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PRESCRIBING PATTERNS IN ADOLESCENT PSYCHIATRIC PRACTICE: AN IMPORTANT ROLE OF ANTIPSYCHOTICS

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SUMMARY

Background: *Many adolescents affected by psychiatric disorders require pharmacological treatment. Knowing which medication is being used is of utmost importance. Our main objective was to gain insight into prescribing patterns at the Department of child and adolescent psychiatry, Clinical Hospital Centre Rijeka. In addition, we looked for potential differences between adolescents regarding their pharmacotherapy status.*

Subjects and methods: *The data from medical charts of 227 adolescents (55% females), age 12-18 years (16.4±1.18) were analysed. All of them were treated as outpatients during one year period (2014/15). Medical charts were obtained from the computerized archive system of Clinical Hospital Centre. Prescribed drug patterns were taken into account if patients have been taking medication for at least one month.*

Results: *Most of the patients, 162 (71.4%), were treated with psychiatric medication. In the pharmacologically treated group, adolescents were older ($t=-4.678$; $p<0.001$), predominately male ($\chi^2=5.175$, $p=0.023$) and hospitalized ($\chi^2=20.612$, $p<0.0001$). Accordingly, male (OR=2.09, P<0.05) and hospitalized (OR=15.32, P<0.001) adolescents were more disposed to be medicated. Psychotic disorder was the most commonly diagnosed disorder (51 patients). There were 454 different prescribing patterns, mostly prescribed antipsychotics, 36.6% of all prescriptions; followed by 31.5% anxiolytics' and 23.7% antidepressants' prescriptions. However, number of patients receiving antipsychotics, anxiolytics and antidepressants was quite similar (103: 110: 99). The highest number of patients was treated with sertraline (58), followed by those treated with risperidone (48). Majority of the patients (104/227) were treated with polytherapy.*

Conclusion: *Prescribing psychiatric pharmacotherapy for adolescents is a common clinical practice. Adolescents that were prescribed pharmacotherapy were significantly older; hospitalized and male adolescents were more prone to be medicated. Antipsychotics were most frequently prescribed drugs. The prescribing patterns are generally consistent with international trends and guidelines; however caution regarding high proportion of polytherapy is necessary.*

Key words: *adolescent - antipsychotic - pharmacotherapy - prescription - psychiatry*

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INTRODUCTION

A number of studies have shown that mental disorders come to be more prevalent from childhood to adolescence (Costello et al. 2003). The prevalence of psychiatric disorders in adolescence is estimated to be in the range from 10% to 20% (Costello et al. 2011, Herpertz-Dahlmann et al. 2013). So called internalizing mental disorders (depression, anxiety) are more frequent in girls, with prevalence ranges from 12% to 23%; contrary to that, externalizing or disruptive disorders are more common in boys, with prevalence ranges from 5% to 10% (Herpertz-Dahlmann et al. 2013). Knowing the possible harmful and long-lasting consequences of the psychiatric disorders, early diagnosis and treatment during adolescence becomes of crucial importance. Consequently, there is also a rise in evidence related to the psychosocial and pharmacological treatment approaches.

Research suggests a growing trend in the use of psychotropic medication in children and adolescents (Rani et al. 2008, Gilat et al. 2011, Olfson et al. 2012, Steinhausenn & Bisgaard 2014). Simultaneously, such a trend carries the danger of excessive and unnecessary pharmacotherapy (Carton et al. 2015, Pennap et al. 2018). Psychopharmacotherapy of children and adolescents is a complex and demanding discipline. The evaluation of efficacy is often hard to perform because is difficult to judge whether this improvement is the consequence of drug efficacy or child's psychological maturation (Kocijan Hercigonja et al. 2002). Therefore, it is important to know which psychiatric remedies are used today in adolescent population and how effective and safe they are to use.

There is some evidence that prescribing antipsychotics for children and adolescents has increased in many developed countries (Hálfdánarson et al. 2017, Kalverdijk et al. 2017); and it is presumed that many of these prescriptions were off-label (Toteja et al. 2014, Carton et al. 2015). The experts agree that psychopharmacology prescription trends, regarding child and adolescent psychiatry, must be monitored regularly. There is some evidence that countries are markedly different regarding these trends (Steinhausen 2015, Piovani et al. 2016), and there is only one related research conducted in Croatia (Maršanić et al. 2012).

Due to all of the above mentioned, we considered of value to investigate patterns of prescribing medication in adolescent outpatients treated at the Department of child and adolescent psychiatry, Psychiatry Clinic, Clinical Hospital Centre Rijeka. The first goal was to establish the proportion of pharmacologically treated adolescents during one-year period. In addition, we investigated the number and proportion of patients treated with a particular drug, dosage ranges and the proportion of patients on monotherapy or polytherapy. We examined whether the patients with or without medication were different regarding different socio-demographic and treatment variables.

METHODS AND SUBJECTS

We researched medication prescribing patterns for adolescent outpatients treated at the Department of child and adolescent psychiatry, Clinical Hospital Centre Rijeka, from May the 1st, 2014. till May the 1st, 2015. The data were analysed from patients' medical charts available through the computerized archive system of Clinical Hospital Centre, Rijeka (IBIS Information System). The research involved adolescent outpatients aged 12-18 who were examined at least once during this period.

The total number of patients was 227, 125 girls and 102 boys. Data in the medical charts were recorded by three psychiatrists, subspecialists in child and adolescent psychiatry, during the usual check-up appointments. The aforementioned psychiatrists had at least ten years of experience in psychiatric treatment of adolescents at that time. Data collected form medical charts were age, sex, family characteristics, heredity for psychiatric illness, diagnosis, administered treatment and psychotherapy. Prescribed drug patterns were taken into account provided the patients had been consuming medication for at least one month in succession. Anxiolytics that were prescribed 'as needed' were not taken in consideration. The number of prescribed medications and patterns is higher than the number of patients due to the facts that patterns were changed during the observed period, and/or patients had to take several different drugs at the same time.

Demographic variables were tabulated and analysed using descriptive statistics. To test the differences between the two groups (patients with or without medication) regarding socio-demographic or therapy variables, we used t-test for independent samples (for age), and chi-square test (with Yates correction) for other features. To explore possible association between observed features and a pharmacological treatment we calculated the odds ratio value (OR). The level of statistical significance was set at $p<0.05$. Statistical analyses were performed with the Statistical Package for Social Sciences for Windows v.11.0 (SPSS Inc., Chicago, IL, USA). This research implies only reviewing and analyzing data collected from medical records. The confidentiality of the collected data was ensured.

RESULTS

Socio-demographic features and modalities of psychiatric treatment of the patients

Over one year period 227 adolescents aged 12-18 years were treated as outpatients. There were slightly more girls: 125 (55%) versus 102 (45%) young men. The mean age of all patients was 16.4±1.18 year. A majority of patients have been treated pharmacologically, 162 of 227 (71.4%). The mean age for pharmacologically treated patients was 16.6±1.06 year, and of those without pharmacological treatment was 15.9±1.12 year. A t-test was used to determine the difference between the groups regarding age, and pharmacologically treated children were significantly older ($t=-4.678$; $p<0.0001$) in this sample. The two groups of outpatients, those with or without pharmacotherapy, were significantly different in terms of sex, too: there were significantly more boys in the group with pharmacotherapy ($\chi^2=5.175$, $p=0.023$). During the observed period 55 adolescent patients were hospitalized, 50 adolescents were included in the psychotherapy programmes through Day hospital, 85 patients were treated with individual psychotherapy, and 8 participated in family psychotherapy. Heredity for psychiatric disorders was found in 33 patients, 33 lived in dysfunctional families, 40 adolescents were living with a single parent, 17 were living in institutions (institutions for homeless children or institutions for upbringing) (Table 1). Notable number of patients were included in more than one tretment modality during the observed time period.

The two groups of outpatients (with or without pharmacotherapy) were significantly different in terms of hospitalization status, there were more hospitalized adolescents among patients with pharmacotherapy ($\chi^2=20.612$, $p<0.0001$). There were no significant differences between groups regarding: involvment in daily hospitals ($\chi^2=0.996$; $p=0.318$), involvment in individual psychotherapy ($\chi^2=0.065$; $p=0.799$), involvment in family psychotherapy ($\chi^2=0.927$; $p=0.335$), positive heredity for psychiatric disorders ($\chi^2=1.843$; $p=0.175$), living in dysfunctional family ($\chi^2=0.492$; $p=0.483$), living with a single parent ($\chi^2=0.163$; $p=0.687$) and living in an institution ($\chi^2=0.829$; $p=0.463$).

As a measure of association between abovementioned features and pharmacological treatment as the outcome, we calculated odds ratio (OR) values (Table 1). The results indicate that male adolescents (OR=2.09, $P<0.05$) and hospitalized adolescents (OR=15.32, $P<0.0001$) were more prone to be treated with drugs in our sample (Table 1).

Psychiatric morbidity

In this sample, most adolescents had psychotic disorders, 51 of them (Table 2). Psychotic disorder (code F20-29 according to the International Classification of diseases, 10th edition ICD-10) as a single diagnosis was found in 39 patients, more often in boys. It should be

mentioned that 12 other patients had the diagnosis of nonspecific acute or transient psychotic disorder (F23.9) as a comorbid diagnosis. Psychotic disorders were closely followed by various reactive conditions (F43), counting 37 patients, most of them were diagnosed with adjustment disorder (F43.2). The number of patients treated for various anxiety disorders was 34, mostly girls. In our sample, conduct disorders (F91, F92) were found in 26 patients (14 male vs. 12 female). Affective or mood disorders (depressive episodes, recurrent depressive disorder, and bipolar affective disorder) have been diagnosed in 24 adolescents; two thirds of them were girls. The number of patients being treated for 'Other behavioural and emotional disorders that occur in childhood and adolescence' (F98) diagnosis was 23, mostly female (20 vs. 3). In this diverse group of clinical entities listed are: enuresis, encopresis, eating disorders of childhood, stereotypic disorders, stuttering, speech disorders, and nonspecific emotional early childhood disorders. Twelve patients were diagnosed with emotional disorders that occur in childhood (F93). Different clinical pictures were described here: separation anxiety, childhood phobia, social anxiety in childhood, sibling rivalry, other and non-specific emotional disorders. There were 12 patients with mental retardation (F70-F79) (Table 2).

Other psychiatric diagnoses were noted in less than ten patients during the observed period: developmental disorders of learning or school abilities (F81, F83), eating disorders (F50), attention and hyperactivity disorder (ADHD, F90) and substance abuse or addiction (F10-F19) (Table 2). Disorders diagnosed in less than five patients were: pervasive developmental disorders (autistic spectrum disorders, F84), mental disorders caused by palsy, brain damage and dysfunction (F07), inorganic sleep disorder (F51), psychiatric and behavioural disorders within other diseases (F54) and tic disorder (F95).

The number of diagnoses (253) exceeds the number of patients because many patients (101, 44.5%) had two and more diagnosed disorders.

Prescription patterns

During the observed one year period, there were 454 different prescribing patterns. Most of the prescriptions were for antipsychotics (166), 36.6% of all prescriptions, followed by anxiolytics' (31.5%) and antidepressants' (23.7%) prescriptions. Mood stabilizers were prescribed in only 5.3% of all prescriptions. The remaining prescriptions (2.9%) prescribed

Table 1. The odds ratio value (OR) between socio-demographic or treatment features and prescribed pharmacological treatment to patients

Socio-demographic and treatment features***	Patients with pharmacotherapy N=162 (71.4%)	Patients without pharmacotherapy N=65 (28.6%)	OR	95% CI	p
Male	81	21	2.09	1.145-3.834	0.016*
Psychiatric heredity	22	4	2.39	0.792-7.249	0.122
Dysfunctional family	25	7	1.51	0.619-3.691	0.364
Living with one parent	27	13	0.80	0.384-1.668	0.552
Living in institutions	10	7	0.54	0.198-1.499	0.240
Hospitalization	53	2	15.32	3.609-65.004	0.000**
Daily hospital	39	11	1.55	0.741-3.268	0.242
Individual psychotherapy	62	23	1.13	0.622-2.061	0.685
Family psychotherapy	4	4	0.39	0.094-1.592	0.188

* P<0.05; **P<0.001; *** Patients could be involved in more than one treatment modality

Table 2. Number of patients diagnosed with specific psychiatric disorder

Psychiatric disorder (ICD 10 code)	Male	Female	Total*
Psychotic disorders (F20-F29)	29	22	51
Psychological reaction to stress or trauma (F43)	16	21	37
Anxiety disorders (F40-F48, excluding F43)	11	23	34
Conduct disorders (F91, F92)	14	12	26
Affective or mood disorders (F30-F39)	8	16	24
Other behavioural and emotional disorders (F98)	3	20	23
Emotional disorders that occur in childhood (F93)	5	7	12
Mental retardation (F70-F79)	8	4	12
Developmental disorders of learning or school abilities (F81, F83)	5	1	6
Eating disorders (F50)	-	5	5
Attention and hyperactivity disorder (F90)	5	-	5
Substance abuse or addiction (F10-F19)	3	2	5

* Patients could be diagnosed with more than one psychiatric disorder; ICD 10 - International Classification of Diseases, 10th edition

Table 3. Features of antipsychotic prescription patterns

Antipsychotic drug	Percentage of prescriptions*	DD range (mg)	Commonly pre scribed DD (mg)	Number of patients
Risperidone	29%	0.25-4	1	48
Quetiapine	26.6%	12.5-400	50	34
Olanzapine**	10.2%	5-15	5	17
Aripiprazole	10.2%	3.75-40	10	15
Promazine	7.2%	12.5-125	25	12
Clozapine	5.4%	25-250	25	7
Ziprazidone	4%	40-120	40	6
Fluphenazine	1.2%	1-3	1	2
Paliperidone palmitate***	7.2%	50-150 mg monthly	100 mg monthly	11

DD - daily dose; * Percentage of prescriptions in all antipsychotic prescription; ** One patient was receiving long-lasting form of olanzapine; *** Long-lasting (depot) form of risperidone active metabolite

other psychotropic drugs (methylphenidate, hypericum perforatum, propranolol, atenolol, biperiden). The most commonly prescribed drugs were: alprazolam among anxiolytics, sertraline among antidepressants and risperidone among antipsychotics.

However, if we look at the number of patients treated with specific class of drugs, the list is slightly different. Most of the patients (110) were ordered to take anxiolytics, closely followed by patients taking antipsychotics (103) and patients taking antidepressants (99). The highest number of patients was treated with sertraline (58), followed by those treated with risperidone (48).

During the observed period, there were 162 patients ordered to take pharmacotherapy. In our sample monotherapy (just one drug at the same time) was prescribed for 58 patients: 26 patients were taking anxiolytics, 17 antidepressants, 13 antipsychotics, and 2 of them were on mood stabilizers. Majority of the patients were treated with polytherapy (104/162). For 50 patients the prescribed treatment included two drugs taken together. The combinations were as follows: antidepressant + anxiolytic for 21 patients; antipsychotic + anxiolytic for 19 patients and antipsychotic + antidepressant for 10 patients. There were 48 patients ordered to take a combination of three drugs, most of them were treated with combination of antipsychotic + antidepressant + anxiolytic. Only 6 patients were treated with four different classes of drugs simultaneously, and the combination was: antipsychotic + antidepressant + anxiolytic + mood stabilizer. In almost all modalities of prescribing, the proportions of male and female patients were not considerably different, with one exception: combination of antipsychotic + antidepressant + anxiolytic was proscribed more often to the girls (34 female versus 13 male).

Prescribed antipsychotics

Within the one year period, antipsychotics were prescribed 166 times, 36.6% of all prescribed drugs (454). Risperidone makes for 29% of the prescribed antipsychotics and it was the most prescribed antipsychotic in this research (Table 3). It was prescribed to 48 patients during one year. Paliperidone palmitate, an active metabolite of risperidone in depot form, makes for 7.2% of all prescribed antipsychotics, 11 patients received this drug. Quetiapine makes for 26.6% of prescribed antipsychotics; it was prescribed to 34 patients. Olanzapine makes for 10.2% of prescribed antipsychotics. In the examined year it was prescribed 17 times to 17 patients. One of these patients was receiving long-lasting (depot) form of olanzapine. Aripiprazole makes for 10.2% of prescribed antipsychotics. It was given to 15 patients. Promazine makes for 7.2% of prescribed antipsychotics for 12 patients. At the end of the list were: clozapine, ziprasidone and fluphenazine (Table 3).

Side effects linked to antipsychotics were recorded in medical charts nine times. Excessive drowsiness was noted in one patient after initiation of risperidone (0.25 mg) in addition to previously prescribed 25 mg of clozapine and 50 mg of sertraline, daily. One of the patients developed dermatitis after increasing the doses of quetiapine (DD 150 mg), which was prescribed in combination with promazine 25 mg and fluvoxamine 200 mg, daily. One of the patients developed swelling of fingers after consumption of olanzapine (DD 5 mg), however the patient was already receiving paliperidone palmitate (150 mg monthly) and fluvoxamine (DD 100 mg). One patient developed arrhythmia at a dose of 10 mg of aripiprazole, taken together with previously prescribed fluvoxamine DD 200 mg. Another patient developed hyperprolactinemia, with itching, redness and dandruff-like urticaria at a dose of 20 mg of aripiprazole, combined with fluvoxamine DD 100 mg. One patient complained of stomach ache while using aripiprazole at a DD of 10 mg as a monotherapy. At the DD of 25 mg of promazine, one of the patients developed increased salivation, combined with DD 5 mg of aripiprazole and 20 mg of diazepam. Another patient gained 5 kg in three weeks after increasing DD of promazine to 100 mg, combined with DD of aripiprazole 30 mg and sertraline 50 mg. There were five more notifications of side effects; some of them emerged during medication with antipsychotics, but clinicians linked these side effects to other groups of psychotropic drugs which were taken concomitantly.

Table 4. Features of antidepressant prescription patterns

Antidepressants	Percentage of prescriptions*	DD range (mg)	Commonly prescribed DD (mg)	Number of patients
Sertraline	49%	25-200	50	58
Fluvoxamine	27.8%	50-200	100	29
Escitalopram	7.4%	5-15	10	9
Tianeptine	7.4%	12.5-50	37.5	8
Venlafaxine	3.7%	37.5-150	-	3
Mirtazapine	1.8%	15-30	-	2
Fluoxetine	1.8%	20-40	-	1
Paroxetine	0.9%	20	-	1

DD - daily dose; * Percentage of prescriptions in all antidepressant prescription

Prescribed antidepressants

Within the aforementioned year, antidepressants were prescribed 108 times, and that is 23.7% of all prescriptions. Sertraline makes for 49% of prescribed antidepressants and is the most prescribed antidepressant, used in 58 patients (Table 4). Fluvoxamine makes for 27.8% of prescribed antidepressants, used in 29 patients. Third place on the list is for escitalopram (9 patients), closely followed by tianeptine (8 patients). Rarely prescribed antidepressants (less than 5 patients) were: venlafaxine, mirtazapine, fluoxetine and paroxetine (Table 4). Side effects were noted in four patients, three of them with sertraline as a monotherapy. One patient, at a daily dose of 50 mg of sertraline, was extremely irritable; another developed hypomanic-like behaviour and epistaxis at the same dose. Another patient developed pain in the epigastric region at a daily dose of 100 mg. One patient developed sweating and restlessness at a daily dose of 112.5 mg of venlafaxine, prescribed together with quetiapine 300 mg and alprazolam 1 mg, daily.

Prescribed anxiolytics and hypnotics

Within the year, anxiolytics have been prescribed for the adolescents 143 times, 31.5% of all prescriptions. In the analysis of pharmacotherapy prescribing patterns only those anxiolytics that had been prescribed to patients as continuous, daily therapy for at least one month were taken into account. Alprazolam makes for 55.2% of prescribed anxiolytics and is the most prevalent anxiolytic. It was used in 25 patients (DD range from 0.0625 to 3 mg; most usual DD 0.25 mg). Diazepam makes for 28.7% of prescribed anxiolytics, used in 25 patients (DD range 2-25 mg, usual DD 5 mg). Rarely prescribed anxiolytics were: oxazepam prescribed for 2 patients (DD range 10-30 mg); bromazepam (1 patient, DD 1.5 mg). The most prescribed hypnotic drug was zolpidem, it was involved in the treatment of 8 patients (DD range 5-10 mg, usual DD 5 mg). Midazolam was used to treat only one patient (DD 15 mg), same as zaleplon (DD 10 mg) and flurazepam (DD 15 mg). No side effects have been linked to these groups of drugs in inspected medical charts.

Prescribed mood stabilizers

Within the year, mood stabilizers were prescribed in the said population only in 24 cases. Seven patients used valproate during the year (DD range 150-800 mg), same as lamotrigine (7 patients, DD range 50-300 mg). Carbamazepine was used to treat 6 patients (DD range 150-600 mg). Clonazepam is known for its anxiolytic action and was used to treat 4 patients in this sample, DD range was 0.125-2 mg. One side effect linked to mood stabilizers was recorded during one year: a patient developed a marked daily drowsiness at a dose of 75 mg of lamotrigine; however it was prescribed together with 50 mg of sertraline, 120 mg of ziprasidone and 2 mg of alprazolam.

Prescriptions of other psychotropic drugs

There were nine patients on therapy with other psychotropic drugs. Biperiden, which is taken to suppress extrapyramidal side effects, was prescribed for three patient; methylphenidate (2 patients), propranolol (2 patients), atenolol (1 patient); and herbal antidepressant St. John's wort (hypericum perforatum) for one patient in our sample.

DISCUSSION

Main findings of this study are: 1) majority of the patients were treated with psychiatric medication; 2) in the pharmacologically treated group, adolescents were older, predominately male and hospitalized; 3) psychotic disorder was the most commonly diagnosed disorder and antipsychotics were most commonly prescribed class of drugs; 4) majority of the patients were treated with polytherapy.

Discussion about studied prescription patterns must take in consideration some characteristics of the sample. From the data obtained it is evident that at the Department of child and adolescent psychiatry there was approximately equal number of male and female outpatients, slightly favouring the female (55%). The fact that internalizing mental disorders (depression, anxiety, eating disorders) are more common in adolescent girls (Herpertz-Dahlmann et al. 2013), could explain more girls in our sample. Mental disorders are more common in boys

before puberty, and after that time females predominate (Herpertz-Dahlmann et al. 2013). Also, it is possible that adolescent girls are more inclined to seek professional mental help, compared to young men, similar to trend noticed in adult population (Pattyn et al. 2015).

The prevalence of serious mental disorder in adolescence is estimated to be around 10%; and approximately one in five adolescent suffers from a mental disorder (Herpertz-Dahlmann et al. 2013). Prevalence of internalizing mental disorders is estimated to be in ranges from 12-23%; prevalence of disruptive or conduct disorders 5-10% (Herpertz-Dahlmann et al. 2013). The global coverage of prevalence data for mental disorders in children and adolescents is still limited (Erskin et al. 2017). According to Austrian epidemiological study (3615 adolescents, 10-18 years), the highest lifetime prevalence rates are for anxiety disorders (15.6%), followed by neurodevelopmental disorders (9.3%), attention deficit hyperactivity disorder (5.2%) and depressive disorders (6.2%); and almost half of adolescents with a lifetime psychiatric disorder had a second diagnosis (Wagner et al. 2017). The diagnostic category most commonly found in our sample of adolescent outpatients was psychotic disorder. One of the possible reasons for that is the highest incidence of schizophrenia in adolescent population. This domination of serious psychotic disorders in our sample can be explained as the consequence of the stigmatization. Therefore, only those with the most severe disabilities seek aid at the Psychiatric Clinic. Majority of individuals with lesser disturbances, particularly those suffering from anxiety or mild depression, tend to seek out help outside the psychiatry (paediatric clinic, private psychologist or psychotherapist, free counselling for students etc.).

There was an interesting finding that mostly girls were diagnosed with 'various disorders that typically occur in childhood and adolescence' (F98), usually 'unspecified' category (F98.9). This ICD-10 code was usually noted when clinicians understood clinical presentation as an adolescent crisis. The concept of adolescent crisis implicate that psychological symptoms are extreme manifestations of normal developmental processes. The affected adolescent usually regains 'normality'; however it is possible that these clinical pictures are early manifestations of a personality or psychotic disorder. Nevertheless, this result could indicate the possible gender bias. Another possible explanation is that affective disorders, almost underdiagnosed in this sample, were 'hidden' in atypical clinical manifestations.

Surprisingly, in our sample there were only five patients with attention deficit and hyperactivity disorder (ADHD) and five girls with diagnosed eating disorders. It is likely that patients with ADHD are being treated at the paediatric services because this disorder is by and large diagnosed in preschool and school children. Similar to that, it is possible that girls suffering from eating disorders are also treated at paediatric departments, as current studies indicate that eating disorders are becoming more common among children (Halmi 2009). Comparing our sample with known epidemiological findings, there is more psychotic disorders and less mood and anxiety disorders than expected.

In our sample most of the patients (71.4%), were treated with psychiatric medication. This is not a surprise knowing that recent international trends of prescribing psychotropic medication for children and adolescents are on the rise, (Rani et al. 2008, Gilat et al. 2011, Olfson et al. 2012, Steinhausen & Bisgaard 2014), more in USA than in Europe (Bachmann et al. 2016). Proposed explanations for this rise are numerous. For example, puberty starts earlier; gap between adult and youth medication rates has narrowed; more children and adolescent seek professional help; the pro-pharmacy impact of pharmaceutical companies (Steinhausen 2015, Pennap et al. 2018).

The results revealed that antipsychotics were the most prescribed drugs. That is in concordance with latest studies showing significant increases in the use of antipsychotics in children and adolescents, globally (Olfson et al. 2012, Pringsheim et al. 2014, Bachmann et al. 2014, Sohn et al. 2016). A study by Patel reported that the usage of antipsychotics in children and adolescents increased 1.5 to 3-fold from 1996. to 2001. (Patel et al. 2005). The overall prevalence of psychotropic drug prescription in Italy from 2006. to 2011. was stable, and no significant trend was found, however there was a slight increase in antipsychotic prevalence and a decrease in antidepressants prevalence (Piovani et al. 2016). On the contrary, one research showed that antipsychotic prescription percentages (USA sample of children and adolescents) were lower than antidepressant, with a peak in adolescence (Sultan et al. 2018).

Risperidone prevails in our study, like in many others (Baeza et al. 2014, Liu et al. 2014, Rettew et al. 2015, Piovani et al. 2016, Park et al. 2018). In abovementioned study in Italy (Piovani 2016), risperidone was the most prescribed antipsychotic, as well as the most prescribed psychotropic medication in the overall population and in school-aged children. Risperidone was the most commonly prescribed antipsychotic for a Medicaid insured children and adolescents in Vermont (USA), followed by quetiapine and aripiprazole; together, these three medications comprised 90% of the antipsychotic prescriptions (Rettew et al. 2015). It is interesting that proportions of prescribed risperidone and quetiapine are very similar to proportions in our sample. The study conducted in Korea (Park et al. 2018) discovered that most prescriptions for children and adolescents with schizophrenia were risperidone and aripiprazole prescriptions. Olanzapine was less frequently prescribed in our sample which may be the consequence of its most unpleasant side effect: weight gain. Quetiapine shows a more favourable side effect profile and wider dosage range. That's probably one of the reasons why it is so often prescribed for adolescents in this sample. It should be noted that observed prescribing of antipsychotics complies with the range of recommended daily doses for minors (Findling 2008,

Taylor et al. 2009, Croatian Psychiatric Society guidelines 2016, National Institute for Health and Care Excellence (NICE) UK guidelines 2015), with only one exception of aripiprazole (DD 40 mg for one patient). Guidelines show that treating psychosis in children is similar to treating them in adults, in addition to requiring better monitoring due to possibility of developing metabolic disorders (Kumra et al. 2008). Looking at the antipsychotic prescribing patterns, researchers concluded that these patterns may reflect the heterogeneity of disorders and conditions treated with antipsychotics (Sultan et al. 2018).

In our research 99 (out of 227) patients were prescribed with antidepressants. Some studies did report decrease in antidepressant prescriptions for children and adolescence since FDA black-box warning in 2004 (Friedman et al. 2014); but recent research from five Western countries showed that there is an increase in youth cohorts from 2005 through 2012 (Bachmann et al. 2016). Antidepressant use increases with age and peak prevalence is highest for young adults age 24 (Sultan et al. 2018). The research conducted in Korea explored prescription patterns of antidepressants for children and adolescents during 2013 (Myong-Wuk et al. 2017). Among the prescriptions, escitalopram (24.1%) and fluoxetine (20.5%) were the two most frequently prescribed drugs (Myong-Wuk et al. 2017). The multi-centric survey conducted in ten Asian countries revealed that fluoxetine, sertraline, and escitalopram were the most common among prescribed antidepressants for children and adolescents (Chee et al. 2016). According to international guidelines and analyses, the first line of antidepressants should be selective serotonin reuptake inhibitors (SSRI) (Findling 2008, Strawn et al. 2015, Croatian Psychiatric Society guidelines 2016, National Institute for Health and Care Excellence (NICE) UK guidelines 2015). Our data show that these guidelines were respected. All SSRIs were prescribed within the recommended doses range. In should be noted that in Germany and UK there is a notable proportion of tricyclic antidepressant prescription, even in 2012 (Bachman et al. 2016). In our research it is evident that tricyclic antidepressants were not used at all.

This research showed that anxiolytics are the most prescribed medication even when disregarding patients who use anxiolytics only when needed. That may be a potentially worrying fact, although doses that were prescribed were low, up to eighth of the adult doses. Danish study finds this class of drugs prescribed only in small proportions for children, with no significant change over time (Steinhausen & Bisgaard 2014). Mood stabilizers, as a group of drugs, were initially used to treat epilepsy in children and adolescents. For that reason, theirs action and side-effects are well known in the paediatric practice. In the studies of prescription patterns, there were no special considerations for this class of drug. It is possible that atypical antipsychotics (second and third generation) are favourable by clinicians due to their safety and side-effect profile.

Majority of the patients in our sample (104/227) were treated with polytherapy. One study of prescription patterns also discovered that antipsychotics were rarely used as monotherapy; mostly they were combined with stimulants, adrenergic agents and antidepressants (Rettew et al. 2015). Contrary to that, in the Croatian study (Maršanić et al. 2012) atypical antipsychotics were used as monotherapy in 62.2% of outpatients. The Korean research (Myong-Wuk et al. 2017) discovered that majority of antidepressant's prescriptions (60.5%) included concomitant psychotropic agents, consisting of antipsychotics (26.7%), sedatives (26.3%) and stimulants (24.4%). Published data suggest that a significant number of children and adolescents are treated with psychotropic polytherapy (Wilens et al. 1995, Toteja et al. 2014, Saldaña et al. 2014). Psychiatric polypharmacy may be associated with increased side-effects, non-adherence and greater costs. On the other hand, this research has shown relatively few side effects. Most likely reason for this finding is that side effects were not recorded if they were transient or low in intensity. It should be pointed out that most of the side effect occurred in patients on polytherapy. This is a significant finding, asking for further investigation in more detailed research.

In the pharmacologically treated group, adolescents were older, predominately male and hospitalized. Similar results were obtained in larger studies. Multicentre Italian study showed that psychotropic drug prevalence increased with increasing children's age; and males were more exposed to psychotropic drugs than females (Piovani et al. 2016), same was found in Taiwan retrospective study (Hsu et al. 2013). Similar to that, retrospective study conducted in USA (2006-2010) disclosed that males were more likely than females to use antipsychotics, especially during childhood and adolescence (Olfson et al. 2015). Comparable retrospective study from Croatia (Maršanic et al. 2012) revealed that antipsychotic therapy was significantly more common in boys and in adolescents than children. Annual antipsychotic prescription percentages for males were higher than corresponding percentages for females in USA children and adolescent (Sultan et al. 2018). Our research discovered that hospitalized adolescents were more disposed to be medicated. This result is logical and expected; it stems from the fact that patients suffering from more severe mental disorders also need more 'severe' treatment interventions, such as medication and hospitalization.

The main limitations of this retrospective study are small sample, short period of observation and prescribed patterns of only three psychiatrists, therefore it can hardly be representative for general population of adolescents. Furthermore, there is markedly different proportion of several psychiatric disorders, compared to those usually found in adolescent population. In conclusion, for more precise data about prescribing patterns, we should include the psychiatrists working outside of the psychiatry clinic. In this study we didn't explore the proportions of off-label use of antipsychotics and corre-

lations between diagnosed disorders and prescribed medication. Regarding the fact that the medications were prescribed by experienced subspecialists, it can be assumed that their experience and knowledge makes it possible for them to individualize the treatment according to the patient, even though it makes them disregard official indications. Despite these limitations, our findings show that our subspecialist prescribing practice mostly follows professional guidelines and international trends.

CONCLUSION

Prescribing psychiatric pharmacotherapy for adolescents is a common clinical practice. Majority of the outpatients received psychotropic prescription; most of them were treated with polytherapy. Psychotic disorder was the most commonly diagnosed disorder and the greatest number of prescription included antipsychotics. However, number of patients receiving antipsychotics, antidepressant and anxiolytics was quite similar. Adolescents with pharmacotherapy were significantly older; hospitalized and male adolescents were more prone to be medicated, consistent with recent findings. The prescribing patterns are generally consistent with trends and guidelines; however caution regarding high proportion of polytherapy is necessary.

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All authors contributed equally to the paper design, writing and edits of the manuscript drafts. All authors read and approved the final manuscript.

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