Psychiatr. Pol. 2026; 60(1): 21–36
PL ISSN 0033-2674 (PRINT), ISSN 2391-5854 (ONLINE)
www.psychiatriapolska.pl
DOI: https://doi.org/10.12740/PP/200518

Current challenges in pharmacotherapy of depression in children and adolescents – a contemporary perspective

Agnieszka Rakus[1], Agnieszka Słopień[2], Filip Rybakowski[1], Edmund Grześkowiak[3], Agnieszka Bienert[1]

[1] Department of Adult Psychiatry, Poznan University of Medical Sciences, Karol Jonscher Clinical Hospital

[2] Department of Child and Adolescent Psychiatry, Poznan University of Medical Sciences, Karol Jonscher Clinical Hospital

[3] Department of Clinical Pharmacy and Biopharmacy, Poznan University of Medical Sciences, Karol Jonscher Clinical Hospital

Summary

Depression in children and adolescents poses a significant health issue that requires effective treatment strategies. According to epidemiological data, depression among children and adolescents is becoming increasingly prevalent, reaching up to 10% of this population. It can lead to tragic outcomes, including suicides, which are one of the leading causes of death among young people. Diagnosis of depression relies on recognizing the presence of at least five characteristic symptoms for at least two weeks, one of which needs to be: persistent low mood or loss of interest or pleasure in activities. In children, diagnosis may be more difficult due to masked behavioral symptoms, frequent irritability, as well as its atypical course (including the duration of symptoms and their variability within a short period of time). There are many predisposing factors for depression, including gender, family history of mental disorders, subclinical depressive symptoms, anxiety disorders, and stressful life events. Treatment primarily involves medications such as selective serotonin reuptake inhibitors (SSRIs). However, due to the limited availability of approved medications, off-label use is common. Fluoxetine is an important medication for treating depression in children, demonstrating efficacy and good tolerability. However, patients should be monitored for suicidal thoughts. Sertraline, although not approved for the treatment of pediatric depression, is often used off-label and has demonstrated a positive response. Escitalopram, approved for the treatment of depression in children over 12 years of age, is more potent and more selective than citalopram, but its approval is based on limited clinical trials. The dosing of SSRIs typically starts with low doses, gradually increased as therapy progresses until clinical response or the occurrence of adverse effects. However, selecting the appropriate therapy can be challenging due to the diversity of symptoms and limited scientific research in the field of child and adolescent psychiatry. It is currently recommended that antidepressant therapy be personalized and based on achieving

optimal therapeutic drug concentrations in the blood. Children and adolescents have distinct pharmacokinetic and pharmacodynamic profiles, which necessitates an individualized approach to pharmacological treatment. Therapeutic Drug Monitoring (TDM) can be a significant tool in treating depression in this patient group, allowing for dose adjustment to individual needs and minimizing adverse effects. TDM also facilitates understanding of drug interactions, reasons for treatment non-response, and the impact of genetic variability. This way TDM can help to optimize treatment and minimize adverse effects. Thus the role of pharmacists in monitoring antidepressant therapy in children and adolescents is also valuable, which may contribute to improving clinical outcomes.

This article examines the efficacy and safety of antidepressants in children and adolescents, with an emphasis on SSRIs, and identifies issues related to treatment selection, with particular emphasis on personalized care and the growing role of TDM.

Key words: children, depression, therapeutic drug monitoring

Introduction

Depression is increasingly becoming a major challenge in both public health and social contexts. According to the World Health Organization (WHO), approximately 280 million people worldwide suffer from depression, accounting for about 3.8% of the global population [1]. It is the second most common mental disorder, following only anxiety disorders in prevalence [2]. It is now understood that depression affects not only adults; it is estimated that up to 10% of children and adolescents suffer from depressive disorders. In its most severe form, depression can lead to suicide, which is the fourth leading cause of death among individuals aged 15 to 19 years [2–4]. The diagnosis of depressive episodes in children and adolescents is based on two widely used classification systems: the *International Classification of Diseases 11th Revision* (ICD-11) and the *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition* (DSM-5) [5]. The diagnosis of depression relies on the identification of at least five characteristic symptoms persisting for a minimum of two weeks, which include: a persistently depressed mood throughout the day, loss of interest and pleasure in life, weight loss, sleep disturbances, feelings of chronic fatigue, difficulty concentrating, and the presence of suicidal thoughts. Diagnosing depression can often be challenging due to the possibility of its symptoms being "masked" by behavioral manifestations such as aggression, hyperactivity, and learning difficulties [6].

Among children and adolescents, various predisposing factors for depression have been observed. One of these factors is female gender, which is likely related to hormonal imbalances and increased vulnerability to stress. A confirmed correlation exists between the onset of depression in children and the presence of this disorder in the family, especially when one of the parents is affected. This aspect is considered one of the strongest risk factors for depression due to both genetic and environmental influences. Diagnosing subclinical depression in a child may predispose them to a full depressive episode in the future, similarly to the occurrence of anxiety disorders and exposure to stressful life events such as the loss of a loved one or experiencing physical or psychological abuse [7]. It has been demonstrated that the implementation of

depression prevention programs in schools and the use of cognitive-behavioral therapy at the subclinical symptom level can contribute to symptom reduction, but they do not influence the likelihood of developing severe mental disorders within the next 12 months [8, 9].

In child and adolescent psychiatry, the amount of scientific data is significantly more limited than in adult psychiatry. As a result, clinicians are frequently confronted with the need to make difficult decisions regarding the appropriate therapy for pediatric patients. Many of the treatment strategies for depression in the pediatric population are derived from adult treatments [7, 8]. It is now known that data obtained from adult patients should not be extrapolated to children and adolescents. This is due, among other factors, to the observed increased risk of suicidal thoughts in individuals under 24 years of age using SSRI antidepressants, as well as the lack of efficacy of tricyclic antidepressants (TCA) [10].

The limited availability of medications approved for treating depressive episodes in children and adolescents is a significant concern. Currently, the FDA (Food and Drug Administration) has approved escitalopram (from age 12) and fluoxetine (from age 8) for depression treatment. In treating obsessive-compulsive disorder, sertraline is recommended (from age 6) [11–13]. These drugs belong to the group of selective serotonin reuptake inhibitors (SSRIs), the most commonly used group of medications for treating mental disorders in both children and adults [14]. The dosing of SSRIs often begins with low doses that are gradually increased during therapy until a clinical response is achieved. The appearance of side effects often necessitates reducing the SSRI dose or discontinuing therapy [15]. The lack of sufficient data in the pediatric population frequently leads to the off-label use of medications, raising concerns about safety and efficacy [16]. The percentage of antidepressants used off-label in children is approximately 50% [17]. Due to the dynamic biochemical and physiological changes that occur in the developing bodies of children and adolescents, significant differences in pharmacokinetic and pharmacodynamic parameters are observed compared to adults. As a result, the need for a more personalized therapeutic approach for this patient group is evident.

Therapeutic Drug Monitoring (TDM), based on the analysis of drug concentrations in plasma or other body fluids, can be an important tool in the treatment of depressive disorders in children and adolescents. TDM allows for the adjustment of drug dosages to the individual needs of the patient, ensuring optimal therapeutic effectiveness and minimizing the risk of adverse effects [16, 18, 19]. TDM offers the opportunity to utilize the individual variability in the pharmacokinetics of antidepressants to understand drug-drug interactions, identify the cause of treatment failure, and comprehend the impact of genetic variability [15].

The literature review was conducted by searching the PubMed and Google Scholar databases from January 2024 to May 2024. The search terms included keywords related to diseases and adverse events (AEs) such as “Pharmacotherapy of depression,” “SSRI,” “Therapeutic Drug Monitoring,” “Depression,” and “Childhood depression.” The

analysis includes a review of literature from the last 10 years on the pharmacotherapy of depression in children and adolescents, including analyses of clinical trials, FDA guidelines and data on off-label drug use. The review also covers the pharmacokinetics and pharmacodynamics of drugs in this age group and the application of therapeutic drug monitoring (TDM) in clinical practice.

The article aims to present the current knowledge on the efficacy and safety of antidepressants in the treatment of depression in children and adolescents, with a particular focus on selected SSRIs. The article also seeks to identify issues related to selecting appropriate therapy, with a particular emphasis on personalized treatment and the growing role of TDM in this process.

Pharmacological treatment

Selective serotonin reuptake inhibitors (SSRIs) are commonly used as first-line therapy in the treatment of depression and other psychiatric disorders in children, adolescents and adults. Their popularity stems from their mild side effect profile, safety, and good patient tolerance. The most frequently used SSRIs include fluoxetine, sertraline, citalopram, escitalopram, and paroxetine. Despite their varied chemical structures, they share the same mechanism of action. They inhibit the serotonin reuptake transporter (SERT) located on presynaptic neuron membranes, resulting in increased serotonin concentration in the synaptic cleft and enhanced serotonin availability in the brain. It has been demonstrated that SSRIs cause fewer side effects than tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) due to their lesser impact on adrenergic, cholinergic, and histaminergic receptors.

FDA-approved indications for SSRIs extend beyond depression treatment and include anxiety disorders, bulimia, obsessive-compulsive disorder, premenstrual tension, and post-traumatic stress disorder [20, 21]. In the first weeks of treatment with some antidepressants from the SSRI and SNRI classes, there has been an observed increase in the risk of suicidal behavior, particularly in children and adolescents. A 2020 meta-analysis noted an increased risk of suicidal behavior in children and adolescents with depression treated with venlafaxine, and in those with anxiety disorders treated with paroxetine. However, sertraline was associated with a reduced likelihood of suicidal behavior in children and adolescents. In 2004, a warning was added to the labels of antidepressants registered for depression treatment (citalopram, fluvoxamine, paroxetine, fluoxetine, sertraline, venlafaxine, mirtazapine, bupropion), indicating a potential increase in the risk of suicidal thoughts and behaviors [22]. However, the increased number of suicidal behaviors did not translate into a rise in completed suicides [23]. Due to these concerns, the FDA recommends that physicians adhere to certain guidelines when treating children and adolescents with antidepressants:

– Always consider the appropriateness of prescribing antidepressants and explore alternative therapies, such as family therapy or cognitive-behavioral therapy.

- Start treatment with a low dose, typically ½ or ¼ of the adult dose, and gradually increase the dosage.
- Regularly conduct follow-up visits and monitor for symptoms such as hopelessness, aggression and suicidal thoughts or tendencies.
- Consider combining pharmacotherapy with psychotherapy [24].

However, this warning was based on analyses of randomized controlled trials (RCTs) that were sponsored by the pharmaceutical industry and published over a decade ago. In recent years, an increasing number of studies have highlighted the methodological limitations of the FDA analyses [25]. In most RCTs evaluating the efficacy of SSRIs in treating depression in patients under the age of 18, the rates of suicidal thoughts emerging or worsening during observation are similar to those observed in the placebo groups. Suicide attempts are rare, and isolated cases are reported in both active treatment and placebo groups. Only venlafaxine therapy, in the short-term treatment period, has shown a significant increase in the risk of suicidal behaviors and/or suicidal ideation compared to placebo [26].

In Poland, the primary role in patient care within psychiatric facilities is held by physicians, psychotherapists and psychologists. Review articles have confirmed the competencies of pharmacists in detecting, preventing and resolving drug-related problems. Additionally, the provision of pharmaceutical care in psychiatric wards has a positive impact on improving clinical and economic outcomes. In one study conducted on patients hospitalized for more than 6 months with schizophrenia, the absence of a clinical pharmacist on the team was associated with an increased number of adverse events (a 34.9% increase) and a higher mortality rate (a 53.64% increase) per 100 beds. The pharmacists' tasks involved addressing drug-related problems (DRPs). Among 49 patients, 71 DRPs were identified, with 1 to 4 DRPs occurring per patient. Due to their specialized knowledge, pharmacists can play a crucial role in monitoring and optimizing antidepressant therapy in patients [27].

Fluoxetine

In the treatment of severe depressive disorders in individuals under 18 years of age, fluoxetine is the first-line medication, demonstrating efficacy both as monotherapy and in combination with cognitive-behavioral therapy, as confirmed by clinical studies [3, 28]. Fluoxetine stands out for its high effectiveness in reducing depressive symptoms and its good tolerance, with relatively infrequent discontinuation due to adverse effects. This may be attributed to the fact that fluoxetine was the first SSRI to be thoroughly studied, whereas data on other drugs in this class are limited. Studies have also confirmed that fluoxetine is more effective than placebo in preventing relapses and prolonging the time between the end of therapy and the reappearance of symptoms [29].

During the implementation of fluoxetine therapy, patients must be continuously monitored due to the potential for suicidal thoughts, suicide attempts, and hostility,

which are more frequently observed in children taking antidepressants compared to the placebo group. However, when compared to other drugs in the same class, such as paroxetine (OR = 1.77) and venlafaxine (OR = 2.43), where the highest risk of suicidal thoughts and attempts was noted, fluoxetine (OR = 1.33) is associated with only moderately increased risk, making it relatively safer in this study [30, 31]. The long half-life of fluoxetine is correlated with a lower risk of withdrawal syndrome compared to other SSRI drugs [30, 32].

When considering fluoxetine therapy, all its pharmacokinetic properties must be taken into account (Table 1). The long half-life of fluoxetine and its active metabolites can be both an advantage and a disadvantage. This drug may be a preferred therapeutic option for patients who are observed to have poor medication adherence. This is because even after missing a dose, the concentration of active metabolites decreases only slightly. On the other hand, when there is a need to switch medications, the washout period for fluoxetine and its active metabolites from the body is prolonged. As a result, a delay in initiating another therapy may be necessary due to the potential for adverse effects or the development of serotonin syndrome [33].

Sertraline

Currently, sertraline is not approved for the treatment of depression in individuals under 18 years of age. The only indication for its use in children and adolescents (from 6 years old) is for the treatment of obsessive-compulsive disorder. Nevertheless, many clinicians choose to use sertraline off-label based on numerous clinical studies that confirm its efficacy in treating depression. In a randomized clinical trial conducted by Wagner et al. in 2003 [32] on a pediatric population, a positive response to treatment was observed in 69% of patients receiving sertraline compared to 59% of patients receiving placebo. Sertraline treatment was generally well-tolerated, as evidenced by the fact that only 9% of patients discontinued treatment due to persistent adverse effects, including diarrhea, vomiting, and anorexia. Statistically significant improvement in patient condition was observed after 3 weeks of initiating therapy [32].

In a study conducted on a limited research sample, Tierney et al. [34] proposed a hypothesis of a potential advantage of sertraline over fluoxetine. This was attributed to the absence of observed exacerbation of suicidal thoughts and attempts following sertraline administration, contrasting with the results for fluoxetine [34]. To determine appropriate dosing, it is necessary to consider the pharmacokinetic properties of sertraline (Table 1).

Escitalopram

Escitalopram, the (S)-enantiomer of citalopram, is a selective serotonin reuptake inhibitor (SSRI) [35]. Compared to citalopram, escitalopram shows significantly higher response to treatment rates. The advantage of escitalopram is particularly pronounced

in patients with more severe forms of the disorder, suggesting that it acts more strongly and selectively [36]. Escitalopram has been approved by the FDA for the treatment of major depressive episodes in children and adolescents over the age of 12, both in acute and maintenance phases. The adverse effects of escitalopram are similar to those of citalopram but occur much less frequently. The most common adverse effects reported by patients include nausea, vomiting, and headaches. The approval of escitalopram for use in children is based solely on two randomized clinical trials, which means it should not be considered a first-line treatment [37]. Periclou et al. [38] compared the pharmacokinetics of a single oral dose of escitalopram (10 mg) in adolescents aged 12–17 years and healthy adults aged 18–35 years, finding no clinically significant differences in parameters such as clearance, peak concentration, half-life, and bioavailability [38] (Table 1).

Table 1. **Pharmacokinetic properties of fluoxetine, sertraline, and escitalopram [11–13]**

	Fluoxetine	Sertraline	Escitalopram
Absorption	it is well absorbed after oral administration food intake does not affect bioavailability	food has no significant effect on bioavailability food intake increases C_{max} by 25% and reduces t_{max} from 8 to 5.5 hours	it is well absorbed after oral administration, regardless of food intake
Distribution	it binds to plasma proteins (95%) the volume of distribution is 20-40 l/kg steady-state plasma concentration is achieved after several weeks of drug administration	it binds to plasma proteins (98%) the average volume of distribution is 20 l/kg steady-state plasma concentration is achieved after one week of once-daily dosing	it binds to plasma proteins (<80%) the volume of distribution is 12-26 l/kg steady-state plasma concentration is achieved after approximately one week
Metabolism	nonlinear pharmacokinetics disproportionate increase in concentration following dose escalation maximum plasma concentration occurs 6–8 hours after administration metabolized primarily by the polymorphic enzyme CYP2D6 to the active metabolite: norfluoxetine	dose-proportional pharmacokinetics within the range of 50 to 200 mg maximum plasma concentration occurs 4.5 to 8.4 hours after administration. Primarily metabolized by CYP3A4, CYP2C19, and CYP2B6	linear pharmacokinetics maximum plasma concentration occurs 4 hours after administration biotransformation to demethylated metabolites primarily involves the CYP2C19 enzyme
Elimination	the half-life ranges from 4 to 6 days excretion primarily occurs through the kidneys	the average half-life is 26 hours metabolites are excreted primarily through feces and urine in roughly equal amounts	the half-life is approximately 30 hours metabolites are primarily excreted in the urine

A review of meta-analyses conducted by Janas-Kozik et al. [26] does not currently allow for definitive conclusions regarding the efficacy of specific selective serotonin reuptake inhibitors (SSRIs) in the treatment of major depression in children and adolescents. The obtained results remain inconclusive, which presents a significant limitation in precisely determining which drugs in this pharmacological group demonstrate the highest therapeutic efficacy in the pediatric population. This highlights the urgent need for clinical pharmacokinetic and pharmacodynamic studies in this age group of patients.

Therapeutic drug monitoring

Therapeutic drug monitoring involves the measurement and quantitative analysis of drug concentrations in plasma to optimize the therapeutic process. This method takes into account interindividual variability in pharmacokinetics and drug properties, allowing for the adjustment of therapy to meet the patient's individual needs. TDM also involves determining a "therapeutic reference range" of drug concentrations that ensures maximum effectiveness while maintaining safety. This is defined by setting the lower and upper boundaries of therapeutically effective and tolerated concentrations. In the absence of reliable data, the therapeutic reference range can be estimated by determining the mean ± standard deviation of drug concentrations in individuals who respond to treatment. The upper limit of the therapeutic range is often set by increased risk of adverse effects, while the lower limit is determined by assessing the minimum concentration needed for clinical efficacy [18].

A significant limitation of established therapeutic reference ranges is their lack of evaluation concerning efficacy and safety in children, adolescents, and elderly patients [19]. The use of TDM in psychiatry and neurology may be particularly beneficial for the following patient groups:

- children and adolescents,
- pregnant women,
- elderly patients,
- individuals with intellectual disabilities,
- patients with pharmacokinetic disorders.

After administering the same dose of medication, plasma concentrations can vary more than twentyfold. Such variations may result from individual differences in drug absorption, distribution, metabolism, and excretion, which can be influenced by age, comorbid conditions, and genetic differences [18]. Physicians should consider incorporating therapeutic drug monitoring in cases where:

- there is no response after administering therapeutic doses,
- there is suspicion of non-adherence to prescribed therapy,
- there is an intolerance to the treatment [18].

International guidelines on therapeutic drug monitoring in neuropsychopharmacology define levels of recommendation for the use of TDM (Table 2).

Table 2. **Levels of TDM recommendations [18]**

Levels	Description	Antidepressant medication
Level 1 "highly recommended"	therapeutic reference ranges have been established controlled clinical trials have demonstrated the beneficial effects of TDM.	**Citalopram,** amitriptyline, clomipramine, imipramine, nortriptyline
Level 2 "recommended"	therapeutic reference ranges were obtained based on drug concentrations at therapeutically effective doses TDM is recommended for dose determination and troubleshooting	bupropion, **escitalopram,** desipramine, doxepin, duloxetine, fluvoxamine, maprotiline, mirtazapine, **sertraline**, trazodone, venlafaxine, vortioxetine
Level 3 "useful"	drug concentrations associated with therapeutic effects are not well established or are based on retrospective TDM data, individual cases, or unsystematic clinical experience	**fluoxetine,** mianserin, paroxetine, reboxetine, tianeptine
Level 4 "Probably useful"	drug concentration does not correlate with clinical effects due to the drug's unique pharmacokinetics TDM is not recommended for dose determination but may be useful for troubleshooting.	agomelatine, tranylcypromine
Level 5 "not recommended"		

Currently, therapeutic drug monitoring (TDM) is highly recommended for most tricyclic antidepressants. However, for selective serotonin reuptake inhibitors (SSRIs), there is a weak but significant association between clinical improvement and dosage, while tolerance decreases with higher doses. Among SSRIs, citalopram is highly recommended (Level 1 recommendation) for TDM, while other SSRIs are rated at Level 2 or 3. For these other SSRIs, there is a lack of definitive studies on the clinical significance of TDM; nevertheless, TDM is still advised at this level to determine the appropriate dosage of the medication. Optimal neuropsychopharmacotherapy should aim to establish the "individual optimal therapeutic range," which may vary depending on the population group and the severity of the mental disorder. Approximately 50–60% of patients do not respond to first-line therapy. In cases of non-response, there are three strategies to consider:

(1) dose escalation;
(2) augmentation by adding another medication;
(3) switching to a different medication within the same class [39].

Non-adherence to medical recommendations is a common cause of lack of clinical response to treatment, especially among pediatric populations. TDM serves as an essential tool for monitoring patient compliance by measuring drug concentrations in plasma. If low or undetectable drug levels are found in the blood after administering standard doses, non-compliance on the part of the patient may be suspected [40]. One factor contributing to non-compliance may be the delayed onset of antidepressant effects. Achieving full clinical benefits often requires a prolonged waiting period, lasting weeks or even months. During this time, a range of adverse effects may be observed, which can mimic either untreated depression or overdose symptoms (such as persistent gastrointestinal disturbances, mood swings, anxiety, and tension). TDM can help determine whether these adverse effects are due to inappropriate plasma concentrations [39, 41]. Additionally, therapeutic drug monitoring allows for the assessment of the relationship between plasma drug levels and the occurrence of idiosyncratic reactions in the patient, helping to establish if an uncontrolled, rare drug reaction is associated with high plasma concentrations [41].

In TDM, the interpretation of results is as important as the results themselves. The full clinical profile of the patient must be considered. Factors influencing the interpretation of results include pregnancy, age, weight, sex, genetics, heart, kidney, and liver diseases, poor nutrition, hypoalbuminemia, and concomitant medications [33]. Therapeutic drug monitoring (TDM) allows for the assessment of whether an increase in drug dosage is justified in cases of insufficient clinical improvement and absence of adverse effects. Conversely, if adverse effects occur alongside clinical improvement, TDM provides information on whether it is safe to reduce the drug dosage.

Despite documented benefits of monitored therapy in psychiatric practice, established therapeutic concentration ranges for children and adolescents that correlate with therapeutic effects are lacking. These ranges are based on those observed in adults; however, it should be noted that changes due to growth and maturation can affect both pharmacokinetics (PK) and pharmacodynamics (PD) of drugs [15, 18]. PK and PD change throughout development and growth, suggesting that data from adults cannot be directly transferred to children. Data should be evaluated individually for each substance, as literature provides varying information. Differences in plasma drug concentrations may be due to varying activities of drug-metabolizing enzymes, which depend on factors such as age and coexisting kidney and liver diseases. It is worth noting that all SSRIs are characterized by intense hepatic metabolism and a highly variable ability to inhibit CYP450 isoenzymes. The use of TDM provides a better understanding of drug interactions in patients undergoing polytherapy. One example of drug interaction is the combination of fluoxetine and bupropion. Both fluoxetine and bupropion are strong inhibitors of CYP2D6 and CYP3A4. The use of this combination may therefore lead to a significant increase in bupropion levels and the emergence of dangerous adverse effects such as seizures, delirium, and anxiety [42].

In addition to considering drug interactions, it is also crucial to address the impact of commonly used substances on the metabolism of antidepressant medications. Significant clinical relevance has been demonstrated with concurrent smoking (>10 cigarettes per day) and the use of drugs that are substrates of CYP1A2, including clozapine, duloxetine, and olanzapine. CYP1A2, responsible for the metabolism of these drugs, is induced by components of cigarette smoke (polycyclic aromatic hydrocarbons). Therefore, it is advisable to consider dose reduction of these medications when a patient stops smoking to avoid increased drug levels in the plasma [18].

Currently, there is an increase in the use of cannabis among children and adolescents, including THC (tetrahydrocannabinol) and CBD (cannabidiol). It is estimated that adolescents suffering from depression are twice as likely to use cannabis. Cannabis is a moderate to strong inhibitor of cytochrome CYP450 and interacts with SSRIs, potentially increasing their plasma concentrations. The adverse event reporting system database has shown that co-administration of CBD and SSRIs metabolized by CYP2C19 increases the risk of some SSRI-related adverse effects, such as diarrhea, dizziness, and fatigue. There is a suspicion that these side effects may be related to increased SSRI levels [43]. Particular attention should be given to fluoxetine, due to the fact that its inhibition of CYP enzyme activity can persist for several weeks after discontinuation of the medication. This is attributed to the long half-life of fluoxetine and its active metabolite, norfluoxetine [43].

Many drug interactions have been discovered through TDM or retrospective analysis of TDM databases. A thorough analysis of potential drug interactions is essential when using SSRIs in combination with other medications. Drug-metabolizing enzymes, especially CYP isoenzymes, exhibit genetic variability [18, 42]. The population can be classified into several types based on the ratio of the parent drug excreted by the kidneys to its metabolites:

- ultra-rapid metabolizers (UM),
- rapid metabolizers (EM),
- intermediate metabolizers (IM),
- poor metabolizers (PM).

Genetic polymorphisms of drug-metabolizing enzymes have clinical significance. In poor metabolizers (PM), there may be an increased risk of unexpected adverse effects and toxicity due to high drug concentrations, whereas ultra-rapid metabolizers (UM) may experience a lack of therapeutic response due to subtherapeutic drug levels in the blood [18, 44]. Patients may not respond to treatment due to the presence of allelic variants in CYP2D6, CYP2C19, or CYP2B6 genes that affect the biotransformation of antidepressant medications. Sertraline, citalopram, and escitalopram are primarily metabolized by CYP2C19, so variations in its activity lead to different levels of exposure to these drugs. Patients in the CYP2C19 UM group are more likely to discontinue treatment or require medication changes compared to those with normal metabolism (NM). Therefore, dose adjustments or the use of

medications not predominantly metabolized by CYP2C19 should be considered for these patients [45]. For escitalopram, a dose of 10 mg/day is appropriate for poor metabolizers (PM), while a dose of 30 mg/day may be needed for ultra-rapid metabolizers (UM) to achieve plasma concentrations similar to those of individuals with normal metabolism receiving 20 mg/day. For sertraline, poor metabolizers should be started on a dose of 100 mg/day, while ultra-rapid metabolizers may require 200 mg/day to achieve AUC and C_{max} values comparable to those of normal metabolizers receiving 150 mg/day [27, 44]. Since the activity of CYP2D6, CYP2C19, and CYP2B6 reaches levels comparable to adults early in childhood, extrapolation of adult data to the pediatric population under close supervision may be considered. However, further studies in children and adolescents are needed to investigate the relationship between CYP2C19, CYP2B6, CYP2D6 activity and treatment tolerance and efficacy [45].

Conclusions

Pharmacotherapy for depression in the pediatric population requires a complex and personalized approach. Individual differences in drug metabolism and treatment response are crucial and must be taken into account.

This review of the literature highlights the challenges of modern pharmacotherapy for depression in children and adolescents. Currently, data on the correlation between drug concentrations, clinical response, and adverse effects in the pediatric population are still limited, which may increase the risk of dosing errors and expose young patients to potential adverse effects. Establishing therapeutic concentration ranges and implementing therapeutic drug monitoring could help minimize the occurrence of adverse drug reactions, leading to better drug tolerance and improved patient compliance. It is now understood that data from adults cannot be directly extrapolated to children for antidepressant medications. Considering factors (such as pharmacological influences, risk of disorders, and interpersonal factors) related to suicidal thoughts should guide cautious prescribing and monitoring. In this context, integrating a clinical pharmacist into the hospital team could be beneficial.

Future directions should focus on increasing both the quantity and quality of research conducted in children, as well as evaluating the benefits of introducing pharmaceutical care in psychiatric settings.

References

1. Institute of Health Metrics and Evaluation. *Global Health Data Exchange (GHDx)*. https://vizhub.healthdata.org/gbd-results/ (retrieved: 4.03.2023).
2. Sipowicz K, Podlecka M, Mokros Ł, Pietras T. *Lonely in the city – sociodemographic status and somatic morbidities as predictors of loneliness and depression among seniors preliminary results*. Int. J. Environ. Res. Public Health 2021; 18(14): 7213. Doi: 10.3390/ijerph18147213.
3. Zhou X, Teng T, Zhang Y, Del Giovane C, Furukawa TA, Weisz JR et al. *Comparative efficacy and acceptability of antidepressants, psychotherapies, and their combination for acute treatment of children and adolescents with depressive disorder: A systematic review and network meta-analysis*. Lancet Psychiatry 2020; 7(7): 581–601. Doi: 10.1016/S2215-0366(20)30137-1.
4. Zwolińska W, Dmitrzak-Węglarz M, Słopień A. *Biomarkers in child and adolescent depression*. Child Psychiatry Hum. Dev. 2023; 54(1): 266–281. Doi: 10.1007/s10578-021-01246-y.
5. Beck A, LeBlanc JC, Morissette K, Skidmore B, Colquhoun H, Lang E et al. *Screening for depression in children and adolescents: A protocol for a systematic review update*. Syst. Rev. 2021; 10(1): 24. Doi: 10.1186/s13643-020-01568-3.
6. Seiffge-Krenke I. *Depression bei Kindern und Jugendlichen: Prävalenz, Diagnostik, ätiologische Faktoren, Geschlechtsunterschiede, therapeutische Ansätze* [*Depression in children and adolescents: Prevalence, diagnosis, etiology, gender differences and therapeutic approaches*]. Prax. Kinderpsychol. Kinderpsychiatr. 2007; 56(3): 185–205. Doi: 10.13109/prkk.2007.56.3.185. PMID: 17451150.
7. Garber J. *Depression in children and adolescents: Linking risk research and prevention*. Am. J. Prev. Med. 2006; 31(6 Suppl 1): 104–125. Doi: 10.1016/j.amepre.2006.07.007. PMID: 17175406.
8. Jonge-Heesen de KWJ, Rasing SPA, Vermulst AA, Scholte RHJ, Ettekoven van KM, Engels RCME et al. *Randomized control trial testing the effectiveness of implemented depression prevention in high-risk adolescents*. BMC Med. 2020; 18(1): 188. Doi: 10.1186/s12916-020-01645-3.
9. Do R, Lee S, Kim JS, Cho M, Shin H, Jang M et al. *Effectiveness and dissemination of computer-based cognitive behavioral therapy for depressed adolescents: Effective and accessible to whom?* J. Affect. Disord. 2021; 282: 885–893. Doi: 10.1016/j.jad.2020.11.027.
10. Hosenbocus S, Chahal R. *SSRIs and SNRIs: A review of the discontinuation syndrome in children and adolescents*. J. Can. Acad. Child Adolesc. Psychiatry 2011; 20(1): 60–67. PMID: 21286371; PMCID: PMC3024727.
11. Charakterystyka produktu leczniczego „Fluoxetine Vitabalans". https://rejestry.ezdrowie.gov.pl/rpl/search/public (retrieved: 10.04.2024).
12. Charakterystyka produktu leczniczego „Escitalopram Actavis". https://rejestry.ezdrowie.gov.pl/rpl/search/public (retrieved: 10.04.2024).
13. Charakterystyka produktu leczniczego „Zoloft". https://rejestry.ezdrowie.gov.pl/rpl/search/public (retrieved: 10.04.2024).
14. Dwyer JB, Bloch MH. *Antidepressants for pediatric patients*. Curr. Psychiatr. 2019; 18(9): 26–42F. PMID: 31511767; PMCID: PMC6738970.
15. Strawn JR, Poweleit EA, Uppugunduri CRS, Ramsey LB. *Pediatric therapeutic drug monitoring for selective serotonin reuptake inhibitors*. Front. Pharmacol. 2021; 12: 749692. Doi: 10.3389/fphar.2021.749692. PMID: 34658889; PMCID: PMC8517085.

16. France K, Ammend D, Brown J. *Pharmacogenetic testing and therapeutic drug monitoring of sertraline at a residential treatment center for children and adolescents: A pilot study*. Innov. Pharm. 2022; 13(4): 10.24926/iip.v13i4.5035. Doi: 10.24926/iip.v13i4.5035. PMID: 37305603;PMCID: PMC10256290.
17. Dörks M, Langner I, Dittmann U, Timmer A, Garbe E. *Antidepressant drug use and off-label prescribing in children and adolescents in Germany: Results from a large population-based cohort study*. Eur. Child Adolesc. Psychiatry 2013; 22(8): 511–518. Doi: 10.1007/s00787-013-0395-9. Epub 2013 Mar 3. PMID: 2345562.
18. Hiemke C, Bergemann N, Clement HW, Conca A, Deckert J, Domschke K et al. *Consensus guidelines for therapeutic drug monitoring in neuropsychopharmacology: Update 2017*. Pharmacopsychiatry 2018; 51(1–02): 9–62. Doi: 10.1055/s-0043-116492. Epub 2017 Sep 14. Erratum in: Pharmacopsychiatry 2018; 51(1–02). PMID: 28910830.
19. Schoretsanitis G, Paulzen M, Unterecker S, Schwarz M, Conca A, Zernig G et al. *TDM in psychiatry and neurology: A comprehensive summary of the consensus guidelines for therapeutic drug monitoring in neuropsychopharmacology, update 2017; A tool for clinicians*. World J. Biol. Psychiatry 2018; 19(3): 162–174. Doi: 10.1080/15622975.2018.1439595.PMID: 29493375.
20. Edinoff AN, Akuly HA, Hanna TA, Ochoa CO, Patti SJ, Ghaffar YA et al. *Selective serotonin reuptake inhibitors and adverse effects: A narrative review*. Neurol. Int. 2021; 13(3): 387–401. Doi: 10.3390/neurolint13030038. PMID: 34449705; PMCID: PMC8395812.
21. Chu A, Wadhwa R. *Selective Serotonin Reuptake Inhibitors*. [Updated 2023 May 1]. StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. https://www.ncbi.nlm.nih.gov/books/NBK554406/.
22. Ho D. *Antidepressants and the FDA's Black-Box Warning: Determining a rational public policy in the absence of sufficient evidence*. Virtual Mentor. 2012; 14(6): 483–488. Doi: 10.1001/virtualmentor.2012.14.6.pfor2-1206.
23. Kaizar EE, Greenhouse JB, Seltman H, Kelleher K. *Do antidepressants cause suicidality in children? A Bayesian meta-analysis*. Clin. Trials 2006; 3(2): 73–90; discussion 91–8. Doi: 10.1191/1740774506cn139oa. PMID: 16773951.
24. Pawełczyk T, Pawełczyk A, Rabe-Jabłońska J. *Ryzyko zachowań samobójczych w trakcie terapii lekami przeciwdepresyjnymi: czy uzasadnione są ostrzeżenia?* [*Risk of suicidal behavior during antidepressant treatment: are the warnings justified?*]. Post. Psychiatr. Neurol. 2010; 19(3): 227–234.
25. Boaden K, Tomlinson A, Cortese S, Cipriani A. *Antidepressants in children and adolescents: Meta-review of efficacy, tolerability and suicidality in acute treatment*. Front. Psychiatry 2020; 11: 717. Doi: 10.3389/fpsyt.2020.00717. eCollection 2020.
26. Janas-Kozik M, Słopień A, Remberk B, Siwek M. *The place of selective serotonin reuptake inhibitors (SSRIs) in the treatment of depressive disorders in children and adolescents. Recommendations of the Main Board of the Polish Psychiatric Association. Part I. Clinical efficacy and areas of application*. Psychiatr. Pol. 2023; 57(5): 899–916.
27. Ilickovic IM, Jankovic SM, Tomcuk A, Djedovic J. *Pharmaceutical care in a long-stay psychiatric hospital*. Eur. J. Hosp. Pharm. 2016; 23(3): 177–181. Doi: 10.1136/ejhpharm-2015-000718. Epub 2015 Nov 27. PMID: 31156842; PMCID: PMC6451613.
28. Hazell P. *Updates in treatment of depression in children and adolescents*. Curr. Opin. Psychiatry 2021; 34(6): 593–599. Doi: 10.1097/YCO.0000000000000749. PMID: 34456305.
29. Emslie GJ, Kennard BD, Mayes TL, Nightingale-Teresi J, Carmody T, Hughes CW et al. *Fluoxetine versus placebo in preventing relapse of major depression in children and adoles-*

cents. Am. J. Psychiatry 2008; 165(4): 459–467. Doi: 10.1176/appi.ajp.2007.07091453. PMID: 18281410; PMCID: PMC2824429.

30. Yan T, Goldman RD. *Time-to-effect of fluoxetine in children with depression*. Can. Fam. Physician 2019; 65(8): 549–551. PMID: 31413023; PMCID: PMC6693597.
31. Barbui C, Esposito E, Cipriani A. *Selective serotonin reuptake inhibitors and risk of suicide: A systematic review of observational studies*. CMAJ 2009; 180(3): 291–297. Doi: 10.1503/cmaj.081514. PMID: 19188627; PMCID: PMC2630355.
32. Wagner KD, Ambrosini P, Rynn M, Wohlberg C, Yang R, Greenbaum MS et al; Sertraline Pediatric Depression Study Group. *Efficacy of sertraline in the treatment of children and adolescents with major depressive disorder: Two randomized controlled trials*. JAMA 2003; 290(8): 1033–1041. Doi: 10.1001/jama.290.8.1033.
33. Fiaturi N, Greenblatt DJ. *Therapeutic drug monitoring of antidepressants*. Handb. Exp. Pharmacol. 2019; 250: 115–133. Doi: 10.1007/164_2018_161. PMID: 30194543.
34. Tierney E, Joshi PT, Llinas JF, Rosenberg LA, Riddle MA. *Sertraline for major depression in children and adolescents: Preliminary clinical experience*. J. Child Adolesc. Psychopharmacol. 1995; 5(1): 13–24. Doi: 10.1089/cap.1995.5.13.
35. Landy K, Rosani A, Estevez R. *Escitalopram*. StatPearls. Treasure Island, FL: StatPearls Publishing; 2024. https://www.ncbi.nlm.nih.gov/books/NBK554406/. Accessed January 2024. PMID: 32491666.
36. Auquier P, Robitail S, Llorca PM, Rive B. *Comparison of escitalopram and citalopram efficacy: A meta-analysis*. Int. J. Psychiatry Clin. Pract. 2003; 7(4): 259–268. Doi: 10.1080/13651500310003408. PMID: 24930412.
37. Carandang C, Jabbal R, Macbride A, Elbe D. *A review of escitalopram and citalopram in child and adolescent depression*. J. Can. Acad. Child Adolesc. Psychiatry 2011; 20(4): 315–324. PMID: 22114615; PMCID: PMC3222577.
38. Periclou A, Rao N, Sherman T, Ventura D, Abramowitz W. *Single-dose pharmacokinetic study of escitalopram in adolescents and adults* [Abstract]. Pharmacotherapy 2003; 10: 1361–1362.
39. Ruhé HG, Huyser J, Swinkels JA, Schene AH. *Dose escalation for insufficient response to standard-dose selective serotonin reuptake inhibitors in major depressive disorder: System atic review*. Br. J. Psychiatry 2006; 189: 309–316. Doi: 10.1192/bjp.bp.105.018325. PMID: 17012653.
40. Mandrioli R, Mercolini L, Saracino MA, Raggi MA. *Selective serotonin reuptake inhibitors (SSRIs): Therapeutic drug monitoring and pharmacological interactions*. Curr. Med. Chem. 2012; 19(12): 1846–1863. Doi: 10.2174/092986712800099749. PMID: 22414078.
41. Piacentino D, Bianchi E, De Donatis D, Florio V, Conca A. *Therapeutic drug monitoring of antidepressants: An underused but potentially valuable tool in primary care*. Front. Psychiatry 2022; 13: 867840. Doi: 10.3389/fpsyt.2022.867840. PMID: 35422716; PMCID: PMC9002103.
42. Hamrin V, Scahill L. *Selective serotonin reuptake inhibitors for children and adolescents with major depression: Current controversies and recommendations*. Issues Ment. Health Nurs. 2005; 26(4): 433–450. Doi: 10.1080/01612840590922452. PMID: 16020058.
43. Hemeryck A, Belpaire FM. *Selective serotonin reuptake inhibitors and cytochrome P-450 mediated drug-drug interactions: An update*. Curr. Drug Metab. 2002; 3(1): 13–37. Doi: 10.2174/1389200023338017. PMID: 11876575.
44. Leon de J, Susce MT, Pan RM, Fairchild M, Koch WH, Wedlund PJ. *The CYP2D6 poor metabolizer phenotype may be associated with risperidone adverse drug reactions and discontinuation*. J. Clin. Psychiatry 2005; 66(1): 15–27.

45. Bousman CA, Stevenson JM, Ramsey LB, Sangkuhl K, Hicks JK, Strawn JR et al. *Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for CYP2D6, CYP2C19, CYP2B6, SLC6A4, and HTR2A Genotypes and Serotonin Reuptake Inhibitor Antidepressants*. Clin. Pharmacol. Ther. 2023; 114(1): 51–68. Doi: 10.1002/cpt.2903. Epub 2023 May 30. PMID: 37032427; PMCID: PMC10564324.

Corresponding author: Agnieszka Rakus
agnieszkajaros0@gmail.com