

IMPORTANCE OF THE NEWER GENERATIONS OF ANTIPSYCHOTICS IN REDUCING SCHIZOPHRENIA HOSPITALIZATION RATES

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SUMMARY

Throughout history, given the lack of understanding of schizophrenia and lack of effective treatment options, patients were often committed to asylums and later psychiatric institutions, often for prolonged periods of time. First antipsychotic medications helped to bring about changes in approach to these patients and facilitated deinstitutionalization, and discovery of new drugs with differing side-effects profiles introduced new options in treating schizophrenia patients. Data on hospitalization of patients in University Psychiatric Hospital Vrapče from the mid-1990s, as well as data on national level, suggests a trend of drop in hospitalization of schizophrenia patients. At the same time, that period saw significant increase in a number of available newer-generations antipsychotics and the rise in their use compared to first-generation one. Although far from being the only contributing factor, seem to play an important role in continuing the trend of reducing hospitalization rates for schizophrenia patients that started with first antipsychotics. Newer antipsychotics with a more tolerable side-effects profile promote better compliance and further reduce rate of relapse and hospitalizations. No less important is the contribution of newer antipsychotics with new receptor profiles to the personalized psychopharmacotherapy approach that is in tune with emerging conceptualizations of schizophrenia as a complex syndrome with a number of separate symptom domains, whose specific combinations produce specific individual clinical presentation and in turn ask for a specific individual approach to the patient.

Key words: antipsychotics – schizophrenia - hospitalization

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INTRODUCTION

With all the psychopathological phenomena that appear as part of the clinical presentation of schizophrenia, often including significant changes in almost all mental processes and altering the way person interacts with the surrounding, it has always been linked to severe social dysfunction and disability. Same complex psychopathology, along with the inability to effectively treat it, or for a long time even to alleviate some of the most pronounced symptoms, influenced the society's attitudes and reactions to those suffering from schizophrenia, and along with marked social dysfunction and a number of other factors contributed to stigmatization and subsequent isolation of schizophrenia patients. On the wave of rampant institutionalization that was often seen not just as adequate but as the only way to treat those with mental disorders, people suffering from schizophrenia ended up being some of the most common "tenants" of asylums, and later with development of modern institutional psychiatry of psychiatric hospitals (Porter 2006). Institutionalization, especially the early one, even with rudimentary attempts at treating mental disorders that more than often amounted up to ethically questionable practices, was primarily focused on the containment and "protection" of the society from the "insane". Far from facilitating modern treatment approaches, "containment approach" also strengthened the stigmatization and the appearance of complete social dysfunction and financial burden for the society.

Many factors, stemming from more than just changes in medicine and psychiatry and spilling into the areas of social, philosophical and economic considerations, influenced the inevitable approach of deinstitutionalization. However, even with accepting the complexity of many contributing factors and their interactions, almost all will agree that the development of new pharmacological treatment options starting in the mid-20th century with lithium carbonate, chlorpromazine, reserpine, imipramine, and other drugs, changed the perception of "untreatable" conditions and opened the doors for significant reduction in the number of those hospitalized in psychiatric institutions. The introduction of chlorpromazine and other drugs to treat psychiatric conditions helped to move psychiatry towards mainstream medicine and influenced the development of psychopharmacology (Ban 2007), but also proved to be vital for the development of community-based treatment options that appeared few decades earlier but never had the strength to break the primacy of institutional approach. Individual reports comparing discharge of patients suffering from what we today consider to be schizophrenia in 1920s and 1930s to the discharge of the same diagnostic category of patients in the period following the introduction of chlorpromazine found that percentage of those discharged rose from under 10% to well over 60%, resonating the reports of general significant drop in the number of residents of psychiatric institutions in United States and across the world (Thuillier 1999). Introduction of chlorpromazine and the revolution in treating schizophrenia patients in

helped to bring about also highlighted the heterogeneity of the condition in its response to treatment and the existing unmet need that paved the way to developing other drugs and new drug classes in line with the developing and changing conceptualization of the biological basis of the disease itself (Ban 2007). Discovery of new classes of antipsychotics led to the significant improvement of treatment by showing superior effect in certain patient populations, through novel mechanisms of action at the receptor level, but not less importantly by causing less extrapyramidal side-effects that previously seriously affected patient compliance and quality of life (Jukić et al. 2003). Though initially enthusiastically moved to the place of first-line treatment as a replacement for the class of first-generation antipsychotics (Jukić et al. 2008), the fact that they proved not to be the “silver bullet” for majority of patients that everyone had hoped for, and that they are accompanied by significant cost and somewhat different but nonetheless serious spectrum of side-effects, led to the questioning of their comparative advantage over first-generation drugs in terms of efficacy (Jones et al. 2006, Kahn et al. 2008, Sikich et al. 2008, Rosenheck 2008).

With all the doubts and ongoing debate it is however interesting to consider and discuss the possible influence of newer antipsychotics on the treatment of patients suffering from schizophrenia and schizophrenia-spectrum disorders, in the context of conceptual revolution that first antipsychotics introduced and the wave of reductions in hospitalization they fostered.

HOSPITALIZATION AND AVAILABILITY OF NEWER ANTIPSYCHOTICS DATA

In order to illustrate the changes in hospitalization of schizophrenia patients and set the stage for discussion on possible influence of the newer antipsychotics we report data from University Psychiatric Hospital Vrapče, Zagreb, Croatia, on patients demitted from the hospital during the period from 1996 till 2012, as well as data on hospitalization of schizophrenia patients in Croatia.

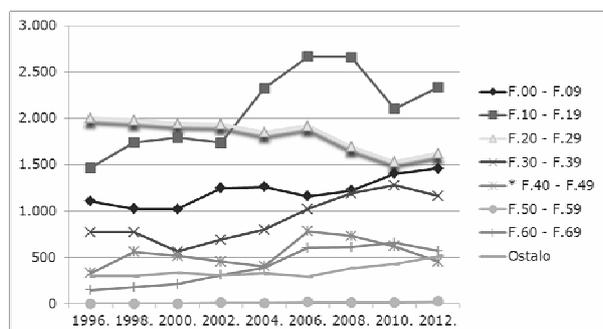


Figure 1. Patients by diagnosis, discharged from University Psychiatric Hospital Vrapče in the period from 1996 to 2012

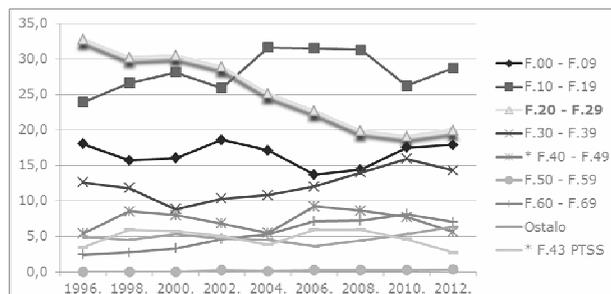
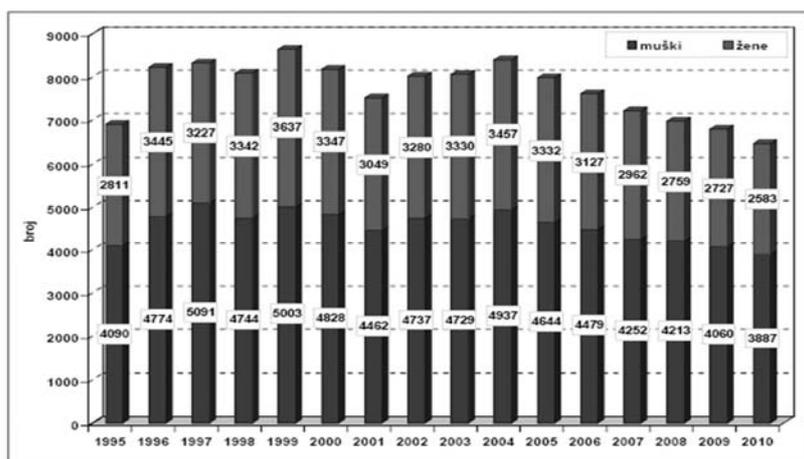


Figure 2. Analysis of relative number of patients by diagnosis, discharged from University Psychiatric Hospital Vrapče (1996-2012)

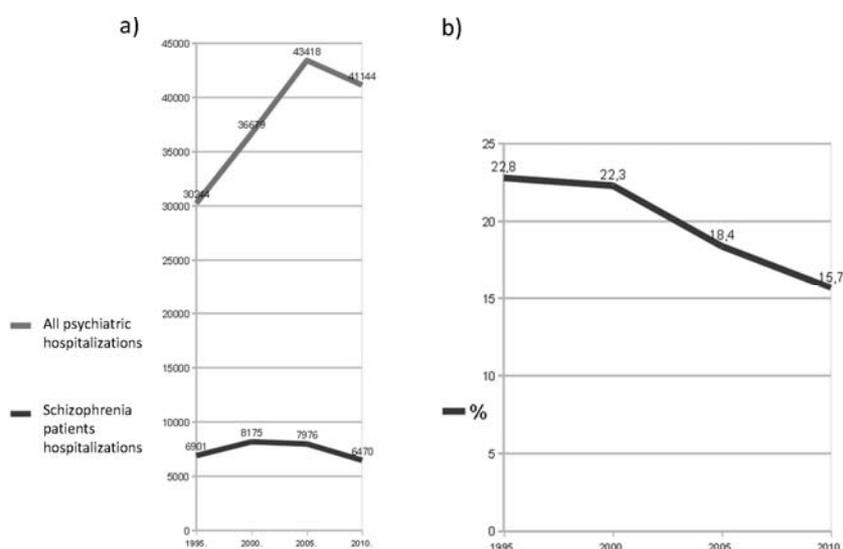
When patients who were demitted from University Hospital Vrapče are divided into groups based on the diagnostic group they belong to, with schizophrenia being lumped together with the group including other psychotic disorders (ICD-10 code F20-F29), it can be seen that there is a discreet but visible trend of reduction of number of patients from that group even while most other groups show general stagnation or increase (Figure 1). Illustrating that even more accurately is the relative number of discharged patients in the same period, again showing a definite trend of reduction in the F20-F29 group, with every third patient being discharged in 1996 (32.4%) and every fifth in 2012 (19-20%) belonging to that diagnostic group (Figure 2). Accounting for possibility that the trend might be a local phenomenon limited to a specific institution but not seen on a national level, we also report data from Croatian Institute for Public Health on the number of hospitalizations of schizophrenia patients in the period from 1995 till 2010, showing that by the end of last century around 8000 schizophrenia patients were hospitalized annually, while that number fell to around 6500 hospitalizations in recent years (Figure 3). It is also important to note that the ratio of hospitalized men and women throughout that period remains unchanged. If we compare total number of psychiatric hospitalization to that of hospitalization of schizophrenia patients on the national level, it is clear that after an initial slight increase there is a decrease in number of hospitalized schizophrenia patients starting from year 2000, while total psychiatric hospitalizations show steep increase that stops only in 2005 as is then followed by a downward trend (Figure 4a). The trend is perhaps better illustrated by showing relative proportion of schizophrenia patients’ hospitalizations from the total number of psychiatric hospitalizations in the same period, reflecting a marked constant drop from almost every fourth patient in 1995 (22.8%) to almost every sixth in 2010 (15.7%) (Figure 4b).

As a general illustration we also report the change in availability of different antipsychotics in republic of Croatia over time reflecting constant addition of new antipsychotics, with the first atypical antipsychotic being introduced in 1996 (Table 1), and the comparison of use of typical and atypical antipsychotic in republic of Croatia for the period between 2006 and 2009,



Source: Croatian Institute for Public Health - Mentalni poremećaji u Republici Hrvatskoj

Figure 3. Number of hospitalizations of schizophrenia patients in Republic of Croatia from 1995 till 2010. Color coding reflects differences by sex (blue-male; red-female)



Source: Croatian Institute for Public Health

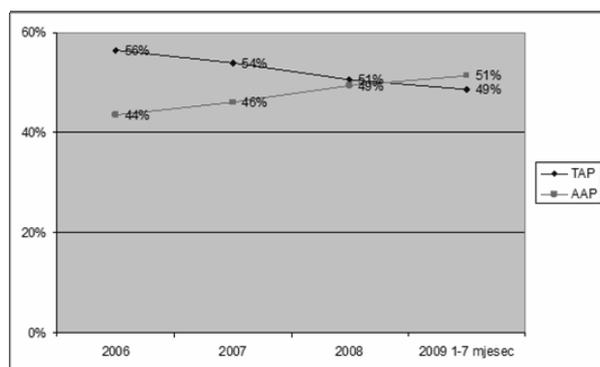
Figure 4. Pattern of change in hospitalizations in republic of Croatia from 1995 till 2010 reflecting a) absolute number of total psychiatric hospitalizations and schizophrenia hospitalizations, as well as; b) proportion of schizophrenia patients hospitalized in the same period

Table 1. Antipsychotics on drug lists from 1989 till 2011

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

Table adapted with permission from Jukić et al. 2011

showing a marked increase in use of atypical and decrease in use of typical antipsychotics, with atypical antipsychotics converging and finally overtaking typical ones in year 2008 and 2009 when 51% of those used were atypical antipsychotics (Figure 5). It is important to note that Table 1 doesn't reflect recent additions to the list of antipsychotics, original or generic parallels, like the addition of long-acting formulation of paliperidone.



TAP/ Typical antipsychotics: levomepromazine, promazine, fluphenazine, haloperidol, zuclopenthixol;
 AAP/ Atypical antipsychotics: clozapine, sulpiride, olanzapine, quetiapine, risperidone, ziprasidone, sertindole;
 Figure adapted with permission from Jukić et al. 2011.

Figure 5. Use of typical and atypical antipsychotics in Croatia

DISCUSSION

When trying to explain complex phenomena with numerous contributing social, economic, medical, and other factors, one necessarily ends up being reductionist, and any discussion on the role of newer antipsychotics on changes in schizophrenia hospitalization rates will have to fall victim to the same reductionism as well. Nonetheless, even taking that into account, as well as the fact that data reported can at best be used as general illustration of just a part of that complex phenomenon, we still find ourselves confronted with the fact that there is a notable trend of decrease in proportion of hospitalizations of schizophrenia patients when compared to other diagnostic groups, in the University Psychiatric Hospital Vrapče but on the national level in Republic of Croatia as well. If we take as a fact that the prevalence and incidence rates of schizophrenia seem to be relatively constant, we will have to look for a reason of such a decrease elsewhere (Goldner et al. 2002). It can be said that there is a general trend of reducing the number of beds in psychiatric institutions and destigmatization of psychiatric patients that helps their inclusion in the society, which might at least partially explain the decrease in hospitalizations of schizophrenia patients. However, when we take a look at population of schizophrenia patients relative to other diagnostic groups, we see the trend of decrease conserved relative to other diagnostic groups, pointing to some other additional factors that

influence the decrease for that population specifically. Introduction of antipsychotic of newer generations and their increased use both seem to coincide with the period in which decrease in hospitalization rates happened. There are also a number of well-established or novel psychosocial therapeutic approaches being increasingly used in work with schizophrenia patients, and their effect on reduced hospitalization needs to be taken into account, but given the lack of systematic approach to those psychosocial programs and instruments on the national and most of the times even on an institutional level, it seems that availability of newer antipsychotics throughout the observed period presented a stronger stable factor contributing to the phenomenon. The fact that those patients treated with newer generations of antipsychotics seem to be treated more often as outpatients and experience less rehospitalizations has previously been described, and unrestricted reimbursement policy for atypical antipsychotics resulted in decrease in hospital admissions even though not in reduced cost (Herceg et al 2008, O'Reilly et al. 2007).

How can we then reconcile these facts with those findings that challenge the competitive advantage of newer antipsychotics? Can we in truth be content with the claim of comparable efficacy of first-generation and newer antipsychotics and start making medical decisions based on economic considerations? When talking about possible advantages of newer antipsychotics we necessarily need to put primary antipsychotic effect temporarily aside and talk about side-effects. Even though newer drugs do carry a risk of serious, mostly metabolic, side-effects it is obvious that the profile of those side-effects is different from those of first-generation antipsychotics, and that these side-effects overall seem to be subjectively tolerated better by patients (Awad et al. 1999). How patients tolerate medications we give them and what type of side-effects they have to incorporate in their daily functioning is an integral part of creating adequate therapeutic alliance and promoting therapy compliance. It is possible that "better", for the patient more tolerable, side-effects profile and consequently more adequate compliance with newer antipsychotics in the end effectively translate into a lower risk of relapse and lower hospitalization rate (Sun et al. 2007).

Some studies comparing different antipsychotics as expected found important differences in side-effects, but also robust albeit small differences in efficacy (Leucht et al. 2013). Those differences in efficacy, no matter how small they might be, combined with changes in our conceptualization of schizophrenia, tentatively put a crack in the concept of "shared antipsychotic effect" for all antipsychotics. Understanding of schizophrenia is shifting towards conceptualizing it as a syndrome and not a monolithic diagnosis, giving rise to an increased focus on different disease domains making up the specific clinical presentation. Different domains are hypothesized to have specific underlying neurobiology that will respond differently to antipsychotic medications of

different profile. Every new antipsychotic, having different receptor profile, gives us another therapeutic instrument that allows us respect specific neurobiology underlying identified symptom domains and, following principles of personalized medicine and pharmacotherapy, address specific set of symptoms, possibly only in specific population of schizophrenia patients, thus increasing their quality of life and every-day functioning, allowing for reduction of hospitalization and increase in a community-based approach.

CONCLUSION

Collectively, we can say that newer antipsychotics, although far from being the only contributing factor, seem to play an important role in continuing the trend of reducing hospitalization rates for schizophrenia patients that started with first antipsychotics. Newer antipsychotics with a more tolerable side-effects profile promote better compliance and further reduce rate of relapse and hospitalizations. No less important is the contribution of newer antipsychotics with new receptor profiles to the personalized psychopharmacotherapy approach that is in tune with emerging conceptualizations of schizophrenia as a complex syndrome with a number of separate symptom domains, whose specific combinations produce specific individual clinical presentation and in turn ask for a specific individual approach to the patient.

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