

VISUOMENĖS SVEIKATA

Analysis of antidepressant prescribing tendencies in Lithuania in 2003–2004

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Key words: consumption of antidepressants; defined daily doses; depression.

Summary. Depression is one of the leading causes of disability worldwide, affecting 121 million people in whole world. In many developed countries, the number of prescriptions for antidepressants increased steeply during the 1990s. The objective of the present study was to evaluate the antidepressant prescribing patterns in all regions of Lithuania during 2003–2004, to analyze the use within different antidepressant groups, and to examine trends in age- and gender-specific antidepressant use. Antidepressants were classified into three groups according to Anatomic Therapeutic Chemical (ATC) Classification specifying the defined daily doses. The results of our study show an increase in the use of reimbursed antidepressants except tricyclic in 2004 when compared to 2003. Increase in the use of selective serotonin reuptake inhibitors and other nontricyclic antidepressants is probably related to their better tolerability, improved risk-benefit ratio, and less toxicity in overdose. There was no increase in the percentage of consumed selective serotonin reuptake inhibitors in elderly patients when compared with younger ones, despite elderly patients are most likely to benefit from reduced sedation, less antimuscarinic and less cardiac toxicity of selective serotonin reuptake inhibitors. The prevalence of the antidepressant use is the highest among middle-aged people (40–59 years), while the young (under 20) and elderly (older than 70) patients receive mostly selective serotonin reuptake inhibitors. Additional studies should be carried out in order to assess drug-prescribing patterns in accordance with the guidelines of depression treatment in Lithuania considering diagnosis, dosage, and duration of treatment.

Introduction

World Health Organization (WHO) reports that depression is one of the leading causes of disability worldwide, affecting 121 million people in whole world (1). Depression can affect individuals at any stage of the life cycle although the incidence is highest in a middle-aged population. It often goes untreated, largely because it is hard to recognize the illness or notice the patterns, blaming the symptoms on flu, stress, lack of sleep, or poor diet. If left untreated, depression could eventually lead to suicide. The rate of suicide per 100 000 inhabitants in 2001 was four times higher in Lithuania than in other European Union countries.

Moreover, depression is more common among women than men. Antidepressant drugs (ADs) are effective across the full range of severity of major depressive episodes (1). In many developed countries, the number of prescriptions for antidepressants increased steeply during the 1990s, after the introduction of selective serotonin reuptake inhibitors (SSRIs) (1–4). In some countries, the increased rate of prescribing coincided with a fall in suicide rates (2–4).

Many studies show that the use of antidepressants continues to increase because of the increase in the use of new ADs following to a big proportion of all AD consumption (2–5). A part of antidepressant drugs

in Lithuania are fully or partly reimbursed. However, because of low prices of tricyclic antidepressants, which are dispensed with common prescriptions, only part of them is reimbursed. Still it is important to assess the proportion of the different groups of antidepressant drugs reimbursed in Lithuania.

In the study, we have not tried to determine the relationship between use rate of the antidepressants and suicide rate. Therefore, the aim of the present study was to evaluate the antidepressant prescribing patterns in all Lithuanian regions in two years (2003 and 2004), to analyze their use within different AD groups, to examine trends in age and gender specific antidepressant use, and to compare the results with the prescribing recommendations of AD given by the order of Ministry of Health.

Material and methods

Antidepressant prescription data were retrieved from Lithuanian Patient's Fund database. A total of 541 732 prescriptions for antidepressant drugs reimbursed in 10 counties of Lithuania (Alytus, Kaunas, Klaipėda, Marijampolė, Panevėžys, Šiauliai, Tauragė, Telšiai, Utena, and Vilnius) were collected between January 2003 and December 2004.

According to the WHO recommendations, antidepressant use was quantified in terms of defined daily doses (DDDs) when the DDD is the assumed average maintenance dose per day for antidepressants used for its main indication in adults. Data were calculated using Anatomic Therapeutic Chemical (ATC)/DDD methodology and expressed in DDDs per 1000 inhabitants per day (6). The obtained prescription data of patients' records included the information about patient's gender, age, and the place where prescription had been dispensed. The patients and the use of antidepressant were divided into subgroups in accordance with these aspects.

The data have been collected and processed using MS Excel software. The analysis did not include statistical significance, since the objective of the study was to estimate the antidepressant prescribing patterns in Lithuania only in two years (2003 and 2004) and to analyze the use within different subgroups of users, divided according to age, gender, region. The general objective of the study implies descriptive analysis rather than inferential. Moreover, the trends in antidepressant use can be due to external factors (such as Lithuania's entry to the European Union) rather than to drug-related or patient-related factors.

Classification of antidepressants. In this study, all prescribed antidepressants were classified into three

groups according to ATC classification specifying the DDD values (7):

1. Tricyclic antidepressants (TCAs): amitriptyline;
2. SSRIs: citalopram, sertraline, paroxetine, escitalopram;
3. Other antidepressants: mirtazapine, bupropion, tianeptine, venlafaxine, reboxetine.

As there are no medicinal products with monoamine oxidase inhibitors (MAOI) marketed in Lithuania, these products are not dispensed (8).

Results

The total use of reimbursed antidepressant drugs in Lithuania increased by 18.5% over the studied period (from 5.54 DDDs/1000 inhabitants per day in 2003 to 6.80 DDDs/1000 inhabitants per day in 2004). Although the population of Lithuania decreased by 0.52% (from 3 454 000 inhabitants in 2003 to 3 436 000 inhabitants in 2004), the number of patients treated with antidepressant drugs increased by 6.9% (from 52 146 to 56 029, respectively) as well as the number of the prescriptions by 13.7% (from 251 010 to 290 722, respectively) (9).

Fig. 1 shows the comparison of antidepressant prescribing patterns in different regions of Lithuania, where the regions with the highest use of ADS were Tauragė, Telšiai, and Marijampolė regions.

The highest rates of antidepressant use were observed in 40–59-year-old patients. SSRIs were the most used drugs in every age group and accounted for 70% of total AD use (Fig. 2 and 3). Fig. 2 illustrates how the prevalence of the use differed by age. The proportion of TCAs used increased with patient's age, while the proportion of other ADs used remained almost stable except ADs use by the patients younger than 20 years, as they mostly received SSRIs.

The results of our study show that women were prescribed antidepressants 3.6 times more frequently than men were. Moreover, the female proportion increased with age, especially after 70 years (Table).

Discussion

This is the first study providing information on prevalence of the use of antidepressants reimbursed in Lithuania during 2003–2004 as the data of previous years were not available because the data have been collected not in an electronic format, so it was almost impossible to prepare detailed statistical analysis of earlier years.

During the study period, the total use of reimbursed ADs increased by 18.5% due to marked overall increase of SSRI (by 16%) and other (newer) AD (by

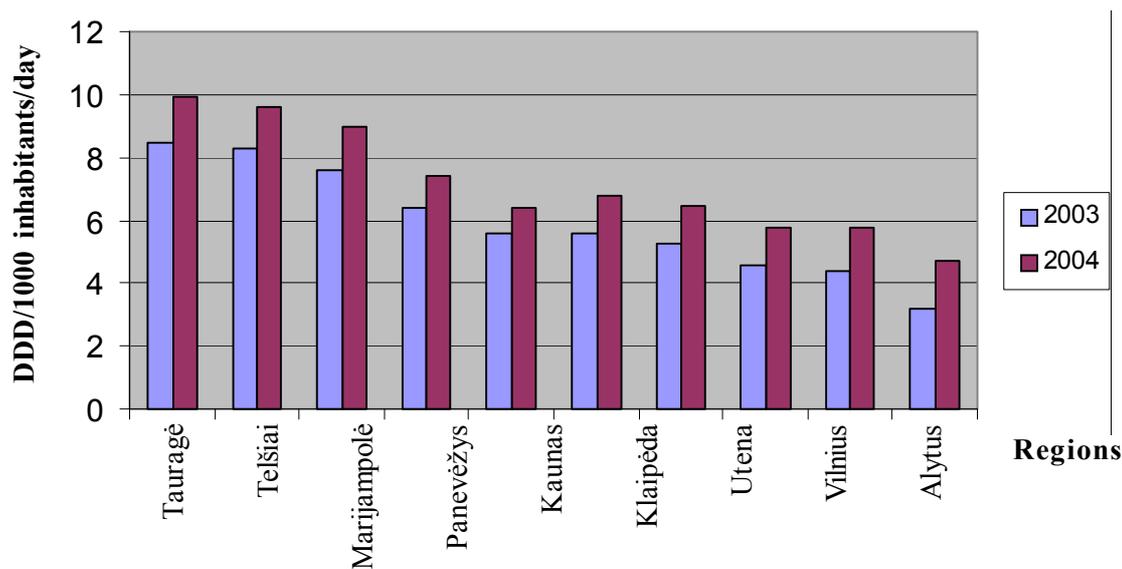


Fig. 1. Antidepressant prescribing patterns (expressed as DDD/1000 inhabitants per day) in different regions of Lithuania in 2003 and 2004

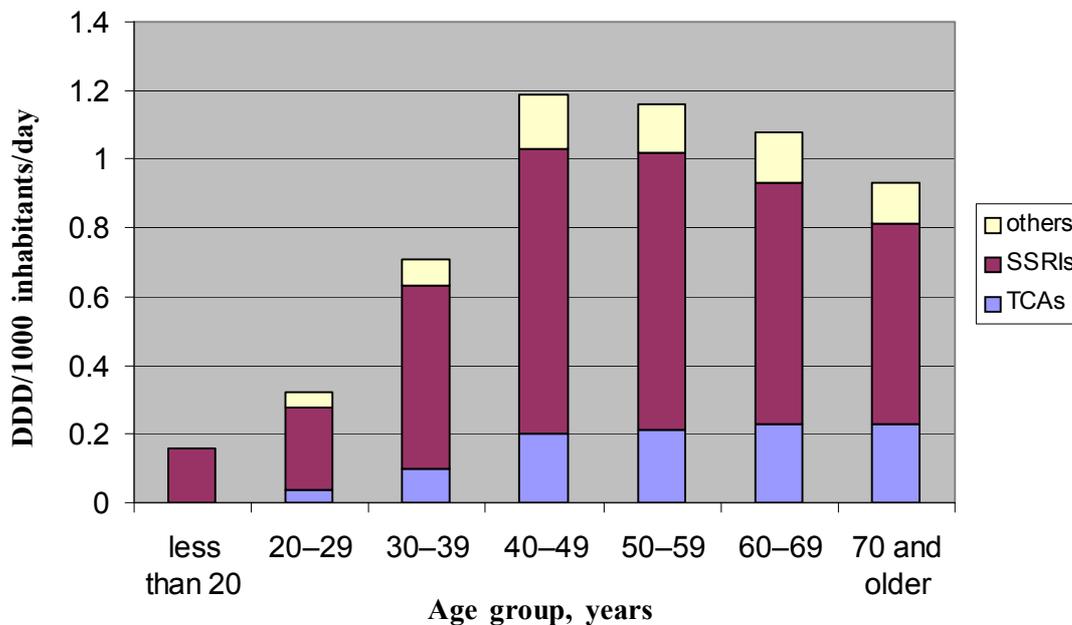


Fig. 2. Prevalence of the use of different antidepressant drugs by age groups in 2003
SSRIs – selective serotonin reuptake inhibitions; TCAs – tricyclic antidepressants.

44%) use. In SSRI group, sertraline was prescribed most commonly (which accounted for 40% and 45.5% of SSRIs for each year, respectively). In addition, similar studies in other countries reported the increased rates of SSRI use (10–13). Moreover, the total use of ADs in other countries is much higher than our results show in Lithuania. The lower prevalence of ADs use could be explained by the fact that ADs were prescribed only for the severe depression; however, ADs are also indicated in conditions other than depression: various states of anxiety, panic disorder, obsessive-compulsive disorder, posttraumatic disorder, bulimia. Furthermore,

general practitioners do not recognize some depressed people, and some patients with recognized depression do not receive adequate drug therapy (14). Underdiagnosis and undertreatment of major depression can be associated with factors relating to patients, their physicians, and the health care systems that provide their care (15). Hence, the prevalence of AD use for the treatment of depression may be less evaluated; also, the total rates of AD prescribing do not correspond to rates of depression and need further investigations to be done by analyzing the patients' medical records.

Following the low consumption of ADs, we have

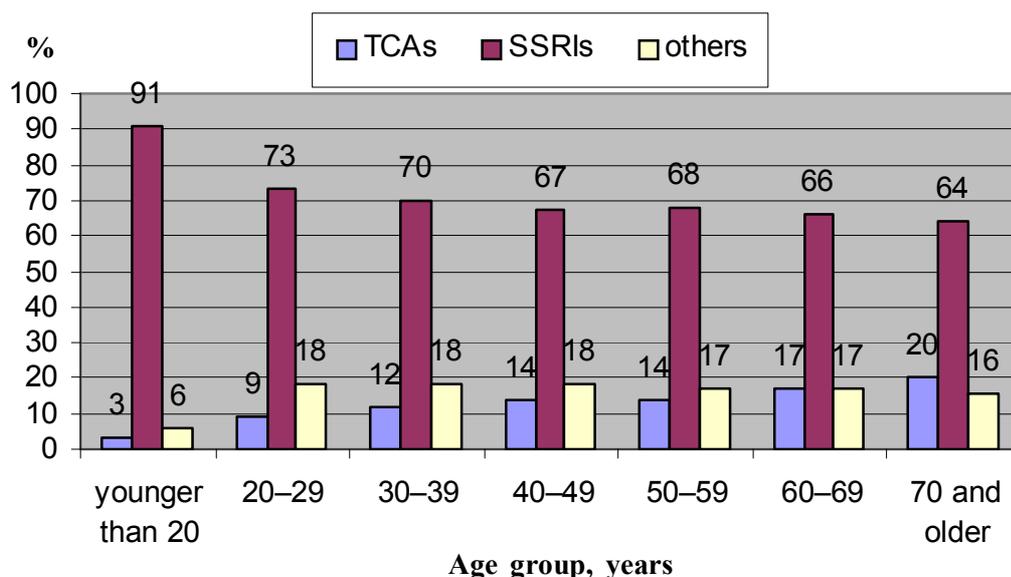


Fig. 3. The proportions of different antidepressant groups use in each age group in 2004
TCAs – tricyclic antidepressants; SSRIs – selective serotonin reuptake inhibitors.

Table. Yearly prevalence of antidepressant use by age and gender
(expressed as number of patients per 10 000 inhabitants)

Age group (years)	Females, n		Males, n		Total number		Female-to-male ratio	
	2003	2004	2003	2004	2003	2004	2003	2004
Younger than 20	40	49	25	28	65	78	1.6:1	1.7:1
20–29	72	82	33	36	105	119	2.2:1	2.3:1
30–39	162	178	50	53	212	231	3.3:1	3.4:1
40–49	254	281	69	73	323	355	3.7:1	3.8:1
50–59	263	297	68	72	331	369	3.9:1	4.1:1
60–69	283	311	71	73	354	384	4.0:1	4.3:1
70 and older	297	330	66	73	363	403	4.5:1	4.5:1
Total	1372	1530	382	409	1753	1939	3.6:1	3.7:1

collected only prescriptions of drugs reimbursed by the Lithuanian Patient's Fund; part of the drugs that were dispensed with ordinary prescriptions was not included in the study. Therefore, considering the low price of TCAs, a big part of these ADs was supposed to have been dispensed without reimbursement. However, in accordance with the recommendation of depression treatment and the priority of AD selection in Lithuania, the drug of choice for the treatment of depression should be amitriptyline unless tricyclic antidepressants are contraindicated in a patient and/or his/her age is under 18 years or more than 65 years (16). In view of the big proportion of SSRI drugs, the use of ADs was not consistent with recommendations for the treatment of depression in Lithuania. According

to Italian researchers, if the restriction of first-choice drugs were revoked, the use of antidepressants would change, resulting in the higher prescribing rates for SSRI and newer AD group (17).

Due to high toxicity of TCAs, these antidepressants are used less frequently and for shorter period than recommended (18–20). However, SSRIs are not proven to be as effective as TCAs in hospitalized patients (21). Several meta-analysis studies reported little difference in efficacy among the different classes of antidepressants (22, 23); the prescribing rates for SSRIs were the highest as these drugs are better tolerated with significantly lower rates of treatment discontinuations overall and due to fewer side effects (24, 25).

As it is shown in Fig. 1, the highest prevalence of AD use is in the west regions of Lithuania (Tauragė, Telšiai, Marijampolė counties), which do not include either city with high population or more health care institutions than other regions. In the study by Tansella and Micciolo, no correlation was found between consumption rate and population density (26). Other study showed that depressive disorders concentrated in city areas, which were centrally located and were characterized by high population density (27). However, our study demonstrated that higher population density was not related to higher AD use, as the use of ADs was not highest in the regions with the highest population (Vilnius, Kaunas, Klaipėda counties). Table shows gender-related differences in the use of ADs. These data are consistent with higher prevalence of depression in females (28–30). However, our study showed the significant difference in the rates of AD use between females and males. The difference was extremely high comparing the groups of patients older than 70 years (by 4.5 times). However, women do not experience more mental illnesses than men; they are simply more prone to depression and anxiety, whereas men are more likely to have addictive disorders and personality disorders (31). The effects of stress, violence, poverty, inequality, sexism, care giving, relational problems, low self-esteem, and ruminative cognitive styles probably increase vulnerability to depression in women (32). Predictive factors for depression include previous depression, feeling out of control or overwhelmed, chronic health problems, traumatic events in childhood or young adulthood, lack of emotional support, lone parenthood, and low sense of mastery (31, 33). Special considerations are required for analyzing the risk factors influencing the women's physical health.

The results in Fig. 2 show that the highest use of ADs was among patients aged 40 to 59 years. In 2004, the proportion of consumed TCA was lowest in patients under 20 years (3%) and highest in ones aged more than 70 years (20%). This finding is not consistent with higher prevalence of conditions that increase risk of TCA toxicity in elderly, including hypertrophy of

prostate, angle-closure glaucoma, and coronary heart disease. As it is reported, the diagnosis of mood disorders in adolescents is problematical due to the increased risk of suicide and substance abuse in young people (34). Furthermore, the difficulties in diagnosing depression especially among elderly may have doubts about the appropriateness of drug therapy.

Some limitations of this study must be acknowledged. The same patient could be included in more than one group if he/she had received combination therapy or the treatment had changed and drug of different group had been prescribed. Moreover, some patients took their drugs in different regions of Lithuania over the studied period, and we could underestimate the prevalence of AD use.

Conclusions

The results of our study show an increase in the use of reimbursed antidepressants except tricyclic antidepressants in 2004 as compared to 2003. Increased use of selective serotonin reuptake inhibitors and other nontricyclic antidepressants is probably related to their better tolerability, improved risk-benefit ratio, and less toxicity in overdose. Surprisingly, there is no increase in the percentage of consumed selective serotonin reuptake inhibitors in elderly patients when compared with younger ones, despite elderly patients are most likely to benefit from reduced sedation, less antimuscarinic and less cardiac toxicity of selective serotonin reuptake inhibitors. This may be due to insufficient consideration of disease-related factors by Lithuanian physicians when choosing antidepressant. The prevalence of the antidepressant use is highest among middle-aged (40–59 years) people, while the young (under 20) and elderly (older than 70) patients receive mostly selective serotonin reuptake inhibitors. As there are no medicinal products with monoamine oxidase inhibitors marketed in Lithuania, these products are not dispensed. Additional studies should be carried out in order to assess drug-prescribing patterns in accordance with the guidelines of depression treatment in Lithuania considering diagnosis, dosage, and duration of treatment.

Antidepresantų išrašymo tendencijos Lietuvoje 2003–2004 metais analizė

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Raktažodžiai: antidepresantų vartojimas, nustatytos dienos dozės, depresija.

Santrauka. Depresija yra viena dažniausių nedarbingumo priežasčių pasaulyje. Šia liga serga apie 121 milijonas žmonių. Daugelyje išsivysčiusių pasaulio šalių antidepressantų skyrimas labai padidėjo nuo 1990 metų.

Tyrimo tikslas. Įvertinti antidepressantų skyrimo tendencijas visuose Lietuvos regionuose 2003–2004 metais, išanalizuoti skirtingų antidepressantų grupių suvartojimą ir išnagrinėti antidepressantų vartojimo pagal amžių bei lytį tendencijas. Antidepressantai klasifikuojami į tris grupes pagal anatominę, terapinę, cheminę (ATC) klasifikaciją nurodant nustatytas dienos dozes. Tyrimo duomenimis, kompensuojamųjų antidepressantų, išskyrus triciklius, vartojimas 2004 metais padidėjo palyginti su 2003 metais. Selektyvūs serotonino receptorių inhibitoriai ir kitų netriciklių antidepressantų vartojimo padidėjimas gali būti susijęs su geresniu jų toleravimu, geresniu rizikos ir naudos santykiu bei mažesniu toksiškumu perdozavus. Senyvo amžiaus žmonių, vartojusių selektyvius serotonino receptorių inhibitorius, procentinio padidėjimo nebuvo palyginus su jaunais žmonėmis, nepaisant to, kad senyvo amžiaus pacientams galima didesnė nauda dėl mažesnės šių vaistų sedacijos, mažesnio antimuskulinio poveikio ir mažesnio kardiotoksiškumo. Antidepressantų vartojimo paplitimas didžiausias tarp vidutinio (40–59 metų) amžiaus žmonių, o jauni (iki 20 metų) ir senyvo amžiaus (per 70 metų) pacientai dažniausiai vartoja selektyvius serotonino receptorių inhibitorius. Turėtų būti atliekami papildomi tyrimai, siekiant nustatyti vaistų išrašymo modelius pagal depresijos gydymo Lietuvoje rekomendacijas atsižvelgiant į diagnozę, dozę bei gydymo trukmę.

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References

1. The World Health Report, 2001. Mental Health: New understanding, new hope. Available from: URL: http://www.who.int/whr/2001/en/whr01_en.pdf
2. Rosholm JU, Andersen M, Gram LF. Are there differences in the use of selective serotonin reuptake inhibitors and tricyclic antidepressants? A prescription database study. *Eur J Clin Pharmacol* 2001;56(12):923-9.
3. Balestrieri M, Bragagnoli N, Bellantuono C. Antidepressant drug prescribing in general practice: a 6-year study. *J Affect Disord* 1991;21(1):45-55.
4. Rosholm JU, Gram LF, Isacson G, Hallas J, Bergman U. Changes in the pattern of antidepressant use upon the introduction of the new antidepressants: a prescription database study. *Eur J Clin Pharmacol* 1997;52(3):205-9.
5. Isacson G, Boethius G, Henriksson S, Jones JK, Bergman U. Selective serotonin reuptake inhibitors have broadened the utilisation of antidepressant treatment in accordance with recommendations. Findings from a Swedish prescription database. *J Affect Disord* 1999;53(1):15-22.
6. WHO International Working Group for Drug Statistics Methodology. Introduction to drug utilization research. Available from: URL: <http://www.who.int/medicines/library/qsm/IDUR.pdf>
7. WHO Collaborating Centre of Drug Statistics Methodology. ATC/DDD version January, 2005. Available from: URL: <http://www.whooc.no/atcddd/>
8. Sveikata A, Mickis A. Naujieji antidepressantai ir jų veikimo būdai. (New antidepressants: mechanisms of action.) *Medicina (Kaunas)* 2001;37(3):1087-91.
9. Data of the State Statistics Department. Available from: URL: <http://www.std.lt>
10. McManus P, Mant A, Mitchell PB, Montgomery WS, Marley J, Auland ME. Recent trends in the use of antidepressant drugs in Australia, 1990–1998. *Med J Aust* 2000;173(9):458-61.
11. Poluzzi E, Motola D, Silvani C, De Ponti F, Vaccheri A, Montanaro N. Prescriptions of antidepressants in primary care in Italy: pattern of use after admission of selective serotonin reuptake inhibitors for reimbursement. *Eur J Clin Pharmacol* 2004;59(11):825-31.
12. Mant A, Rendle VA, Hall WD, Mitchell PB, Montgomery WS, McManus PR, et al. Making new choices about antidepressants in Australia: the long view 1975–2002. *Med J Aust* 2004;181(7 Suppl):S21-4.
13. Soos G, Viola R, Csukonyi K, Nagy G. Comparison the in- and outpatient's utilization of antidepressants. 33rd European Symposium on Clinical Pharmacy, 2004.
14. McManus P, Mant A, Mitchell PB, Montgomery WS, Marley J, Auland ME. Recent trends in the use of antidepressant drugs in Australia, 1990–1998. *Med J Aust* 2000;173(9):458-61.
15. Davidson JR, Meltzer-Brody SE. The underrecognition and undertreatment of depression: what is the breadth and depth of the problem? *J Clin Psychiatry* 1999;60 Suppl 7:4-9.
16. The order of Minister of Health Care Ministry of the Republic of Lithuania, No V-570 (Aug 11, 2004). *Valstybės žinios* 2004;128:4617.
17. Poluzzi E, Motola D, Silvani C, De Ponti F, Vaccheri A, Montanaro N. Prescriptions of antidepressants in primary care in Italy: pattern of use after admission of selective serotonin reuptake inhibitors for reimbursement. *Eur J Clin Pharmacol* 2004;59(11):825-31.
18. Lawrenson RA, Tyrer F, Newson RB, Farmer RD. The treatment of depression in UK general practice: selective serotonin reuptake inhibitors and tricyclic antidepressants compared. *J Affect Disord* 2000;59(2):149-57.
19. MacDonald TM, McMahon AD, Reid IC, Fenton GW, McDervitt DG. Antidepressant drug use in primary care: a record linkage study in Tayside, Scotland. *BMJ* 1996;313(7061):860-1.
20. Donoghue J, Tylee A, Wildgust H. Cross sectional database analysis of antidepressant prescribing in general practice in the United Kingdom, 1993–1995. *BMJ* 1996;313(7061):861-2.
21. Anderson IM. SSRIS versus tricyclic antidepressants in depressed inpatients: a meta-analysis of efficacy and tolerability. *Depress Anxiety* 1998;7 Suppl 1:11-7.
22. Montgomery SA, Henry J, McDonald G, Dinan T, Lader M, Hindmarch I, et al. Selective serotonin reuptake inhibitors: meta-analysis of discontinuation rates. *Int Clin Psychophar-*

- macol 1994;9(1):47-53.
23. Song F, Freemantle N, Sheldon TA, House A, Watson P, Long A, et al. Selective serotonin reuptake inhibitors: meta-analysis of efficacy and acceptability. *BMJ* 1993;306(6879):683-7.
 24. Martin RM, Hilton SR, Kerry SM, Richards NM. General practitioners' perceptions of the tolerability of antidepressant drugs: a comparison of selective serotonin reuptake inhibitors and tricyclic antidepressants. *BMJ* 1997;314(7081):646-51.
 25. Ferguson JM. SSRI Antidepressant medications: adverse effects and tolerability. *Prim Care Companion J Clin Psychiatr* 2001;3(1):22-7.
 26. Tansella M, Micciolo R. Trends in the prescription of antidepressants in urban and rural general practices. *J Affect Disord* 1992;24(2):117-25.
 27. Maylath E, Weyerer S, Hafner H. Spatial concentration of the incidence of treated psychiatric disorders in Mannheim. *Acta Psychiatr Scand* 1989;80(6):650-6.
 28. Stewart DE, Gucciardi E, Grace SL. Depression. *BMC Womens Health* 2004;4 Suppl 1:S19.
 29. Lawrenson RA, Tyrer F, Newson RB, Farmer RD. The treatment of depression in UK general practice: selective serotonin reuptake inhibitors and tricyclic antidepressants compared. *J Affect Disord* 2000;59(2):149-57.
 30. Poluzzi E, Motola D, Silvani C, De Ponti F, Vaccheri A, Montanaro N. Prescriptions of antidepressants in primary care in Italy: pattern of use after admission of selective serotonin reuptake inhibitors for reimbursement. *Eur J Clin Pharmacol* 2004;59(11):825-31.
 31. Stewart DE, Rondon M, Damiani G, Honikman J. International psychosocial and systematic issues in women's mental health. *Arch Women's Mental Health* 2001;4:13-7.
 32. Mazure CM, Keita GP, Blehar MC. Summit on women and depression: proceedings and recommendations. Washington, DC: American Psychological Association 2002. Available from: URL: <http://www.apa.org/pi/wpo/women&depression.pdf>
 33. Danilevičiūtė V, Sveikata A. Šiuolaikinis požiūris į farmakologines ir kliniškes naujų antidepressantų savybes. (Contemporary approach to pharmacological and clinical aspects of novel antidepressants.) *Medicina (Kaunas)* 2002;38(12):1147-56.
 34. Carta MG, Altamura AC, Hardoy MC, Pinna F, Medda S, Dell'Osso L, et al. Is recurrent brief depression an expression of mood spectrum disorders in young people? Results of a large community sample. *Eur Arch Psychiatry Clin Neurosci* 2003;253(3):149-53.

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