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ARTICLE



## Comparison of psychotropic medication use in the Baltic countries

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### ABSTRACT

**Purpose:** While the pivotal role of pharmacotherapy in psychiatry is universal, significant regional differences exist in drug use patterns. Herewith we compare the use of ATC psychotropic drugs (N05, psycholeptics and N06A, antidepressants) in 2010–2015 in the three Baltic Countries with reference to the Nordic Countries.

**Methods:** Data were obtained from the national authorities on medicines as expressed in DDD per 1000 inhabitants per day. A semi-structured questionnaire was used for expert statements on the rationale of current use of medicines.

**Results:** During the observation period the use of antipsychotics, anxiolytics, hypnotics and sedatives, and antidepressants steadily increased, while the growth in use of anxiolytics stagnated in the more recent years. Antipsychotic use was the largest in Lithuania and the lowest in Estonia. The use on anxiolytics in Lithuania was more than twice of that in Estonia and Latvia. Conversely, the use of hypnotics and sedatives was about three times higher in Estonia than in Latvia or Lithuania. Antidepressant use was dominated by the selective serotonin reuptake inhibitors in all three countries, but overall was much lower in Latvia as compared to Lithuania and Estonia. As compared to the Nordic Countries in 2015, antidepressants are used at much lower level throughout Baltics, probably reflecting underdiagnoses of depression and anxiety disorders.

**Conclusion:** While the health-care expenditures in Estonia, Latvia and Lithuania are largely similar, as is the cultural and recent political background of these EU member countries, the extent and the pattern of psychotropic drug use is remarkably variable.

### ARTICLE HISTORY

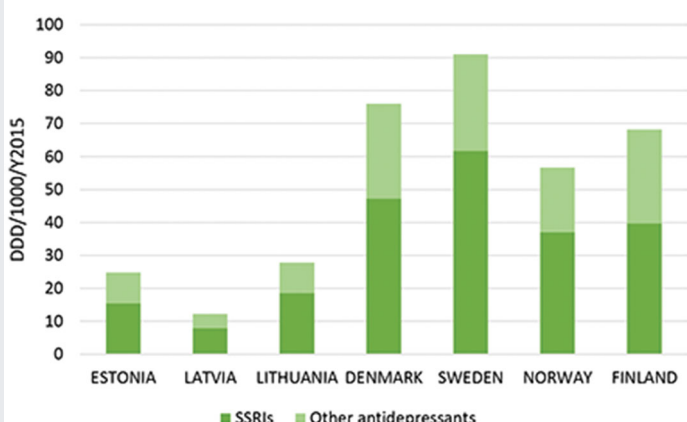
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### KEYWORDS

Psychotropic medicines;  
defined daily dose; cross-  
country comparison;  
Baltic Countries

### Comparison of the consumption of psychotropic medicine in the Baltic and the Nordic countries:

Antidepressant (N06A) use highly variable country-wise, but much lower in the Baltics. Data in the Figure are for 2015.



## Background and aim

Since the emergence of modern antipsychotic, antidepressant and anxiolytic drugs in 1950ies the use of psychotropic medicines has profoundly changed psychiatric practice worldwide [1,2]. Antipsychotics are nowadays the main treatment option for schizophrenia and other psychotic conditions but are also used in many other disorders with issues in regulation of behavior, calling for a new nomenclature [3]. With the arrival of the second generation of antipsychotics in clinical practice the antipsychotics sales increased remarkably in the nineties and especially so in the beginning of the new millennium [4]. While the second generation antipsychotics have secured the prevailing position, the first generation drugs with their serious disadvantage of high risk of extrapyramidal side effects are still in widespread use. Antidepressants and ‘minor tranquilizers’ emerging soon after the first antipsychotics made a similar impact to psychiatry by greatly facilitating the treatment of anxiety and depression, and have a significant level of application outside psychiatry. Especially the exponential increase in the use of selective serotonin reuptake inhibitors has changed the public view on how the mental faculties operate [5].

The pivotal role of pharmacotherapy in psychiatry is universal, but significant regional differences exist in drug use patterns [6–8]. These can be caused by prescribing guidelines, consumer drug advertising, government regulatory restrictions, reimbursement policies, and diagnostic practice, but also attributed to cultural beliefs [9–12]. Both physician- and patient-related factors are known to influence the practice of medication with psychotropics [13].

Transition societies offer a resource to notice and analyze the significance of socioeconomic and cultural factors to medical practice. Estonia, Latvia and Lithuania, often referred to as the Baltic Countries, shared a largely similar political history in the XX century [14], including the ‘return to the Western World’ during the last decade [15]. Rapid economic growth and membership in international alliances, most notably joining the European Union, were expected to contribute to closing the gap with the modernization of medical practice in Europe. Herewith we aimed at comparing the recent use of ATC psychotropic drugs (N05, psycholeptics and N06A, antidepressants) in the three Baltic Countries in the period of 2010–2015, with an attempt to understand reasons for the significant differences that are found in these three nations that are socioeconomically and culturally similar.

## Materials and methods

### National drug use statistics

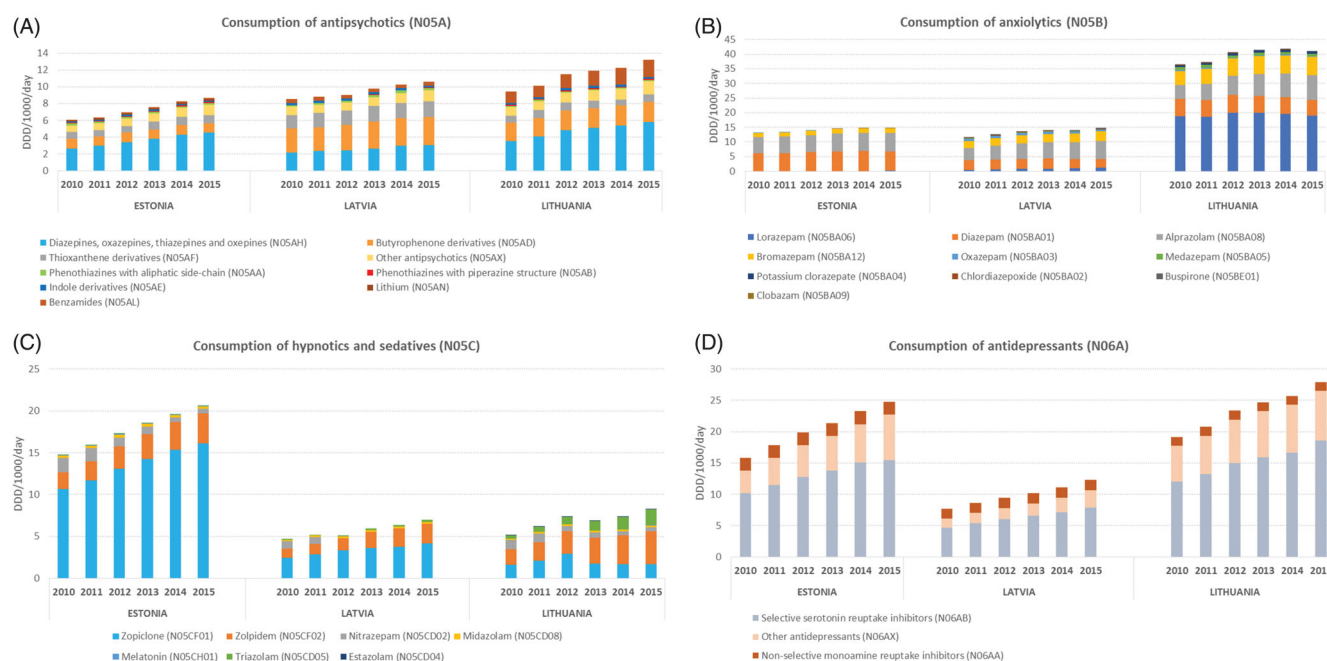
The drug regulatory authorities in Estonia, Latvia and Lithuania and in the Nordic Countries use the Anatomical Therapeutic Chemical (ATC) classification system and the Defined Daily Dose (DDD) as a measuring unit [16] that supports drug use statistics at national level and international comparisons. In the ATC classification system, the active substances are divided into groups according to the organ or system on which they act, and their therapeutic,

pharmacological and chemical properties. Drugs are classified at five different levels. The drugs are divided into fourteen main groups (1st level), with pharmacological/therapeutic subgroups (2nd level). The 3rd and 4th levels are chemical/pharmacological/therapeutic subgroups and the 5th level is the chemical substance. The 2nd, 3rd and 4th levels are often used to identify pharmacological subgroups when that is considered more appropriate than therapeutic or chemical subgroups. The Defined Daily Dose (DDD) is the assumed average maintenance dose per day for a drug used for its main indication in adults. It should be emphasized that the defined daily dose is an arbitrary unit of measurement and does not necessarily reflect the recommended or prescribed daily dose. Doses for individual patients and patient groups will often differ from the DDD and will necessarily have to be based on individual characteristics (e.g. age and weight) and pharmacokinetic considerations. Drug consumption figures are usually presented as numbers of DDD/1000 inhabitants/day. The use of a drug expressed as DDD/1000 inhabitants/day is derived by calculating the overall amount of a drug being used over a specified period of time (e.g. a year) and dividing this by the DDD multiplied by the population and the number of days in the period. Sales data presented in DDD/1000 inhabitants/day provides a rough estimate of the proportion of the population within a defined area treated daily with certain drugs. For example, the figure 10 DDD/1000 inhabitants/day indicates that 1% of the population on average gets a certain treatment daily. Because wholesalers do not accumulate drug reserves, the DDD methodology provides the most adequate representation of drug use at the level of actual sales in the whole country. While the purchased drugs are not consumed entirely, there is no ground to believe that failure of compliance at this level were different between demographically similar regions.

Data for the Baltic Countries have been published as the reports by the respective authorities for 2010–2012 [17] and 2013–2015 [18]. The comparison data of 2015 for the Nordic countries were derived from the following reports and online databases: Denmark [19], Finland [20], Norway [21], and Sweden [22].

### Semi-structured questionnaire to focus group

A link to internet-based custom-made questionnaire was sent to 8 psychiatrists (2 in Estonia, 4 in Latvia, 2 in Lithuania) who were identified as internationally visible figures and influential at the national level, and who attended a meeting in Riga, Latvia in December 2017 that recognized differences in psychotropic use between the respective countries. The questionnaire was in English but possibility to respond in mother tongue was offered (and eventually used by two participants). All of those invited filled in the questionnaire. They provided personal assessment whether the psychotropic drug use in their own and neighboring countries is either optimal or below or above the real need, as well as of the potentially contributing factors to that state. Questions on factors potentially influential in shaping the



**Figure 1.** Consumption of psychotropic medicines in Estonia, Latvia and Lithuania in 2010–2015. A: antipsychotics (N05A); B: anxiolytics (N05B); C: hypnotics and sedatives (N05C); D: antidepressants (N06A).

practice of psychotropic drug prescription were accompanied with response variants on Likert-scale (strongly agree, agree, neither agree or disagree, disagree, strongly disagree), and the respondents were invited to free comments. For semi-quantitative assessment these responses were converted to a scale ranging from  $-2$  to  $+2$ , and the mean (95%CI) was calculated and Spearman correlation analysis applied. The questionnaire is available upon request as well as more detailed summary of the outcome.

## Results

### *Use of psychotropic medicines in 2010–2015 in the Baltic countries*

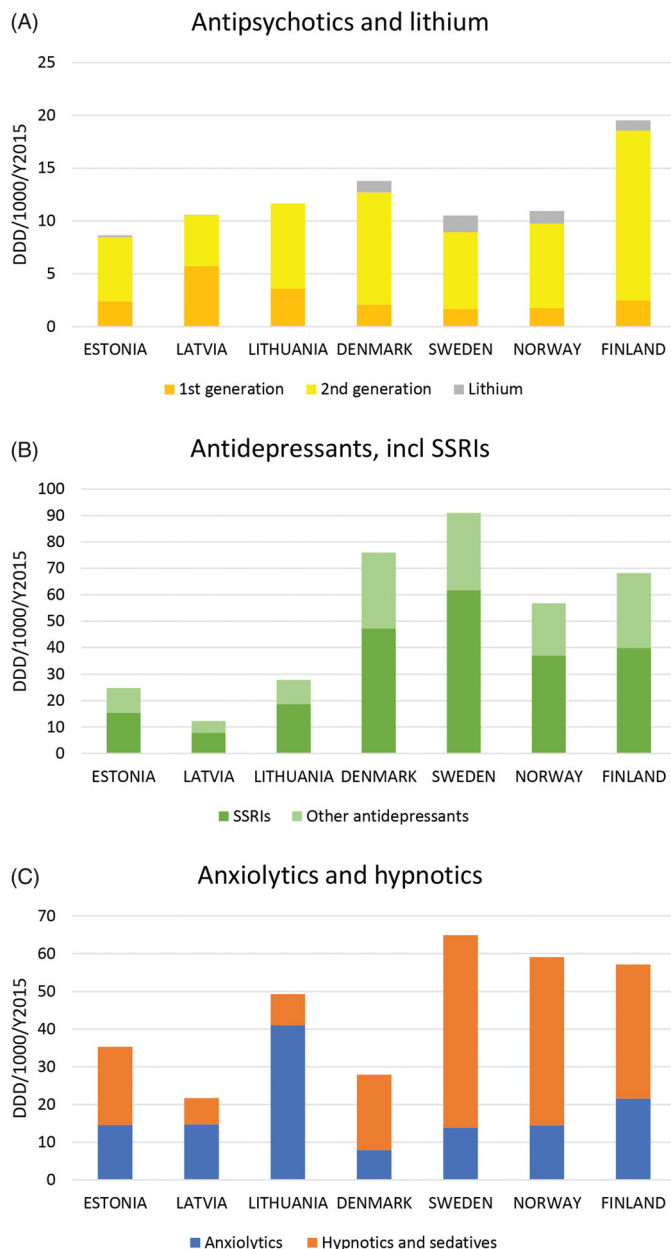
During the period of 2010–2015 the use of antipsychotics, anxiolytics, hypnotics and sedatives, and antidepressants, as expressed in DDD per 1000 inhabitants per day, steadily increased in all three countries, while the growth in use of anxiolytics stagnated in the more recent years. Antipsychotic use was the largest in Lithuania and the lowest in Estonia (Figure 1(A)). The N05AH group (diazepines, oxazepines, thiazepines and oxepines) was prescribed in Estonia almost at the level of Lithuania, but lower was the prescription of butyrophenones and benzamides. In Latvia, butyrophenone derivatives were the most common antipsychotics, and thioxanthenes relatively popular. Lithium was by far more often used in Lithuania than in the other two countries.

The use of anxiolytics (N05B) in Lithuania was more than twice of that in Estonia and Latvia; to a large extent this difference was made by frequent prescription of lorazepam while other drugs, especially bromazepam, also contributed (Figure 1(B)). In Estonia diazepam and alprazolam held the

lion's share of the market. Conversely to the anxiolytics, the use of hypnotics and sedatives (N05C) was about three times higher in Estonia than in Latvia or Lithuania, mostly owing to the extensive use of zopiclone in Estonia (Figure 1(C)). Zolpidem was the second most common hypnotic, and in Lithuania it was preferred to zopiclone. Lithuania was using triazolam to a much higher level than Estonia or Latvia. Antidepressant use was dominated by the selective serotonin reuptake inhibitors in all three countries, but overall the use was twice lower in Latvia as compared to Lithuania and Estonia (Figure 1(D)).

### *Comparison of the use of psychotropic medicines in the Baltic and Nordic countries in 2015*

To put the levels of psychotropic drug use in the Baltics into broader perspective, we have compared the use of medicines in 2015 to that in the Nordic countries. Use of antipsychotics in Latvia had grown to the level of Scandinavian countries by 2015 but remained slightly lower in Estonia; Lithuania had a higher consumption rate but well below Finland where the antipsychotics use is higher (Figure 2(A)). The N05AH group (diazepines, oxazepines, thiazepines and oxepines) formed more than half of antipsychotic use in the Nordic Countries, Estonia and Lithuania becoming rather similar in this regard. Anxiolytics were used in Estonia and Latvia at the level of Sweden and Norway; Lithuania would compare to the higher Finnish level if omitting the exceptional lorazepam use that doubles the figure (Figure 2(C)). Use of hypnotics was much lower in the Baltic countries, and use of antidepressants very much lower than in the Nordic countries (Figure 2(B)).



**Figure 2.** Comparison of the consumption of psychotropic medicines in Denmark, Finland, Norway and Sweden with the Baltic Countries in 2015. A: antipsychotics (N05A); B: antidepressants (N06A); C: anxiolytics (N05B), and hypnotics and sedatives (N05C).

### Focus group assessment of psychotropic drug use and contributory factors

The majority of expert psychiatrists thought of psychotropic use in the Baltics as too low but this was not a consensual position. Almost unequivocal, however, was the assessment of use of antidepressants as too low (data not shown).

Expert assessment of the reasons for quantitative and qualitative differences in psychotropic drug use between the three countries suggested similarity between countries (own vs. other; Spearman  $\rho = 0.803$ ;  $p = .021$ ). Of the significance of the potential reasons for these differences (Table 1), psychiatrists suggested the dissimilar reimbursement practices, the relative role of general practitioners, and stigma

**Table 1.** Focus group assessment of contributory factors to country-wise differences in psychotropic drug use patterns.

Factors	Own country	Other countries
Clinical tradition of drug selection	0.63 (0.19–1.06)	0.25 (–0.34–0.84)
Differences in diagnostics	–0.25 (–1.12–0.62)	0.75 (0.01–1.49)
Overall socio-economic conditions	0.13 (–0.70–0.95)	0.38 (–0.25–1.00)
Relative role of general practitioners	1.13 (0.59–1.66)	1.13 (0.59–1.66)
Reimbursement system	1.50 (1.05–1.95)	0.25 (–0.49–0.99)
Recipe specifics	0.75 (0.16–1.34)	0.38 (–0.39–1.14)
National drug control specifics	0.38 (–0.25–1.00)	0.75 (0.16–1.34)
Stigma	1.00 (0.37–1.63)	0.38 (–0.51–1.26)

Assessment was made on a scale from –2 to +2. Mean ( $n = 8$ ) and 95%CI presented.

associated with psychiatric treatment as the most obvious sources of difference.

### Discussion

We have observed large qualitative and quantitative differences between the three Baltic countries, Estonia, Latvia and Lithuania, in the use of psychotropic medicines. This occurs despite of the shared recent socio-economic history. In comparison to the Nordic countries, consumption of hypnotics and antidepressants was significantly lower.

This analysis was based on DDD that is most informative in general terms as respondent based methods have difficulty with estimating the level of use. Simple prevalence rates and duration of treatment have been found as relative independent measures [7]. The DDD based approach does not capture most of aspects of clinical practice but provides objective record of overall level of medicine use for cross-cultural overview.

Gradual increase in the use of antipsychotics since the emergence of the second generation drugs is a world-wide phenomenon [23,24]. This is reflected in the presented statistics for the Baltics where the growth in the consumption of second generation antipsychotics in the period of observation has brought the antipsychotic use to the level of Nordic countries. As throughout the transition period the Baltic Countries have related closely with Nordic countries, and while the level of economic development still differs it is of primary relevance to compare psychotropic drug use with this region. Economic factors may have only limited effect on drug consumption measures and have not prevented the increase in antipsychotic use elsewhere [24]. Apparently antipsychotics are used at the level corresponding to essential need, and where economic factors may weigh in this could be represented in relatively higher use of butyrophenones as in the case of Latvia.

Huerta et al. [25] compared benzodiazepine prescriptions in five European countries between 2001 and 2009 and by this method found up to three-fold difference in drug use prevalence. They also reported regional differences in terms of hypnotic vs. anxiolytic use: While the former was more common in the UK and Denmark, the latter prevailed in Spain, the Netherlands and Bavaria. As an extreme example to the higher end, the benzodiazepine use in Croatia was 74.4 DDD/1000/day in 2015 [26]. These authors proposed



that the preference of either hypnotics or anxiolytics is mainly owing to marketing activities and physician habits.

The Nordic countries have been using significantly more of hypnotics than anxiolytics. The levels of use of both, especially hypnotics, have recently declined in Finland, but Finland still uses these drugs at the level of Lithuanian anxiolytics and Estonian hypnotics use combined. In Norway, the use of anxiolytics has declined but hypnotics use has remained stable, the former is at about the level of Estonia but the latter twice the level of this comparator. In Sweden, the use of anxiolytics is about the same as in Estonia and Latvia, while the use of hypnotics is between that of Norway and Finland. Zopiclone was the by far most prescribed hypnotic medicine in Estonia. Since 2005 when the use of zopiclone was similar to diazepam and alprazolam the prescription rate has been steadily increasing [27]. Benzodiazepines are more frequently used by older people and by females but the populations in the Baltic Countries are similar in such demographic aspects. The remarkable consumption level of lorazepam in Lithuania has a long tradition, and in this tradition even other medicines classified as anxiolytics are often used as sleep aid, often for rather long periods at low doses.

Antidepressant use has largely increased over the past two decades in many countries. This increase has been estimated to have leveled off in countries with the highest consumption, such as Canada [28]. Differences in methods do not permit direct comparison of the level of antidepressant use but Canada had been ranked as a top user of antidepressants in international comparison. Antidepressant use has also remained stable in Finland while the level of consumption has been more than three times higher than in Estonia and in Lithuania by 2015. Similar to Finland is the antidepressant consumption in Denmark, and even higher in Sweden. Norway consumes less but still the use is more than twice the level of Estonia and Lithuania. Underdiagnostics of depression in the Baltics is thus highly likely, and the low figures may be reinforced by using doses too low.

Most differences in psychotropic use prevalences between and within countries have been attributed to diverse prescription habits of physicians [25,29] but also to regional economic development [30]. Similarly is the large variability in the Baltics apparently related to reimbursement regulation that is most generous in Lithuania and at lower level in Latvia where relatively higher use of antipsychotics may be explained by the role of cheaper antipsychotics in place of other sedative medications. Adherence to treatment may also contribute to overall drug use and can be affected by general pharmacophobia or skepticism toward prescribed medication dependent on culture [31]. The attitudes of patients toward mental health help-seeking can vary by country and by this means contribute to differences in prescribing [25]. Whether patients seek psychiatric help appears to be related to stigma, still much felt in the Baltics, and fear of side effects, overfeatured in the variety of Internet sources particularly with regard to antidepressants.

Primary care in the three Baltic Countries has been described as largely similar in terms of legislative framework,

principles of financing, coordination of services, service delivery and quality requirements [32]. Nevertheless, at a more granular level, substantial differences are reflected in medicine use pattern. The dense network of primary mental health centers in Lithuania (in total 103 primary mental health centers/10 regions) [33,34] has provided easy access, not gated by family doctors, and likely been contributing toward overall higher psychotropic use as compared to Estonia and Latvia.

Nevertheless it is possible that genuine differences in mental health contribute to drug use patterns. In a population-based study that used the CIDI-3.0 interview in five European countries on more than twenty thousand individuals it was found that not only had less than one-third of subjects with major depressive disorder been taking antidepressants, but seeking help for emotional problems was a more important predictor of use of either antidepressants or benzodiazepines than a formal psychiatric diagnosis [35]. The Nordic experience of pharmacoepidemiology that rests on prescription databases with their extensive linkage potential, including the outcome [36] should be followed in future medical practice and studies to reveal the effectiveness and safety of drug therapy in real-life settings and thus elucidate how appropriate are the regional differences in prescription practice.

## Conclusion

While the health-care expenditures in Estonia, Latvia and Lithuania are largely similar, as is the cultural and recent political background of these EU member countries, the extent and the pattern of psychotropic drug use has within a few decades become remarkably variable. The reasons for such differences require clarification. While differences in compensation mechanisms may explain some of the variance, other factors such as clinical traditions, access to mental health services, and prescription patterns by general practitioners potentially contribute.

## Disclosure statement

JH is a Faculty Member of the Lundbeck International Neuroscience Foundation (LINF). KP is an employee of the Lundbeck Eesti AS. Neither Lundbeck nor LINF had any role in conceiving the idea of compiling this paper or in any aspect of data collection, analysis, and writing. Other authors report no potential conflict of interest.

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