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AVAILABILITY OF PSYCHIATRIC MEDICATIONS TO CROATIAN HEALTHCARE USERS AND THE INFLUENCE OF AVAILABILITY OF ATYPICAL ANTIPSYCHOTICS ON PSYCHIATRIC HOSPITAL MORBIDITY

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INTRODUCTION

In professional psychiatric circles as well as in the general population there is a constant debate over the issue of availability of drugs through the Croatian Institute for Health Insurance (CIHI) to Croatian healthcare users. While psychiatrists are often frustrated by the lack of access to the newest medications, those that were maybe just recently marketed in the richest countries, at the same time it is suggested to the public that, due to ignorance and negligence of the authorities, many of those drugs that are widely available in other countries are not available to our patients. Despite our own experiences and impressions, which suggest that in Croatia, at present, in the year 2011, there are no significant problems regarding the availability of the latest psychiatric medications, we decided to test that impression comment on the results in this article.

AIM AND METHODS

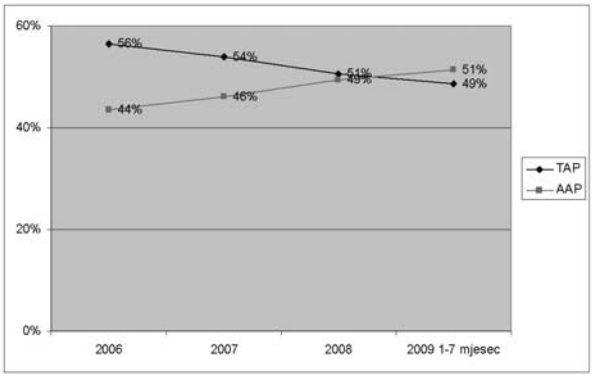
The aim of this research was to check the availability of psychiatric drugs to Croatian citizens, changes in availability of those drugs over time, as well as the dynamics of the introduction of new psychiatric drugs to the list of drugs of the Croatian Institute for Health Insurance (CIHI), and whether and, if so, how the availability of psychiatric drugs, especially anti-psychotics, affected the hospital psychiatric morbidity in Croatia.

In order to analyze the availability and the dynamics of introduction of medications to the list of drugs of CIHI, which in fact represents availability of those drugs to Croatian citizens, we have analyzed all the lists of drugs in Croatia between 1989 and 2011. Changes in use of antipsychotics was evaluated on the example of their use in the University Psychiatric Hospital Vrapče, Zagreb (Jukić et al. 2008), and we have also used the information obtained from the agency that monitors use of medications in Croatia (PharmMis). We also used the example of University Psychiatric Hospital Vrapče to determine changes in hospital morbidity from the time of predominant use of conventional antipsychotics till today when atypical antipsychotics are more frequently used.

RESULTS

The results are presented in Table 1-6 and on Figure 1. By analyzing lists of drugs of the CIHI we obtained the following data. Table 1 shows the increase in number of psychiatric medications, original substances as well as preparations, over the 22-year period from 1998 until 2011.

It is particularly interesting to see the situation in the list of drugs in 1991, the first year of the war, and the introduction of new drugs after 1994 (just before the end of the war). The greatest increase is seen in the group of antidepressants (300%), antiparkinsonics (275%) and antipsychotics (267%).



TAP/ Typical antipsychotics: levomepromazine, promazine, fluphenazine, haloperidol, zuclopenthixol;
AAP/ Atypical antipsychotics: clozapine, sulpiride, olanzapine, quetiapine, risperidone, ziprasidone, sertindole

Figure 1. Use of typical and atypical antipsychotics in Croatia

During 1991 the list contained 6 antipsychotic drugs and 7 preparations, but in the period from 1995 till today that number increased steadily every year, and today we have available 16 antipsychotics and 38 preparations in total, all of them on the primary list of drugs (Table 2). By analyzing dynamics of medications being included and removed in the official list of drugs, it is seen that CIHI list of drugs contained following antipsychotics in 1989: haloperidol, sulpiride, clozapine, sultopride, pimozide; in 1992 fluphenazine, levomepro-

mazine, perazine, periciazine, promazine, and droperidol were added to the list, thioridazine in 1995, risperidone in 1998, olanzapine in 1999, quetiapine in 2002, ziprasidone and zuclopenthixol, sertindole in 2008, amisulpride and droperidol in 2009; in 2011 list contains 16 antipsychotics (38 preparations), 8 preparations of olanzapine, 8 preparations of risperidone, 5 preparations of quetiapine, and of all the other antipsychotics promazine, ziprasidone, clozapine and sulpiride have one parallel of the generic drug.

Table 1. Classes of psychiatric medications on drug lists from 1989 till 2011 by number of preparations

Drug class	1989	1991	1995	2011	Increase %
Antiepileptic original (generic parallel)	7 (7)	7 (7)	10 (10)	12 (24)	171 (343)
Antiparkinsonic original (generic parallel)	4 (5)	4 (4)	7 (8)	11 (15)	275 (300)
Antipsychotics original (generic parallel)	6 (7)	6 (7)	11 (13)	16 (38)	267 (543)
Anxiolytics and hypnotics original (generic parallel)	12 (22)	13 (23)	13 (18)	13 (23)	1 (1)
Antidepressants original (generic parallel)	6 (8)	6 (7)	6 (6)	18 (40)	300 (500)
Psychostimulants original (generic parallel)	2 (2)	2 (2)	1 (1)	3 (3)	1 (1)
Drugs for treating dementia original (generic parallel)	-	-	-	3 (6)	
Drugs for treating addiction original (generic parallel)	-	-	-	6 (10)	

Table 2. Antipsychotics on drug lists from 1989 till 2011

	1989	1991	1995	2011
Antipsychotics original (generic parallel)	6 (7)	6 (7)	11 (13)	16 (38)
	haloperidol lithium carbonate sulpiride clozapin sultopride pimozide	haloperidol lithium carbonate sulpiride clozapin sultopride pimozide	haloperidol pimozide clozapine sulpiride lithium carbonate levomepromazine (1992) promazine (1992) fluphenazine 1992) perazine (1992) periciazine 1992) thioridazin (1995)	Levomepromazine promazine fluphenazine haloperidol lithium carbonate sulpiride clozapine risperidone (1998) olanzapine (1999) quetiapine (2002) zuclopenthixol (2005) ziprasidone (2005) sertindole (2008) droperidol (2009) amilsulpride (2009)

Table 3. Antidepressants on drug lists from 1989 till 2011

	1989	1991	1995	2011
Antidepressants original (generic parallel)	6 (8)	6 (7)	6 (6)	18 (40)
	amitriptyline doxepin clomipramine maprotiline viloxazine trazodone	amitriptyline doxepin clomipramine maprotiline viloxazine trazodone	amitriptyline clomipramine maprotiline viloxazine trazodone moclobemide (1995)	amitriptyline clomipramine maprotiline moclobemide fluvoxamine (1996) fluoxetine (1996) sertraline (1997) tianeptine (1998) paroxetine (1999) reboxetine (2000) hypericin (2000) escitalopram (2005) citalopram (2005) venlafaxine (2005) mirtazapine (2005) duloxetine (2007) bupropion (2009) agomelatin (2010)

Table 4. Anxiolytics and hypnotics on drug lists from 1989 till 2011

	1989	1991	1995	2011
Anxiolytics & Hypnotics original (generic parallel)	12 (22)	12 (23)	13 (18)	13 (23)
	diazepam	diazepam	bromazepam	alprazolam
	bromazepam	bromazepam	diazepam	bromazepam
	clorazepate	clorazepate	lorazepam	diazepam
	chlordiazepoxide	chlordiazepoxide	medazepam	lorazepam
	lorazepam	lorazepam	oxazepam	oxazepam
	medazepam	medazepam	prazepam	flurazepam
	midazolam	midazolam	meprobamate	midazolam
	oxazepam	oxazepam	buspirone	nitrazepam
	prazepam	prazepam	alprazolam (1992)	zolpidem (1999)
	buspirone	buspirone	flurazepam (1992)	Valerian extract (2003)
	hydroxyzin	hydroxyzin	midazolam (1992)	zaleplon (2006)
	meprobamate	meprobamate	nitrazepam (1992)	melatonin (2010)
			triazolam (1992)	Valerian-hop extract (2011)

Table 5. Share of individual antipsychotic in the overall antipsychotics market

Share of individual antipsychotic in the overall antipsychotics market	MS %
Olanzapine	18.82
Haloperidol	15.76
Promazine	15.42
Fluphenazine	15.03
Risperidone	9.88
Clozapine	8.01
Quetiapine	6.81
Sulpiride	4.82
Levomepromazine	2.35
Zuclopentixole	1.53
Ziprasidone	1.37
Sertindole	0.21

Data for period from January till August 2009 refer to days of treatment with specific antipsychotic, source PharmMis

New atypical antipsychotics appeared on Croatian market in 1996, their share in overall consumption of antipsychotics, compared to that of the classical antipsychotics, increased every year until finally in 2008 atypical antipsychotics took the leading role (Figure 1). Review of the share of every individual antipsychotic on Croatian market in 2009 (Table 5) indicates that new atypical antipsychotics take the first place.

In 1991 list of drugs contained 6 antidepressants and 7 preparations, the number increasing every year in the period from 1995 till today, so today we have 18 antidepressants and 40 of their preparations available in total (Table 3). Since 1991 the dynamics of introduction of new antidepressants looked like this: moclobemide in 1995, fluvoxamine and fluoxetine in 1996, sertraline in 1997, tianeptine in 1998, paroxetine in 1999, reboxetine in 2000, citalopram, escitalopram, mirtazapine and venlafaxine in 2005, duloxetine in 2007, bupropion in 2009 and agomelatine in 2010. Of the 18 drugs listed, 5 are not included on the basic (positive) list of drugs but are found on the additional list: fluvoxamine, moclobemide, tianeptine, reboxetine and duloxetine.

Table 6. Patients hospitalized from 2001 till 2010 in University Psychiatric Hospital Vrapče by diagnoses

Diagnosis	2001 %	2002 %	2003 %	2004 %	2005 %	2006 %	2007 %	2008 %	2009 %	2010 %
F.00-F.09	18.39	18.62	18.72	17.13	15.27	13.72	13.95	14.37	15.51	17.46
F.10-F.19	27.14	25.94	31.60	31.61	30.62	31.52	30.99	31.32	30.04	26.21
F.20-F.29	28.02	28.96	25.12	25.12	24.06	22.71	20.69	19.90	19.11	19.09
F.30-F.39	10.18	10.33	10.73	10.83	11.64	12.05	13.96	14.00	14.16	15.89
F.40-F.49	7.50	6.79	6.09	5.47	7.94	9.25	8.88	8.60	8.92	7.72
F.60-F.69	3.84	4.59	3.66	5.29	6.10	7.12	7.21	7.15	7.71	8.15
Other	4.95	4.77	4.08	4.54	4.37	3.64	4.32	4.66	4.55	5.49
Total	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00

Medications for treating addictions and dementia were not included on the list of drugs 20 years ago (Table 1). Drugs for treating dementia were introduced on the list in the following order: donepezil and rivastigmine in 2000, memantine in 2005, and all three of the drugs are today still listed on the additional drug list. In the group of medications for treating addiction buprenorphine was added to the list in 2002, bupropion in 2005, naltrexone in 2007, varenicline and fixed combination of buprenorphine and naloxone in 2008,

and today all but bupropion, varenicline and naloxone are found on the basic drug list.

We have seen that number of anxiolytics and hypnotics (the most prescribed drug classes in the world and in Croatia) has increased only by 1% over the period of 22 years (Table 1). Number of different preparations remained the same although new drugs were introduced on the list since 1989 in the following order: alprazolam, flurazepam, midazolam, nitrazepam and triazolam in 1992, zolpidem in 1999, zaleplon in 2006, and melatonin in 2010. The number of different preparations remained the same because clorazepate, chlordiazepoxide, medazepam, prazepam, hydroxyzine, buspirone and meprobamate were taken off the list. Current basic list contains only two of the anxyolitics, diazepam and alprazolam, while oxazepam and lorazepam are found on the additional list. All hypnotics are on the basic list except for the zaleplon.

Table 6 shows analysis of changes in psychiatric morbidity during 10-year period (from 2001 till 2010) in the University Psychiatric Hospital Vrapče, or more correctly it shows analysis of relative number of hospitalized patients by diagnoses. Results indicate reduction in number of hospitalized patients with schizophrenia spectrum disorders (F20.-F29), primarily treated by antipsychotics.

DISCUSSION

In the last 20 years many efficient psychiatric drugs were discovered and marketed. It led to improvement in treating patients suffering from variety of mental disorders (Jones et al. 2006, Jukić et al. 2003). Choosing a certain drug for a specific psychiatric patient depends in big part also on the availability of that drug, on the status of registration of the drug in Croatia, on whether the drug is on the basic (positive) list of drugs or on the additional list and will require co-payment, on what is the price of the drug or what is the actual co-payment required from the patient (Tandon et al. 2008, Traynor 2007).

Analysis of introduction of new drugs on the CIHI drug list over a 22-year period shows that number of drugs in certain classes increased many times, especially antipsychotics and antidepressants whose number grew 5 times.

New atypical antipsychotics caused great enthusiasm and hope among psychiatrists and patients, but also among all those who take part in treating psychotic patients (Kahn et al. 2008). Still, many on the local level were also frustrated because of certain restrictions and limits in application of atypical antipsychotics, mainly because of the high price, while the same medications were used more liberally and without restrictions elsewhere (wealthier Western countries). Although when they were first introduced they were 10 times more expensive than typical antipsychotics, they soon became predominant and in even in professional circles (guidelines for treating schizophrenia and psychotic disorders) were seen as the first-line of treatment of schizophrenia and psychotic disorders (Jukić et al. 2008).

At the time of first atypical antipsychotics coming on the official list of drugs in Croatia, our algorithms stated that that both typical and atypical antipsychotics were first choice for the first-episode schizophrenia, and that atypical antipsychotics can be prescribed only after some of the typical ones were first tried and failed to produce response or caused extrapyramidal or other side effects, even if at that time guidelines of American Psychiatric Association stated that atypical antipsychotics were the first choice in treating schizophrenia, especially in first episodes. The provision explaining when to use atypical antipsychotics said "Only for patients with disease refractory to classical therapy or those not tolerating classical therapy, prescribed by psychiatrist". The clause was applied to all of the atypical antipsychotics that were marketed. Consequently, a new atypical antipsychotic could be prescribed to a patient only in accordance with the mentioned provision and after getting a specific approval from the committee with the CIHI. The approval initially had to be renewed every 6 months, but later only acquired at the initiation of therapy without the need for renewals, with this addition to the original provision "Institute approves start of the treatment without the need for renewing the approval". For many years this was reason for misunderstanding between psychiatrists and CIHI. Psychiatric circles used memos and declarations to warn of the illogic nature of these stipulations which asked for official approval of CIHI for every single case of use of medications, which were according to guidelines drugs of choice. This was corrected two years ago when the disputed stipulation was removed.

Results of the most recent studies came to conclusion that there are no significant differences in efficiency between typical and atypical antipsychotics (Jones et al. 2006, McEvoy et al. 2006, Lewis et al. 2006, Sikich et al. 2008). After 20 years of use of new atypical antipsychotics (15 years in Croatia), data regarding their efficiency gathered from clinical studies are still modified with results from the every-day clinical practice.

The question we can ask is whether the significant increase in number and use of psychiatric medications in recent years (especially antipsychotics and antidepressants) was followed by equally significant improvement of the health of those suffering from mental disorders. Analysis of morbidity in University Psychiatric Hospital Vrapče suggests that greater use of atypical antipsychotics influenced the change in morbidity structure in the hospital in a way that number of patients hospitalized under the diagnosis of schizophrenia and schizophrenia spectrum disorders

was reduced every year. Analysis of psychiatric morbidity during 10-year period (from 2001 till 2010) in the University Psychiatric Hospital Vrapče, or more correctly analysis of relative number of hospitalized patients by diagnoses, indicates reduction in number of hospitalized patients with schizophrenia and schizophrena spectrum disorders (F20.-F29), primarily treated by antipsychotics. It is clear that proportion of those patients in the overall patient population from 2001 till 2010 fell by 9%, from 28% to 19%. Considering the fact that schizophrenia is disease with stabile incidence and prevalence of around 1%, it is obvious that with introduction of more atypical antipsychotic on the list of drugs fewer patients with psychotic disorders are treated in the hospital. They are treated more as outpatients and with fewer rehospitalizations (Herceg et al. 2008). Probably because of the changed side-effects profile and broader spectrum of activity (positive, negative, affective and cognitive symptoms), these patients are now treated more adeqautely and there is probably more of them who function in their family and work environment (Jukić & Herceg 2006).

CONCLUSIONS

New antipsychotics registered in the world, some even in Croatia, but are still not on the CIHI list of drugs are: aripiprazole, paliperidone, iloperidone, zotepine, melperone, long-acting depot formulation of paliperidone (still in clinical trials). Regardless of that, we can be satisfied with the present availability of antipsychotics in Croatia, especially if compared to countries in the region that are not yet part of European Union (Bosnia and Herzegovina, Serbia, Montenegro, Macedonia, Kosovo). What we are missing in the basic drug list are drugs for treating dementia (all three drugs registered in Croatia are in the additional drug list) and some of the mentioned new atypical antipsychotics like paliperidone, iloperidone, zotepine, melperone, long-acting depot formulation of paliperidone.

Today we can say, with regards to psychiatric medications arsenal, we are no longer in the era of pharmacological nihilism of 60 years ago, but in the era of pharmacological hedonism.

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