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Factors influencing the choice of antidepressants: a study of antidepressant prescribing practice at University Psychiatric Clinic in Belgrade

Faktori koji utiču na izbor antidepresiva: analiza propisivanja na Univerzitetskoj psihijatrijskoj klinici u Beogradu

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Abstract

Background/Aim. Antidepressants are a widely used class of drugs. The aim of this study was to investigate different aspects of antidepressant prescribing practice at University Psychiatric Clinic in Belgrade. **Methods.** This cross-sectional study was carried out by retrospective analysis of the patient's medical charts. The study included all patients with antidepressant prescribed at discharge during 2009 (n = 296). The evaluation was focused on patient-related factors (socio-demographic and illness related), psychiatrist-related factors (sex and duration of working experience) and drug related factors (type of antidepressant, dose, polypharmacy and reimbursement by national health insurance). **Results.** Antidepressants were prescribed for unipolar depression (F32-34, ICD X) either without comorbidity (46.2%) or with comorbidity (24.7%), mostly as a monotherapy (91% had one antidepressant), to the patients who were 65% female, aged 50.1 ± 8.9, most of them with 12 years of education (52.6%), married (69.3%) and employed (55.9%). The majority of patients had a history of two hospitalizations (Med 2; 25th–75th perc. 1–4) during nine years (Med 9; 25th–75th perc. 2–15) after the first episode of depression. Among them, 19% were found to be suicidal in a lifetime. The single most prescribed antidepressant was sertraline (20.4%), followed by fluoxetine (13.3%) and maprotiline (11.7%). Utilization of antidepressants was positively correlated with the rate of reimbursement ($p < 0.01$). The most prescribed antidepressant group was selective serotonin reuptake inhibitors (SSRI) (47.8%), followed by tricyclic antidepresants (TCA) (25.3%) and new antidepressants – venlafaxine, tianeptine, mirtazapine, bupropion, trazodone (15.1%). Most of the drugs were prescribed in doses which are at the lower end of the recommended dose-range. Regarding severity of the actual depressive episode, TCA were prescribed for severe depression with psychotic features, while SSRI were choice for episodes with moderate symptom severity ($p = 0.01$). Psychiatrists with longer working age (20–30 years) hesitated to prescribe new antidepressants in comparison to younger colleagues ($p = 0.01$). **Conclusion.** Economic issues in Serbia as developing country influence the choice of antidepressants, as well as a psychiatrist's working age and severity of depression. However, SSRI are the drugs of the first choice, as it was shown in most of the developed countries nowadays.

Key words:
antidepressive agents; drug prescriptions; patients; physicians; pharmaceutical preparations.

Apstrakt

Uvod/Cilj. Antidepresivi (AD) su vrsta lekova koji se široko koriste u lečenju. Cilj rada bio je analiza propisivanja AD i faktora koji utiču na izbor leka. **Metode.** Retrospektivnom studijom obuhvaćeni su svi bolesnici sa propisanim AD na otpustu sa hospitalnog lečenja u Univerzitetskoj klinici u Beogradu tokom 2009. godine (n = 296). Analizirani su faktori koji se tiču bolesnika (sociodemografski podaci, istorija bolesti), psihijatra (pol i godine staža) i samog leka (vrsta, doziranje, polifarmacija, pozicija na listi lekova koji se izdaju na teret zdravstvenog osiguranja). **Rezultati.** Antidepresivi su bili najčešće propisivani za lečenje unipolarne depresije (70,9%), bez komorbiditeta (kod 46,2% bolesnika) ili sa komorbiditetom (2,7%), uglavnom kao monoterapija (≥ 2 AD kod 9%), bolesnicima koji su u 65% slučajeva bili ženskog pola, starosti 50,1 ± 8,9 godina, u proseku sa 12 godina obrazovanja (52,6%), u braku (69,3%) i u statusu zaposlenih (55,9%). Većina bolesnika bila je dva puta hospitalizovana (Med 2; Q1-Q3 1–4) u periodu od devet godina (Med 9; Q1-Q3 2–15) nakon prve epizode depresije. Ukupno 19% bolesnika bilo je suicidno do tada. Najpropisivaniji AD bili su sertralin

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(20,4%), fluoksetin (13,3%) i maprotilin (11,7%). Učestalost propisivanja korelisala je pozitivno sa pozicijom na listi lekova koji se izdaju na teret osiguranja ($p < 0.01$). Selektivni inhibitori preuzimanja serotonina (SSRI) bili su prepisani kod 47,8% bolesnika, triciklični antidepresivi (TCA) kod 25,3%, a „novi" AD (venlafaksin, tianeptin, mirtazapin, bupropion, trazodon) kod 15,1% bolesnika. Većina lekova propisivana je u najnižoj preporučenoj dozi. Kod psihotične depresije TCA su bili značajno češće prepisivani, dok su SSRI bili lekovi izbora kod umereno teške simptomatologije ($p = 0.01$). Psihijatri sa dužim radnim stažom (20–30 godina) ređe su propisivali "nove" AD ($p = 0.01$). **Zaključak.** Ekonomski faktori, dužina radnog staža psihijatra i težina depresivne epizode su faktori koji su uticali na izbor AD kod ispitivanih bolesnika. Podatak da se SSRI koriste najviše u skladu je sa praksom većine razvijenih zemalja.

Ključne reči:
antidepresivi; lekovi, propisivanje; bolesnici; lekari; lekovi.

Introduction

The use of antidepressants (ADs) has been steadily increasing during the last decade [1, 2]. Drugs from this group act predominantly on serotonergic and/or noradrenergic transmission and reduce a spectrum of symptoms – from affective and will-instinctive to cognitive psychopathology.

Following history of development of ADs, it is evident that tricyclic ADs (TCA) such as amitriptiline, clomipramine, maprotiline were the most significant drugs in the treatment of depression from the early sixties to the late nineties all over the world. Later on, the emphasis was on synthesis and the application of selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine, sertraline, paroxetine, citalopram and escitalopram, whose indications are wider [3].

In the last fifteen years the group of ADs has been rapidly enlarged, so that in contrast to the former relatively small number of available drugs, today we are disposed to a large number of ADs. New ADs include a few groups of drugs: selective antagonist reuptake inhibitors (SARIs) (trazodone), noradrenaline dopamine reuptake inhibitors (NDRIs) (bupropion), serotonin noradrenaline reuptake inhibitors (SNRIs) (venlafaxine), noradrenergic and specific serotonergic antidepressants (NaSSAs) (mirtazapine).

Each new generation and class of ADs was expected to have better tolerability, greater safety and preserved efficacy. SSRIs proved to be minimally cardiotoxic in comparison to TCA, more suitable for geriatric population and with favourable dosage profile (autointoxication with TCA frequently appeared in the treatment of depression [4], while the latest ADs were characterised with better initial tolerability, in relation to SSRIs, as well as reduced frequency of side effects). New ADs have been accepted as a chance for theraporesistent cases, as well as for cases where given AD proved to be inefficient.

Enlarged group of ADs is undoubtedly an advantage for clinicians, but with the widen range the choice of the medicine is somehow complicated. Algorithms are an example of the attempt to include a certain coordination in the process of decision making, but it is worth mentioning that in the recently published study by Divac et al. [5] it was shown that only 41.5% of doctors at the University Psychiatric Clinics in Belgrade follow the therapeutic guidelines, published in 2004 [6]. The introduction of the therapeutic guidelines in Serbia is in progress. The legal aspects of its implementation will be carefully considered and regulated.

Even in the countries in which therapeutic guidelines were in use for several decades, there were a number of factors independent of the algorithms themselves to play a role in the choice of ADs[7]. The study [8] published in USA showed that the choice of drug was associated mostly with the type of clinical symptoms and with its side effects profile, while the price and the influence of a visiting representative of a drug manufacturer influenced the drug choice in lesser amount [8.] . On the other hand, psychiatrists from Asia considered demographic factors (patient's age, hospital addmission type) as more important for drug choice than the clinical symptoms [9]. Finally, the choice of AD in Europe [10] was associated with doctor's characteristics (age, specialization), as well as with the factors related to the patient (severity of depression, age, education, the existence of comorbidity).

By searching the literature, we noticed that there were no studies on AD prescription practice in Serbia so far, except a publication from Vojvodina written by Lisulov and Nedic [11] that analyzed practice of general practitioners (primary health care). Therefore, the aim of this study was to analyze prescribing of ADs at the University Psychiatric Clinic in Belgrade and to evaluate which ADs were most frequently used in relation to three types of factors: patient-related factors (sociodemographic and illness related), psychiatrist-related factors (sex and duration of working experience), and drug related factors (type of AD, dose, polypharmacy and reimbursement by health insurance).

Methods

This pharmacoepidemiological cross-sectional study was carried out by retrospective analysis of the patient's medical charts. Analyses included medical documentation of all subjects treated at the Clinic for Psychiatry, Clinical Centre of Serbia, Belgrade (in-patients and day-hospital patients) from January to September 2009 with ADs prescribed at discharge, regardless of the diagnosis.

Following medical chart data were considered: ADs and all other prescribed drugs, ADs daily dose, diagnosis, sex, age, marital status (married, single, divorced, widower), education (less than 12 years of education, more than 12 years of education), employment (employed, unemployed, pensioner, student), duration of the disease, number of hospitalizations and suicidal attempts in patient's history. In parallel, we noted the sex and working experience of psychiatrist who prescribed ADs (a total of 24 doctors; six had less than 10 years of serv-

ice, 11 had 10–19 years of service and 7 had more than 20 years of service). Finally, we considered economic factor by analyzing percentage of every AD refunded by health-insurance (The List of Drugs Prescribed and Issued at the Expense of the Obligatory Health Service – "positive list"; the source was "Official Gazzete of the Republic of Serbia", published in October 2009).

After all charts review, number of patients with at least one AD prescribed at discharge (from January to September 2009) was 296.

For some further analyses, ADs were grouped in the following way: TCAs (amitriptiline, clomipramine, maprotiline); SSRIs (fluoxetine, paroxetine, sertraline and escitalopram); new and the other ADs (venlafaxine, trazodone, mirtazapine, burpopion, tianeptine).

Furthermore, we examined the association of AD prescription with spectrum of diagnostic categories from ICD X.

Statistical analysis included parametric and non-parametric descriptive statistics, depending on the nature of data (arithmetic environment and standard deviation, mediana and inter-qwoter scope, relative frequency). Further analysis included inferential statistics methods (unifactoral analysis of variants, Students' *t* - test, Mann - Whitney's *U*-test, Pearson's, χ^2- test of indepedence, Spearman's rank correlation). Data analysis was performed by PASW Statistics18 (SPSS Inc. Chicago, IL).

Results

The choice of ADs at the University Psychiatric Clinic in Belgrade included SSRIs in 47.8% cases, TCAs in 25.3% cases and new ADs in 15.1.3% cases. ADs were prescribed to the patients with the following International Classification of Diseases (ICD) X diagnoses: unipolar depression (F 32–34) without comorbidity (46.2%) and with comorbidity (24.7%); organic mental disorder (8.7%); anxiety disorders (8.0%); psychotic disorders (7.4%); bipolar disorders (3.7%) and the other diagnoses (personality disorder and psychoactive substances abuse, 1.3%) (Figure 1).

Patients with unipolar depression (n = 137) were 50.1 ± 8.9 years old, 65% females, with high school degree in 52.6%. The first episode of depression occurred 9 years prior

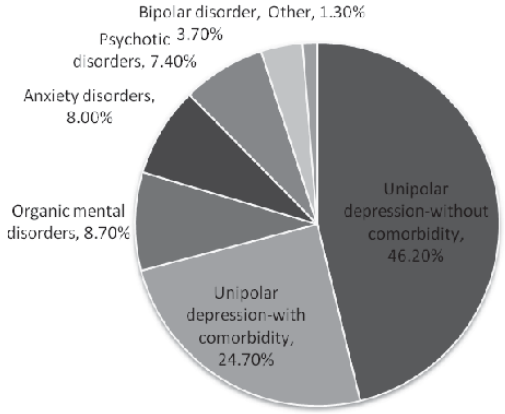

Fig. 1 – Antidepressants in different diagnostic categories – The International Classification of Diseases (ICD) X

to the current (2–15 years); the average number of hospitalizations was 2 (1–4). Patients with the other diagnoses were similar to the unipolar depression group in terms of sociodemographic and clinical parameters (47.6 ± 10.9 years of age, $p = 0.07$; females 56%, $p = 0.11$; high school 54.1%, $p = 0.96$; first diagnosis 8 years prior to the current study (3–16 years), $p = 0.70$; the number of hospitalizations 2 (1–4), $p = 0.10$)). However, the unipolar depression group was significantly different in terms of the two sociodemographic parameters: marital status (more married patients with unipolar depression, $p = 0.03$) and employment (more patients with unipolar depression were employed, $p = 0.01$), compared to the other diagnostic groups.

The frequency of the prescribed ADs is shown in Figure 2. Three most frequently prescribed ADs in monotherapy were: sertraline (20.4%), fluoxetine (13.3%) and maprotiline (11.7%).

At the same time, the most frequently prescribed groups of ADs were: SSRIs (47.8%), followed by TCAs (25.3%) and new antidepressants (15.1%).

In unipolar depression without comorbidity, one AD was prescribed in 91%, while in all other cases there were maximum of two ADs combined. The most frequently used combination of two ADs was maprotiline-clomipramine (in 33% patients). The applied dosages of ADs are shown in Table 1 (the range of recommended doses was added from the official textbook [12]).

Table 1

Antidepressant daily doses (in miligrams)

Drug	Median (mg)	25–75 percentile (mg)	Recommendations [13] (mg)
Amitriptiline	75	25–100	75–300
Clomipramine	75	50–100	75–300
Maprotiline	50	25–75	50–150
Fluoxetine	20	20–20	10–20–80
Paroxetine	20	20–40	20–60
Sertraline	50	50–100	50–200
Escitalopram	10	10–15	10–20–40
Venlafaxine	150	150–225	75–225
Mirtazapine	30	22.5–30	15–45
Moclobemide	300	300–300	150–600
Mianserine	30	30–30	30–150
Trazodone	75	50–125	150–600
Tianeptine	37.5	37.5–37.5	25–50

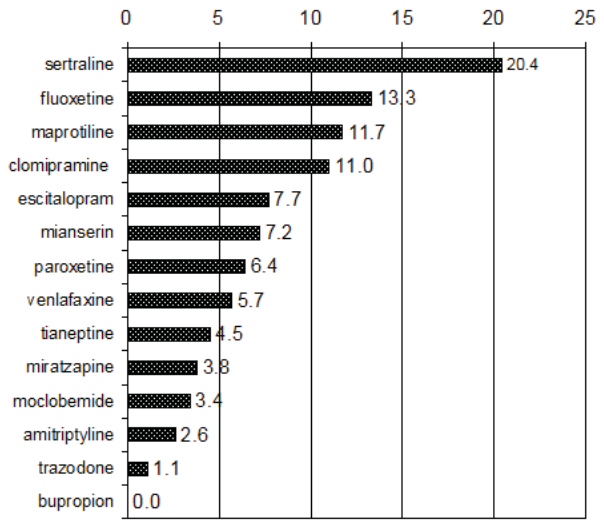

Fig. 2 – The frequency of prescribing a single antidepressant

Analysis of associations between ADs choice and the three groups of factors related to the patient, doctor and the drug, respectively showed that the three factors affected the choice of ADs in our sample of patients with unipolar depression. The first, ADs choice was associated with the severity of the actual depressive episode ($p = 0.02$); the second, economic factor had a significant effect on ADs choice (psychiatrists mostly prescribed ADs refunded in 75%-100% by the National Health Insurance, $p < 0.01$); the third, the physician's years of experience influenced significantly the choice of ADs (i.e. the doctors with more than 20 years in psychiatry were hesitating to prescribe new antidepressants; $p = 0.01$) (Figure 3).

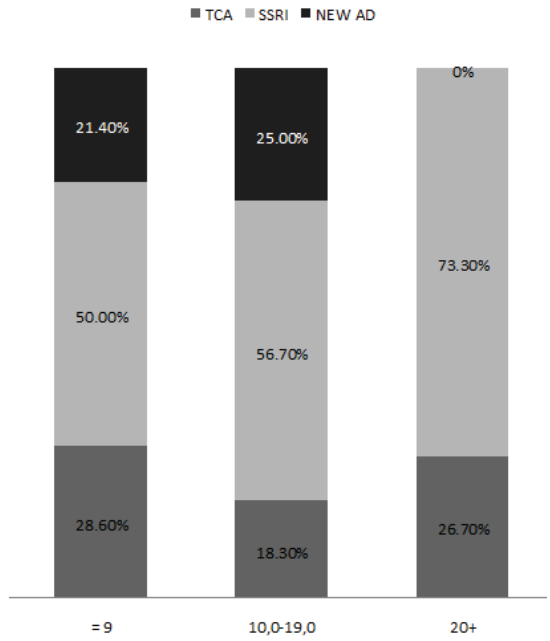

Fig. 3 – Groups of antidepressants (AD) and the frequency of prescription in relation to the psychiatrist's years of practice.

TCA – tricyclic antidepressants; SSRI – selective serotonin reuptake inhibitors

For severe depressive episodes with psychotic symptoms, TCA (60.0%) were ADs of choice, while in 73.3 % patients with moderate depression SSRI were prescribed (Figure 4). Patients' sex ($p = 0.08$), age ($p = 0.29$), employment ($p = 0.71$), duration of the illness ($p = 0.72$), suicidal attempts during the patient's history ($p = 0.89$), as well as the physician's sex ($p = 0.89$) were not associated with the choice of ADs.

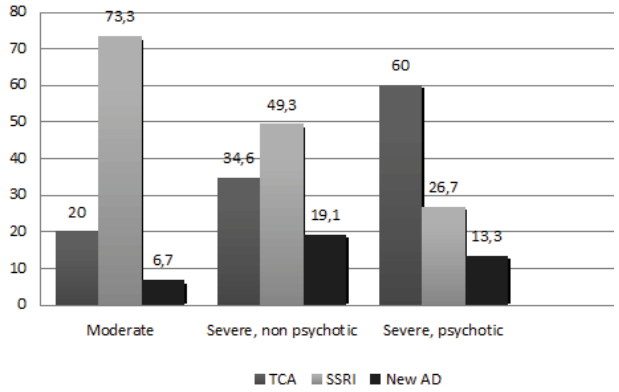

Fig. 4 – The use of antidepressants (AD) in relation to severity of depressive episode

TCA – tricyclic antidepressants; SSRI – selective serotonin reuptake inhibitors

Discussion

The current study showed that ADs were predominately prescribed to the patients diagnosed with unipolar depression, with or without comorbidity, Most frequently prescribed ADs were those from the group of SSRIs. The prescriptions combining two ADs were rare; however, when such combinations were prescribed the doses were moderate to lower in comparison to the recommended dosages. TCA ADs were most often recommended fo patients with major depression with psychotic symptoms, while SSRI were predominantly prescribed for nonpsychotic episodes of depression. In addition to the symptom profile, the most important factors in deciding which drugs to prescribe were also the position of a drug on the positive list, as well as the years of experience of the attending physician.

The results of our study are significant because they delineate the prescribing practice of the University Clinic, the major undergraduate and graduate educational institution, with the highest impact on education and training of psychopharmacologists in the country. It should be noted that the Clinic for Psychiatry experts published Guidelines for the treatment of depression in 2004 [6] as well as two editions of the textbook entitled "Antidepressants" in 2000 and 2006, respectively [12, 13], which have considerably facilitated improvement of psychiatry clinical practice in the country. Nevertheless, the current study showed that the physicians with many years of experience hesitate to prescribe new ADs. It would be of interest to investigate whether the physicians with more than 20 years of service do not prescribe new ADs due to poor experience or because they are satis-

fied with the efficacy of the older generation of drugs and have no need to widen the range. Further studies are needed to answer these questions given that the existing literature does not offer sufficient data to address this issue. Available limited data only indicate that physicians with more years of experience rarely prescribe SSRIs as their first choice of ADs; however, the years of experience have no effect on decision to prescribe new ADs (SNRIs), with an interesting result concerning the gender of the physicians [10]. Namely, the Bauer's et al. [10] study, which involved physicians from several Western European countries, showed that female physicians more often prescribe newer ADs from SNRI group than TCAs, but the authors were unable to explain such findings. The effect of the physician's or the patient's gender on the selection of ADs has not been detected in this country, although there are studies which show that SSRI drugs would be the choice of women in the generative period [14].

The most frequently prescribed ADs in our country are sertraline, fluoxetine, maprotiline and clomipramine. All four of these ADs are on the list of prescription medicine and are covered by the Obligatory Healthcare Coverage without any patient's financial obligation. Similar results were shown in a comprehensive study conducted in the Serbian Autonomic Province of Vojvodina in 2006, which showed that fluoxetine was most frequently prescribed AD and that there is a connection between the prescribing frequency and the reimbursement obtained[11]. More specifically, the fact that the coverage for the drugs from the positive list (e.g. maprotiline, clomipramine and mianserine) only extended to the obligatory participation had a considerable effect on the frequency of prescribing Ads, in general, as well as ADs from the SSRI group (e.g., sertaline, fluoxetine) for which, at the time the study, there was 10%–50% drug price reduction [11].

The effect of drug costs on the treatment choice is to be expected and was well documented in developing countries. A 2004 study by Simon et al. [15] showed that the cost of drugs in St. Petersburg hindered the treatment in 75% of patients, while a similar problem was encountered by only 24% of patients in Barcelona, or 32% in Melburn. Due to a very strong effect of the economic factor and the fact that ADs are predetermined by being listed on the aforementioned positive list, the selection and the percentage of ADs used in the treatment of depression in our country differ from the practices in the European countries. For example, in Great Britain and France, SSRIs are used in about 80% of patients and SNRIs (newer ADs) in about 10% of cases, which nearly eliminated the use of TCAs. The situation is similar in Holland, Sweden and Switzerland, while Germany is an exception, where SSRIs are used in about 31.7% of patients, while TCAs in 26.5%.[10.] With respect to the practice in the rest of the world, a 2007 multicentric study showed that "newer ADs" (i.e., SSRIs and new ADs) are less often prescribed in Japan (49%), but considerably more often in Taiwan, Singapore and China (80–70%) [9]. Despite the above-described factors, there is an increase in the use of SSRIs and new ADs in this country compared to five years ago. More specifically, in some unpublished analyses from our clinic, based on a similar methodology applied to 168 patients who were treated during 2005, TCAs were the medications of choice in 48% patients with unipolar depression, SSRIs in 39%, and new ADs in 13% of patients, respectively.

Subsequently, over the course of the following four years, it became clear that the percentage of TCA used has considerably decreased; however, it is interesting that the ADs from this group were still significantly more often prescribed for major depression with psychotic symptoms than any other ADs. According to the latest Harvard guidelines, the recommended therapy for patients suffering from major depression with psychotic symptoms is electroconvulsive therapy (ECT), followed by either TCAs, or SSRIs in combination with an antipsychotic [16]. Because ECT is used only in treatment of resistant cases, it is clear that the use of TCAs is key and correct strategy for the reduction in the mentioned symptoms. However, it should be noted that TCAs should be avoided in suicidal patients as well as if simultaneous treatment by TCAs and cardiotoxic antipsychotic is applied, in which case the choice of ADs should be an SSRI.

The fact that the doses of the prescribed ADs vary in the range of moderate to lower, which is not affected by the economic factor (the drugs covered by the health insurance are also given in smaller doses) suggests that such a therapy may be inefficient. If we compare the prescribed dosages in our and the Western Europe countries, it may be concluded that our colleagues prescribe similar dosages. However, the dosages of certain ADs prescribed by psychiatrists are considerably different from those prescribed by general practitioners: psychiatrists prescribe higher doses of amitriptiline, sertraline and venlafaxine, while higher doses of trazodone are prescribed by general practitioners [10].

In an effort to counteract an inefficient treatment, or in order to reduce side effects, combinations of two ADs are used worldwide (e.g., in Austria 25%) more often than in case of our patients (9%). The recommended combinations of ADs include the following strategies[17]: serotonergic (SSRI with trazodone), noradrenergic (TCA with bupropion) or combined strategy (venlafaxin and mirtazapine; bupropion and SSRI), respectively. Therefore, it is unclear why in the current sample the majority of combined therapies included two TCA, which, it should be pointed out, may be very risky. Given that recommended combinations of ADs include new ADs, we believe that the physicians will gain necessary skills for the application of combinations of ADs as the result of rational psychopharmacotherapy with longer use and better availability of new drugs.

Conclusion

The current study showed that economic factors, psychiatrist's years of experience and the severity of depression are the major factors that significantly effect drug choice in a particular sample. The fact that SSRIs were most frequently prescribed ADs is consistent with the practice in the majority of developed countries. These results are important because they delineate the practice of the University Clinic, the major undergraduate and graduate educational institution, with the

highest impact on education and training of psychopharmacologists in the country. We suggest that methodologically similar studies need to be conducted at the national level as an important step prior to the official introduction of national algorithms.

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