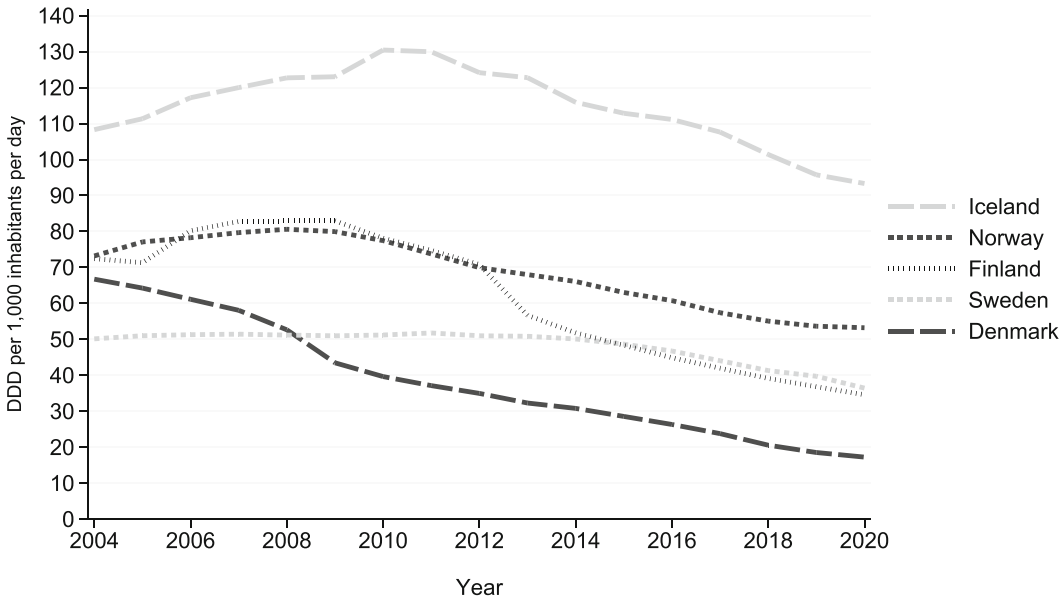

FIGURE 1 Time trend in therapeutic intensity for benzodiazepines and related drugs (DDD sold per 1000 inhabitants per day) overall and by country. Abbreviation: DDD, WHO defined daily doses

130 DDD/inhab./day in 2010, after which it decreased towards 2020 (Figure 1). In 2020, the highest therapeutic intensity of BZ and related drugs was observed in Iceland with 93.3 DDD/inhab./day, followed by Norway (53.3 DDD/inhab./day), Sweden (36.5 DDD/inhab./day), Finland (34.6 DDD/inhab./day), and Denmark (17.2 DDD/inhab./day, Table S1).

From 2004 to 2020, the therapeutic intensity of clonazepam, BZS, and BZH decreased in all five countries, whereas the therapeutic intensity of BZRD increased somewhat in Iceland and Norway, but decreased in Denmark, Finland, and Sweden (Figure 2 and Table S1).

For clonazepam, the therapeutic intensity decreased by 33% to 75%, although the therapeutic intensity in all countries was low between 2004 and 2020 (<2 DDD/1000 inhab./day in all countries, Table S1). For BZS, the largest decrease in therapeutic intensity from 2004 to 2020 was observed in Denmark (79%, from 25.8 to 5.3 DDD/1000 inhab./day, Table S1), followed by Norway (49%), Sweden (47%), Finland (41%), and Iceland (25%). However, the most marked decrease in therapeutic intensity was seen for BZH. The therapeutic intensity of BZH decreased by 100% in Finland between 2004 and 2020 (from 16.4 to 0 DDD/1000 inhab./day, Table S1) and by 94% in Denmark, 92% in Sweden, 79% in Iceland, and by 76% in Norway.

In all countries, BZRD accounted for the majority of amount sold in 2020 (from 78% in Sweden to 55% in Finland, Table 2), followed by BZS (from 44% in Finland to 20% in Sweden), whereas clonazepam and BZH only comprised a minor proportion of the total amount sold in all countries (≤2% and ≤5%, respectively).

In 2020, utilization of BZ and related drugs was comprised by a small number of substances, and with little variation between countries. These individual substances were alprazolam, diazepam, oxazepam, zopiclone, and zolpidem (and additionally in Denmark: clonazepam and nitrazepam; Table S2).

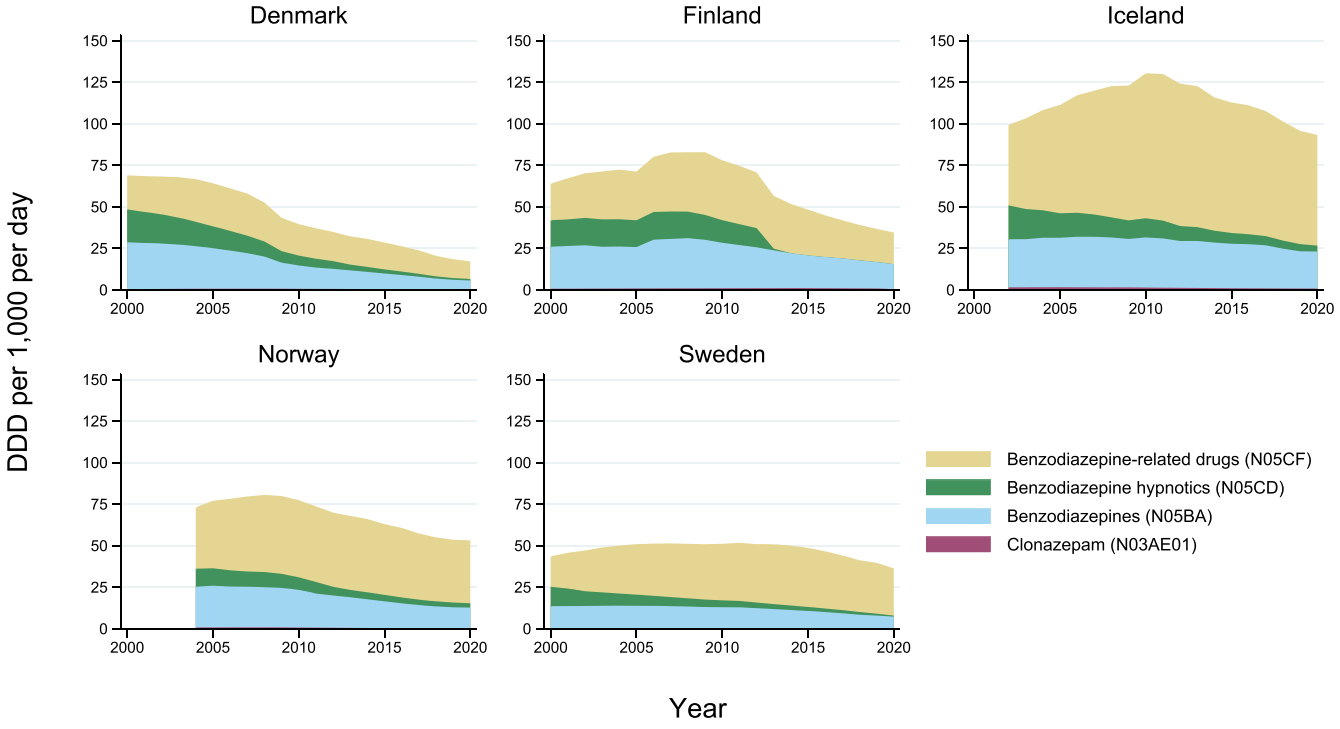

FIGURE 2 Time trend in therapeutic intensity for benzodiazepines and related drugs (DDD sold per 1000 inhabitants per day) by drug class and country. Abbreviation: DDD: WHO defined daily doses

BZRD had the highest annual prevalence in all five countries in 2020, ranging from 31 users/1000 inhabitants in Denmark to 104 users/1000 inhabitants in Iceland (**Table S3**). The drug class with the second highest annual prevalence in all five countries (in 2020) was BZS, also with considerable difference between countries (from 80/1000 inhabitants in Iceland to 21/1000 inhabitants in Denmark). In comparison with BZRD and BZS, the annual prevalence of clonazepam and BZH use was considerably lower in all countries, ranging from 1.2 to 4.5/1000 inhabitants for clonazepam and 0.5 to 5.2/1000 inhabitants for BZH. The annual prevalence of BZ/BZH/BZRD use was considerably higher among females than among males (Table S4).

In all countries, the highest annual prevalence of BZS, BZH, and BZRD use was seen among those aged 80 years and above, whereas the difference in annual prevalence between age groups was minimal for clonazepam (Figure 3). In Denmark, the annual prevalence of BZRD use, but especially BZS use, decreased in all age groups between 2000 and 2020. In Norway and Sweden, the use of BZS decreased somewhat in all age groups from 2004/2006 to 2020, whereas the use of BZRD remained constant over time in all age groups (Figure 3).

4 | DISCUSSION

In this Nordic drug utilization study, we found that the use of BZ and related drugs diminished across all Nordic countries between 2010 and 2020, but also that there were marked differences in the use of these drugs between countries. The use of BZ and related drugs per capita was considerably higher in Iceland than in the other Nordic countries. Furthermore, we found that the use of BZH decreased considerably in all countries and that BZRD were the most used hypnotics in all countries.

Several recommendations and regulations on the use of BZ and related drugs were issued in the Nordic countries during the study period (Table 1). These represent a wide array of actions, including national guidelines on the use of BZ, disease-specific guidelines describing the role of BZ in their treatment (e.g., major depression and various anxiety disorders), structural initiatives as improved register coverage or feedback to prescribers. However, no obvious single initiative coincided with a significant change in the use of BZ or BZRD. From this observation, the decrease in use of BZ and related drugs could be attributable to the sum of initiatives, rather than individual initiatives alone, or from a general, international trend in the perception of BZ use and the associated risks. Furthermore, the observed decreases could also be related to

TABLE 2 Total amount sold and proportion of total amount sold for benzodiazepines and benzodiazepine-related drugs by drug class and country

Drug class/ country	2000[a]		2010		2020	
	Total national sales (1000 DDD)	Proportion of national sales (%)	Total national sales (1000 DDD)	Proportion of national sales (%)	Total national sales (1000 DDD)	Proportion of national sales (%)
Clonazepam						
Denmark	806	1	1098	2	657	2
Finland	1099	1	1757	1	803	1
Iceland	119	2	128	1	88	1
Norway	1038	1	1103	1	370	<1
Sweden[b]	571	1	698	1	542	1
Benzodiazepines						
Denmark	41 818	41	21 452	35	8786	31
Finland	36 157	40	41 375	35	24 052	44
Iceland	2107	29	2499	23	2229	24
Norway	30 273	33	29 658	29	18 898	24
Sweden[b]	33 097	31	33 692	25	20 826	20
Benzodiazepine hypnotics						
Denmark	29 422	29	9080	15	1497	5
Finland	22 714	25	20 605	17	1	<1
Iceland	1485	20	957	9	352	4
Norway	13 430	15	10 243	10	3848	5
Sweden[b]	28 590	27	10 882	8	1810	2
Benzodiazepine-related drugs						
Denmark	30 379	30	28 906	48	17 571	62
Finland	31 475	34	54 729	46	30 389	55
Iceland	3533	49	7241	67	6655	71
Norway	45 756	51	61 285	60	56 903	71
Sweden[b]	45 166	42	89 890	67	82 766	78

Abbreviation: DDD: WHO defined daily doses.

[a]Data from 2002 for Iceland and from 2004 for Norway as registers in these countries were first established in these years.

[b]Data from Sweden include both sales at community pharmacies and hospital use, while data for the remaining countries only cover sales at community pharmacies.

initiatives initiated before the study period; in Denmark and Norway, guidelines on prescription of addictive drugs were issued in the 1980s and 1990s, and in Sweden treatment guidelines on anxiety disorders from 1995 recommended antidepressant drugs as first line treatment in these disorders. Such guidelines were in many cases continuously developed, updated, or reimplemented; thus, only substantially affecting prescription patterns years or decades after their introduction. This phenomenon was observed in Denmark in relation to the use tramadol. Guidelines on the use of opioids (including tramadol) were issued around 2007, but declining use of tramadol was first observed around 2017–2018 after media attention to its adverse effects and subsequent regulatory reclassification of tramadol's prescription status to that of opioids (e.g., only prescription via consultation, only one dispensing per prescription etc.).[27]

The difference between countries, in both amount used and annual prevalence, is striking. Iceland has markedly higher levels of BZ use than any other Nordic country. Conversely, Denmark shows lower levels of BZ use, together with the most pronounced decrease in BZ use of all five countries. Collectively, clonazepam use was low, and the use of BZH almost disappeared during the study period. The higher levels of BZ/BZRD use in Iceland, than in the other four Nordic countries, has been

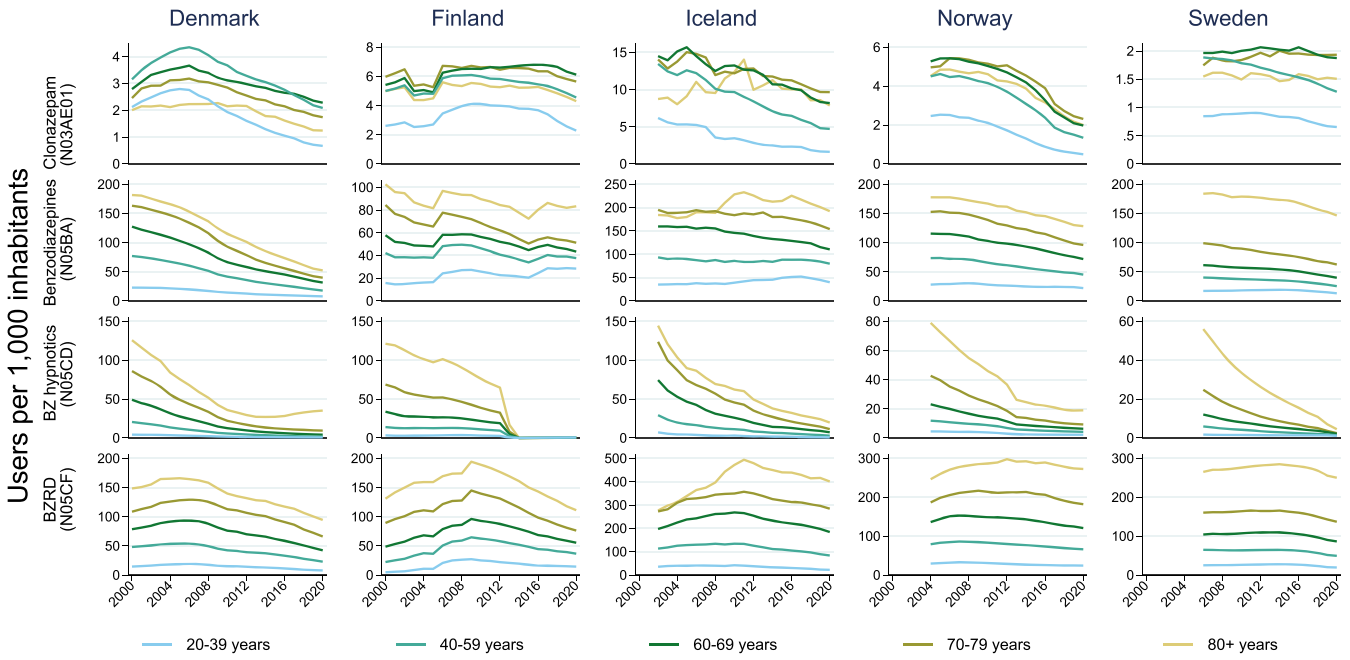

FIGURE 3 Time trend in the annual prevalence of benzodiazepines and related drug-use (annual number of users per 1000 inhabitants) by age group, drug class and country. *Note*: Y-axis differs between countries.

documented as early as in the 1970s.[28] Exact reasons for this higher level of BZ use in Iceland are not known, but relevant factors could include that many individuals do not have a specific general practitioner (or health centre) as is common in Denmark, Norway and Sweden, that the access to specialists is easier, and that many specialists are trained in the USA, where prescriptions practices might be more liberal.[29] Likewise, higher levels of opioid utilization have been observed among older adults in Iceland, compared to the other four countries.[30]

The apparent reduction in BZH use in Finland around 2013 was a result of BZH no longer being reimbursed and thus not recorded in the Finnish Prescription Registry. Finnish wholesale statistics indicate that BZH use is still considerable in Finland with temazepam being the 3rd most commonly sold BZ in 2020.[31] For BZ and BZRD, we found high prevalence in all older age groups, compared to the younger age groups in all countries. Especially in Iceland, Norway, and Sweden, the prevalence of BZRD use was markedly higher among those aged 80 years or older, compared to younger age groups, despite the association of BZRD with various adverse events, including increased risk fractures, falls, and cognitive impairment.[1,3,4] The high rates of BZ and BZRD use among older individuals could reflect an increased attention over the study period to new users of BZ and BZRD, whereas deprescribing efforts in (older) long-term users might have limited success rates.

An important strength of our study was the use of valid and nearly complete data on entire nations. Using these nation-wide data sources, the total study population was about 21 million inhabitants in 2021. However, there are also limitations with the use of these data sources: Firstly, as nation-wide prescription databases had not yet been established in all countries in 2000, data were not available from Iceland, Norway, and Sweden for the first 2–6 years (for Sweden, wholesales data were used for the period of 2000–2005). Secondly, data from Iceland did not include all use in nursing homes prior to 2010, which might lead to underestimation of the use prior to 2010.[20] Thirdly, Swedish legislation did not allow us to include complete data for drugs with only one manufacturer due to confidentiality issues (e.g., clonazepam). Fourthly, Finnish registers are based on reimbursement information, which means that purchases for non-reimbursable products are not registered. Coverage of BZ use by the Finnish prescription register was approximately 90% prior to 2013 and 76% in 2013–2014 after BZs like chlordiazepoxide, nitrazepam, and temazepam were no longer eligible for reimbursement and thus not recorded in the prescription register.[14] This could potentially lead to an underestimation of the true prevalence and amounts sold but might not reflect in the trends observed. Fifthly, the use of benzodiazepines and related drugs in hospitals were not included in analyses of prevalence due to data availability issues. Lastly, the use of aggregate data did

not allow us to assess indications for treatment, duration of use, or whether the decrease in utilization was offset by a channelling to other drug categories, e.g., sedative antihistamines, antidepressants, or low-dose antipsychotics.

Despite recent decreases in the use of BZ and related drugs, attention should still be devoted to their usage. Long-term use among all age groups should be monitored, deprescribing should be actively pursued, and prescribers should be extra cautious with older patients given the high number of users in the light of an increased risk of falls and fractures. Furthermore, the evidence base for pharmacological and non-pharmacological interventions in insomnia in older adults is sparse.[32] It is of note that following the decreasing use of BZ and related drugs in countries like Denmark, Norway, and Sweden, an increase has been observed in use of other psychotropic drugs, such as quetiapine.[33] This increase in the use of quetiapine is likely to reflect a "clinical vacuum" from the increased attention to adverse effects with BZ and related drugs as a large proportion of new users of quetiapine have no records of psychotic disorders (or any psychiatric diagnosis) and the treatment is commonly installed in general practice.[34,35] Therefore, caution should be exerted when reducing use of BZ and BZRD and it should be investigated if reductions in BZ/BZRD use are converted to off-label use of, for example, antipsychotics for anxiolytic/hypnotic purposes.

In conclusion, the use of BZ and related drugs has decreased in all Nordic countries over the last 10 years. However, there was considerable variation between countries in both the number of users and the amount used, but BZRD remained the most commonly used drug class among these drugs. Drivers of the high use among older adults and the high use of BZRD should be the target of future research and initiatives.

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CONFLICT OF INTEREST

MH reports honoraria for consultancy from the Lundbeck Foundation and Otsuka Pharmaceutical Co, unrelated to this study. HZ was an employee of the Centre for Big Data Research in Health, UNSW Sydney, which in 2020 received funding from AbbVie Australia to conduct research, unrelated to this study. AbbVie did not have any knowledge of, or involvement in, this study. AP and JH report participation in research projects funded by Alcon, Almirall, Astellas, AstraZeneca, Boehringer-Ingelheim, Novo Nordisk, Servier, Menarini Pharmaceuticals, and LEO Pharma, all regulator-mandated phase IV studies, all with funds paid to their institution (no personal fees) and with no relation to the work reported in this paper. LSG, JHA, LKS, SS, and JW report no conflict of interest.

DATA AVAILABILITY STATEMENT

The data used for this study can be obtained from public data sources or through application to relevant public authorities in each country (described in Appendix S1).

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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