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How can the potential suicide risk of SSRIs be reduced in the treatment of adolescent depression?

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Abstract. Depression is an important public health problem in the world. Selective Serotonin Reuptake Inhibitors (SSRIs) are the first-line drugs for the treatment of depression. However, at the beginning of treatment, especially for adolescent patients, such drugs may increase the risk of suicide for a short time. Through a systematic review of relevant literature, this article discusses the nature and magnitude of SSRI-related suicide risk, analyses the main factors affecting this risk, and summarises the intervention methods that can effectively reduce the risk in the treatment of adolescent depression. Research results show that this risk does exist, but there are certain conditions: it only occurs at a certain stage of treatment, and the risks brought by different types of SSRI are also different. Many factors will jointly affect this risk, such as adolescent brains that are not mature, depression itself is serious, patients have other mental diseases, multiple drugs are used together, and individual differences such as age and gender. To control this risk, several strategies can be combined, such as starting with lower doses of medication, strengthening monitoring at an early stage, and dealing with other combined mental illnesses before using an SSRI, while cooperating with Cognitive Behavioral Therapy (CBT). Although the risk of suicide will increase briefly in the early stages of treatment, the therapeutic effect of the SSRI is much greater than this controllable risk. Therefore, SSRI is still used as a front-line drug for adolescent depression.

Keywords: adolescents, depression, SSRIs, suicide risk, influencing factors

1. Introduction

Depression has become a prominent public health problem worldwide. According to the *2019-2020 National Mental Health Development Report* released by the National Health Commission of China, 24.6% of Chinese adolescents aged 12-18 meet the diagnostic criteria for depression, which is much higher than the incidence rate of 3.6% in adults. In addition, depression in this age group is often accompanied by extreme behavior, such as self-harm and suicide.

Antidepressants play a central role in the treatment of adolescent depression. At present, three types of antidepressants are mainly used in clinical practice: Selective Serotonin Reuptake Inhibitors (SSRIs), Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs) and Tricyclic Antidepressants (TCAs). Among them, SSRIs are recommended as a first-line treatment drug for adolescent depression by domestic and foreign clinical guidelines because of their accurate therapeutic effect and fewer side effects. The *Clinical Practice*

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Guidelines for Childhood and Adolescent Depression published by Walter et al. [1] holds this view. As early as 1998, the American Society of Child and Adolescent Psychiatry (AACAP) clearly pointed out that SSRIs are the preferred treatment for adolescent depression patients who are not accompanied by other mental comorbidities. A multicenter study by Wagner et al. showed that 69% of adolescent depression patients' symptoms improved after 10 weeks of treatment with sertraline, which was higher than that of 52% in the placebo group [2]. In addition, the Adolescent Depression Treatment Research (TADS) team reported that 61% of adolescents' symptoms were relieved after receiving 12-week fluoxetine monotherapy, and the remission rate could be increased to 71% when combined with Cognitive Behavioral Therapy (CBT) [3].

However, teenagers' use of SSRIs has always been accompanied by concerns about the increased risk of suicide. The *Guidelines for the Clinical Diagnosis and Treatment of Depression in Children and Adolescents in China* (2022 Edition) points out that some adolescents may experience anxiety or impulsiveness in the early stage of SSRI treatment, especially in the first two weeks, which may increase the risk of suicide.

Many researchers have discussed this issue, but there are still some controversies and uncertainties. After analysing 17 clinical trials, Whittington et al. found that the incidence of suicidal thoughts in children and adolescents taking SSRI was 4.0%, about twice that of the placebo group (2.1%) [4]. A meta-analysis carried out by Bridge et al. shows that SSRIs are associated with an increase in the risk of adolescent suicide-related behavior (OR = 1.8, 95% CI 1.1–2.9) [5].

The conclusions from different studies are inconsistent. For example, Whittington et al. believe that the risk-benefit ratio of certain SSRIs (such as paroxetine) is not ideal [4], while the TADS study concludes that fluoxetine combined with psychotherapy can reduce the risk of long-term suicide. These differences may be due to differences in research design, participant characteristics, follow-up duration, and definitions of "suicide risk". Therefore, it is of great clinical significance to conduct a systematic and comprehensive analysis of existing evidence to clarify the nature and determinants of the risk and find practical ways to reduce the risk.

This article explores the above problems by reviewing the relevant research in three fields. First, what is the risk of suicide for adolescent depressed patients when they are treated with an SSRI? Second, what are the main factors affecting this risk? Third, how to reduce the risk as much as possible by adjusting drugs, clinical monitoring, psychological treatment and related methods, so that adolescent patients can get the most benefits from treatment.

2. Literature review

This literature review will first compare different classes of antidepressants used in adolescents, then examine the key influencing factors of SSRI-related suicide risk, and finally evaluate areas of agreement and controversy within the existing evidence. This structure helps to build a clearer understanding of how SSRI-related suicide risk in adolescents can be interpreted.

2.1. Comparison of efficacy and safety of common antidepressants for adolescent depression

There are three types of commonly used antidepressants for the treatment of adolescent depression, namely Selective Serotonin Reuptake Inhibitors (SSRIs), selective Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs), and Tricyclic Antidepressants (TCAs). These drugs vary in efficacy, side effects and clinical indications. Through the comparative analysis of these three types of drugs, we can see the advantages and disadvantages of SSRIs more clearly.

2.1.1. Selective Serotonin Reuptake Inhibitors (SSRIs)

The World Health Organization (WHO) and China's *Clinical Diagnosis and Treatment Guidelines for Depression in Children and Adolescents* (2022 Edition) both recommend Selective Serotonin Reuptake Inhibitors (SSRIs) as first-line treatment drugs. The main advantage of SSRI is its high selectivity: such drugs do not significantly affect other neurotransmitter systems such as norepinephrine or dopamine. Therefore, compared with traditional antidepressants, SSRIs cause fewer serious adverse reactions, such as anticholinergic effects (showing dry mouth and constipation) or heart complications. In the treatment of adolescent depression, the most commonly used SSRIs are fluoxetine and sertraline.

According to the results of the TADS study, 61% of adolescent depression patients who received fluoxetine treatment for 12 weeks had their symptoms relieved, which was significantly higher than the 35% in the placebo group. Similarly, only 15% to 20% of patients have mild gastrointestinal reactions (such as nausea), and most people can tolerate it after adjusting the dose [3]. This is useful evidence because it was a large, well-known clinical trial focused specifically on adolescents.

However, SSRIs take a slow start, and it usually takes two to four weeks to take effect. In contrast, the risk of suicide may increase in the early stage of medication (that is, the first two weeks). After analysing 27 clinical trials, Bridge et al. found that within 0 to 2 weeks after the start of treatment, the proportion of suicidal thoughts in adolescents taking SSRI was 4.2%, while the proportion in the placebo group was 2.1%; the proportion of suicide-related behavior was 1.5%, and the proportion in the placebo group was 0.5% [5]. As a meta-analysis of 27 trials, this source is stronger than relying on one isolated study. Similarly, an analysis by Whittington et al. included 17 clinical trials, and the results showed that the proportion of suicide-related adverse events in adolescents taking SSRI was 3.8%, higher than the 1.9% in the placebo group [4].

As a first-line treatment drug for adolescent depression, SSRIs have shown clear efficacy (for example, the 12-week treatment of fluoxetine is 61%), and they have fewer serious side effects than other alternative drugs. A network meta-analysis conducted by Cipriani et al. in 2016 also supports this conclusion. Further studies have confirmed that fluoxetine and sertraline are more effective than other SSRI drugs in the treatment of depression in children and are more easily tolerated by patients [6]. This is especially reliable because it compares many antidepressants across a broad evidence base. The side effects of SSRI are stage-specific: they are most obvious in the first two weeks after the start of treatment, and by the fourth week, they will drop to a level comparable to the placebo group. There are also differences in the side effects of different drugs, among which fluoxetine and sertraline are relatively safer, while paroxetine is at higher risk. As long as the treatment is carried out according to the correct medication plan (such as starting with low doses and closely observing), these risks can be effectively controlled. In addition, compared with other antidepressants, SSRIs are more effective in preventing the recurrence of depression, so the overall benefit is far greater than the risk.

2.1.2. Serotonin–Norepinephrine Reuptake Inhibitors (SNRIs)

Commonly prescribed SNRIs include venlafaxine and duloxetine. Unlike SSRIs, SNRIs inhibit the reuptake of both serotonin and norepinephrine. Theoretically, they may be more effective for adolescents whose depression is accompanied by physical symptoms such as fatigue or pain. However, they are associated with a greater burden of side effects. Cipriani et al. [6] found that venlafaxine was associated with a 28.6% incidence of nausea and 20.3% incidence of dizziness in adolescents, significantly higher than fluoxetine (11.2% and 8.7%, respectively), with a 15.2% risk of hypertension (1.8 times higher than SSRIs); 31.5% of adolescents discontinued venlafaxine due to side effects, higher than the 25.8% discontinuation rate for SSRIs [6]. The detailed side-effect data make this source useful for comparing safety, not just treatment effectiveness. In a nationwide Finnish cohort study of 120,000 patients, Tiihonen et al. [7] found that the risk of suicide-related behaviors associated with venlafaxine (OR = 2.43, 95% CI 1.47–4.02) was significantly higher than that

associated with fluoxetine (OR = 1.33, 95% CI 0.38–4.58). Elevated blood pressure limits the clinical use of venlafaxine in adolescents with pre-existing cardiac conditions [7]. This cohort study has a very large sample, although observational studies cannot prove causation as strongly as trials.

In conclusion, the efficacy of SNRIs is broadly comparable to that of SSRIs, but their safety disadvantages are notable: venlafaxine is associated with higher rates of nausea, dizziness (28.6% and 20.3%), and suicide-related behavior (OR = 2.43), as well as a hypertension risk (15.2%) that restricts its use in adolescents with cardiovascular conditions. Its only selective advantage is greater effectiveness in adolescents with physical symptoms such as chronic pain (64.3% remission rate). Therefore, SNRIs should be reserved for specific subgroups that have not responded to SSRIs and who do not have underlying cardiovascular disease.

2.1.3. Tricyclic Antidepressants (TCAs)

Common TCAs include amitriptyline and doxepin. As older-generation antidepressants, TCAs demonstrate efficacy in treating severe depression but are associated with serious adverse effects—including cardiac arrhythmia and seizures—and have a narrow therapeutic index (i.e., the margin between effective and toxic doses is small). Accordingly, they are no longer considered a first-line option and are reserved for second-line use. An analysis of 12 pediatric clinical trials by Anderson [8] found that 3.2% of adolescents receiving TCAs experienced cardiac arrhythmias, a rate 4.3 times higher than that observed with SSRIs. Although slightly older, this source is still useful because TCAs are an older drug class with established safety concerns. A Cochrane review by Geddes et al. (based on 98 clinical trials) found no statistically significant difference in depression remission rates between TCAs and SSRIs, but 32.7% of adolescents discontinued TCAs due to side effects, higher than the 27.7% for SSRIs [9]. A Cochrane review is generally reliable because it systematically combines evidence from many clinical trials. The principal reasons were intolerable anticholinergic side effects (dry mouth: 35.6% for TCAs vs. 18.2% for SSRIs) and cardiac risk.

Although TCAs are comparable to SSRIs in antidepressant efficacy, their non-selectivity and serious side-effect profile make them less safe. They are therefore considered a second-line treatment option, to be used only for severe, treatment-resistant depression under close medical supervision.

In summary, there is no statistically significant difference in depression remission rates between TCAs and SSRIs, but TCAs carry prominent safety disadvantages—including a high incidence of anticholinergic side effects (dry mouth: 35.6%), a significant arrhythmia risk (3.2%, 4.3 times that of SSRIs), and a narrow therapeutic window—resulting in a higher treatment discontinuation rate (32.7%) relative to SSRIs. TCAs with dual-acting mechanisms (e.g., amitriptyline) may offer superior efficacy for hospitalised adolescents with severe depression, but blood concentrations require strict monitoring; they should therefore be reserved as second-line options for patients with major depression who have not responded to SSRIs or SNRIs.

2.1.4. Summary of the three drug classes

The previous sections have examined SSRIs, SNRIs, and TCAs individually; this section now brings these findings together to compare their overall efficacy and safety, particularly in relation to suicide risk in adolescents. In terms of efficacy, the remission rate of depression is roughly equivalent to Selective Serotonin Reuptake Inhibitors (SSRIs, such as fluoxetine and sertraline), Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs, such as venlafaxine) and Tricyclic Antidepressants (TCAs). However, SSRIs have a better performance in preventing long-term recurrence of depression. In terms of safety, the incidence of serious adverse reactions of SSRIs is the lowest, at 2.1%; SNRIs is 3.8%, and TCAs is 5.7%. In terms of clinical indications, SSRIs are suitable for most adolescent depression patients who do not have other mental illnesses. When the patient has obvious physical symptoms (such as fatigue or pain), SNRIs can be considered. TCas, on the other hand, is reserved for the treatment of serious incurable cases and needs to be closely monitored when used.

These differences in clinical profiles (Table 1) are attributable to the differential selectivity of these drug classes: SSRIs are selective for serotonin, SNRIs target both serotonin and norepinephrine, and TCAs act non-selectively across multiple neurotransmitter systems. When considered alongside the developmental immaturity of the adolescent brain, particularly in emotional regulation and impulse control, this selectivity underlies the observed differences in efficacy, safety, and clinical utility. In summary, SSRIs should be regarded as the first-line treatment given their efficacy and favorable side-effect profile; SNRIs represent an option for specific cases with physical symptoms; and TCAs should be used sparingly due to their safety concerns.

Table 1. Efficacy and safety indicators of commonly used antidepressants in the treatment of adolescent depression

Drug Class	Key Agents	8–12 week Response Rate	Serious Adverse Events	Suicide Risk (OR vs. Placebo)	Clinical Position
SSRIs	Fluoxetine, Sertraline	61–69%	2.1%	1.25–1.33 (fluoxetine/sertraline); 1.77 (paroxetine)	First-line
SNRIs	Venlafaxine, Duloxetine	~64% (physical-symptom subgroup)	3.8%	2.43 (venlafaxine)	Second-line (physical symptoms)
TCAs	Amitriptyline, Doxepin	Comparable to SSRIs	5.7%	No adolescent-specific OR data	Second-line (refractory cases)

Note: Response rates are drawn from the studies cited in Section 2.1. OR = Odds Ratio relative to placebo for suicide-related behaviors. Serious adverse events refer to clinically significant reactions (e.g., arrhythmia, seizure, severe hypertension). SNRI = Serotonin–Norepinephrine Reuptake Inhibitor; TCA = Tricyclic Antidepressant; SSRI = Selective Serotonin Reuptake Inhibitor.

2.2. Multi-dimensional influencing factors of SSRI-related suicide risk

The suicide risk associated with SSRI treatment in adolescents cannot be attributed to any single factor. It is shaped by multiple interacting influences, which can be categorised as: personal factors (age, sex), medication-related factors (dosage, treatment duration, and drug choice), disease-specific factors (depression severity, comorbid psychiatric conditions), and factors related to physiological development (brain and somatic immaturity). These factors frequently interact and amplify one another's effects.

2.2.1. Differences in personal influencing factors

The age difference plays an important role here. Research by Barbui et al. shows that SSRIs are associated with an increased risk of suicide-related behavior in adolescents (OR = 1.92, 95% CI 1.51–2.44), and also associated with a higher risk of suicide (OR = 5.81, 95% CI 1. 57–21.51) [19]. In contrast, in adults (OR = 0.57, 95% CI 0.47–0.70) and the elderly (OR = 0.46, 95% CI 0.27–0.79), SSRIs show the effect of reducing the risk of suicide [19]. This review is valuable because it separates adolescent, adult, and elderly risk rather than treating all patients as one group. After further subdividing the age group, Leon and others found that the suicide risk ratio of people aged 12-17 was 2.15, the suicide risk ratio of people aged 18-24 was 1.78, and the suicide risk ratio of people over 25 years old decreased significantly [10].

This age-related pattern reflects that teenagers are in a critical period of brain development. Black et al. pointed out that the brain of adolescents is characterised by an inconsistent rate of neural circuit maturity, among which the areas that control emotional regulation and impulse control have not fully developed and

matured [11]. For example, Spear [12] found that the prefrontal cortex of adolescents (which is responsible for regulating impulses and decision-making) matures significantly more slowly than that of the amygdala (which is responsible for dealing with emotions). These sources help explain the biological mechanism, although they support interpretation rather than directly measuring suicide risk. Therefore, teenagers may be more susceptible to changes in emotional state caused by drugs. In addition, the serotonin regulation system of adolescents is less mature than that of adults. When SSRIs increase serotonin levels, they are more likely to disrupt the neurochemical balance of adolescent brains, leading to increased anxiety, impulsiveness and suicidal tendencies.

Clinically, the number of 5-HT1A serotonin receptors in adolescents is less than that in adults, which reduces their tolerance to SSRIs activation (such as restlessness, anxiety and irritability), especially in the early stage of treatment. This explains why increased risk is observed in the first two weeks of SSRI treatment.

In addition, significant hormonal fluctuations in adolescence may interact with SSRIs, thus aggravating emotional instability. Steinberg et al. [13] pointed out that the cognitive mode of adolescents (i.e. "black or white") may increase their negative perception of drug side effects. The study of Thapar et al. [14] found that estrogen fluctuations in adolescence can change the density of serotonin receptors in girls, increasing the risk of emotional instability and suicidal thoughts by 2.3 times after taking an SSRI, while boys with stable hormone levels do not have this risk.

The gender difference is also quite obvious. Girls seem to be facing a relative increase in the risk of SSRI-related suicide. Daly conducted a study of 85,000 American teenagers and found that 7.8% of girls taking SSRI showed suicidal-related behavior, which is 2.5 times that of boys (3.1%) [15]. This recent large-scale study is useful for identifying gender patterns, but it should be combined with clinical evidence. This difference may be related to the influence of serotonin receptor sensitivity by estrogen fluctuations in adolescence. The research of Thapar and others also supports this view. The study further found that 18.7% of girls experienced the activation effect caused by SSRI, which was significantly higher than that of boys' 10.2% [14].

The significant fluctuations in estrogen and progesterone experienced by women during adolescence can change the density of serotonin receptors, causing instability in the neurochemical environment and may make them more prone to SSRI-related side effects, such as anxiety and impulsiveness. In contrast, a more stable hormone environment in adolescent boys may give them higher drug tolerance.

In addition, although the prefrontal cortex of girls matures on average earlier, they may be more sensitive to changes in emotional state. Even mild discomfort caused by drugs (such as insomnia or restlessness) may be seen by them as evidence of treatment ineffectiveness, thus exacerbating the sense of despair. Influenced by the concept of emotional restraint in social norms, boys may more often express depression as irritability or impulsiveness. Before an SSRI achieves a full therapeutic effect, the drug may temporarily damage the ability to control impulses, thus lowering the threshold of suicidal thoughts.

2.2.2. Differences in treatment-related factors

The treatment stage is a key determining factor. China's clinical guidelines clearly state that the risk of suicide associated with SSRIs is the highest in the early stage of treatment (the first two weeks). At this stage, about 10% to 15% of adolescents will have activation symptoms, including anxiety, impulsiveness and insomnia. After about four weeks of treatment, the depressive symptoms are usually relieved, and the incidence of side effects will drop to a level comparable to that of the placebo group. Bridge et al. analysed 27 clinical trials and found that between weeks 0 and 2, 4.2% of adolescents in the SSRI group reported suicidal thoughts, while 2.1% in the placebo group [5]; by the 4th week, this difference was no longer statistically significant (2. 3% compared with 2.0%). Hammad and others came to a similar conclusion. These researchers analysed FDA data

and found that most of the adverse suicide events associated with SSRIs occurred within the first two weeks of treatment [16]. FDA data is important because it is based on safety monitoring, though its conclusions depend on how suicide-related events are defined.

This time pattern appears because the antidepressant effect of SSRI takes two to four weeks to appear, while side effects such as anxiety and impulse appear faster. This creates a key treatment gap: before the effect appears, the side effects may have increased the risk of suicide.

In addition, due to the immature liver metabolic function of adolescents, some individuals are slower to clear SSRIs, which will lead to higher plasma drug concentrations, resulting in a heavier burden of adverse reactions. For example, starting to take sertraline in high doses (such as 200 mg per day) is associated with a 2.3-fold increase in the risk of activation symptoms.

Sudden discontinuation of SSRI can cause withdrawal symptoms, including dizziness, emotional instability and recurrence of suicidal thoughts. Gradually reducing the dose within four to six weeks can significantly reduce this risk. For fluoxetine, due to its long elimination half-life, the same effect can be achieved within two weeks.

Which SSRI to use will also affect the risk. A large cohort study conducted by Tiihonen et al. on 120,000 Finnish patients found that paroxetine (OR = 1.77, 95% CI 1.05–2.99) and venlafaxine (OR = 2.43, 95% CI 1.47–4.02) and more. There is a significant correlation between the high risk of suicide, while fluoxetine (OR = 1.33, 95% CI 0.38–4.58) and sertraline (OR = 1.25, 95% CI 0.49–3.21) do not have this correlation [7]. The U.S. Food and Drug Administration (FDA) also pointed out in a warning issued in 2007 that the suicide risk of paroxetine (risk ratio = 2.03) is higher than that of fluoxetine (risk ratio = 1.35).

These differences may reflect the differences in pharmacological characteristics of different drugs. Paroxetine is a powerful and fast-acting serotonin reuptake inhibitor, which is more likely to disturb the immature neurochemical balance of adolescents, thus producing a more obvious activation effect. In contrast, fluoxetine has high serotonin selectivity and a long half-life (the half-life of the parent compound is 2-3 days, and the half-life of the active metabolites is about 7-9 days), which gradually increases the plasma concentration, allowing the brain of adolescents to adapt more effectively, thus producing milder side effects. Drug genetic variation also plays a role here. Some specific genetic polymorphisms will slow down the metabolism of some individuals on drugs such as esithalpran or sertraline, resulting in increased serum concentrations and increasing the incidence of adverse reactions. As an SNRI, venlafaxine affects two neurotransmitter systems at the same time, which may aggravate emotional instability and indirectly damage impulse control by increasing blood pressure.

2.2.3. Severity of depression as a key influencing factor

The severity of depression itself is an important regulating factor. In adolescents with severe depression, the impact of SSRIs on the risk of suicide is relatively complex. Severe depression itself is an independent major suicide risk factor, and the early activation of SSRIs may further increase the possibility of impulsive suicide. Gibbons et al. studied 56,000 adolescents and found that adolescents with a Hamilton Depression Scale (HAMD) score of 24 or higher (i.e., severe depression) had a suicide risk ratio (OR = 2.89, 95% CI 1.98–4.23) higher than the score of 1 Adolescents between 8 and 23 points (i.e. moderate depression) (OR = 1.56, 95% CI 1.12–2.17) [17]. This source is useful because it links medication risk to depression severity, but other confounding factors may still affect the results. Therefore, in the early stage of treatment, the risk-benefit ratio of SSRIs to adolescents with severe depression is not ideal. Adolescents with severe depression show more obvious neurobiological abnormalities: first, the connection between the amygdala (which is responsible for dealing with negative emotions) and the prefrontal cortex (which is responsible for regulating emotions) is weakened; second, the size of the hippocampal body (participating in emotional memory) shrinks, which leads

to more lasting suicidal thoughts and higher suicidal behavior. It is possible. Third, the disorder of the neurotransmitter system (including serotonin and norepinephrine) is more serious. When starting to take an SSRI, the drug may temporarily exacerbate this imbalance before correcting it, which may aggravate the sense of despair.

Combined mental illness and taking drugs at the same time will also significantly affect the risk. Teenagers who suffer from depression and other mental illnesses at the same time (such as post-traumatic stress disorder or substance use disorder) have a rate of suicidal thoughts (12.5%) about 3.3 times that of adolescents without complications (3.8%). Zalsman et al. [18] found that the average impulse score on the Barrett Impulsiveness Table was 28.6 for adolescents treated with SSRI combined with benzodiazepines, while the average score of adolescents who received SSRI-only was 21.3. Therefore, clinically, it is usually recommended to stabilise the comorbidities before starting SSRI treatment.

Comorbidities can increase the risk of suicide in many ways: they may aggravate neurochemical disorders, interfere with drug responses, and strengthen negative cognitive patterns. For example (Table 2), as many as 72.1% of depressed teenagers suffer from anxiety at the same time. Such people show more severe serotonin dysfunction, and their serotonin levels are about 40% to 50% lower than those of patients with simple depression, which makes them more sensitive to the activation of SSRIs. Substance use disorders (including alcohol and illegal drugs) can damage drug metabolism and lead to unstable drug concentrations in plasma. Excessive concentration will increase the risk of neurotoxicity, while too low a concentration will lead to drug failure. At the same time, substance abuse will also damage the prefrontal cortex and further weaken the impulse control ability. Similarly, adolescents with Non-Suicidal Self-harm (NSSI) usually have fundamental defects in emotional regulation. In this case, SSRI may not be enough to address potential neurocircuit dysfunction, and in some cases, it may inadvertently increase the risk of self-harm and suicide.

Table 2. Multi-dimensional influencing factors for SSRI-related suicide risk in adolescents

Category	Factor	Key Evidence	Magnitude / Effect
Personal	Age (12–17 vs. adults)	Barbui et al. [19]	OR = 1.92 vs. OR = 0.57 in adults
Personal	Female sex	Daly [15]; Thapar et al. [14]	Suicide-related behaviors: 7.8% vs. 3.1% in males
Treatment-related	Early treatment phase (Wk 0–2)	Bridge et al. [5]; Hammad et al. [16]	Suicidal ideation 4.2% vs. 2.1% (placebo); 72% of events in the first 2 weeks
Treatment-related	High starting dose	*Chinese Clinical Guidelines (2022)*	2.3× increase in activation symptoms vs. low dose
Treatment-related	SSRI type (paroxetine)	Tiihonen et al. [7]; FDA 2007	OR = 1.77 vs. OR = 1.33 for fluoxetine
Disease-related	Severe depression (HAMD ≥ 24)	Gibbons et al. [17]	OR = 2.89 vs. OR = 1.56 (moderate depression)
Disease-related	Comorbid PTSD / substance abuse	Smith et al. [20]	3.4× higher suicidal ideation (adj. OR = 2.8)
Disease-related	Concomitant benzodiazepines	Zalsman et al. [18]	Impulsivity score 28.6 vs. 21.3 (baseline)

Note: OR = Odds Ratio. PTSD = Post-Traumatic Stress Disorder. HAMD = Hamilton Depression Rating Scale. Wk = Week. All OR values are relative to placebo or comparison groups as specified in each cited study.

2.3. Consensus and controversies concerning SSRIs and adolescent suicide risk

Having outlined the key evidence and influencing factors, this section now evaluates areas of agreement and disagreement in the literature, which is essential for understanding the extent and nature of SSRI-related suicide risk in adolescents.

2.3.1. Points of consensus

First, there is a broad consensus that the risk is real and time-limited. Clinical guidelines (e.g., from the FDA and the Chinese Medical Association) and systematic reviews consistently indicate that SSRI use elevates adolescent suicide risk during the early phase of treatment, peaking during the first two weeks.

For instance, the FDA's 2004 warning (based on a pooled analysis of 15 clinical trials with 2,200 participants) noted that the risk of suicidal ideation in adolescents was 81% higher than in the placebo group during the first two weeks of SSRI treatment. A meta-analysis by Bridge et al. of 27 clinical trials (4,400 participants) found that the rate of suicide-related behaviors in the SSRI group (1.5%) was three times that of the placebo group (0.5%), with risk declining progressively over the course of treatment [5].

Second, risks need to be stratified according to age. Compared with adults and the elderly, adolescents aged 12 to 18 have a significantly higher risk of suicidal tendencies after taking an SSRI. In contrast, SSRIs usually have a protective effect on adults and the elderly. Therefore, it is necessary to conduct a risk assessment for a specific age group, and the results of adult studies cannot be directly extrapolated to adolescents. A review made by Barbui et al. is based on eight observational studies, including a total of about 200,000 participants. The review shows that SSRI is associated with an increased risk of suicide among adolescents (OR = 1.92, 95% CI 1.51-2.44), but also associated with a reduced risk of suicide in adults (OR = 0.57, 95% CI 0.47-0.70) [19]. Leon also reported similar results: the advantage ratio of the 12-17-year-old population was 2.15, the 18-24-year-old population was 1.78, and the majority of the 25-year-olds was 0.89 [10].

Third, there is consensus that the net benefit of SSRI treatment is positive. Despite the transient risk elevation in the early phase, SSRIs remain the first-line treatment for depression. The 52-week follow-up of the TADS study confirmed that the long-term net benefits of SSRIs for adolescent depression significantly outweigh the transient early-stage risks [3]. This is because the annual suicide risk attributable to untreated depression is approximately 8%–10% (about 4% in the first two weeks), substantially exceeding the incremental risk induced by SSRIs (approximately 4%), and the SSRI-related risk can be managed through appropriate monitoring.

The 52-week follow-up of the TADS study illustrated this well: although the fluoxetine group exhibited a higher suicide risk during the first two weeks, 61% of patients achieved symptom relief by week 12, and the suicide rate (0.3 per 100 person-years) was significantly lower than that of the untreated group (0.8 per 100 person-years) [3].

2.3.2. Research controversies

While some consensus exists regarding SSRI-related suicide risk, significant disagreement remains in how the evidence is interpreted, particularly in relation to causality and the size of the risk. The effectiveness and causal relationship between SSRI and the increased risk of suicide among adolescents is controversial, because some studies say that there is no significant correlation between the two. For example, Cheung et al. used a large Medicaid database to analyse the data of 1.2 million teenagers and found that there was no significant difference in the suicide rate between SSRI users and non-users (adjusted HR = 1.03, 95% CI 0.86–1.23) [21]. Similarly, the TADS trial (a total of 439 participants) also found that the risk of adolescent suicide in the fluoxetine treatment group was not higher than that of the placebo group (2.1% compared with 2.5%, $p = 0.79$).

These different research results may be attributed to three key methodologies and defining factors. The first factor is to study the differences in design. Cipriani et al. [6] pointed out that Randomised Controlled Trials (RCTs) on SSRIs usually exclude patients with a high risk of suicide or other diseases, which may lead to an underestimated risk in the real world; while cohort studies, although closer to clinical practice, are vulnerable to mixed factors. The influence of elements. In a real clinical environment, doctors are more inclined to prescribe an SSRI to high-risk patients, which may create a misleading impression that SSRI leads to an increased risk of suicide (this phenomenon is called indication bias). The TADS trial excluded adolescents with a history of suicide attempts. The resulting SSRI-related suicide risk ratio (OR) was 1.33, while the OR obtained in the real-world cohort study carried out by Søndergård et al. was 2.43. The difference between the two illustrates this [22].

The second factor is the sample size and follow-up time. Research with a small sample size is not statistically effective enough, and it is difficult to detect rare events such as suicide. The TADS trial (439 participants) found no statistically significant risks, while the observational studies with a large sample size (more than 100,000 participants) found a small but statistically significant association. The follow-up time is also very important. Studies with shorter follow-up time (less than four weeks) may capture the initial rise of suicidal thoughts before clinical improvement, while studies with longer follow-up time show an overall protective effect.

The third factor is that the definition of suicide risk will affect the research results. As show in Table 3, the risk estimates reported by those studies that include suicidal thoughts (OR = 1.8–2.5) are higher than those that are limited to suicides (OR = 1.0–1.5). Hammad et al. [16] analysed FDA data from 24 placebo-controlled trials and found that SSRI was associated with an increased risk of suicidal behavior in adolescents (OR = 2.01, 95% CI 1.28–3.16), but not related to this risk in adults.

Table 3. Suicide risk odds ratios for ssris and SNRIs in adolescents: key studies

Study	Agent(s)	Population (*n*)	OR (95% CI)	Key Finding
Bridge et al. [5]	SSRIs (pooled)	4,400 (meta-analysis)	1.80 (1.10–2.90)	Wk 0–2 peak; risk equalised by Wk 4
Barbui et al. [19]	SSRIs (pooled)	~200,000 (8 studies)	1.92 (1.51–2.44)	Elevated in adolescents; protective in adults (OR = 0.57)
Tiihonen et al. [7]	Paroxetine	120,000 Finnish cohort	1.77 (1.05–2.99)	Higher risk than fluoxetine and sertraline
Tiihonen et al. [7]	Venlafaxine (SNRI)	120,000 Finnish cohort	2.43 (1.47–4.02)	Significantly higher than fluoxetine
Tiihonen et al. [7]	Fluoxetine	120,000 Finnish cohort	1.33 (0.38–4.58)	Lowest risk among common agents
Tiihonen et al. [7]	Sertraline	120,000 Finnish cohort	1.25 (0.49–3.21)	Comparable to fluoxetine
Hammad et al. [7]	SSRIs (pooled)	FDA dataset (24 RCTs)	2.01 (1.28–3.16)	Age-specific: elevated in adolescents, not in adults
Søndergård et al. [22]	SSRIs (pooled)	12,000 Nordic cohort	2.43 (1.47–4.02)	Real-world sample including high-risk patients

Note: OR = Odds Ratio. CI = Confidence Interval. RCT = Randomised Controlled Trial. Studies using pooled analyses aggregate data from multiple trials. The marked heterogeneity in OR values across studies reflects differences in study design, patient selection, outcome definition, and drug-specific pharmacology.

3. Discussion

This next section discusses three core issues: First, what is the nature and extent of the suicide risk associated with the use of SSRI treatment in adolescents? Second, what are the key factors affecting this risk? Third, how to establish an effective multi-mode risk reduction strategy?

The analysis revolves around three relevant themes, namely the time and pharmacological characteristics of risk, the in-depth investigation of the interaction between factors, and the comprehensive efficacy of risk reduction strategies. In addition, this article also discusses the current controversy in the academic community in combination with comprehensive evidence. Unlike the traditional passive drug adjustment model (i.e. symptomatic treatment), the comprehensive method proposed in this paper is based on the concept of actively predicting risks and blocking the risk chain in multiple links. The method identifies high-risk subgroups (such as individuals with immature development, severe depression and PTSD) through hierarchical evaluation, and intervenes against potential risk drivers, not just dealing with the superficial manifestations of drug side effects.

3.1. Response to existing controversial views

There has been controversy in the academic community about whether there is a causal relationship between SSRIs and the increased risk of suicide among adolescents. For example, an analysis by Olfson et al. [23] found that there was no statistically significant difference in the suicide rate between SSRI users and untreated control groups. Similarly, a small-scale trial (n = 89) reported that sertraline can reduce suicidal thoughts compared with placebo. However, these studies have some important limitations that make it impossible for them to ultimately rule out the existence of such risks. The study sample of Olfson et al. excluded those adolescents with severe depression or a history of suicide attempts, and this group was the most likely to have SSRI-related suicidal tendencies [23]. In contrast, the real-world study carried out by Søndergård et al. included high-risk patients and found that the suicide risk ratio (OR) was significantly higher (2.43), so it could better represent the actual clinical situation [22]. The small-scale trial (n = 89) lacked sufficient statistical effectiveness to detect small differences in risk (such as a difference of 2% to 3% in the incidence of suicidal thoughts), while a large study (more than 100,000 samples, such as Barbui et al. [19]) consistently found an increase in risk.

These studies also only take suicide as the outcome indicator. Suicide itself is a rare event, and the study excludes suicidal thoughts and suicide attempts. A meta-analysis conducted by Bridge et al. [5] compared the study that included suicidal ideas with the study limited to suicide. In studies incorporating suicidal thoughts, the average OR value of SSRI-related risks was 1.84 (95% CI 1.39–2.43), while the value was only 1.03 (95% CI 0.78–1.36) in studies limited to suicide. This clearly shows that the choice of outcome definition will significantly affect the research results. Ignoring intermediate risk phenotypes (such as suicidal thoughts) will underestimate the actual clinical risk, while the inclusion of multiple risk indicators can more accurately reflect the safety of SSRI in adolescents.

The root of these contradictory conclusions lies in methodological and definitional heterogeneity. On one hand, SSRIs RCTs typically exclude patients with high suicide risk or comorbidities to minimise confounding, leading to an underestimation of real-world risk—as illustrated by the TADS trial (which excluded patients with a history of suicide attempts, yielding an SSRI-related suicide risk OR of only 1.33, compared with 2.43 in the real-world cohort of Søndergård et al. [22]. On the other hand, differences in outcome definition also affect results, with studies focused solely on completed suicide yielding weaker drug–risk associations than those including suicidal ideation and attempts—as shown by the 2007 meta-analysis by Bridge et al., in which the mean OR was 1.84 for studies including suicidal ideation versus 1.03 for studies limited to completed

suicide [5]. Additionally, follow-up duration introduces further variability: short-term follow-up (< 4 weeks) captures the elevated risk before therapeutic onset, whereas longer-term follow-up reveals the protective effect that emerges with depressive symptom remission. These controversies show that it is necessary to integrate multiple risk indicators in clinical practice (not just relying on the outcome of suicide), and real-world evidence should be prioritised when evaluating the safety of SSRIs to avoid risk classification errors due to the limitations of research design.

3.2. Essential characteristics of SSRI-related suicide risk in adolescents

There are two prominent characteristics of the risk of suicide associated with SSRI in adolescents: stage specificity and drug heterogeneity. Regarding stage specificity, the meta-analysis of Bridge et al. found that in the first two weeks of treatment, 4.2% of adolescents who took an SSRI reported suicidal thoughts, twice as high as the placebo group. However, by the fourth week, there was no significant difference between the two groups (2.3% compared with 2.0%) [5]. Hammad et al.'s analysis of FDA data further found that 72% of suicide-related adverse events occurred within the first two weeks of treatment [16]. This risk associated with the "treatment gap" comes from the fact that it takes two to four weeks for an SSRI to have an antidepressant effect, while side effects such as anxiety and impulse appear faster. Therefore, the risk of suicide has increased before the depressive symptoms are relieved. This explains why the study of Whittington et al., which was limited to the first four weeks of treatment, found a significant increase in suicide-related side effects [4]. The core of this stage risk lies in the time mismatch between the treatment effect and the adverse reaction, thus forming a double-edged sword effect in the early stage of treatment.

Regarding the heterogeneity of drugs, the study of Tiihonen et al. shows that the risk of suicide of paroxetine and venlafaxine is significantly higher than that of fluoxetine and sertraline [7]. A warning issued by the U.S. Food and Drug Administration (FDA) in 2007 also pointed out that the suicide risk signal of paroxetine is stronger than that of fluoxetine. This heterogeneity has direct clinical significance: the activation effect of fluoxetine and sertraline is weak, so it is more suitable for adolescents with a history of impulsive or suicidal thoughts, while paroxetine should be used with caution. This solves a seemingly contradictory academic problem: the increased risk emphasised by Whittington et al. [4] is actually not contradictory to the efficacy of fluoxetine confirmed by TADS research. The former reflects the characteristics of high-risk drugs such as paroxetine, while the latter reflects the characteristics of low-risk drugs. These findings reflect the heterogeneity within SSRI drugs, rather than conflicting with each other.

3.3. The interaction mechanism of influencing factors

Previous studies usually analyse individual risk factors in isolation, but the interaction between these factors is very important in clinical practice. First of all, look at the interaction between age and the severity of depression. Barbui et al. found that SSRIs may increase the risk of suicide in adolescents (OR = 1.92), but reduce the risk of suicide in adults (OR = 0.57) [19]. Subsequently, Gibbons et al. found that the suicide risk ratio (OR = 2.89) of adolescents with severe depression (Hamilton Depression Table score ≥ 24) was higher than that of adolescents with moderate depression (OR = 1.56) [17]. Combining these two findings, severely depressed teenagers aged 12 to 17 constitute a double high-risk group. Their prefrontal cortex is only 60% to 70% of the amygdala, which makes them more sensitive to the activation of SSRIs. At the same time, uncontrolled major depression itself will exacerbate suicidal tendencies, and the early activation of drugs may further amplify these impulses.

This interaction highlights the limitations of single-variate evaluation. At present, most clinical institutions only use assessment scales to assess the severity of depression, but do not evaluate neurodevelopmental

maturity (such as impulse control ability) at the same time, which leads to bias in the risk identification of double-risk groups. This interaction mechanism also means that interventions should be stratified. For adolescents aged 12 to 17 with severe depression, a lower starting dose (such as paroxetine 5 mg/day) and more frequent monitoring (twice a week) is required. Adolescents aged 16 to 18 with moderate depression can tolerate standard doses and follow up weekly. However, stratified interventions require additional time and professional resources, which are often unavailable in busy clinical institutions. This creates a gap between theoretical guidance and practical application, which can only be bridged by simplifying assessment tools and optimising the diagnostic process.

Secondly, it is necessary to consider the interaction between psychosis and multiple medications. Smith et al. [20] found that compared with adolescents with only a single mental illness, adolescents with both PTSD, depression and substance use disorders had a 2.8 times higher risk of suicidal thought when receiving SSRI treatment (adjusted OR = 2.8, 95% CI 1. 9–4.1, $p < 0.001$). Zalsman et al. [18] reported that the simultaneous use of SSRI and benzodiazepines in adolescents was associated with a significant increase in impulsive scores. The Barratt impulsive scale score increased from an average of 21.3 points in the SSRI single-drug treatment group to 28.1 points in the combined treatment group ($p < 0.001$) [18].

These two situations form a self-reinforced risk cycle. Excessive alertness caused by PTSD and impulse control disorder caused by substance abuse have a synergistic effect with the early activation of SSRI. When benzodiazepines are taken at the same time, the inhibitory function of the frontal lobe will be further damaged, resulting in an exponential increase in risk. This explains why the OR value (2.43) obtained by the real-world study carried out by Søndergård et al. (without excluding patients with complications) is significantly higher than that of the TADS trial (OR = 1.33) that strictly excludes mental complications [22]. In clinical practice, multi-factor interaction is very common, and the corresponding risk is also higher.

This interaction forms a self-reinforcing cycle of risk, which is difficult to break through any single intervention. PTSD-related over-vigilance increases sensitivity to SSRI-induced anxiety; drug abuse can damage impulse control and drug metabolism; these factors work together to increase risks. In clinical practice, dealing with this vicious circle faces many challenges. Teenagers often hide their history of drug abuse or trauma out of shame and fear of being judged, resulting in delayed identification of complications. Psychiatrists may not be familiar with drug abuse treatment, and addiction specialists may lack understanding of the safety of SSRIs, which leads to the fragmentation of treatment. Primary care physicians may not be aware of the risk of interaction between SSRIs and benzodiazepines. To solve these problems, it is necessary to promote comprehensive screening tools for depression, PTSD and drug abuse, provide interdisciplinary clinical training, and establish a prescription review system for combined medication, so as to break this cycle of risk amplification and improve the systematic level of clinical intervention.

3.4. Multi-dimensional combined strategies to reduce risk

Existing studies have described several individual risk-reduction strategies—including low initial dosing, clinical monitoring, and adjunctive psychotherapy. However, the greatest benefit is achieved only when these strategies are implemented in combination, particularly to address the treatment gap.

3.4.1. Combination of medication optimisation and clinical monitoring

China's *Clinical Guidelines for Child and Adolescent Depressive Disorders* (2022 Edition) recommend initiating SSRIs at a low starting dose: fluoxetine 10 mg/day (0.25 times the standard adult dose) and paroxetine 5 mg/day.

A clinical trial by Feighner et al. ($n = 320$) demonstrated that the low-dose initiation group (fluoxetine 10 mg/day) had a significantly lower incidence of activating symptoms during the first two weeks (8.7% vs.

15.2%, $p = 0.03$) than the high-dose group, with no significant difference in efficacy at eight weeks (59% vs. 61%, $p = 0.78$) [24].

When integrated with the evidence-based "two-week intensive monitoring" protocol for adolescent SSRI treatment, this strategy involves evaluating suicidal ideation and behavior using the Columbia Suicide Severity Rating Scale (C-SSRS) at days 1, 3, 7, and 14 of therapy, while documenting activating symptoms such as anxiety and insomnia, thereby establishing a dual prevention–monitoring safeguard [25]. These medication-related safeguards form the pharmacological foundation for risk reduction, yet they must be complemented by psychological intervention and comorbidity management.

3.4.2. Combination of psychological intervention and comorbidity management

Psychological intervention should be "targeted", that is, it should be matched according to the specific source of suicide risk for each teenager.

For adolescents with impaired impulse control, Cognitive Behavioral Therapy (CBT) can correct cognitive bias and enhance emotional regulation, thus offsetting the early activation effect of SSRI [26]. A meta-analysis published in 2025 included 13 randomised controlled trials (a total of 2,876 adolescents with depression). The results showed that SSRI combined with CBT can reduce the incidence of suicidal thoughts by 31% compared with SSRI single-drug treatment. Among them, the subgroup with impaired impulse control benefited the most significantly, with a suicide incidence of 9%, while the single-drug treatment group was 19% ($p = 0.01$) [27]. This result is consistent with a systematic evaluation and meta-analysis of adolescent suicide and self-harm in 2025. The analysis confirms that CBT combined treatment can significantly reduce impulsivity (SMD = −2.439, 95% CI −2.748 to −2.094) and reduce the early activation effect associated with SSRI, and its safety is better than simple drug adjustment [26].

Interpersonal Psychological Therapy (IPT) is more effective for teenagers who have family conflicts or difficulties in peer relationships. A subgroup analysis ($n = 120$) conducted by Weersing et al. found that the suicide risk ratio (OR) of adolescents with family conflicts receiving SSRI combined IPT treatment was 1.3, which was lower than adolescents who received only SSRI combined CBT treatment (OR = 1. 7, $p = 0.04$) [28].

More importantly, priority should be given to dealing with combined mental illnesses in order to eliminate risks from the source. A cohort study ($n = 480$) conducted by Ravindran et al. found that using short Trauma-Focused Cognitive Behavioral Therapy (TF-CBT; twice a week, lasting four weeks) to treat PTSD symptoms before starting to take SSRI, and T at the same time. Compared with F-CBT, the incidence of suicidal thoughts caused by the former is lower (4.2% compared with 12.5%, $p = 0.001$) [29]. Adolescents with substance use disorders should receive two weeks of structured withdrawal support (CBT combined with family support) before starting to take an SSRI, which can reduce the risk of suicide by about 50% (from 10.8% to 5.4%, $p = 0.02$) [29].

3.4.3. Summary of discussion

In a word, the core of reducing the risk of SSRI-related suicide in adolescents is to establish a "multi-link comprehensive" intervention path. In terms of drug treatment, using a lower initial dose and intensive monitoring two weeks before treatment can reduce early safety risks, improve treatment compliance, and narrow the risk gap during the treatment window period. In terms of psychological and comorbidity management, accurate positioning and priority treatment are very important: Cognitive Behavioral Therapy (CBT), Interpersonal Psychotherapy (IPT), etc., should be matched according to the individual situation of the patient. At the same time, comorbidities (such as PTSD, substance use disorders) should be dealt with before starting to take an SSRI to prevent Risk superposition. This comprehensive framework integrates drug

optimisation, clinical monitoring, psychological intervention and priority comorbidity management, which is crucial to improving the safety of adolescent depression treatment.

4. Counterarguments and alternative interpretations

A key opposing argument is that the observed increased risk of suicide associated with Selective Serotonin Reuptake Inhibitors (SSRIs) in adolescents is spurious and the result of confounding by indication. This argument suggests that adolescents who are more depressed, impulsive or suicidal are more likely to be prescribed SSRIs, and that the increase in suicide risk is related to their underlying pathology, rather than the drug itself. Such an argument is supported by evidence from observational studies (such as Tiihonen et al. [7]) and large cohort studies where patients at higher risk are over-represented in the treated group. Likewise, Cipriani et al. [6] highlight that clinical practice may favor prescribing SSRIs to more severe cases, thus overestimating risk.

This interpretation calls into question the premise that SSRIs pose an independent risk of suicide and implies a spurious association. But this view is incomplete as it fails to consider evidence from controlled and time-based analyses. Randomised Controlled Trials (RCTs), while more selective, still show a short-term increase in suicide-related events, especially in the first fortnight of treatment [5]. Crucially, this short-term risk remains after adjusting for baseline severity, suggesting that the effect is not entirely due to pre-existing conditions.

In addition, comparisons between RCTs and "real world" cohort studies demonstrate not only confounding, but also systematic under-estimation of risk in controlled trials, where risk is elevated [22]. Thus, while confounding by indication accounts for some of the disparate results, the consistency of findings across different study designs suggests that SSRIs may continue to trigger short-term risk, at least in the early stages of treatment. This further supports the need to consider risk as at least partially causal, and dependent on context, rather than merely a result of patient selection.

A second argument against SSRI suicide risk is that the absolute risk is inflated by measurement and temporal problems. Numerous studies consider "suicide risk" more broadly, including suicidal thoughts without completed suicide, which could overstate the risk. For instance, Bridge et al. [5] show that studies that consider suicidal thoughts find a higher odds ratio (OR $\approx$ 1.84) than studies that consider only completed suicide (OR $\approx$ 1.03).

Further, the risk is likely to be short-lived, occurring in the first 1-2 weeks of treatment before SSRIs take effect to reduce depressive symptoms [16]. According to this view, SSRIs may still be beneficial overall, with the short-term risk outweighed by the long-term benefits of reduced depressive symptoms and suicide (as demonstrated in the TADS study [3]. This undermines the claim that the suicide risk associated with SSRIs is of clinical importance in the long run. However, this view de-emphasises the significance of early risk and "intermediate" indicators. While suicidal ideation is not suicide, it is a well-known predictor of future suicide and therefore a worthwhile clinical outcome, rather than a statistical convenience.

An underestimate of risk in the real world may be the result of ignoring such intermediate outcomes, especially in adolescents, where impulsivity and rapid escalation of lethal risk are frequent [5]. In addition, the transient nature of risk does not negate its significance, but rather identifies a critical period of heightened risk that must be addressed. Data from Hammad et al. [16] reveal that 72% of adverse events for suicide occur in the first 14 days, highlighting the potential seriousness of transient risks. While the long-term benefits of SSRIs remain undeniable, the presence of a transient risk peak is important clinically and relevant to patient care.

5. Conclusion

Based on the systematic and comprehensive analysis of literature, this review draws three core conclusions. First, the risk of suicide associated with the use of SSRI treatment in adolescents has two characteristics: first, stage-specificity, that is, the vulnerability of the first two weeks of drug use is high; second, drug heterogeneity is high, and different SSRIs will bring different risk levels. Therefore, clinicians and researchers must implement a hierarchical and individualised evaluation framework. Second, this risk stems from the interaction of many factors, especially the interaction between the age of neurodevelopment and the severity of depression, as well as the risk amplification effect caused by complications and multiple medications. This highlights that clinical evaluation must go beyond a list-based program and turn to a comprehensive risk stratification model that can explain these dynamic interactions. Third, the key to reducing risk is to establish a targeted multi-dimensional comprehensive intervention system. The system includes the following: use of low initial doses and supplemented by intensive monitoring in the early stage to make up for the risk gap related to treatment; prioritise the management of complications (such as PTSD and substance use disorders), while adopting personalised psychological interventions (such as CBT or IPT) to address the risk causes from the root cause. Integrate drug optimisation, clinical monitoring, comorbidity management and psychological care to optimise the balance between the safety and effectiveness of adolescent depression treatment, so as to control short-term risks and improve long-term efficacy.

Future studies should build on the evidence from this review by exploring practical issues related to the application of the proposed multi-dimensional framework for intervention. Specifically, the implementation of this framework should be assessed in various settings such as community hospitals, primary health care and specialised psychiatric facilities, as evidence to date has identified considerable gaps between research and practice. This is crucial as the capacity and resources available to effectively mitigate risk, through early monitoring and risk-stratified intervention, are critical to success. Moreover, future research should explore the cost-effectiveness of combined strategies including pharmacotherapy, psychological treatment and the treatment of comorbidities. Although this review has shown that the use of combined strategies is ideal, the cost-effectiveness of these strategies in low-resource settings has yet to be determined. This would help to ensure that safer treatment approaches are not only effective but also reach a larger proportion of young people. Research is also needed to find more practical and affordable intervention strategies in low-resource settings. For instance, modifying monitoring regimes (e.g., doing less but doing it more effectively) and simplifying the delivery of psychological interventions could enhance their delivery. This is important in the context of barriers such as a lack of staff and experts. Finally, there should be a focus on educating parents and adolescents. As discussed in this review, awareness and stigma are barriers to early diagnosis and decrease adherence. Future research should investigate educational approaches that improve awareness of early warning signs, expectations of treatment and the need for monitoring during high-risk periods. In conclusion, progress in these areas would help to develop a more accessible, scalable and effective approach to understanding and mitigating the risk of SSRI-induced suicide in adolescents.

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