TREATMENT PATTERNS OF SCHIZOPHRENIA BASED ON THE DATA FROM SEVEN CENTRAL AND EASTERN EUROPEAN COUNTRIES

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SUMMARY

Objective: *The aim is to analyze how schizophrenia is pharmacologically treated in seven CEE countries: Croatia, Estonia, Hungary, Poland, Serbia, Slovakia and Slovenia.*

Methods: *Psychiatrists from selected centers in each of participating countries were asked to complete a pre-defined questionnaire on their current clinical practice. Information on protocols and resource utilization in schizophrenia treatment was included and derived from randomly selected patient medical records. Expert opinions on country-wide treatment patterns were additionally sought. This sub-analysis focuses on pharmacological treatment patterns in the last six months and over the course of the disease.*

Results: *961 patients' data show that during last six months the most commonly prescribed medications were oral atypical anti-psychotics: olanzapine (n=268), clozapine (n=234) and risperidone (n=160). The most frequently prescribed atypical antipsychotics over course of disease were: risperidone (54.5%), olanzapine (52.4%) and clozapine (35.1%), along with haloperidol (39.3%). Experts reported risperidone (four countries) and olanzapine (three countries) as first-line treatment, with the same two medications prescribed as second-line treatment. Clozapine was the most reported medication for refractory patients. Approximately 22% of patients received polypharmacy with antipsychotics in at least one period over the disease course. Mean time since diagnosis was 13.1 years and on average 4.8 treatment courses received during that period. Anxiolytics (70%), antidepressants (42%), mood-stabilizers (27%) were also prescribed, with diazepam (35.4%), sertraline (10.5%), valproic acid (17.5%) the most commonly reported, respectively, in each group. The most frequently reported treatment change was switch from one oral atypical antipsychotic to another (51%).*

Conclusion: *Oral atypical antipsychotics, mostly older drugs (risperidone, olanzapine, clozapine), were most commonly prescribed for schizophrenia treatment in participating countries. Given that results are from the first large-scale analysis of RWD, we believe these findings can be a benchmark for future real-world studies, which could contribute to the optimization of treatment for this debilitating disease.*

Key words: *schizophrenia - burden of disease - European countries - treatment patterns - antipsychotics*

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INTRODUCTION

Schizophrenia is a severe psychiatric disease with a heterogeneous course and symptom profile characterized by the presence of positive and negative symptoms. Positive symptoms include delusions and hallucinations. Negative symptoms include social withdrawal, lack of motivation and lack of emotional reactivity. Positive symptoms may reflect an excess or distortion of normal functions, with negative symptoms reflecting a diminution or loss of normal function (European Medicines Agency 2012).

Conventional treatment with antipsychotics has two clear aims: 1) acute treatment primarily to control posi-

tive symptoms; and 2) maintenance treatment to consolidate stabilized control of symptoms and to prevent exacerbations (European Medicines Agency 2012). Though the degree of supporting evidence varies, there are three main reasons why antipsychotic treatment is typically initiated: 1) to treat the presenting psychotic symptoms; 2) to delay, prevent or reduce the severity of the onset of a psychotic illness and 3) to intervene as soon as psychosis develops, in order to improve overall outcome (Barnes 2011).

International treatment guidelines of organizations, such as World Federation of Societies of Biological Psychiatry (WFSBP), British Association for Psychopharmacology (BAP), National Institute for Health and Care Excellence (NICE) or The Schizophrenia Patient Outcomes Research Team (PORT), stress that pharmacotherapy with antipsychotic medicines, accompanied by adequate psychotherapy, is the key to effective schizophrenia treatment. The effectiveness of antipsychotic medications is well established with evidence from numerous clinical trials. The optimal treatment regime, in terms of antipsychotic selection, dosage, duration, efficacy and tolerability, for each individual patient is less clear and patient cooperation is a major concern of all organizations (European Medicines Agency 2012, Barnes 2011, Hasan et al. 2013, Kuipers et al. 2010, Kreyenbuhl et al. 2010, Dixon et al. 2009).

There are a few publications focusing on the treatment of patients with schizophrenia in Central and Eastern Europe (CEE). A targeted literature review did not identify any studies with cross-sectional data on disease management or treatment patterns in countries outside of Western Europe or the US.

The overarching study analysed multiple aspects of schizophrenia, its diagnosis and treatment in seven CEE countries, collecting information on clinical guidelines, epidemiology, treatment patterns, costs and presence of symptoms. The objective of the present sub-analysis was to characterize patterns in the pharmacological treatment of patients with schizophrenia among the different countries. Analyses utilized the available literature and information gathered during a retrospective data collection in seven participating CEE countries (Szkultecka-Debek et al. 2013). International and national guidelines for the chosen countries were consulted to take into account general recommendations for schizophrenia treatment (Walczak et al. 2013).

To our knowledge, this is the first study to use patient medical records to document local clinical practice in this region of Europe.

SUBJECTS AND METHODS

Project description

The Schizophrenia and Negative Symptoms – Burden of Disease in Seven CEE Countries study consisted of two parts: a literature review and a retrospective data collection. In part one, international, medical databases and local, country-specific sources were searched for relevant information. In part two, retrospective data were collected from patient medical records and the independent opinion of medical experts was sought. The participating countries were: Croatia, Estonia, Hungary, Poland, Serbia, Slovakia and Slovenia. A detailed description of the study methodology has been previously described by Szkultecka-Debek et al. (Szkultecka-Debek et al. 2013). Here we present a sub-analysis focusing on pharmacological treatment patterns only.

Study sites

The study involved three to six different types of medical centers (university hospital, psychiatric hospital, psychiatric ward of a general hospital or outpatient clinic) from different regions within each country. In total, 29 medical centers participated in this project (Table 1).

Sampling

According to each of the participating countries' regulations, ethics committees were either notified (in Poland) or the necessary approval was obtained (in Slovenia, Croatia, Estonia, Hungary, Serbia) prior to the initiation of data collection and analysis. In Slovakia, the project did not require Ethics Committee approval.

Patients with schizophrenia who were treated within the last five years were eligible for this study. International Classification of Diseases (ICD)-10 criteria were used for schizophrenia type definition, and the following were included in the study: (F20.0) Paranoid schizophrenia, (F20.1) Hebephrenic schizophrenia, (F20.2) Catatonic schizophrenia, (F20.3) Undifferentiated schizophrenia, (F20.4) Post-schizophrenic depression, (F20.5)

Table 1. The regional study centers, by country

Country	Number of centers	Regions
Croatia	5	Zagreb (2), Rijeka, Split, Osijek
Estonia	3	Tallinn, Tartu, Pärnu
Hungary	4	Budapest, Győr, Balassagyarmat, Vác
Poland	6	Lublin, Bialystok, Cracow (2), Warsaw, Gdansk
Serbia	4	Beograd (2), Nis, Novi Sad
Slovakia	4	Bratislava (3), Trnava
Slovenia	3	Begunje, Ljubljana, Maribor

Residual schizophrenia, (F20.6) Simple schizophrenia, (F20.8) Other schizophrenia, (F20.9) Schizophrenia, unspecified. A sample of medical records was identified and assessed at each center. The sample included both inpatients and outpatients in proportions adjusted to reflect local practices. The records of newly diagnosed patients (less than six months since diagnosis) comprised no more than 20% of the sample. Random sampling was used where possible (Szkultecka-Debek et al. 2013).

Retrospective data were collected via questionnaire and, where possible, covered the whole course of the disease from first diagnosis. When this information was not available, data from the last five years were collected. In total, data were extracted from 961 patient medical records (Croatia: n=123, Estonia: n=150, Hungary: n=150, Poland: n=165, Serbia: n=120, Slovakia: n=81, Slovenia: n=172). Treatment-related sections of the questionnaire collected information on hospitalizations, pharmacotherapy and psychotherapy. Data collection took place between February and December 2013.

Expert opinion

In order to gain valuable information from a different perspective, local psychiatry experts were asked to express their experience of treating patients with schizophrenia in their everyday medical practice. These additional questionnaires were designed to characterize schizophrenia care in each country and included information on the schizophrenia population, treatment patterns and protocols, social aspects of schizophrenia, resource use and management of adverse events, and provided a broad insight into the disease and its treatment. Whilst the majority of the data was extracted from patient medical records, expert opinion served an important role by providing additional information, allowing for a more detailed comparison of treatment patterns in different countries.

A total of 39 expert psychiatrists participated in this part of this study: four from Croatia, seven from Estonia, seven from Hungary, six from Poland, six from Serbia, four from Slovakia and five from Slovenia. It should be noted that there were some significant differences in opinion among experts from the same country.

Analyzed data

To establish local market differences, the availability of particular antipsychotics in the seven CEE countries was determined. Based on expert experience, the most commonly used treatment options were identified in three categories: first-line treatment, second-line treatment and medications prescribed for refractory patients. Patient records, supplemented with expert opinion, were used to identify patterns in the prescription of antipsychotics over the last six months, and to analyze changes in the last few years in prescribing practices over the complete history of the disease. Analyses included the number of treatment courses with the respect to disease duration, additional, non-antipsychotic prescriptions for co-administration and switching patterns with antipsychotic treatments.

Statistical analysis

Results presented are expressed in percentages calculated both from the total sample and country-specific samples. Where data represent sample characteristics, the main statistics are presented as the arithmetic mean and dispersion is assessed using minimum and maximum values. Results derived from expert opinions are presented as percentage values, estimated using the arithmetic mean of all available expert questionnaires from a particular country. Some patients received polypharmacy with antipsychotics in at least one period over the disease course; therefore, the percentages of patients with particular substances used in the first-line, second-line treatment and refractory strategy may not equal 100%.

RESULTS

Availability of antipsychotics

Availability and, more importantly, reimbursement are the most relevant factors affecting the use of particular antipsychotic drugs for the treatment of patients with schizophrenia. On average, nine to 10 atypical antipsychotics and four to five typical antipsychotics are reimbursed in each participating country (Table 2).

Table 2. Reimbursed antipsychotic drugs by country

| Country	Number of reimbursed drugs*		
	Atypical antipsychotics	Typical antipsychotics	Total
Croatia	10	5	15
Estonia	10	6	16
Hungary	10	4	14
Poland	9	8	17
Serbia	5	4	9
Slovakia	13	6	19
Slovenia	10	7	17

* The group of substances reimbursed in all seven countries includes oral formulations of: clozapine, haloperidol, olanzapine, quetiapine, risperidone, ziprasidone and zuclopentixol and the parenteral form of risperidone and zuclopentixol. The other widely reimbursed oral drugs are: amisulpride and sulpride (except in Serbia), aripiprazole (except in Serbia and Croatia) and sertindole (except in Serbia and Slovenia)

## First-line, second-line and refractory strategy based on expert opinion

In the seven participating CEE countries, schizophrenia treatment was initiated with an atypical antipsychotic. In four countries, the drug of first choice for psychiatrists was risperidone (36–53%), with olanzapine prescribed in the other three (33–40%). Other frequently used drugs for first-line treatment included haloperidol (the only typical antipsychotic), olanzapine (second choice in Croatia and Slovakia, third choice in Hungary and Serbia), risperidone (second choice in Estonia and Poland, third choice in Slovenia), aripiprazole and quetiapine (Figure 1).

Olanzapine was the most popular choice of second-line treatment (28–37%) according to expert experience (Figure 2). In Croatia, the proportion of patients treated with risperidone was 37%, with 36% treated with olanzapine. In Slovenia, four drugs were reported to be equally prescribed (20%): olanzapine, risperidone, amisulpride and quetiapine. This indicates that quetiapine is more popular as a second-line treatment than a first-line treatment in Slovenia. In Serbia, haloperidol and clozapine were frequently prescribed as second-line treatment.
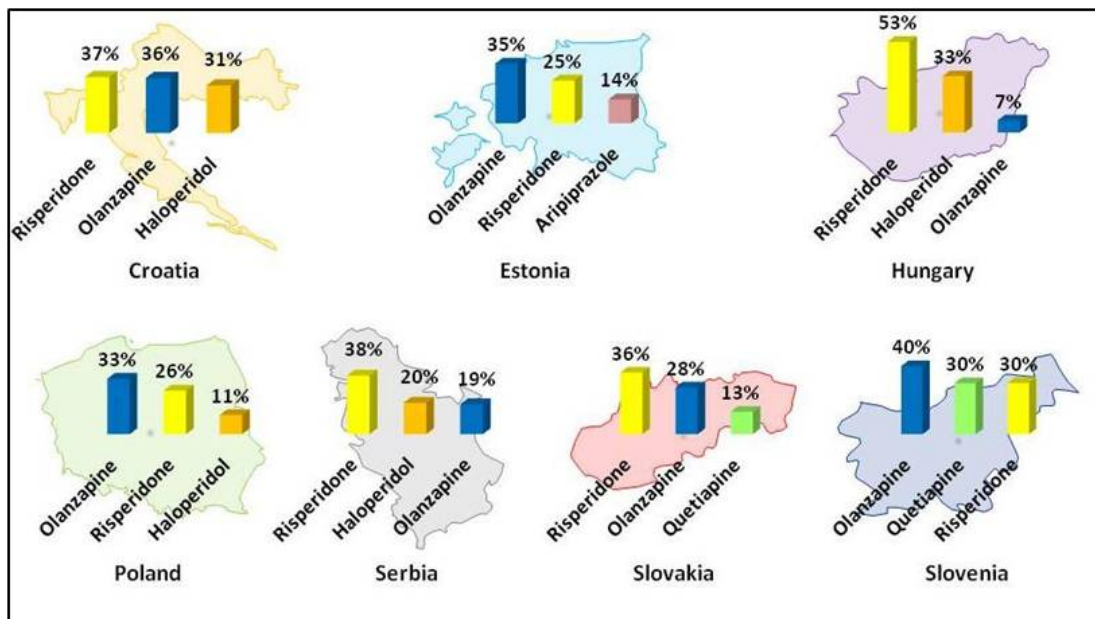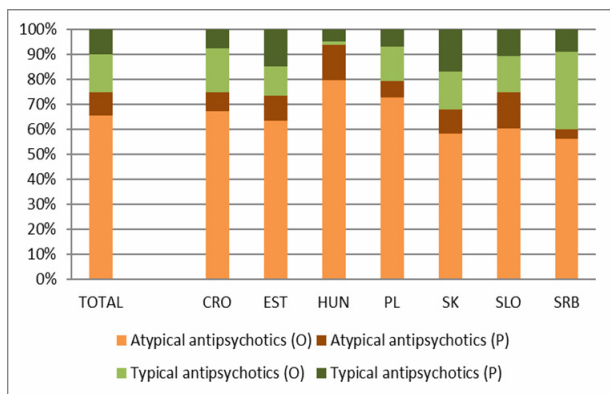

Figure 1. First-line treatment of schizophrenia in seven CEE countries based on expert opinion (percentages of patients treated with the three most frequently prescribed substances)
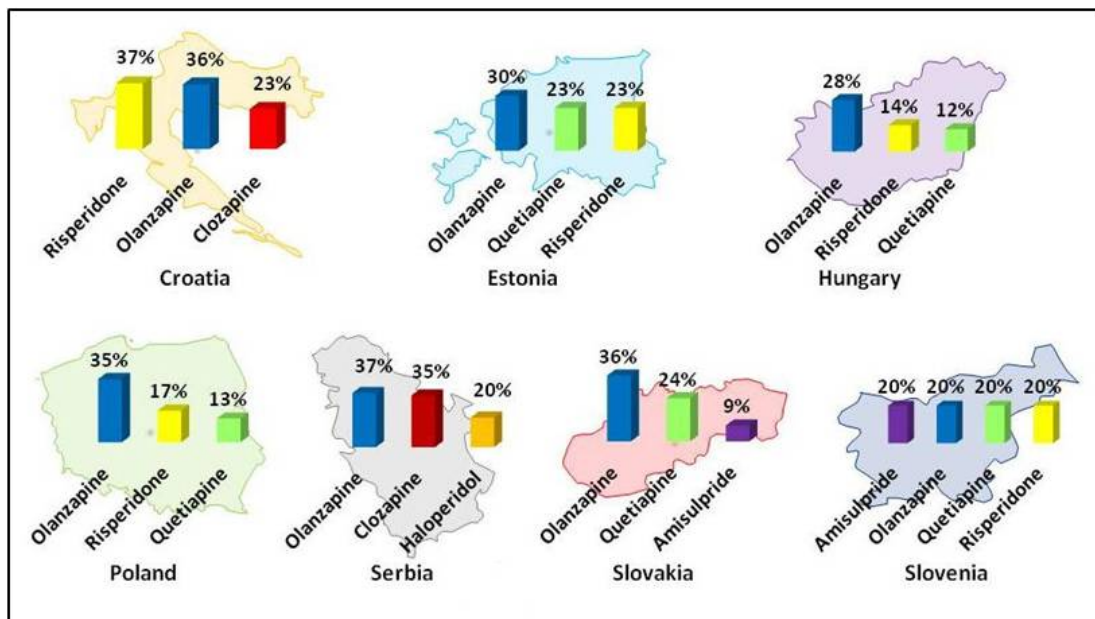
Figure 2. Second-line treatment of schizophrenia in seven CEE countries on the basis of experts' opinion (percentages of patients treated with three most frequently used substances)
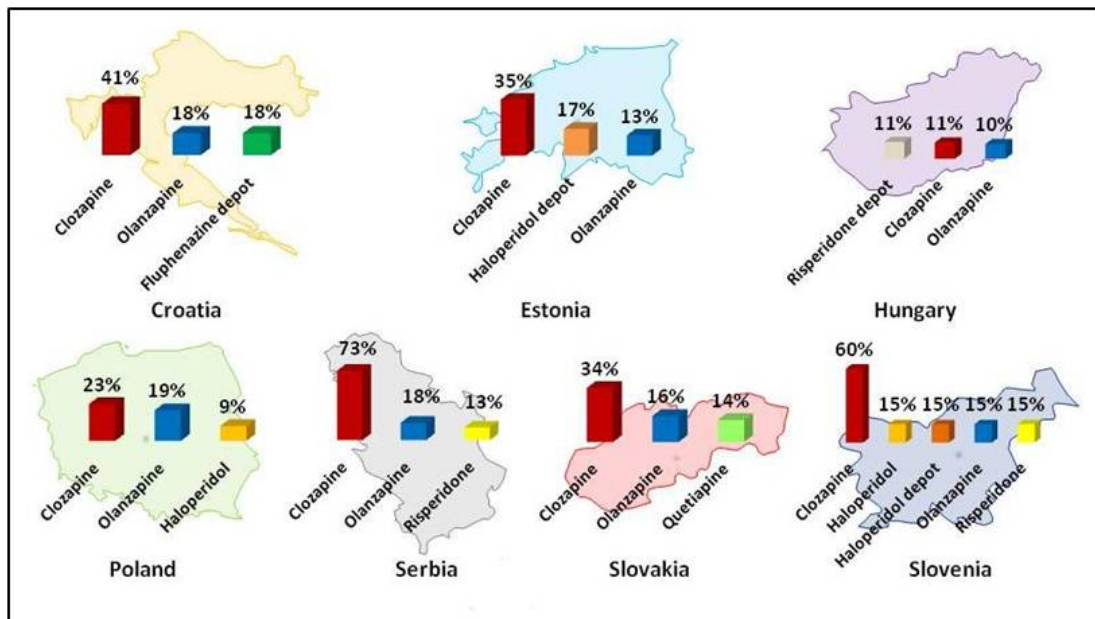
Figure 3. Treatment of refractory patients in seven CEE countries based on expert opinion (percentage of patients treated with the three most frequently prescribed drugs)
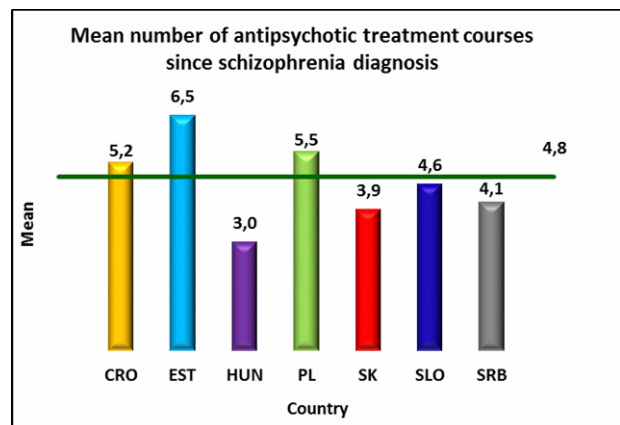

Figure 4. Differences in antipsychotic prescriptions (last six months) between countries

Figure 5. Mean number of antipsychotic treatment courses since schizophrenia diagnosis (horizontal line represents mean value from total sample)

It was reported in all seven countries that refractory patients (i.e. patients who are non-responders to previous treatments) were mostly treated with clozapine, with the percentage of patients ranging from 11% to 73%. In Hungary, risperidone depot had a similar frequency of use to clozapine. Olanzapine was also reported as the second or third most frequently chosen drug for refractory patients (Figure 3).

Recently prescribed antipsychotics

Analysis of patient medical records (N=961) identified a total number of 1,518 antipsychotics prescriptions in the last six months, of which 65.4% were oral atypical antipsychotics.

The second largest group was oral typical antipsychotics, with 15.3% of prescriptions, followed by 9.5% and 9.4% of typical and atypical parenteral antipsychotics, respectively. Hungary reported the highest percentage oral atypical antipsychotic prescriptions, with

the lowest reported in Serbia (79.8% vs 56.2%, respectively) (Figure 4). In the prior six months, the most commonly prescribed antipsychotic was olanzapine (n=268), followed by clozapine (n=234) and risperidone (n=160).

Antipsychotics used during the whole course of disease

To explore how standard treatment has changed during the past few years, the most frequently used antipsychotics prescribed during the defined period (time since diagnosis or last five years) were identified. Using data derived from patient medical records (N=961), the most frequently used drug was risperidone, which was prescribed for 54.5% of all patients. This percentage was highest in Hungary and lowest in Slovakia (78% vs 31%, respectively).

Table 3. Percentage of patients treated with each antipsychotic drug: between country differences during the whole course of disease

	Risperidone	Haloperidol	Olanzapine	Clozapine	Quetiapine	Amisulpride	Aripiprazole
Mean value from total sample	54.5	39.3	52.4	35.1	24.1	14.5	21.0
Croatia	46.3	41.5	56.9	52.0	19.5	12.2	1.6
Estonia	50.7	36.7	46.0	29.3	34.0	9.3	32.0
Hungary	78.0	39.3	58.0	24.0	39.3	30.7	24.7
Poland	46.7	47.3	72.7	24.8	29.1	24.2	27.9
Slovakia	30.9	25.9	50.6	18.5	22.2	7.4	12.3
Slovenia	56.4	33.1	49.4	40.1	17.4	10.5	33.1
Serbia	62.5	47.5	26.7	56.7	1.7	0.0	0.8

Table 4. Mean percentage of patients treated with other (non-antipsychotic) drugs

	Anxiolytics	Antidepressants	Mood-stabilizers
Mean value from total sample	69.9	42.0	26.8
Croatia	74.8	39.8	33.3
Estonia	63.3	43.3	10.7
Hungary	80.0	38.7	28.0
Poland	70.9	47.9	44.8
Slovakia	34.6	33.3	16.0
Slovenia	67.4	45.9	43.0
Serbia	85.8	29.2	40.8

The second most frequently used antipsychotic reported during the whole duration of treatment was olanzapine, prescribed for a mean of 52.4% of all patients. The highest proportion of patients treated with olanzapine was in Poland (73%) and the lowest in Serbia (27%). Haloperidol was indicated more frequently than clozapine across the whole treatment duration, but the difference was small (39.3% vs 35.1%, respectively). Three other atypical antipsychotics were often prescribed: quetiapine (24.1%), aripiprazole (21%) and amisulpride (14.5%). Approximately 22% of patients received polypharmacy with antipsychotics in at least one period over the disease course. Table 3 presents the differences between countries in the usage of specific antipsychotic drugs during the whole course of disease.

Number of antipsychotic treatment courses since schizophrenia diagnosis

The mean number of antipsychotic treatment courses undertaken during the full disease course was 4.8, based on data from patient records (N=691). A treatment course was defined as a period in which a previously unused pharmacological treatment was taken. The smallest number of courses (3.0) was observed in Hungary, with the highest (6.5) in Estonia (Figure 5). In our sample, the average age of patients was 40.7 years (range: 18–79 years), whereas the age of first diagnosis of schizophrenia was 27.3 years (range: 7–69 years). The mean time since first diagnosis of schizophrenia in the sample was 13.1 years (range: 0–46 years), with the minimal

length in Slovenia and maximal in Poland (11.0 vs 14.5 years). Taking into account both data, patients appear to change treatment on average every 2.7 years.

Other (non-antipsychotic) drugs prescribed

Anxiolytics were the largest group of non-antipsychotic medications prescribed over the full course of disease, used by 70% of all patients analyzed. The most frequently reported anxiolytic was diazepam (35.4%), followed by lorazepam (15.8%) and alprazolam (14.2%).

Antidepressants were taken by 42% of the total study population. Sertraline, escitalopram and citalopram were the most commonly prescribed, taken by 10.8%, 7.4% and 7.3% of patients, respectively.

The third largest group of non-antipsychotic drugs was mood-stabilizers, used by 27% of patients. In this group, the most frequently reported drug was valproic acid (17.5%), followed by carbamazepine (7.3%) and lamotrigine (4.4%). These results are summarized in Table 4.

Switching patterns

In the whole cohort of this study, 92.4% of patients had experienced primary negative symptoms at some time since their initial schizophrenia diagnosis. Using data derived from patient medical records, the switching of antipsychotics was the most commonly reported intervention for the treatment of negative symptoms. In 51% of cases, a switch from one oral atypical antipsychotic to another was reported and this was a consistent pattern in almost all of the participating countries.

The second most frequent switch was a change from oral typical to oral atypical antipsychotic (reported in 26% of cases). The specific reasons for switching antipsychotics were not reported.

Serbia presented a different treatment pattern, with patient records most commonly reporting a switch from oral typical to oral atypical antipsychotic, rather than oral atypical to oral atypical, a finding confirmed by expert opinion. This is due to the low number of reimbursed atypical antipsychotics in Serbia (five drugs) compared with the other participating countries (10 drugs on average). There was no one particular switch that would be assumed as the common scheme in all countries; however, the change from risperidone to olanzapine was seen in four countries (Estonia, Hungary, Slovenia and Serbia) as one of the most frequently reported treatment modifications. When analyzing the two most commonly presented patterns, differences between countries were clearly demonstrated. However, in some of the countries it was difficult to find one 'popular' switch.

DISCUSSION

This study is part of a larger, overarching investigation that is the first to compare data on the burden and treatment of schizophrenia in seven CEE countries. The situation in Western Europe is well described, for example in the European Schizophrenia Cohort (EuroSC) study, where data from France, Germany and the UK were presented (Bebbington et al. 2005, Heider et al. 2009), or in the European multinational EPSILON study, which was carried out in The Netherlands, Denmark, the UK, Spain and Italy (Becker et al. 1999, Chisholm & Knapp 2002, Knapp et al. 2002). In our study, we analyzed a sample of 961 patient medical records, compared with 1208 patients in the EuroSC study and 404 subjects involved in EPSILON.

In this substudy we used patient medical records to collect retrospective data on pharmacological treatment patterns for patients with schizophrenia. The most frequently prescribed drugs, both in the last six months and in the whole course of treatment, were atypical antipsychotics. Olanzapine was prescribed for the highest percentage of patients during the months immediately prior to the start of the study. Risperidone was the most frequently prescribed over the whole history of treatment. Expert experience and opinion indicated that these drugs are prescribed more often in first- and second-line treatment. Haloperidol and clozapine were the next most commonly used medications, followed by the new atypicals: quetiapine, aripiprazole and amisulpride. The six-month data (i.e. recently prescribed antipsychotics) included all patients regardless of disease state, from newly diagnosed to refractory.

With parenteral antipsychotic prescription, the differences in reimbursement between the seven CEE countries are quite significant; however, some of the drugs are currently administered to patients during hospitalization. In this scenario, hospitals (in some countries) usually have the opportunity to give patients non-reimbursed drugs as the cost is included in the overall cost of hospitalization. Therefore, reimbursement has a smaller impact on the availability of such treatment to patients with schizophrenia in these countries.

Prescription of additional, non-antipsychotic drugs was comparable between countries with relation to anxiolytics and antidepressants. In six countries, anxiolytics were taken by 63–86% of patients, whereas only 35% of patients in Slovakia took these medications. Differences in antidepressant use between countries were even smaller. With regards to the third category of substances, mood stabilizers, the seven countries split into two groups: those with a small proportion of patients (11–16%; Estonia, Slovakia and Slovenia) and those with a much higher proportion of patients (33–45%; Croatia, Hungary, Poland and Serbia) treated with mood stabilizers.

This study presents cross-sectional, retrospective data from each participating country, both individually and as a summary of the total sample (N=961), which can be used as a benchmark for future studies. Mean differences between countries were not tested for statistical significance for several reasons. Firstly, the number of selected patient medical records differed between countries. In smaller countries, such as Slovenia or Estonia, the selected sample closely corresponded to the overall population of people with schizophrenia. Conversely, Poland, which is the largest country in our study, submitted the second highest number of questionnaires (n=165), but the total number of patients with schizophrenia in Poland is disproportionately greater. The proportion of records from hospitals and outpatients clinics in each country was influenced by local access to the centers. Factors of great importance are the differences between health care systems and in the Gross Domestic Product (GDP) of each participating country. For example, in 2012 the real GDP per capita varied from 3.100 EUR per inhabitant in Serbia to 8.500–9.400 EUR per inhabitant in Croatia, Poland, Hungary, Slovakia and Estonia, to 15.000 EUR per inhabitant in Slovenia (European Commission 2014).

Information on the availability of reimbursed antipsychotics were gathered through literature review at one time point (first quarter of 2013) to compare data between countries. Some local changes in the reimbursement of new drugs may therefore have taken place.

CONCLUSION

Oral atypical antipsychotics, mostly the older ones (risperidone, olanzapine and clozapine), are most commonly used for the treatment of schizophrenia in

seven CCE countries. Over the entire course of disease, more than 50% of patients received either olanzapine or risperidone, with clozapine the most commonly pre-scribed antipsychotic for refractory patients. Conco-mitant treatment, particularly with anxiolytics, was frequent and consistent across the participating coun-tries; however, there were clear differences in the use of mood stabilizers. These real-world data, the first to be collected from non-Western European countries, may serve as a benchmark or comparator for future studies of treatment patterns in schizophrenia.

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