

Research article Ερευνητική εργασία

Psychotropic medication use in children and adolescents in an inpatient setting

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Psychiatriki 2011, 22:314–319

Medication can be an effective part of treatment for several psychiatric disorders of childhood and adolescence but its use should be based on a comprehensive psychiatric evaluation and treatment plan. The aim of this study was to evaluate psychotropic medication use for children and adolescents treated as inpatients and to compare it with principles of rational pharmacotherapy, thus identifying possible downsides of current practices and pointing a way towards safer and more efficient practices. This is a descriptive study of prescribing trends at the Clinical Department for Children and Adolescents of the Institute of Mental Health in Belgrade, during the period from September 2009 to September 2010. Analyzed demographic data (age, gender) and the number of hospitalizations were obtained from medical histories, while diagnoses were obtained from discharge notes. Prescribed therapy was copied from medication charts. Drug dosages were analyzed as average daily doses prescribed during the hospitalization. Psychiatric diagnoses were classified according to The International Classification of Diseases and Related Health Problems, 10th Revision (ICD-10). During the examined time period, 264 patients were hospitalized (61.4% males), with an average age of 11.4 ± 5.1 years. We have found that 66.3% of admitted patients were treated with pharmacotherapy in addition to other treatment modalities. There was a highly significant correlation between the age of patients and the prescribed dosage (Spearman's $\rho = 0.360$, $p < 0.001$) as well as the number of prescribed drugs (Spearman's $\rho = 0.405$, $p < 0.001$). The most commonly diagnosed psychiatric disorders were: autism spectrum disorders (20.8%), conduct disorders (19.7%), mixed developmental disorder (14.8%), adjustment disorder (7.2%), mental retardation (7.2%), acute psychosis (4.5%), and ADHD (2.3%). The most commonly prescribed medications were antipsychotics (45.9%), followed by antidepressants (17.2%), mood stabilizers (16.1%), benzodiazepines (14.4%), and other psychotropic drugs (6.4%). The most commonly prescribed antipsychotic was risperidone, used for more than 50% of the patients treated with antipsychotics. Taken together risperidone and chlorpromazine were more than 75% of all prescribed antipsychotics. 98.4% of prescribed antidepressants belonged to the SSRIs, with sertraline and fluoxetine accounting for almost 90% of them. All prescribed dosages were in accordance with the official guidelines. This is the first survey in Serbia to document the practice of prescribing psychotropic medication in the field of child and adolescent psychiatry. Current drug-prescribing practices at the Clinical Department for Children and Adolescents of the Institute of Mental Health in Belgrade are in accordance with current practices in the United States and Europe. Not every child with symptoms of mental health problems needs pharmacological treatment; when they do, the general rule of thumb should be "start low, go slow, and taper slowly". Follow-up studies are necessary to assess the change of trends, as well as studies in different patient populations and health centers, in order to globally evaluate psychotropic medication use in children and adolescents in Serbia.

Key words: Psychopharmacology, medication, children, adolescents, inpatients

Introduction

Pediatric psychopharmacology is a field in rapid growth according to the expanding research and regulatory action. At the same time, this area is frequently the object of different and controversial debates in the media and the general public because of the very delicate issue concerning the application of psychotropic agents in treatment of children and adolescents with mental disorders.

Key elements in the field of pediatric psychopharmacology include the specificities of the child development (in particular, the developing brain), psychopathology, chemical compounds that act on the brain, and the therapeutic objectives. Because of that, clinicians must integrate information from variety of sources in order to achieve coherent conclusions about treatment effects. However, pharmacological treatment during childhood and adolescence when the organism undergoes marked developmental changes may result in toxicities not seen in adults.^{1,2} The administration of agents acting on neurotransmitter systems in rapid development may interfere with normal processes and result in unwanted long-lasting changes.

Even though psychotropic drugs are increasingly more present in the treatment of psychiatric disorders of children and adolescents, the efficacy and safety have been tested in only several groups of drugs. The vast majority of psychotropic drugs are still prescribed "off-label".³⁻⁵ The off-label use of drugs is not in itself an inappropriate practice, because it is often supported by considerable empirical evidence and is consistent with treatment guidelines. However, it is important to inform parents that medication is going to be prescribed off-label before making treatment decisions for their child.

Testing the safety and efficacy of psychotropic drugs in child psychiatry is particularly significant because of the huge differences in the metabolism of certain drugs that were discovered in different age groups, i.e. a varying absorption rate, metabolism and excretion rates, frequently leading either to sub-dosing of medication or pronounced side-effects.⁶

The decision to use psychotropic agents has to be grounded on a good diagnosis with the aim to improve the patient's well-being and to enable his or her optimal growth and development.³ The general rule of thumb for introducing medication to children and adolescents is "start low, go slow, and taper slowly".⁷

Pharmacoepidemiological analyses of the use of medication world-wide have shown great differences in frequency of prescribing medication in clinical practice in different countries or even different mental health centers of the same country, depending on the predominant theoretical approach, medication prices, or availability of drugs on the market.⁶ For example, two thirds of antipsychotic medication prescribed to children and adolescents in the USA belong to the class of atypical antipsychotics, whereas the same class of drugs is prescribed in only 5% of cases in Germany.⁵ Over 70% of children and adolescents with mental health problems in Australia are receiving two or more psychotropic drugs simultaneously, while only 5% of child psychiatrists prescribe stimulants and antipsychotics to children younger than 3 years. Roughly around 40% of indications for prescribing are off-label indications.⁸

According to existing data, there is a trend of prescribing atypical antipsychotics (risperidone, clozapine) as well as an increase of antidepressant prescriptions in Serbia's adult population.⁹ An assessment of drug prescribing trends in Serbia's child and adolescent population is necessary in order to evaluate current therapeutic practice and to compare it with principles of rational pharmacotherapy worldwide, thus identifying possible downsides of current practices and point a way towards safer and more efficient practices.^{5,10}

Materials and method

This is a descriptive study of prescribing trends at the Clinical Department for Children and Adolescents of the Institute of Mental Health in Belgrade, Serbia, during the period from September 2009 to September 2010.

Analyzed demographic data (age, gender) and the number of hospitalizations were obtained from medical histories, while diagnoses were obtained from discharge notes. Prescribed therapy was copied from medication charts. Drug dosages are presented as average daily doses prescribed during the hospitalization. Dosages are analyzed and compared to the recommended daily dose, average age of patients, as well as to gender and number of previous hospitalizations.

Psychiatric diagnoses are classified according to The International Classification of Diseases and Related Health Problems, 10th Revision (ICD-10),¹³ while drugs

are classified according to The Anatomical Therapeutic Chemical (ATC) Classification System.¹⁴

The study was approved by the Ethical Committee of the Institute of Mental Health.

Data were analyzed using descriptive and analytical statistical methods (t-test, Spearman correlation test) using the SPSS 16.0 software.

Results

During the examined time period, 264 inpatients were treated at the Clinical Department for Children and Adolescents, 61.4% of which were male, and 38.6% female. Of the total number of inpatients in the studied period, 66.3% that were treated with psychotropic agents in addition to other treatment modalities were included in the study.

The average age of inpatients was 11.40 years (SD=5.09) ranging from 3 to 17 years. On average, male patients were younger (10.17 years; SD=4.79) than females (13.35 years, SD=4.16); the difference is statistically highly significant ($t=5.14$, $p<0.01$). Average number of hospitalizations per patient was 1.91 (SD=2,557), ranging from 1 to 32. No significant statistical difference was found in number of hospitalizations per gender.

There was no significant difference in drug dosing nor the number of prescribed psychotropic drugs per gender. However, there was a highly significant correlation between the age of patients and the prescribed dosage (Spearman's $\rho=0.360$; $p<0.001$). When the number of prescribed drugs were compared with the patient age, a positive, highly significant correlation was found (Spearman's $\rho=0.405$; $p<0.001$).

The most commonly diagnosed psychiatric disorders were: autism spectrum disorders (20.8%), conduct disorders (19.7%), mixed developmental disorder (14.8%), adjustment disorder (7.2%), mental retardation (7.2%), acute psychosis (4.5%), and ADHD (2.3%).

The most commonly prescribed medications were antipsychotics (45.9%), followed by antidepressants (17.2%), mood stabilizers (16.1%), benzodiazepines (14.4%), and other psychotropic drugs (6.4%)

Table 1 shows the most frequently prescribed drugs. The most commonly prescribed antipsychotic was risperidone, used for more than 50% of the patients treated with antipsychotics. Taken together risperidone and chlorpromazine were more than two thirds of all

prescribed antipsychotics. Two most commonly used antidepressants, sertraline and fluoxetine, accounted for almost 90% of all applied antidepressants.

Our analysis has shown that 6.4% of prescribed drugs did not belong to any of the mentioned categories – 30% of those was methylphenidate (average dose was 30.12 mg; SD=0.27), 54.2% was biperiden with an average dose of 1.92 mg (SD=0.27), zolpidem in 8.3% (average dose of 5 mg), as well as propranolol in 4.2%, dosed at 30 mg per day.

Antidepressants were most commonly prescribed for the following diagnoses: F92 (31.1%), F43 (24.6%), F42 (11.5%). The most frequent indications for antipsychotics were F92 (22.3%) and F84 (18.0%). The total amount of antipsychotics prescribed for disorders from the psychotic spectrum (F20–F29) was 13.6%, while 27.3% of mood stabilizers were prescribed for patients diagnosed as F92; 18.2% was prescribed for F84, and 9.1% for F70. As for mood stabilizers, in 4.5% they were prescribed for the bipolar disorder – sodium valproate, carbamazepine, and lamotrigine account for 98.3% of used stabilizers.

Discussion

This is the first survey in Serbia to document the practice of prescribing psychotropic medication in the field of child and adolescent psychiatry.

The results of our study have shown that two thirds of inpatients during the studied period of time were treated with a combination of psychotropic drugs and other treatment modalities –individual, group, and occupational therapy– whereas one third of patients were not treated with medication at all. Younger patients were given smaller doses and fewer drugs, with dosages and the number of prescribed drugs increasing with age. These findings are consistent with the “start low, go slow” dosing principle, as well as with the caution advised when prescribing psychotropic drugs for younger children.^{3,7}

We have found that a wide range of psychotropic medication has been prescribed on a regular basis, with antipsychotics being the most prescribed drugs, which is not consistent with studies conducted in countries such as Australia or USA, reporting that stimulants are by far the most commonly prescribed drugs.^{7,8} Antipsychotics are most commonly prescribed for conduct disorders and autism, as well as for psychotic disorders, all of which are official indications. All pre-

Table 1. Most frequently prescribed psychotropic agents at the Clinical Department for Children and Adolescents

| <i>Drug</i> | <i>(%)</i> | <i>Dosage (mg)</i> | <i>SD</i> |
|-------------------------|------------|--------------------|-----------|
| <i>Antipsychotics</i> | | | |
| Chlorpromazine | 20.9 | 69.18 | 28.39 |
| Risperidone | 56.4 | 2.44 | 7.49 |
| Haloperidol | 7.6 | 2.08 | 1.37 |
| Levopromazine | 4.1 | 104.69 | 85.03 |
| Olanzapine | 1.2 | 6.25 | 1.77 |
| Clozapine | 5.2 | 188.89 | 123.82 |
| Quetiapine | 2.3 | 38.75 | 10.31 |
| Fluphenazine | 2.3 | 2.75 | 1.50 |
| <i>Antidepressants</i> | | | |
| Sertraline | 65.6 | 70.62 | 36.64 |
| Paroxetine | 8.2 | 20.00 | 0.00 |
| Fluoxetine | 23.0 | 20.00 | 0.00 |
| Escitalopram | 1.6 | 10.00 | 0.00 |
| Mianserin | 1.6 | 30.00 | 0.00 |
| <i>Mood Stabilizers</i> | | | |
| Carbamazepine | 18.3 | 327.27 | 228.43 |
| Lamotrigine | 21.7 | 78.85 | 58.72 |
| Sodium valproate | 58.3 | 786.14 | 533.42 |
| Topiramate | 1.7 | 325.00 | 0.00 |
| <i>Benzodiazepines</i> | | | |
| Lorazepam | 55.8 | 3.12 | 2.51 |
| Diazepam | 28.8 | 9.77 | 5.35 |
| Alprazolam | 3 | 68.58 | 118.140 |
| Clonazepam | 5 | 2.40 | 0.89 |

scribed doses were within the recommended range.^{6,7} Almost two thirds of antipsychotics belonged to the second generation atypical antipsychotics, which is in accordance with trends shown in adult psychiatric population in Serbia.⁹ Worldwide trends vary with similar percentage of atypical antipsychotics prescribed in the USA.⁵

Chlorpromazine, a low-potency phenothiazine, makes up for 20.9% of total antipsychotics prescribed. Although nowadays it is considered a second choice medication for psychotic disorders, chlorpromazine was used to manage agitation, which justifies its extensive use. However, because of its well known anticholinergic and sedative side-effects, and its greater potential to produce hypotension and lower the seizure threshold than haloperidol, it ought to be used with caution.^{4,7}

The second most frequently prescribed class of drugs in our study were SSRIs, shown to have reliable efficacy and a good safety profile when used for treating children and adolescents. Clinical studies have confirmed

that fluoxetine has the largest effect size, yet it is the third most commonly prescribed SSRI in our study. Knowing that all antidepressant drugs have significant risk when given to children and young people, fluoxetine is the only antidepressant for which clinical trial evidence shows that the benefits outweigh the risks.¹⁵

All of the prescribed antidepressants were dosed within recommended dose ranges.^{6,7} Even though two thirds of used antidepressants were prescribed for official indications, the single most common diagnosis for which they were prescribed was the mixed emotional and conduct disorder (F92), for which antidepressants are not officially indicated. Significant acting out frequently occurs among children and adolescents with major depression and dysthymic disorder, so there are many common symptoms in the groups of conduct and affective disorders in children and adolescents. Also, the co-existence of major depression with conduct disorder increases the risk of impulsive suicidal behavior.¹⁴

The mood stabilizers were most commonly prescribed for conduct disorders, and only rarely for bipolar disorder, even though it is the main indication for this class of drugs. This discrepancy is due to the fact that conduct disorders make up a larger percent of inpatients. The modes of prescribing mood stabilizers were in accordance with international guidelines.^{6,7} However, the most frequently used mood stabilizer, sodium valproate, is associated with several serious side-effects, such as polycystic ovary syndrome, weight gain, as well as CNS toxicity.^{4,7}

Benzodiazepines make up for only 14.4% of prescribed psychiatric medication for children and adolescents, a conspicuously smaller percentage than the one found in Serbia's adult psychiatric population. Also, most commonly prescribed drug from this group was lorazepam, whereas for adults it is diazepam.⁹

The limitation of our study was that our results are not generalizable. In order to have a more precise picture of child and adolescent psychopharmacological trends in Serbia it would be necessary to study other mental health centers as well. Beside this, it should be kept in mind that hospitalization is required for serious and otherwise unmanageable patients, and that, very likely, this sample doesn't represent the population of outpatients. In the future, follow-up studies are necessary to assess the change of trends, as well as studies in different patient populations and health centers, in or-

der to evaluate in greater detail current child and adolescent psychotropic medication practices in Serbia.

Conclusion

Our findings have shown that current drug-prescribing practices at the Clinical Department for Children and Adolescents of the Institute of Mental Health in Belgrade, Serbia are in general accordance with current therapeutic practices in the United States and Europe.

Psychotropic medication should not be offered to a child or a young person with a mental disorder except in combination with a psychological treatment. It is well known that not every child with symptoms of mental health problems needs pharmacological treatment; when they do, the general rule should be "start low, go slow." However, the prescribing psychiatrist should monitor the child or young person's progress on a regular basis, carefully looking for adverse drug reactions, while continuously reviewing mental state.

The recent debate about the safety of prescribing and using the SSRI antidepressants in children has highlighted the need for careful evaluation and monitoring of the specificities of the psychopharmacological treatment. One obvious implication is that practicing rational pharmacotherapy requires integration of knowledge at different levels, including developmental psychopathology, pharmacology, drug regulations, and bioethics, as well as a considerable investment of time on the part of the treating clinician and the child's parent. Clinicians should use psychotropic drugs based on research evidence of their efficiency, those authorized in each country for age groups and indications, and in respect to each person's individual capacity to metabolize medication. Even though as mental health professionals we have a special responsibility to our youngest patients, it is very important to resist the pressure to "do something" rapidly with medication, particularly in those cases when a more patient and cautious approach is advised.

Χρήση ψυχοτρόπων φαρμάκων σε νοσηλευόμενα παιδιά και εφήβους

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Ψυχιατρική 2011, 22:314–319

Η φαρμακευτική αγωγή αποτελεί δυνητικά αποτελεσματικό συστατικό της αντιμετώπισης πολλών ψυχικών διαταραχών της παιδικής και της εφηβικής ηλικίας, αλλά η χρήση της πρέπει να έχει ως βάση την περιεκτική ψυχιατρική αξιολόγηση και τον θεραπευτικό σχεδιασμό. Σκοπός αυτής της μελέτης ήταν η αξιολόγηση της χρήσης της φαρμακοθεραπείας σε νοσηλευόμενα παιδιά και εφήβους και η σύγκρισή της με τις αρχές της λελογισμένης φαρμακοθεραπείας, ώστε να εντοπίσει πιθανές αδυναμίες των σημερινών πρακτικών και να υποδείξει για το μέλλον ασφαλέστερες και αποτελεσματικότερες πρακτικές. Πρόκειται για περιγραφική μελέτη των συνταγογραφικών τάσεων στο Κλινικό Τμήμα Παιδιών και Εφήβων του Ινστιτούτου Ψυχικής Υγείας Βελιγραδίου κατά την περίοδο από τον Σεπτέμβριο του 2009 έως τον Σεπτέμβριο του 2010. Τα δημογραφικά στοιχεία των ασθενών (ηλικία, φύλο) και ο αριθμός των νοσηλείων τους ελήφθησαν από τα ιατρικά ιστορικά τους, ενώ οι διαγνώσεις από τα εξιτήρια. Η χορηγηθείσα θεραπεία αντιγράφηκε από τις καρτέλες φαρμάκων. Οι δόσεις των φαρμάκων καταγράφηκαν ως οι μέσες ημερήσιες δόσεις κατά τη νοσηλεία. Οι ψυχιατρικές διαγνώσεις ταξινομήθηκαν βάσει του ICD-10. Κατά την περίοδο της μελέτης, νοσηλεύθηκαν 264

ασθενείς (61,4% άρρενες), μέσης ηλικίας 11,4±5,1 ετών. Βρέθηκε ότι στο 66,3% των νοσηλευθέντων ασθενών χορηγήθηκε φαρμακοθεραπεία σε συνδυασμό με κάποια άλλη θεραπεία. Υπήρχε στατιστικά σημαντική συσχέτιση ανάμεσα στην ηλικία των ασθενών και τη δόση ($\rho=0,360$, $p<0,001$) καθώς και τον αριθμό των χορηγούμενων φαρμάκων ($\rho=0,405$, $p<0,001$). Οι συνηθέστερες διαγνώσεις ήταν: διαταραχές του αυτιστικού φάσματος (20,8%), διαταραχές διαγωγής (19,7%), μικτή αναπτυξιακή διαταραχή (14,8%), διαταραχή προσαρμογής (7,2%), νοητική υστέρηση (7,2%), οξεία ψύχωση (4,5%), και ΔΕΠΥ (2,3%). Τα συνηθέστερα χορηγούμενα φάρμακα ήταν τα αντιψυχωσικά (45,9%), ακολουθούμενα από τα αντικαταθλιπτικά (17,2%), τα σταθεροποιητικά (16,1%), τις βενζοδιαζεπίνες (14,4%), και άλλα ψυχοτρόπα (6,4%). Το συνηθέστερα χορηγούμενο αντιψυχωσικό ήταν η ρισπεριδόνη, που δόθηκε σε άνω του 50% των ασθενών που έλαβαν αντιψυχωσικά. Η ρισπεριδόνη και η χλωροπρομαζίνη μαζί αποτέλεσαν πάνω από 75% του συνόλου των χορηγηθέντων αντιψυχωσικών. 98,4% των χορηγηθέντων αντικαταθλιπτικών ήταν SSRI, με τη σερτραλίνη και τη φλουοξετίνη να αποτελούν σχεδόν το 90% αυτών. Όλες οι συνταγογραφηθείσες δοσολογίες ήταν σε συμφωνία με τις επίσημες οδηγίες. Πρόκειται για την πρώτη μελέτη των πρακτικών συνταγογράφησης στην ψυχιατρική παιδιών και εφήβων στη Σερβία. Οι τρέχουσες συνταγογραφικές πρακτικές στο Κλινικό Τμήμα Παιδιών και Εφήβων του Ινστιτούτου Ψυχικής Υγείας Βελιγραδίου συμφωνούν με τις σύγχρονες πρακτικές στις ΗΠΑ και την Ευρώπη. Δεν απαιτείται φαρμακοθεραπεία για κάθε παιδί με συμπτώματα ψυχικής διαταραχής, στις περιπτώσεις όμως που απαιτείται ακολουθείται ο κανόνας «ξεκίνα με χαμηλή δόση, αύξησε τη δόση αργά, μείωσε τη δόση αργά». Απαιτούνται μελέτες παρακολούθησης για την εκτίμηση των μεταβολών των συνταγογραφικών τάσεων, καθώς και μελέτες σε διαφορετικούς πληθυσμούς ασθενών και κέντρα υγείας για τη συνολική εκτίμηση της χρήσης της φαρμακοθεραπείας στα παιδιά και στους εφήβους στη Σερβία.

Λέξεις ευρετηρίου: Ψυχοφαρμακολογία, φάρμακα, παιδιά, έφηβοι, νοσηλευόμενοι ασθενείς

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