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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 2. Pharmacological properties and safety of use

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Summary

Antidepressants are generally effective and well tolerated by children, but unfortunately 31% to 48% will not respond and up to 25% of children treated with antidepressants experience physical, emotional or behavioral adverse reactions to the drug that may lead to discontinuation of treatment or require an alternative treatment. The aim of the study was to review studies evaluating the pharmacodynamic properties of selective serotonin reuptake inhibitors (SSRIs) and their safety. A different pharmacodynamic profile causes that SSRIs are characterized by a different risk of some side effects in the patient (considered common for SSRIs) and they differ in the degree of adjustment to the clinical picture of depression and co-occurring psychopathology, as well as preferences characteristic of a particular patient. SSRIs in patients <18 years of age sometimes have different pharmacokinetic parameters compared to in adults, which has a significant impact on their effectiveness and tolerance. This is related, among others, to the fact that the activity of CYP450 isoenzymes, regardless of the action of inhibitors and inducers, evolves with the patient's age and – in the case of CYP2D6, 2C9 and 2B6 – depends on genetic polymorphisms. The concentration of fluoxetine, fluvoxamine or paroxetine is about two times higher in children compared to adolescents and adults, which should be taken into account at the stage of both drug introduction and setting

target doses. The T1/2 of paroxetine and sertraline at a dose of 50 mg/day (but not at higher doses) is significantly shorter in patients <18 years of age than in adults; therefore, in cases of non-optimal efficacy or the appearance of withdrawal symptoms during the day, use of them in divided doses, twice a day should be considered.

In the event of significant problems with the selection of the drug and/or dose of the drug due to unsatisfactory efficacy and/or tolerance in a patient <18 years of age, examination of the dominant polymorphism for the metabolism of a given isoenzyme may be very important. This applies in particular to CYP2C19 in the case of escitalopram treatment, and to a lesser extent during treatment with sertraline, and CYP2D6 in the case of fluoxetine or paroxetine. SSRIs are generally well tolerated in patients less than 18 years of age and the majority of adverse reactions (TEAEs) during treatment are mild or moderate. In most RCTs evaluating the efficacy of SSRIs in depression in patients <18 years of age, rates of suicidal ideation or the occurrence of suicidal ideation during follow-up are comparable to placebo, suicide attempts are rare, and isolated cases occur in both the active treatment groups and the placebo arm.

There was no statistically significant increased risk for antidepressants (including all SSRIs) or psychotherapy or combinations of antidepressants with psychotherapy (except venlafaxine). Only venlafaxine therapy was associated with an increased risk of suicidal behavior and/or ideation in short-term therapy compared to placebo.

Key words: child and adolescent psychiatry, depression, SSRIs – pharmacokinetics and safety of their use

Introduction

Antidepressants are one of possible intervention strategies for many mental health disorders in both adults and adolescents. Although antidepressants are generally effective and well tolerated by children, between 31% and 48% of them will not respond, and up to 25% of children treated with antidepressants experience physical, emotional, or behavioural adverse reactions to the drug, which may lead to withdrawal of treatment or require alternative treatment. What is more, evidence from the adult population suggests that pharmacogenetic information may help identify those most at risk of poor response or adverse drug effects, but the evidence base in the paediatric populations is less clear [1]. This paper reviews trials evaluating the pharmacodynamic properties of selective serotonin reuptake inhibitors (SSRIs), as well as the safety of their use.

Pharmacodynamic properties of SSRIs

The ability to block serotonin reuptake is essentially the only element the SSRIs have in common, and beyond this, the drugs show more pharmacodynamic differences than similarities. The fact that each member of the SSRI group has a different pharmacodynamic profile means that these drugs will be characterised by a different risk of certain adverse effects (considered common for SSRIs) in a given patient and, above all, will differ in their degree of adaptation to the clinical picture of depression and co-occurring psychopathology and patient-specific preferences (Table 1) [2, 3].

Table 1. **Pharmacodynamic properties of SSRIs and consequent therapeutic implications [2-5]**

	SSRI				
	Citalopram/ Escitalopram	Sertraline	Paroxetine	Fluoxetine	Fluvoxamine
Additional mechanisms of action other than SERT blockade	Weak H_1-receptor blockade (applies to citalopram and results from R-citalopram activity)	Dopamine transporter blockade Binding to σ_1 receptors	Antagonism to M_1 cholinergic receptors Weak norepinephrine transporter blockade NO synthase blockade H1-receptor blockade 5HT2a and 2b agonism	Weak norepinephrine transporter blockade 5HT2C receptor antagonism Norfluoxetine – noradrenergic effect	Binding to σ_1 receptors
Effects of additional mechanisms	The only "pure" SSRI Citalopram – additional sedative effect	Dopaminergic effect Activating potential A lower risk of hyper PRL? Pro-cognitive potential? Reduced anhedonia? Greater risk of diarrhoea/loose stools? Bound to Sigma receptors Additional anti-anxiety mechanism?	↑ undesirable central or peripheral anticholinergic effects ↑ sexual dysfunctions Increased risk of weight gain Additional anti-anxiety and sedative effects	Activating and anxiety-provoking potential of norfluoxetine	Sigma – additional anti-anxiety mechanism?

Pharmacokinetic properties of SSRIs and risk of drug interactions in children and adolescents

All SSRIs are characterised by extensive hepatic metabolism and a significant but highly variable ability to block CYP450 isoenzymes, which translates into a different interaction risk for each SSRI representative (Table 2).

Table 2. **SSRIs – their hepatic metabolism and the risk of affecting the metabolism of other drugs through CYP450 inhibition [3-6]**

SSRI	CYP450 blockade by SSRI						SSRI as a substrate for CYP450 or other metabolic pathways
	3A4	2D6	1A2	2B6	2C19	2C9	
Citalopram	+	+	+	0	+	0	2C19* > 3A4/2D6
Escitalopram	0	+	0	0	0	0	2C19* >3A4 /2D6
Fluoxetine	++	+++	+	0	++	++	2D6* >3A4/3A5, 2C9/2C19, 2B6/1A2
Fluvoxamine	++	+	+++	+	++	++	2D6* **>**1A2/3A4
Paroxetine	+	+++	+	+	+	+	2D6* >3A4/1A2/2C19
Sertraline	+	+ (++ ≥ 150 mg)	+	+	++	+	2C19*>2D6=3A4 =2C9 =2B6*

0 – no effect; + weakest inhibition; ++ moderate inhibition; +++ strongest inhibition;

* isoenzyme activity varies according to genetic polymorphism. The following subgroups of metabolisers can be distinguished in the population: normal, intermediate, rapid, ultra-rapid and poor metabolisers. The slower the activity of a given isoenzyme, the greater the risk of adverse effects and interactions of drugs metabolised by that isoenzyme, but also the lower the dose of drug needed to cause both a significant clinical effect and an adverse event. On the other hand, those in the group of rapid and especially ultra-rapid metabolisers for a particular isoenzyme will have the lowest risk of interactions, will require significantly higher doses to achieve a clinical effect and will experience significantly fewer adverse effects when using drugs metabolised by that isoenzyme.

It is important to remember that antidepressants and other substances that inhibit the activity of particular CYP450 isoenzymes or compete for a particular isoenzyme due to its intensive use in metabolic processing, will contribute to increased blood concentrations of drugs metabolised by these isoenzymes, which may lead to exacerbation of adverse effects (including uncommon and rare ones) and even to complications and toxic effects [3, 7]. From a practical point of view, the ability of paroxetine, fluoxetine and higher doses of sertraline to block CYP2D6, the strong blockade of CYP1A2 by fluvoxamine and the ability of fluoxetine, fluvoxamine and, to a lesser extent, sertraline and citalopram or escitalopram to inhibit CYP2C19 and CYP3A4 activity deserve particular attention in this respect [3, 6].

These properties should be taken into account, inter alia, in the planned combination of the above-mentioned drugs with antipsychotics, whose clearance and therefore tolerability may be significantly reduced. To avoid this phenomenon, it is necessary to reduce the dose of the antipsychotic or to choose a different molecule. For example, CYP3A4 and 2D6 play a key role in the metabolism of aripiprazole, risperidone and

cariprazine, the metabolism of clozapine and olanzapine is largely mediated by CYP1A2 and to a lesser extent by 2D6, while the metabolism of quetiapine and lurasidone is almost exclusively mediated by CYP3A4/5 [6].

Given the age group discussed in the article, the risk of interaction between SSRIs and phytocannabinoids also requires special attention. Both cannabis and its THC (tetrahydrocannabinol) and CBD (cannabidiol) derivatives have the ability of clinically relevant blockade of CYP450, 2D6, 3A4, 2C19, 1A2, 2B6, and 2C9, while CBG (cannabigerol) inhibits the activity of 2C9 and 3A4 [4, 8]. Previous analyses in adolescents suggest that combining sertraline, citalopram or escitalopram with THC and/or CBD increases the maximum concentration of the drug in the blood (Cmax) and area under the curve of change in drug concentration over time (AUC) of the above drugs and increases the risk of adverse effects such as cough, diarrhoea, flu-like symptoms, fatigue and dizziness [9, 10]. SSRI tolerability may also be adversely affected by oral contraception. Both progesterone and ethinylestradiol may inhibit CYP2C19 and show weak induction of 3A4. It is also worth remembering about the increased risk of interaction when SSRIs are combined with non-steroidal anti-inflammatory drugs, which will translate not only into an increased risk of bleeding, but also, in the case of the use of ibuprofen, diclofenac or celecoxib, into the risk of a number of other adverse effects resulting from pharmacokinetic interactions. Ibuprofen is a substrate for CYP450, 2C9 and 2C19, diclofenac a substrate for 2C9, 2C19, 3A4, 1A2, 2B6 and an inhibitor of CYP 3A4, and celecoxib significantly inhibits CYP2D6 activity.

The risk of interaction of SSRI with proton pump inhibitors (PPIs) is also noteworthy. As omeprazole, esomeprazole, rabeprazole and lansoprazole show significant ability to modify CYP450 3A4, 2D6, 2C, 1A2 activity, when PPIs are required with concomitant SSRI therapy, pantoprazole or dexlansoprazole should be considered as first-line drugs [4-6]. In the context of SSRI interactions, it should also be remembered that enzyme inducers can cause – due to an increase in the activity of individual CYP450 isoenzymes – a significant decrease in the level of the antidepressant drug metabolised by the isoenzyme in question, which may result in a weakening or decrease in the therapeutic effect, or even its loss [7]. Particular attention must be paid to the risks arising from the use of certain antiepileptic drugs that are strong CYP inducers, such as carbamazepine, phenytoin, oxcarbazepine or cenobamate [4-6].

Patient age and genetic polymorphisms as a factor influencing SSRI tolerability and efficacy in children and adolescents

SSRIs in patients aged <18 are sometimes characterised by different pharmacokinetic parameters compared to adults, which has a significant impact on the efficacy and tolerability of SSRIs (Table 3). This is due, among other things, to the fact that the activity of CYP450 isoenzymes, irrespective of the action of inhibitors and inducers, evolves with the age of the patient (Table 4) and, in the case of CYP2D6, 2C9 and 2B6, depends on genetic polymorphisms [11-13]. At the same doses, concentrations

of fluoxetine, fluvoxamine or paroxetine are approximately 2x higher in children compared to adolescents and adults, which should be taken into account at both the drug introduction and target dose setting stages [14-18]. The T1/2s of paroxetine and sertraline used at a dose of 50 mg/day (but not at higher doses) are significantly shorter in patients aged <18 than in adults, and as they are less than 20 hours, in these cases, consider using those drugs in divided doses, twice a day, in order to maintain their therapeutic concentration throughout the day and avoid the appearance of withdrawal symptoms during the day (Table 4) [16, 19].

Table 3. **Key pharmacokinetic parameters of SSRIs, including differences in patients aged <18 [4, 5, 14-20, 22-25]**

Drug	T_{max}*	T1/2 of main drug and active metabolites**	C_{max} and/or mean blood concentration
Citalopram	3	36 Metabolites with questionable/low clinical activity: demethylcitalopram didemethylcitalopram	Lack of sufficient comparisons between age groups Relationships probably analogous to those observed with escitalopram
Escitalopram	4	27-32 Children and adolescents, depending on genetic polymorphism: NM – 23.02 h PM – 57.55 h IM – 35.97 h RM – 16.93 h# UM – 12.51 h#	Testing in patients aged <18 Blood concentrations of the drug, depending on CYP2C19 polymorphism: PM – 217% NM IM – 144% NM RM – 80% NM UM – 65% NM AUC/C_{max} depending on CYP2C19 polymorphism: RM/ UM < IM/PM
Fluoxetine	6-8	4-6 days Non-linear kinetics in all age groups Active metabolite: Norfluoxetine – 4-16 days	C_{max}/AUC: Ch (2x) > A = D Testing in patients aged <18 Coefficient [FLU/(s)-nor-FLU]: EM = 2 x UM IM = 3 x UM PM = 5 x UM Negatively correlated with CYP2D6 activity
Fluvoxamine	3-8	17-22 Non-linear kinetics	C_{max}/AUC: Ch (1.7-2.7x) > A = D

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Paroxetine	4-6	21-24 Non-linear kinetics Children and adolescents: 11.1 ± 5.2# Non-linear kinetics	C_{max}/AUC: Ch > A = D Testing in patients aged <18: Correlation between drug clearance and CYP2D6 activity due to polymorphism AUC/C_{max} depending on CYP2D6 polymorphism: RM/UM/IM < PM
Sertraline	4.5-8.5	Adults: 22-36 Linear kinetics demonstrated with a single administration Adolescents: Single administration: 26.7 ± 5.2 Steady state at dose of 50 mg/day: 15.3 ± 3.5# Steady state at dose of 100-150 mg/day: 20.4 ± 3.4 Steady state at dose of 200 mg – values comparable to adults (27-28h on average) Non-linear or linear kinetics (depending on testing) Children and adolescents, depending on genetic polymorphism NM – 22.13 h PM – 31.84 h IM – 26.08 h RM – 20.15 h NM – 19.22 h	C_{max}/AUC: Ch = A = D Testing in patients aged <18: Blood concentrations of the drug, depending on CYP2C19 polymorphism: PM = 134% NM IM = 114% NM RM = 78% NM UM = 75% NM AUC/C_{max} depending on CYP2C19 polymorphism: RM/UM < IM/PM

* T_{max} – the time after which the maximum blood concentration of a drug is observed from the moment of administration. As the concentration increases until T_{max} is reached, it is possible that immediate/short-term, desirable, and undesirable clinical effects of the drug may increase, reaching their climax around T_{max} and then gradually weakening. Knowledge of T_{max} allows an assessment of how much of the patient's observed beneficial (e.g. relaxation, activation, ease of falling asleep, etc.) or adverse effects (e.g. sedation, dizziness, anxiety, etc.) are likely to be related to the drug administration; NM – normal metaboliser; PM – poor metaboliser; IM – intermediate metaboliser; RM – rapid metaboliser, UM – ultra-rapid metaboliser;

** T1/2 is the time taken for the drug concentration in the blood to decrease to half of the baseline value, after the absorption and distribution phases have been completed; it allows the estimation of the time after which significant elimination of the drug from the body will occur if its administration is discontinued, which generally takes place after 5-7x T1/2 and is important when adverse effects/complications occur and we are waiting for them to be resolved, as well as when planning the introduction of another preparation and wishing to avoid the risk of interaction with the discontinued antidepressant. Importantly – where active metabolites exist, some desirable and undesirable clinical effects of the drug will persist for a multiple of T1/2 (5-7x) of the metabolite – from the time the

drug is discontinued. T1/2 also indicates after how long the drug will reach steady state when administered regularly. For most SSRIs, they reach stable concentrations after approximately 7-14 days, for fluoxetine – due to the very long T1/2 – this only happens after 3-4 weeks. C_{max} – maximum concentration of a drug in the blood; AUC – area under the curve of change in drug concentration over time – reflects the amount of drug that enters the bloodstream after administration; # – consider administering 2x/day

Table 4. **Activity of selected CYP450 isoenzymes and patient age under 18 years [11-13]**

Isoenzyme	Developmental pattern
2D6	Foetal life – minimal or no activity Up to 1 week of age – beginning of activity Up to 1 month of age – 20% of adult activity 3-5 years of age – adult-like activity
2C9	Foetal life – none Up to 1 month of age – the beginning of activity Up to 6 months of age – adult-like activity Childhood period – activity higher than in adults (!) – gradually normalising after puberty
2C19	Postnatal period – activity at 30% of adult level Up to 10 years of age – level slightly lower than or comparable to adults 10-18 years of age – slow build-up to levels comparable to adults
1A2	Foetal life – none Up to 4 months of age – adult-like activity 1-2 years of age – activity higher than in adults (!) – gradually normalising after puberty
3A4	Foetal life – minimal or no activity Up to 1 month of age – 30-40% of adult activity Up to 6 months of age – adult-like activity 1-4 years of age – activity higher than in adults (!) – gradually normalising after puberty

Studies in adolescents further suggest that in this age group, the use of sertraline at a daily dose of 50 mg, due to the faster metabolism of the drug, may be insufficient and potentially associated with a weaker central nervous system effect compared to adults treated with the same dose. Indeed, platelet serotonin reuptake, a reflection of this phenomenon in the central nervous system (CNS), was shown to be inhibited in adolescents by 61 ± 15% after approximately 2 weeks of administration of sertraline at a dose of 50 mg/day. That was a weaker result than in older age groups and suggests a potential need for doses of > 50 mg/day to achieve a response to treatment [19].

In cases of significant problems with drug selection and/or drug dose due to unsatisfactory efficacy and/or tolerability in a patient aged <18, it may be very important to investigate the polymorphism of the predominant isoenzyme for the metabolism of the drug in question [11]. It has been shown that in juvenile patients with rapid or ultra-rapid CYP2C19 activity, the T1/2 of escitalopram is less than 20h and, in

addition, blood concentrations of the drug, at the same dose, are significantly lower than in intermediate or poor metabolisers. Thus, poor metabolisers needed a dose of 10 mg and rapid metabolisers a dose of 30 mg to achieve escitalopram concentrations equivalent to those observed with a 20 mg dose in normal metabolisers [20]. The above data may provide – in the case of suboptimal response to treatment – an indication for the use of escitalopram in divided doses – twice daily and combined higher doses in rapidly metabolising patients. On the other hand, poor metabolisers may require lower doses than initially assumed by the clinician and experience a higher risk of adverse effects. For example, a population-based cohort study on 17,297 subjects born between 1981 and 2005 with a diagnosis of depression between 1996 and 2012, using single nucleotide polymorphism genotyping data, showed that in children and adolescents with CYP2C19 poor metaboliser status who were (es) citalopram-treated, the risk of antidepressant treatment switching and suicide attempt or self-harm was higher [21].

For sertraline, analogous differences in pharmacokinetic parameters were observed, depending on CYP2C19 activity. However, they were much less pronounced. It appears they do not require adjustment in drug dosage and do not significantly translate into sertraline tolerability. Sertraline concentrations in the most rapidly metabolising patients were about 25% lower and in the poor metabolisers about 35% higher than those of normal metabolisers [20]. In the aforementioned cohort study, in young adults with CYP2C19 poor metaboliser status who were treated with sertraline, the risk of drug switching was higher. No such relationship was found for the subpopulation of children and adolescents [21].

In the case of fluoxetine and paroxetine, an inverse correlation between CYP2D6 activity and drug concentration has been observed, which in some cases may translate into the need for dosage adjustments [15, 16, 22, 23]. In contrast, there are no reliable data for fluvoxamine or citalopram in this aspect (Table 3).

Adverse effects of SSRIs in children and adolescents

SSRIs are generally well tolerated in patients aged <18 and most treatment-emergent adverse effects (TEAEs) are mild to moderate in severity. Based on the analysis of the individual randomised clinical trials with placebo control (RCTs), the proportions of patients reporting at least 1 TEAE after SSRIs are comparable to the placebo groups or numerically (but not statistically significantly) higher than in the placebo groups. A similar situation, in most single RCTs, applies to rates of treatment discontinuation due to adverse effects (Table 5) [26-37]. This is also confirmed by meta-analyses. In the most recent of them, conducted by Zhou et al. [38], which included not only antidepressants but also psychotherapy and its combination with antidepressants, only imipramine therapy was associated with a significantly higher risk of treatment discontinuation for any reason than placebo. For each of the SSRIs (as for the other active treatments analysed), this risk was comparable to placebo. As

with adults, the dynamics, location during therapy and severity of individual adverse effects vary. Insomnia, vivid, exhausting dreams, restlessness, nausea, abdominal pain, drowsiness and fatigue and dry mouth mainly occur at the beginning of treatment and tend to reduce in severity or disappear during the first 12 weeks of therapy. On the other hand, sweating, constipation, diarrhoea, flatulence, or sexual dysfunction are most often persistent, with no clear tendency to change over time [39].

Individual SSRIs have different effects on body weight in patients aged <18. In a study by Calarge et al. [40], somatically healthy patients aged 15-20 (n = 264) with a diagnosis of depression or generalised anxiety who had not previously taken an SSRI or within one month of starting an SSRI were followed prospectively for 1.51 ± 0.76 years. Citalopram and escitalopram therapy were most strongly associated with increases in all body composition measures, including visceral fat mass. A weaker association was shown for fluoxetine therapy, while sertraline therapy did not differ from treatment without SSRIs in terms of the aforementioned analysed parameters. Due to insufficient subgroup size, the authors did not include paroxetine in the statistical analyses, but other studies indicate that, along with citalopram and escitalopram, it is associated with the highest risk of weight gain in patients aged <18 treated with SSRIs or SNRIs [41]. In single short-term RCTs, a slight decrease in body weight was observed within a few weeks of treatment with fluoxetine or sertraline [42]. The aforementioned risk of weight gain during therapy with citalopram or escitalopram is dependent on the CYP2C19 polymorphism and is greatest for patients who metabolise these drugs more slowly [43].

SSRIs and the risk of suicide

There is a particular focus on the information that the use of SSRIs (but not exclusively) in children and adolescents is associated with increased suicidal thoughts and behaviour. Since 2004, the Food and Drug Administration has included a specific warning (Black Box Warning) about the risk of suicide in the information on antidepressants. However, the increase in suicidal behaviour did not imply an increase in successful suicides [44]. Moreover, following the warnings, a reduction in the prescription of antidepressants was observed in some countries in subsequent years [45] and this phenomenon was associated in time with an increase in suicide rates In the majority of RCTs evaluating the efficacy of SSRIs in the treatment of depression in patients aged <18, rates of severity or occurrence of suicidal ideations during follow-up are comparable to placebo, suicide attempts are rare, and isolated cases occur in both the active treatment groups and the placebo arm (Table 5) [26-37]. In the meta-analysis of RCTs cited above by Zhou et al. [38], only venlafaxine therapy was associated with an increased risk of suicidal behaviour and/or ideations in short-term therapy compared to placebo. In contrast, there was no statistically significant increased risk for other antidepressants (including all SSRIs) or psychotherapy or the combination of antidepressants and psychotherapy.

In contrast, a Cochrane database review of RCTs [46] concluded that there is low-confidence evidence that escitalopram may 'at least slightly' reduce the risk of suicidal behaviour or ideations compared with placebo. Also, low-confidence evidence, according to the authors, indicates that fluoxetine, paroxetine or sertraline and venlafaxine may 'at least slightly' increase the risk of suicidal ideations or behaviour compared to placebo. These analyses do not address the risk of successful suicides. Analyses of cohort and case-control studies (i.e. without placebo control and often without correction or identification of multiple factors modifying the results of the analysis) are somewhat different, as exemplified by the work of Li et al. [47], who showed that exposure to antidepressants significantly increased the risk of suicide and suicide attempts compared with no antidepressant use among children and adolescents. In subgroup analysis, the risk of suicide attempts during use of antidepressants in general, and use of SSRIs was significantly increased, while the overall suicide risk for antidepressants in general and for SSRIs was not statistically significant. In addition, the risk of suicide and suicide attempt between SSRIs and other antidepressants was similar. It is important to remember that analysis of cohort and case-control data is always subject to important limitations. Firstly, the authors did not analyse the temporal relationship between drug prescription and suicide risk due to the lack of reliable data. Secondly, they did not have the capacity to account for many baseline differences between patients and confounding factors in their analyses.

SSRIs have varying degrees of safety and contraindication profiles in somatic diseases. Table 6 presents the suggested safety of SSRIs in selected clinical conditions in patients aged <18. However, it should be emphasised that due to insufficient data, these suggestions are largely based on extrapolation of data and recommendations for adult patients.

Table 5. **Adverse reactions and adverse events observed in RCTs with SSRIs [26-37]**

Author	Description of the trial	Tolerability results
Fluoxetine		
Findling et al. 2022 [26]	Age: 12-17 Observation: 8-week RCT N = 784 Groups: Flu – 20 mg/day Vor – 10 mg/day Vor – 20 mg/day PBO	TEAE: PBO – 40.9% Vor – 10 mg – 46.9% Vor – 20 mg – 59% Flu – 49.0% SAE: PBO – 0.6% Vor – 10 mg – 4.3% Vor – 20 mg – 4.3% Flu – 2.0% Discontinuation of treatment due to TEAE: Vor = Flu = PBO Most commonly observed TEAEs in Flu group, in descending order of prevalence (from 6.5% to 3.9%): nausea/headaches/upper respiratory tract mucositis vomiting diarrhoea vertigo Occurrence of suicidal ideations, leading to discontinuation of treatment: PBO – 0.0% Vor – 10 mg – 0.7% Vor – 20 mg – 1.9% Flu – 1.3% Adverse effects related to suicidal ideations (suicidal thoughts, suicide attempt): Vor – 10 mg – 1.4% Flu – 3.9%

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Findling et al. 2020 [27]	Age: 7-17 Observation: 8-week RCT N = 473 Groups: Flu – 20 mg/day Vil – 15-30 mg/day PBO	TEAE: PBO – 50.0% Flu – 49.5% Vil – 67.4% SAE: PBO – 0.5% Flu – 5.2% (increased depression, hallucinations, overdose, suicidal ideations) Vil – 0.0% Discontinuation due to adverse effects: PBO – 1.6% Flu – 6.2% Vil – 4.8% Most commonly observed TEAEs in Flu group, in descending order of prevalence (from 10.3% to 4.1%): headache insomnia/nausea upper respiratory tract infection/suicidal ideations gastrointestinal symptoms (vomiting, abdominal pain) upper respiratory tract mucositis Incidence of suicidal ideations during follow-up: PBO – 13.4% Flu – 14.4% Vil – 8.0% Suicide attempts during follow-up: PBO – 4.3% Flu – 2.1% Vil – 2.7%
Atkinson et al. 2014 [28]	Age: 12-17 Observation: 10 weeks N = 337 Groups: Flu – 20-40 mg/day Dul – 60-120 mg/day PBO	TEAE: Dul – 59.8% Flu – 62.4% PBO – 66.0% Treatment discontinuation due to TEAEs: Dul = Flu = PBO SAE ratio: Dul = Flu = PBO Increase in suicidal ideations during follow-up: Dul – 7.1% Flu – 8.0% PBO – 6.8 % Suicide attempts: 1 person in the entire study group (treated with Flu)

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Emslie at al. 2002 [29]	Children: n = 122 Adolescents: n = 97 Observation: 8 weeks Groups: Flu – 20 mg/day PBO	Overall frequency of adverse effects: FLU = PBO Headaches: Flu > PBO Treatment discontinuation due to adverse effects: FLU = PBO
Emslie at al. 2014 [30]	Age: 7-17 Observation: 10 weeks N = 463 Groups: Flu – 20 mg/day Dul – 60 mg/day Dul – 30 mg/day PBO	Treatment discontinuation due to adverse effects: Flu – 20 mg/day – 5.1% Dul – 60 mg/day – 11.1% Dul – 30 mg/day – 6.0% PBO – 3.3% Overall frequency of adverse effects: Dul 60mg – 73.1% Dul 30mg – 57.8% Flu – 61.5% PBO – 58.2% Dul 60mg > Dul 30mg and PBO Adverse effect reported in ≥10% of patients receiving Flu: headaches Increase in suicidal ideations during follow-up: Dul 60mg – 6.7% Dul 30mg – 5.2% Flu – 8.0% PBO – 9.4% Self-harm unrelated to suicidal ideations: Dul 60mg – 2.9% Dul 30mg – 2.7% Flu – 1.8% PBO – 4.3% Suicide attempts during follow-up: Flu – 1 person Dul – 0 persons PBO – 1 person

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Weihs et al. 2018 [31]	Age: 7-17 Observation: 8 weeks N = 339 Groups: Flu – 20 mg/day Desv – 25-50 mg/day PBO	TEAE: Desv – 28.7% Flu – 32.1% PBO – 34.8% SAE: Desv – 1.7% Flu – 5.4% PBO – 3.6% Increase in suicidal ideations during follow-up: Desv – 7.8% Flu – 10.3% PBO – 6.7% Suicide attempts: 1 person after the end of the trial Treatment discontinuation due to TEAE: Flu = Desv = PBO Most commonly observed TEAEs in the group of children receiving Flu, in descending order of prevalence (from 11.1% to 2.2%): vomiting nausea/falls upper respiratory tract infection/rash/fatigue/upper respiratory tract mucositis insomnia/joint pains Most commonly observed TEAEs in the group of adolescents receiving Flu, in descending order of prevalence (from 13.4% to 3%): nausea upper respiratory tract mucositis insomnia diarrhoea/fatigue dizziness/joint pains

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Escitalopram		
Emslie at al. 2009 [32]	Age: 7-17 Observation: 8 weeks N = 312 Groups: Escit – 10-20 mg/day PBO – PBO	Treatment discontinuation due to adverse effects: Escit – 2.6% PBO – 0.6% SAE: Escit – 2.6% PBO – 1.3% Exacerbation of suicidal ideations: 1 patient in Escit group Most commonly observed TEAEs in Escit group, in descending order of prevalence: headaches – 25.2% menstrual cramps – 10.9% insomnia/nausea – 10.3% abdominal pain – 9.0% upper respiratory tract mucositis – 8.4% fatigue – 7.7% flu-like symptoms – 7.1% vomiting – 6.5% diarrhoea/upper respiratory tract infection – 5.2%
Wagner et al. 2006 [33]	Age: 6-17 Observation: 8 weeks N = 264 Escit – 10-20 mg/day PBO	Treatment discontinuation due to adverse effects: Escit – 1.5% PBO – 1.5% TEAE: Escit – 68.7% PBO – 67.7% Suicide behaviours during follow-up: Escit – 1 person PBO – 2 persons Most commonly observed TEAEs in Escit group, in descending order of prevalence: headaches – 22.9% upper respiratory tract mucositis – 11.4% abdominal pain – 10.7% nausea – 7.6% vomiting – 5.3% upper respiratory tract infection – 5.3%

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Citalopram		
Wagner et al. 2004 [34]	Age: 7-17 Observation: 8 weeks N = 174 Groups: Cit – 20-40 mg/day PBO	Treatment discontinuation due to adverse effects: Cit – 5.6% PBO – 5.9% SAE: none Most commonly observed TEAEs in Cit group, in descending order of prevalence: rhinitis/nausea – 13.5% abdominal pain – 11.2% flu-like symptoms – 6.7% fatigue/diarrhoea/lower back pain – 5.6%
Paroxetine		
Emslie at al. 2006 [35]	Age: 7-17 Observation: 8 weeks N = 206 Groups: Par – 10-50 mg/day PBO	TEAE: Par – 70.3% PBO – 60.8% SAE: Par – 5.8% PBO – 1% TEAEs related to suicidal behaviour: Par – 1.92% PBO – 0.0% Suicide attempt: Par – 2 persons PBO – 1 person Discontinuation due to adverse effects: Par – 8.6% PBO – 1.96% Adverse effects occurring 2x more frequently in the Par group than in the PBO group: cough – 5.9% dyspepsia – 5.9% vomiting – 5.9% dizziness – 5.0%

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Berard et al. 2006 [36]	Age: 13-18 Observation: 12 weeks N = 286 Groups: Par – 20-40 mg/day PBO	TEAE: Par – 65.9% PBO – 59.1% Treatment discontinuation due to TEAE: Par – 10.7% PBO – 7.1% Most commonly observed TEAEs in Par group, in descending order of prevalence: nausea – 24.2% headaches – 18.7% dizziness – 10.4% drowsiness – 9.3% decrease in appetite – 7.7% (the only TEAE 2x more frequent than in the PBO group) infection – 7.7% asthenia – 6.6% Suicide attempts during follow-up: Par – 3 persons (1.7%) PBO – 2 persons (2.1%)
Sertraline		
Wagner et al. 2003 [37]	Age: 6-17 Observation: 10 weeks Total of 2 RCTs, results combined for both RCTs N = 376 Groups: Ser – 50-200 mg/day PBO	SAE: Ser – 3.7% PBO – 3.2% Increase in suicidal ideations during follow-up: Ser – 1.6% PBO – 0.0% Suicide attempts during follow-up: Ser – 2 persons (1.1%) PBO – 2 persons (1.1%) Most commonly observed TEAEs in the group of adolescents receiving Ser, in descending order of prevalence: vomiting – 7.8% diarrhoea – 6.8% Most commonly observed TEAEs in the group of children receiving Ser, in descending order of prevalence: insomnia – 19.8% diarrhoea – 15.1% lack of appetite – 10.5% vomiting – 9.3% excitation – 8.1% urinary incontinence – 7.0% skin redness – 5.8%

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PBO – placebo; Flu – fluoxetine; Cit – citalopram; Escit – escitalopram; Ser – sertraline; Par – paroxetine; Ago – agomelatine; Desv – desvenlafaxine; Dul – duloxetine; Vor – vortioxetine; Vil – vilazodone

Table 6. **Safety of SSRIs in selected clinical conditions [3, 48, 49]**

Active substance	Heart diseases	Epilepsy	Glaucoma	Diabetes mellitus / metabolic syndrome	Renal failure	Risk of hepatotoxicity	Pregnancy	Breast-feeding
Citalopram	M[1]	L	M/L[3]	L	M/L[10]	L/M	M	L2
Escitalopram	M[1]	L	M/L[3]	L	M/L[10]	L/M	M	L2
Fluoxetine	L/M[2]	L	M/L[3]	L[7]	M[8,9,10]	L/M	M	L2
Fluvoxamine	L	L	M/L[3]	L	M[9,10]	L	M	L2
Paroxetine	L	L	H[4]	M[5, 6]	M[9,10]	M	H	L2
Sertraline	L	L	M/L[3]	L	M[8,9,10]	M	M	L2

Risk of complications: H – high, M – moderate, L – low; 1 – moderate risk of QTc prolongation: should not be used in patients with current QTc prolongation or cumulative risk factors for QTc prolongation; in overdose, the drug poses a significant risk of cardiac arrhythmias; 2 – mild risk of QTc prolongation, increasing with significant doses and overdose; 3 – in the first 7 days of SSRI treatment, there is an increase in intraocular pressure and risk of acute glaucoma attack, then the risk becomes very low and is associated with a reduction in intraocular pressure; 4 – significant risk of acute glaucoma attack due to the anticholinergic effect of the drug; 5 – highest risk of weight gain among SSRIs; 6 – the drug may cause hyperglycaemia; 7 – the risk of inducing hypoglycaemia and confounding adverse drug effects with hypoglycaemia; 8 – the risk of accumulation and associated risk of serotonin syndrome in advanced renal failure; 9 – dose reduction of ≤ 50% required; 10 – as GFR decreases, the risk of haemorrhagic complications after SSRIs increases;

L – Safety criteria for use of drugs during breastfeeding (Hale's Lactation Risk Category): L2 (drug probably suitable) – A drug that has been taken by a limited number of lactating mothers whose infants had no increase in adverse effects.

Summary

1. The different pharmacodynamic profile means that SSRIs have a different risk of certain adverse effects (considered common for SSRIs) and differ in their degree of adaptation with the clinical picture of depression and co-occurring psychopathology and patient-specific preferences.
2. SSRIs in patients aged <18 are sometimes characterised by different pharmacokinetic parameters compared to adults, which has a significant impact on the efficacy and tolerability of SSRIs. This is due, among other things, to the fact that the activity of CYP450 isoenzymes, irrespective of the action of inhibitors and

inducers, evolves with the age of the patient and, in the case of CYP2D6, 2C9 and 2B6, depends on genetic polymorphisms.
   a. Concentrations of fluoxetine, fluvoxamine and paroxetine are approximately 2x higher in children compared to adolescents and adults, which should be taken into account at both the drug introduction and target dose setting stages.
   b. The T1/2 of paroxetine and sertraline used at a dose of 50 mg/day (but not at higher doses) are significantly shorter in patients aged <18 than in adults; therefore, in cases of sub-optimal efficacy or if withdrawal symptoms become apparent during the day, the use of the drugs in divided doses, twice a day, should be considered.
   c. In cases of significant problems with drug selection and/or drug dose due to unsatisfactory efficacy and/or tolerability in a patient aged <18, it may be very important to investigate the polymorphism of the predominant isoenzyme for the metabolism of the drug in question. This applies in particular to:
      i. CYP2C19 during treatment with escitalopram, and to a lesser extent during treatment with sertraline;
      ii. CYP2D6 when using fluoxetine or paroxetine.
3. SSRIs are generally well tolerated in patients aged below 18 and most treatment-emergent adverse effects (TEAEs) are mild to moderate in severity.
4. In the majority of RCTs evaluating the efficacy of SSRIs in the treatment of depression in patients aged <18, rates of severity or occurrence of suicidal ideations during follow-up are comparable to placebo, suicide attempts are rare, and isolated cases occur in both the active treatment groups and the placebo arm.
5. In contrast, there was no statistically significant increased risk for other antidepressants (including all SSRIs) or psychotherapy or the combination of antidepressants and psychotherapy (except venlafaxine).
6. Only venlafaxine therapy was associated with an increased risk of suicidal behaviour and/or ideations in short-term therapy compared to placebo.

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