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The Significance Of Increase Of The Antidepressant/Anxiolytic Ratio In The Treatment Of Depressive And Anxiety Disorders.

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ABSTRACT

The aim of this study was to analyse the prescription of antidepressants and anxiolytics by gender, to determine the correlation between them and to determine the antidepressants/anxiolytics ratio in Slovenia from 2009 until 2016. Data from the Slovenian Database of Outpatient Prescriptions were used based on the WHO Anatomical-Therapeutic-Chemical methodology. Data were anonymised. Compiled data were processed by means of descriptive statistics, contingency tables, Pearson correlation coefficient and linear regression analysis. Outpatient prescription showed a statistically significant increase in prescription of antidepressants (N06A) from 43.9 defined daily doses per 1000 inhabitants per day in 2009 to 58.8 defined daily doses per 1000 inhabitants per day in 2016 and statistically significant declining pattern of anxiolytics (N05B) from 19.3 defined daily doses per 1000 inhabitants per day in 2009 to 14.7 defined daily doses per 1000 inhabitants per day in 2016. Antidepressants/anxiolytics ratio increased from 2.3 in 2009 to 4.0 in 2016. The correlation coefficient between the prescribing anxiolytics and antidepressants from 2009 until 2016 was negative (-0.97). Increase of antidepressants/anxiolytics ratio could be an indicator of better quality treatment of depressive and anxiety disorders and tool for monitoring changes.

Keywords: mental health, antidepressive agents, anxiety disorders, anxiolytics, depression, drug prescriptions

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INTRODUCTION

Slovenia has one of the highest suicide rates in the EU (1). It is known that at least 90% and as many as 98% of those who committed suicide had a psychiatric diagnosis at the moment of death, most frequently depressive disorders (2,3). However depressive and anxiety disorders are the most common groups of mental disorders worldwide (4).

Among mental disorders depression represents a global public health problem and it contributes significantly to the global burden of disease. The World Mental Health Survey conducted in 17 countries found that on average about 1 in 20 people reported having an episode of depression in the previous year (5,6). Severe form of depression is one of the most common psychiatric disorders (7,8).

Depression can become chronic or recurrent and lead to substantial impairments in an individual's ability to take care of his or her everyday responsibilities. Many patients with depression suffer from other diseases and have multiple diagnoses (9).

Suicide is considered to be the worst consequence of untreated depression. In fact, depression is the leading cause of disease burden for women in both high-income and low- and middle-income countries (5,10).

Nowadays, depression can be treated successfully. Medicinal products for treating depression function on different biochemical substances in the biological processes in the brain, but the effect appears only after three or four weeks. Antidepressants (AD) do not cause addiction and do not have lasting adverse consequences. Anxiolytics (ANX) have been useful in the treatment of anxiety disorders only for short period otherwise may lead to addiction, so treatment with AD is recommended also in case of anxious disorder as well (11).

However, the prescription of AD and ANX has been monitored through the years. In the past prescribing of AD in Slovenia was probably too low compared to Scandinavian countries (12). In Slovenia there was a 2.33-fold increase in the rate of AD prescriptions among primary care physicians after participation in the educational program on depression treatment and suicide risk recognition from 2002 - 2003 (13). It is possible to observe a significant change in the prescription. Previously, ANX were preferred and mostly prescribed medicines. Nowadays, physicians prescribe more AD or a combined AD/ANX therapy (13,14,15). Authors reported a decrease in total number of prescribed ANX by 11.1 % in Zagreb and by 58.7 % in Sarajevo in the period from 2006 to 2010 (16).

Based on the above results the aim of the present study was to analyse the outpatient prescription of AD and ANX in Slovenia in the period from 2009 until 2016, to determine the correlation between prescribed AD and ANX and to determine the AD/ANX ratio.

MATERIAL AND METHODS

The source for the retrospective observational analysis was the »Database of prescriptions for outpatients« of the Republic of Slovenia at the National Institute of Public Health (17).

Medicinal products were classified according to the Anatomical Therapeutic Chemical (ATC) Classification System and Defined Daily Doses (DDD) per 1,000 inhabitants per day (hereinafter DDD/TID) were used. The subgroups of prescribed psychoanaleptics (ATC code N06) i.e. AD (ATC code N06A) and psycholeptics (ATC code N05) i.e. ANX (ATC code N05B) were analysed in order to identify the reasons for the changing trend (18).

Data were analysed using statistical software IBM SPSS Version 21 (SPSS Inc., Chicago, IL, USA). Compiled data were processed by means of descriptive statistics, contingency tables, Pearson correlation coefficient and linear regression analysis (19,20).

This study does not require ethics committee approval as all data used for statistical analysis were anonymised and part of routine and compulsory data collection based on formal legal base (17).

RESULTS

ANX (alprazolam, lorazepam, and diazepam) are the most commonly prescribed subset among psycholeptics (N05) in the period from 2009 to 2016. The prescriptions of ANX gradually dropped from 245 prescriptions/1000 inhabitants in 2009 to 207 prescriptions/1000 inhabitants in 2016, the number of DDD/TID for ANX decreased from 19.3 in 2009 to 14.7 in 2016. There were prescribed 24.6 DDD/TID for women and 13.8 DDD/TID for men in 2009, while there were prescribed 18.3 DDD/TID for women and 11.0 DDD/TID for men in 2016. The prescription of ANX was present in greater extent among females during observed period, but the ANX ratio of DDD/TID females to males decreased and was 1.8 : 1 in 2009 while it was 1.7 : 1 in 2016. In the observed period, the most commonly prescribed AD were selective serotonin reuptake inhibitors (SSRIs) (N06AB). There was an increase in the prescribed DDD/TID of escitalopram and sertraline. The number of prescriptions/1000 inhabitants for AD increased from 213 in 2009 to 271 prescriptions in 2016. The number of DDD/TID increased from 43.9 in 2009 to 58.8 in 2016.

There were prescribed 61.4 DDD/TID of AD for females and 26.1 DDD/TID for males in 2009, while there were prescribed 80.5 DDD/TID for females and 36.6 DDD/TID for males in 2016. Among females, there was a greater extension of prescription of AD than among males. On the other side DDD/TID ratio of AD females to males decreased from 2.4 : 1 in 2009 to 2.3 : 1 in 2016.

There was statistically significant increase in the prescription of AD, while the prescription of ANX statistically significantly decreased in all Slovenian statistical regions with the consequence of statistically significant increase in AD/ANX ratio. Total AD/ANX ratio in Slovenia gradually increased from 2.3 in 2009 to 4.0 in 2016.

The relationship between the two variables in the whole population is statistically significant. Consumption of AD was higher in women aged 60 years and older compared with younger patients. The value of the correlation coefficient between the prescribing ANX and AD from 2009 until 2016 was negative (- 0.97). Regression model is $DDD/TID\ ANX = 34.032 - 0.3234\ DDD/TID\ AD$.

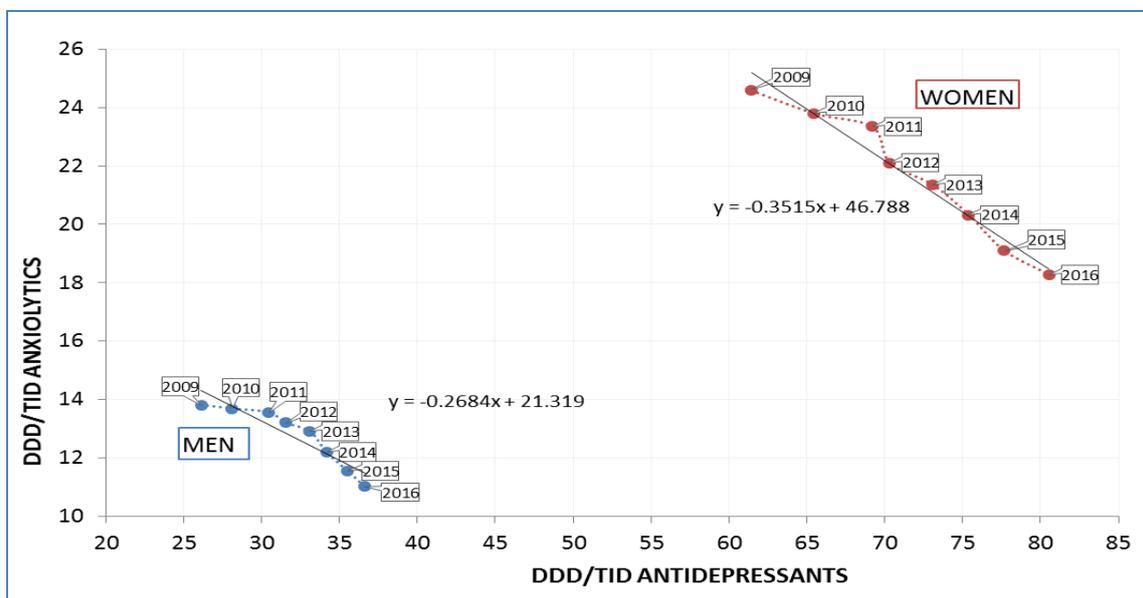


Figure 1: Trend of prescribing antidepressants (AD) and anxiolytics (ANX) by gender from 2009 to 2016

DISCUSSION

Study results pointed to several favourable features, the prescribed DDD/TID of AD statistically significantly increased while the prescribed DDD/TID of ANX statistically significantly decreased with the same trend in both genders. However, the prescription of AD in women is one more time higher than in men and the prescription of ANX is 60% higher in women. This is not surprising as women are more frequently affected by depressive and anxiety disorders in comparison with men (4).

On the other hand there was a decreasing number of reported treated cases of depressive and anxiety disorders on primary and secondary outpatient healthcare services, i.e. decreasing number of reported outpatient cases of depression from 33526 in 2009 to 25450 in 2015 and decreasing number of outpatient cases of anxiety from 28164 in 2009 to 27512 in 2015 (21). Since general trends in other countries usually show a certain rise in treated prevalence of anxiety and mood disorders, our results are somewhat discordant with these data and need further elaboration in separate studies.

The AD/ANX ratio, which is growing significantly, could be one of the indicators of quality in prescribing medicinal products as well as indicator of better pharmacological treatment. There is a negative correlation between prescribed AD and ANX, as shown on the Figure 1. Prescription of AD is increasing while prescription of ANX is decreasing. Among men and women, the consumption of ANX decreased approximately linearly with the increase of consumption of AD, suggesting that general practitioners (GPs) were probably switching ANX for AD in this period of time (22).

Pharmacological treatment guidelines recommend AD, specifically **selective serotonin reuptake inhibitors** (SSRIs) as the first-line treatment as well as for the prolonged treatment not only for depressive but also for anxiety disorders. Besides SSRIs, other AD are recommended instead of ANX for long term treatment usually performed in outpatient primary care settings (8, 23, 24, 25).

The high use of ANX, consequently decrease in prescription units in 2009 - 2016 period and increase in AD/ANX ratio suggests that ANX were often prescribed instead of the AD. Slovenian psychiatrists made a wide educating campaign for the primary care doctors during 1990 - 2000 who are now becoming more aware of the problem of diagnosing an appropriate medical treatment in line with guidelines (13, 14, 26).

Increase in AD prescription in Slovenia in observed period in recent years could be the result of the improvement of primary care physicians' skills in diagnostic and treatment of anxiety and depression. The reason could also be a more frequent request for pharmacological treatment and more severe cases of clinical depression and anxiety disorders during recession and global crisis. In fact, in Slovenia recession and economic crisis emerged in 2009 (14, 22, 27).

Based on the publications Slovenian psychiatrists strongly believe that the decrease in the suicide rate observed in Slovenia between 2000 and 2010 was due to the outcome of education and programmes leading to the shift in the treatment, i.e. prescription of AD rather than ANX by general practitioners (14, 26, 28).

Additionally, Slovenia is among those EU countries where every unit of increase in DDD/TID for AD reduces the standardised death rate for suicide by 0.088 (10).

In Slovenia, the number of physicians and outpatient psychiatric services per capita is low (29). Lower number of psychiatrists and family physicians can be associated with lower recognition of mental disorders and prescription of AD and ANX (14, 30). The highest AD/ANX rates were observed in the central regions, where the majority of family physicians and psychiatric facilities are located. The differences in AD/ANX rates prescription of medicinal products could be also associated with the different availability and inequality in medical treatment (rural regions vs major cities). However, in all Slovenian regions an increase in prescription of AD as well as an increase in AD/ANX ratio and decrease in prescription in ANX units were observed in the period of evaluation of rationality in prescribing. These results are certainly important from the public health perspective, but educational and other activities need to be continued in the future since their effects may diminish over time.

The main limitation of the study was that only outpatient prescriptions were included, as hospital data on prescription is not yet available. Of course the inpatient population is less numerous and also not comparable to outpatients due to the severity of their disorders so our data still reflect the current state in the majority of patients with anxiety and mood disorders. The study was presented on a national basis, it was based on a routine data collection and made in accordance with a law. The prescriptions are being regularly monitored. A particular strength of the study is that a nation-wide database on outpatient prescriptions were used.

CONCLUSIONS

Using the WHO ATC/DDD methodology and rationality indicators in the assessment of trends in the outpatient utilization of selected psychopharmaceuticals over a seven-year period proved efficiency in the evaluation of prescribing rationality (18).

Prescription (standard unit) of AD and ANX shows indirect insight in the health situation of the population. The data suggested that AD/ANX ratio increased in Slovenia in the period from 2009 to 2016 and a further trend toward improvement in medical treatment was noted as statistically significant increase in prescription of AD and statistically significant decrease in prescription of ANX were reported.

Statistically significant increase in prescription of AD and statistically significant decrease in prescription of ANX indicate improvement in pharmacological treatment according to clinical guidelines and education of physicians in Slovenia.

However, increase in prescription of AD could also be the consequence of the impact of economic crisis on mental health of population in Slovenia. Nevertheless, increase of AD/ANX ratio indicate improvement in pharmacological treatment according to clinical guidelines and higher level of education of Slovenian physicians in the field of the treatment of depression. The trend of outpatient prescription of ANX decrease proportionately with AD increase in the period from 2009 to 2016. There was an obvious tendency to follow international recommendations in prescribing AD and ANX. Increase of AD/ANX ratio in outpatient prescribing practice could be an indicator of better quality of treatment of depressive and anxiety disorders and an effective tool for monitoring changes.

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