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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 I. Clinical efficacy and areas of application

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Summary

In the adult population of patients with major depression, both psychotherapeutic and pharmacological interventions are effective, but antidepressants remain the mainstay of treatment. In the case of child and adolescent psychiatry, there is still controversy over whether to use pharmacological interventions and which drug to prefer. Although psychotherapeutic treatment is still considered a first-line treatment, antidepressants are widely used to treat depression in children and adolescents, and the number of medications prescribed for this indication has increased over time. In Poland, about 57,000 patients under 18 years of age currently use reimbursed antidepressants. Antidepressants are generally effective and well tolerated by children, but between 31% and 48% will not respond to them and up to 25% will experience side effects.

The aim of the study was to present the effectiveness and tolerance of antidepressants used in depression in the pediatric population. Among all SSRIs, the largest amount of data from short-term RCTs and their meta-analyses indicate the effectiveness of fluoxetine in patients diagnosed with depression < 18 years of age, which still makes it the drug of first choice in this

indication. However, the results of meta-analyses do not allow to draw clear conclusions as to the effectiveness of individual SSRIs in the treatment of depression in children and adolescents. Single placebo-controlled studies show the efficacy of sertraline, escitalopram and citalopram in the treatment of depression in patients < 18 years of age, making them important treatment options worth considering. There is no reliable evidence on the effectiveness of fluvoxamine.

Key words: child and adolescent psychiatry, depression, SSRIs – clinical effectiveness and areas of application

Introduction

According to the ICD-11 definition, depressive disorders are characterised by depressed mood (sad, irritable, feeling of emptiness) or loss of pleasure, accompanied by other cognitive, behavioural or neurovegetative symptoms that significantly affect a person's ability to function. Depressive disorder may present with a single episode and be mild, moderate with or without psychotic symptoms, severe with or without psychotic symptoms, or it may be recurrent depressive disorder with an identical picture, with a single episode [1].

Prevalence of depressive disorders

According to the WHO (2001), depression is the fourth most common cause of disease burden worldwide and is expected to show an increasing trend over the next 20 years. Similarly, major depressive disorder is one of the most common mental disorders in children and adolescents. The point prevalence is 2.8% in school-aged children (6-12 years) and 5.6% in adolescents (13-18 years). However, compared to adults, children and adolescents with major depressive disorders are underdiagnosed and therefore also untreated, probably because the symptoms of depressive disorder in this population are uncharacteristic and highly variable [2]. In a nationwide epidemiological study on a representative sample of children and adolescents in Poland, EZOP II [3], the prevalence of depression was estimated at 1.9% in children aged 12-13, 4% in the group of 14-15 years and 7% in adolescents aged 16-17. In turn, the total number of patients in the age range 0-17 years under psychiatric care (excluding addiction treatment) in 2021 was 211,880. More than 25,000 people up to 18 years of age with disorders of a depressive nature received healthcare services in 2021. In 2021, 11,000 patients aged 0-17 years with 'depressive episode' or 'recurrent depressive disorder' benefited from the services. The vast majority of patients were in the age group of 12-17 years [4].

Prevalence of antidepressant use in children and adolescents and indications for their use

In the treatment of major depression, both psychotherapeutic and pharmacological interventions in the adult patient population are effective; however, antidepressants

remain the mainstay of treatment [5]. In the case of child and adolescent psychiatry, the situation is different, and it is still controversial whether to use pharmacological interventions and which drug to prefer, and although psychotherapeutic treatment is still considered to be the first-line therapy, antidepressants are widely used in the treatment of depression in children and adolescents, and the number of drugs prescribed for this indication has increased over time [2, 6]. Over the past 20 years, the consumption of antidepressants (mainly – selective serotonin reuptake inhibitors – SSRIs) has increased dramatically in many countries [2]. Between 2005 and 2012, the prevalence of antidepressant use increased from 1.3% to 1.6% in the US; from 0.7% to 1.1% in the UK; from 0.6% to 1.0% in Denmark; from 0.5% to 0.6% in the Netherlands; and from 0.3% to 0.5% in Germany [6]. In Poland, reimbursed antidepressants are currently used by approximately 57,000 patients under the age of 18. A spike in the number of patients using antidepressants was observed in 2021. This compilation includes those filling prescriptions for selected antidepressants regardless of indication. Sertraline is the most commonly used drug, with approximately 21,000 patients under the age of 18 filling prescriptions for this drug in 2018. A steady increase in the number of patients using particular antidepressants is being observed [4].

Table 1 shows the extent of SSRI registration in Poland and internationally for different age groups. Table 2 shows how SSRIs are listed in the recommendations for children and adolescents. In contrast, Table 3 shows other uses of SSRIs discussed in the subject literature.

Table 1. **The extent of SSRI registration [7-9]**

Drug	Poland	EU	FDA
Citalopram	Adults	Adults	Adults
Escitalopram	Adults	Adults	Depression from the age of 12
Fluoxetine	Moderate or severe depression in combination with psychotherapy from the age of 8	Moderate or severe depression in combination with psychotherapy from the age of 8	From the age of 7 in OCD From the age of 8 in major depression From the age of 10 in combination with olanzapine in a depressive episode in the course of Bipolar I Disorder
Fluvoxamine	OCD from the age of 8 Other indications OCD from the age of 8 Other indications from the age of 18	OCD from the age of 8 Other indications – adults	From the age of 8 in OCD
Paroxetine	Adults	Adults	Adults
Sertraline	OCD from the age of 6 Other indications – adults	OCD from the age of 6 Other indications – adults	From the age of 6 in OCD

Table 2. **The way SSRIs are listed in the recommendations for children and adolescents [10-20]**

Source	Anxiety disorders in children and adolescents	Depression in children and adolescents	OCD in children and adolescents	Bipolar disorder in children and adolescents	Other
AACAP practice parameter	GAD, social anxiety, separation anxiety and PD – in children aged 6-17: **SSRI**. For all drugs in this group, this is an off-label use in this indication (Walter et al. 2020) [10]	Major depressive episode: **SSRIs** with the exception of paroxetine For some drugs in this group, this is an off-label use in this indication (Walter et al. 2023) [11]	In combination with CBT, **SSRIs**[1] (Geller et al. 2012) [12]		
American Academy of Paediatrics (Cheung et al. 2018) [13]		Depressive disorders: **SSRIs** (paroxetine treatment should not be initiated in the OPD setting). For some drugs in this group, this is an off-label use			
Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) 2018 guidelines (Yatham et al. 2018) [14]				In a depressive episode in the course of BD – as third-line treatment **olanzapine + fluoxetine**	

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[1] AACAP standards published earlier than 5 years ago should be considered as in need of updating

Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 clinical guidelines for the management of adults with major depressive disorders (MacQueen et al. 2016) [15]		Depressive episode: first-line treatment: psychotherapy, second-line treatment: **fluoxetine** (level of evidence 1), **escitalopram, citalopram, sertraline** (level of evidence 2) If no response to treatment with **SSRI** (general) + psychotherapy, change to another SSRI (general)			
Canadian practice guidelines for the treatment of children and adolescents with eating disorders (Couturier et al. 2020) [16]					Anorexia nervosa: case reports on the positive effects of **fluoxetine** and **sertraline** Bulimia nervosa: scarce data on **fluoxetine** ARFID – reports on improvement after the use of **fluoxetine, sertraline, escitalopram and paroxetine**
NICE CG31 [17], NG134 [18]		**Fluoxetine –** possible use in moderate or severe depression in combination with psychotherapy from the age of 5 **Fluoxetine, citalopram, sertraline**: possible use in severe treatment-resistant depression, recurrent depression, psychotic depression	**Fluvoxamine** – in case of failure of psychosocial interventions (bearing in mind that use under the age of 8 is an off-label use) **Sertraline** – in case of failure of psychotherapeutic interventions (bearing in mind that use under the age of 6 is an off-label use) **Fluoxetine** – if OCD is accompanied by clinically significant depression		Body Dysmorphic Disorder – **fluoxetine**

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WFSBP guidelines for treatment of anxiety, obsessive-compulsive and posttraumatic stress disorders – Version 3. Part I: Anxiety disorders (Bandelow et al. 2023) [19]	GAD, separation anxiety, mixed anxiety disorders: **fluvoxamine** (strength of recommendation 1), **sertraline** and **fluoxetine** (strength of recommendation 2) Social phobia: **paroxetine** (strength of recommendation 2), **fluoxetine** (strength of recommendation 3) Selective mutism: single studies on **citalopram**, **escitalopram**, **fluoxetine** and **sertraline** (strength of recommendation 3)				
WFSBP guidelines for treatment of anxiety, obsessive-compulsive and posttraumatic stress disorders – Version 3. Part II: OCD and PTSD (Bandelow et al. 2023) [20]			**Fluvoxamine, fluoxetine, sertraline (**strength of recommendation 1) Paroxetine, citalopram – inconclusive data (recommendation class 4)		PTSD: **sertraline** was assessed, inconclusive data (strength of recommendation 4)

Explanation of abbreviations: AACAP – American Academy of Child and Adolescent Psychiatry, CBT – cognitive-behavioural therapy, GAD – generalized anxiety disorder, NICE – National Institute of Health and Care Excellence, OCD – obsessive-compulsive disorder, OPD – outpatient department, PTSD – posttraumatic stress disorder, WFSBP – World Federation of Societies of Biological Psychiatry

Table 3. **Other uses of SSRIs discussed in the literature [21-25]**

Source	Indication
The World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the treatment of adolescent sexual offenders with paraphilic disorders (Thibaut et al. 2016) [21]	**SSRIs** (particularly **fluoxetine** and **sertraline**) may find use in the treatment of paraphilic disorders in juvenile sex offenders
Autism Review of the literature on the pharmacotherapy of axial symptoms (Maniram et al. 2022) [22] 2. Meta-analysis on the effects of antidepressants on specific types of symptoms (Liang et al. 2022) [23] 3. Meta-analysis on the efficacy of pharmacotherapy against repetitive stereotypic behaviours (Yu et al. 2020) [24]	**Fluoxetine** – one clinical trial showed improvement in repetitive stereotypic behaviours **Antidepressants** (in general) showed improvement in repetitive stereotypic behaviours **SSRIs** do not help
Self-harm (Eggart et al. 2022) [25]	The efficacy of **SSRIs** has not been confirmed

Reasons behind antidepressant use in the child and adolescent population

Despite this increase in prescription rates and despite their licensed indication in many disorders, the use of antidepressants in major depression in young people has been questioned in light of the high placebo response rate of 22% to 62% and the 'black box warning' issued by the FDA in 2004 reporting an increased risk of suicidal behaviour among children treated with SSRIs [2, 6]. The FDA's warning was based on an analysis published more than a decade ago on sponsored randomised controlled trials (RCTs). However, by this time, an increasing number of studies are questioning the methodological rigour of the FDA analysis [6]. It should also be noted that antidepressants are generally effective and well tolerated by children, but between 31% and 48% of them will not respond to them and up to 25% will experience adverse effects. 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 population is smaller and this aspect requires further, detailed research [26].

Efficacy and tolerability of antidepressants used for depression in the paediatric population

In a meta-analysis, Cipriani and his team (2016) [2] compared the efficacy and tolerability of antidepressants for acute depression in children and adolescents (mean duration of follow-up – 8 weeks). The authors reviewed 31 articles published between 1986 and 2014, describing 34 RCTs involving 5,260 patients (mean age 13.6 years, SD = 2.87), in which the effects of 14 antidepressants and placebo were compared (3,106 trial participants took drugs and 2,154 took placebo). Drugs used in therapeutic doses only were included in the analysis, they included: amitriptyline, citalopram, clomipramine, desipramine, duloxetine, escitalopram, fluoxetine, imipramine, mirtazapine, nefazodone, nortriptyline, paroxetine, sertraline and venlafaxine. RCTs including participants with drug-resistant depression treated for less than 4 weeks and a study group of less than 10 patients were excluded from the analysis. In the meta-analysis, the authors took into account the change in severity of depressive symptoms, the frequency of treatment discontinuation due to the emergence of adverse effects, and the emergence of suicidal thoughts and behaviours. To assess changes in depressive symptoms in the trials reviewed by the authors, the following were used: *Children's Depression Rating Scale – Revised (CDRS-R), Beck Depression Inventory (BDI)* and *Children's Depression Inventory (CDI)*. The number of patients whose depressive symptom scores decreased by at least 50% or whose Clinical Global Impression (CGI) scores improved significantly was considered an indicator of improvement.

In the analyses performed, only fluoxetine was found to be more effective than placebo (SMD = – 0.51, 95% CrI: –0.99 to –0.03). Nortriptyline was significantly less effective than the seven antidepressants and placebo (SMD = – 1.65 to – 1.14). In contrast, there were no statistically significant differences in clinical efficacy between all the drugs included in the meta-analysis – including no evidence of an advantage of fluoxetine over the other antidepressants. Fluoxetine was significantly better tolerated than duloxetine (OR = 0.31; 95% CrI: 0.13 to 0.95) and imipramine (OR = 0.23; 95% CrI: 0.04 to 0.78). Citalopram and paroxetine were significantly better tolerated than imipramine (OR = 0.27; 95% CrI: 0.04 to 0.96 and OR = 0.22; 95% CrI: 0.08 to 0.87, respectively). Imipramine was significantly worse tolerated compared to placebo (OR = 5.49; 95% CrI: 1.96 to 20.86), venlafaxine (OR = 3.19; 95% CrI: 1.01 to 18.70) and duloxetine (OR = 2.80; 95% CrI: 1.20 to 9.42). Venlafaxine compared to placebo (OR = 0.13; 95% CrI: 0.00 to 0.55) and 10 other therapeutic interventions (citalopram, escitalopram, fluoxetine, fluoxetine + CBT, duloxetine, imipramine, family therapy, desvenlafaxine, CBT and placebo + CBT) was associated with a significant risk of increased suicidal thoughts and/or behaviour.

In another publication, Feeney et al. (2022) [27] included in their meta-analysis 34 double-blind, placebo-controlled randomised trials involving 6,161 patients. Medications used for acute depression in children and adolescents included fluoxetine, duloxetine, citalopram, escitalopram, paroxetine, sertraline and vortioxetine. The standardised mean difference (SMD) across all studies was very small and amounted

to 0.12 (CI: 0.08-0.17; $p < 0.001$), it was significantly lower than that observed in the trials in adults. When the meta-analysis was restricted to trials with a low mean placebo response, the SMD increased to 0.19 and then to 0.22 when trials with at least a 50% chance of receiving placebo were included. The authors note that most of the research was conducted among older children and younger adolescents. This does not answer the question of the efficacy of the drugs in older adolescents.

Teng et al. (2022) [28] included 17 RCTs involving 2,537 participants (patients aged from 6 to 18; mean age 13.7 years) into a systematic review and meta-analysis from 7,284 publications. They proved that antidepressants improved patient functioning (SMD = 0.17; 95% CI: 0.09–0.25; $p < 0.0001$), but did not affect quality of life (SMD = 0.11; 95% CI: – 0.02 to 0.24; $p = 0.093$). Second-generation antidepressants (fluoxetine, paroxetine, sertraline, escitalopram, nefazodone), especially fluoxetine, escitalopram and nefazodone, had a particular effect on improving functioning in children and adolescents treated for depression. Such an effect was not observed with first-generation drugs (nortriptyline, imipramine, desipramine).

In contrast, Zhou et al. (2020) [29] included 71 RCTs comprising 9,510 patients aged between 3 and 20 years (mean age 14 years) in their analyses. It was found that fluoxetine in combination with cognitive-behavioural therapy, CBT (SMD = – 0.73; 95% CI: – 1.39 to – 0.07) and fluoxetine alone (SMD = – 0.51; 95% CI: – 0.84 to – 0.18) were more effective compared to placebo in the treatment of depression in children and adolescents. Fluoxetine + CBT was more effective than CBT in monotherapy (SMD = – 0.78; 95% CrI: – 1.55 to – 0.01) and psychodynamic therapy (SMD = – 1.14; 95% CrI: – 2.20 to – 0.08). Nortriptyline (SMD = 1.04 to 2.22) showed the worst effect compared to all other active effects. Nefazodone and fluoxetine were associated with less frequent trial discontinuation compared to sertraline, imipramine and desipramine. In contrast, the use of imipramine was associated with a higher rate of early termination compared with placebo, desvenlafaxine, fluoxetine and vilazodone. Venlafaxine was significantly more likely to have an increased risk of suicidal thoughts and behaviours compared to placebo and 10 other interventions (citalopram, escitalopram, fluoxetine, fluoxetine with CBT, duloxetine, imipramine, family therapy, desvenlafaxine, CBT and placebo with CBT).

In a Cochrane library meta-analysis that included 26 RCTs examining the efficacy of different antidepressants in patients aged 6-18 years, Hetrick et al. (2021) [30] showed that most antidepressants could be associated with a 'small and non-significant' reduction in depressive symptoms on the CDRS-R scale compared with placebo and that differences in this aspect between individual antidepressants were also 'small and non-significant'. On the basis of an analysis of the efficacy of the drugs and the risk-benefit balance, the authors conclude that if pharmacotherapy for depression is required for a patient aged ≤18, fluoxetine, sertraline, escitalopram or duloxetine should be considered as first-line drugs.

However, these meta-analysis results, most of which suggest the most beneficial clinical effects associated with fluoxetine use, require additional commentary. Firstly,

fluoxetine has so far been the most studied antidepressant in the age group in question – both in terms of its comparisons to placebo and as an active comparator, making the group of patients receiving fluoxetine included in the meta-analyses by far the largest. It can therefore be assumed that the results for other antidepressants (including other SSRIs) are not as well represented as those for fluoxetine, and their efficacy in child and adolescent depression remains an open question and requires further research. Secondly, it is worth noting that the positive effects of fluoxetine treatment are mainly indicated by the oldest studies, including registration studies sponsored by the manufacturer. In the case of more recent studies – in which fluoxetine acted as an active comparator – it usually had comparable efficacy (or comparable inefficacy) to the other drug that was used in the clinical trial. Finally, it is worth noting the single RCTs suggesting the efficacy of sertraline, citalopram and escitalopram in children and adolescents and the exclusively negative trials on paroxetine (Table 4) [31-47]. It should be noted that the studies included in the meta-analyses are short-term observations and do not allow conclusions to be drawn about the usefulness of individual antidepressants (including individual SSRIs) in the long-term treatment of depression in patients under the age of 18.

Table 4. **Summary of major RCTs in children and adolescents on the efficacy of SSRIs and/or its comparison with the efficacy of antidepressants with a different mechanism of action [31-47]**

Drug	Author	Description of the trial	Efficacy results
Fluoxetine	Findling et al. 2022 [31]	Age: 12-17 Observation: 8-week RCT N = 784 Groups: Flu – 20 mg/day Vor – 10 mg/day Vor – 20 mg/day PBO	Reduction in depression severity (CDRS-R): Vor = PBO Flu > PBO
	Findling et al. 2020 [32]	Age: 7-17 Observation: 8-week RCT + 26-week OL N = 473 Groups: Flu – 20 mg/day Vil – 15-30 mg/day PBO	Reduction in depression severity (CDRS-R): Flu = Vil = PBO

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Fluoxetine	Findling et al. 2009 [33]	Age: 12-17 Observation: 8-week RCT N = 34 (MDD+ SUD) Groups: Flu 10-20 mg PBO	Reduction in depression severity (CDRS-R): Flu = PBO
	Atkinson et al. 2014 [34]	Age: 12-17 Observation: 10 weeks N = 337 Groups: Flu – 20-40 mg/day Dul – 60-120 mg/day PBO	Reduction in depression severity (CDRS-R): Flu = Dul = PBO
	Emslie at al. 2002 [35]	Children: n = 122 Adolescents: n = 97 Observation: 8 weeks Groups: Flu – 20 mg/day PBO	Reduction in depression severity (CDRS-R): Flu > PBO Remission rates: Flu > PBO Therapeutic response rates: Flu = PBO
	Emslie at al. 1997 [36]	Age: 7-17 Observation: 8 weeks N = 96 Groups: Flu – 20 mg/day PBO	Reduction in depression severity (CDRS-R): Flu > PBO Remission rates: Flu = PBO
	Emslie at al. 2014 [37]	Age: 7-17 Observation: 10 weeks N = 463 Groups: Flu – 20 mg/day Dul – 60 mg/day Dul – 30 mg/day PBO	Reduction in depression severity (CDRS-R): Flu = Dul = PBO

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Fluoxetine	Weihs et al. 2018 [38]	Age: 7-17 Observation: 8 weeks N = 339 Groups: Flu – 20 mg/day Desv – 25-50 mg/day PBO	Reduction in depression severity (CDRS-R): Flu = Desv = PBO Therapeutic response rates Flu > PBO Desv = PBO
	Arango et al. 2022 [39]	Age: 7-17 Observation: 12 weeks N = 466 Groups: psychosocial counselling +: Flu – 10-20 mg/day Ago – 10 mg/day Ago – 25 mg/day PBO	Reduction in depression severity (CDRS-R): Flu = Ago (25mg) > PBO (only in adolescents)
Escitalopram	Emslie at al. 2009 [40]	Age: 7-17 Observation: 8 weeks N = 312 Groups: Escit – 10-20 mg/day PBO – PBO	Reduction in depression severity (CDRS-R): Escit > PBO Therapeutic response rates (CGI): Escit > PBO Remission rates: Escit (CDRS-R) = PBO
	Wagner et al. 2006 [41]	Age: 6-17 Observation: 8 weeks N = 264 Escit – 10-20 mg/day PBO	Reduction in depression severity in the whole group (CDRS-R): Escit = PBO Reduction in depression severity in adolescents (age: 12-17): Escit > PBO
Citalopram	Wagner et al. 2004 [42]	Age: 7-17 Observation: 8 weeks N = 174 Groups: Cit – 20-40 mg/day PBO	Reduction in depression severity (CDRS-R): Cit > PBO Therapeutic response rates: Cit > PBO

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Citalopram	von Knorring et al. 2006 [43]	Age: 13-18 Observation: 12 weeks N = 244 Groups: Cit – 10-40 mg/day PBO	Therapeutic response rates (MADRS): Patients receiving concurrent psychotherapy: Cit = PBO Patients without psychotherapy: Cit > PBO Remission rates (MADRS): Patients receiving concurrent psychotherapy: Cit = PBO Patients without psychotherapy: Cit > PBO
Paroxetine	Emslie et al. 2006 [44]	Age: 7-17 Observation: 8 weeks N = 206 Groups: Par – 10-50 mg/day PBO	Reduction in depression severity (CDRS-R): Par = PBO Therapeutic response rates: Par = PBO Remission rates: Par = PBO
	Berard et al. 2006 [45]	Age: 13-18 Observation: 12 weeks N = 286 Groups: Par – 20-40 mg/day PBO	Reduction in depression severity (K-SADS-L): Par = PBO Therapeutic response rates (MADRS): The whole group: Par = PBO Patients aged >16: Par > PBO
	Le Noury et al. 2015 [46]	Age: 12-18 Observation: 8 weeks N = 275 Groups: Par – 20-40 mg/day Imi – 200-300 mg/day PBO	Reduction in depression severity (HAM-D): Par = Imi = PBO Reduction in depression severity (K-SADS-L): Par = Imi = PBO Therapeutic response rates: Par = Imi = PBO
Sertraline	Wagner et al. 2003 [47]	Age: 6-17 Observation: 10 weeks Total of 2 RCTs, results combined for both RCTs N = 376 Groups: Ser – 50-200 mg/day PBO	Reduction in depression severity (CDRS-R): Ser > PBO Therapeutic response rates Ser > PBO

Explanation of abbreviations: PBO – placebo, Flu – fluoxetine, Cit – citalopram, Escit – escitalopram, Ser – sertraline, Par – paroxetine, Ago – agomelatine, Desv – desvenlafaxine, Dul – duloxetine, Vor

– vortioxetine, Vil – vilazodone, Imi – imipramine, CGI – Clinical Global Impression, CDRS-R – Children's Depression Rating Scale—Revised; MADRS – Montgomery Asberg Depression Rating Scale; K-SADS-L – Kiddie-Schedule for Affective Disorders and Schizophrenia for School Age Children; HAM-D – Hamilton Depression Scale

Summary

1. Of all the SSRIs, the largest amount of data from short-term RCTs and their meta-analyses indicate the efficacy of fluoxetine in patients with a diagnosis of depression aged <18, which continues to make it the drug of first choice for this indication.
2. The results of meta-analyses do not allow firm conclusions on the efficacy of individual SSRIs in the treatment of depression in children and adolescents.
3. Single placebo-controlled trials indicate the efficacy of sertraline, escitalopram and citalopram for the treatment of depression in patients aged <18, making them important therapeutic options worthy of consideration.
4. There is a lack of robust evidence on the efficacy of fluvoxamine.

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