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Review

A Narrative Review: Serotonin Reuptake Inhibitors and the Risk of Suicidal Ideation in Adolescents

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Abstract: Abstract: Serotonin reuptake inhibitors (SSRIs) are currently the first-line treatment for adolescents suffering from major depressive disorder, even though a black box warning concerns suicidal ideation was put forth in 2004. Numerous trials have been conducted evaluating this risk in adult patients, with less being done surrounding pediatric patients. Trials that have focused on this specific risk in adolescents have shown either a strong connection, conflicting results, or non-significance. Trials comparing other non-SSRI antidepressants have also demonstrated some risk of suicidal ideation, suggesting the risk may not be specific to this class of drugs. Other data have also suggested that the risk is linked to treatment duration, genetics, and/or simply that the adolescent patients with major depressive disorder are an at-risk population. Herein, a review is presented of the trials conducted surrounding SSRIs, their use in adolescents, and their risk in terms of developing suicidal ideation.

Keywords: SSRIs; adolescents; suicidal ideation

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1. Introduction

In 2004, with the input of numerous committees reviewing pediatric trials, the FDA issued a black box warning for certain antidepressants, specifically selective serotonin reuptake inhibitors (SSRIs) [1]. It had been reported that antidepressants used in pediatric patients may lead to an increase in suicidal ideation (i.e., thoughts of killing oneself). SSRIs were first introduced in 1987 with fluoxetine (Prozac) from Eli Lilly. Subsequent analogs became more popular in the 1990s due to the reportedly lowered risk of anticholinergic and cardiovascular toxic adverse events, compared to older antidepressants such as tricyclic antidepressants (TCAs). These SSRIs are now first-line treatments in pediatric patients for mood ailments, including major depressive disorder (MDD), bipolar disorder (BPD), and dysthymic disorder (DD). Unfortunately, the adverse events that have been observed for those taking SSRIs are treatment-emergent suicidal ideation (TESI) or treatment worsening of suicidal ideation (TWOSI). It has been suggested that these may have been underreported in previous trials, as suicidal ideation is often grouped together with other emotional disturbances [1]. Although suicidal ideation may have a connection to SSRI use in pediatrics, suicidality (i.e., suicidal ideation, gestures, and/or attempts) among this patient population have revealed the opposite trend, calling into question the true nature of the debate [2,3].

There is also interest in the relationship with the amount of serotonin (5-HT) in the body, not just in the brain as a neurotransmitter, but also in plasma levels [4–6]. One trial that tested SSRIs, their impact on patients' 5-HT levels, and suicidal ideation, reported an increase in platelet 5-HT receptor density as a result of treatment. Patients also displayed an increase in suicidal ideation, although the authors acknowledged larger sample sizes are

needed for conformation [4]. Trials with different SSRIs, such as paroxetine and sertraline, have also been conducted, in addition to other serotonin-affecting drugs, such as serotonin norepinephrine reuptake inhibitors (SNRIs) (i.e., venlafaxine) and the serotonin antagonist and reuptake inhibitor (SARI) (i.e., trazodone) [7,8]. Some trials and meta-analyses have indicated that other antidepressants that effect serotonin, as well as bupropion, which effects norepinephrine and dopamine, also carry a risk for suicidality and/or suicidal ideation [9–11]. There has also been evidence to support that older antidepressants, such as TCAs and some SNRIs, carry a higher risk of TESI and/or TWOSI [12,13]. However, medication is not the sole treatment for depression, as cognitive behavioral therapy (CBT) is also recommended, with dual therapy and medication preferred in most guidelines [14–16].

Pediatric patients are also not alone in suffering from a risk of TESI and TWOSI. Generally, psychotropic medications have had more reported adverse events in preadolescents and adolescents than in adults in safety trials [17]; however, there remains a risk of adults developing suicidal ideation after starting on an antidepressant [18]. The first few weeks of antidepressant treatment have been reported to be the highest-risk period for suicidal ideation among adults, but that the risk lessens with treatment duration [19,20]. This is similar to the risks seen in placebo-controlled trials for SSRIs and cohort studies that suggest treatment duration may play a role in pediatric patients [21,22]. Some others have suggested that, in adults, the risk of TESI or TWOSI is relatively low, as well as that their suicidal ideation had decreased [23,24]. One trial reported a decrease in suicidality in adults above the age of 24 when treated with either citalopram, sertraline, or paroxetine [25]. The same trial reported that those between 18 and 24 showed a neutral effect in terms of suicidality, suggesting that the risk regarding suicidal ideation and SSRIs may be age-specific [25]. Another trial tested SSRIs in patients 7 years old and younger and found no suicidal ideation throughout the study [26]. Further trials suggest there may be a connection between neutrophils, lymphocytes, and inflammatory cytokines, although there remains limited evidence of this [27,28]. Overall, any connection between SSRIs and suicidal ideation depends on a multitude of factors. Herein is a review of the many different trials, meta-analyses, and studies that reflect the relationship that SSRIs [specifically: fluoxetine, paroxetine, sertraline, citalopram, escitalopram, and fluvoxamine, see Table 1] have with suicidal ideation, both before and after the 2004 FDA decision, as well as possible mitigation strategies to reduce these risks.

2. Selective Serotonin Reuptake Inhibitors (SSRIs)

To identify all potential publications, no specific date ranges, filters, or limits were set. The following electronic databases were used in this search: PubMed, Web of Science, and SciFinder. The database searches utilized search terms in titles and/or abstracts for "suicidal ideation", "selective serotonin reuptake inhibitors", "SSRI", "antidepressants", and "adolescents". In addition, a manual search of relevant studies on Google Scholar and relevant journals was carried out. This involved a thorough examination of the reference sections of articles to identify any additional records that could be potentially relevant. The research was conducted from June to December 2023.

2.1. Fluoxetine

Fluoxetine was the first SSRI introduced to the market to incur a black box warning, despite having been studied 6 years prior to the FDA's decision for adolescent use. The Treatment for Adolescents with Depression Study (TADS), across thirteen US academic and community clinics, between the spring of 2000 and the summer of 2003, tested the effectiveness of fluoxetine, cognitive behavioral therapy (CBT), a combination of the two, or a placebo, in adolescents diagnosed with MDD for a 12-week period [29]. In

total, 439 patients, 12 to 17 years of age, were randomized, with 216 receiving fluoxetine (10 mg/day with an increase to 40 mg/day by week 8) either as monotherapy or in combination with CBT, and 223 receiving either placebo or CBT alone. The primary outcomes were based on the children's depression rating scale—revised (CDRS-R), as well as a positive score using the clinical global impressions (CGI) scale. Baseline improvements in CDRS-R scores were seen in all groups, with the group receiving fluoxetine and CBT improving from 61 to 34. The groups that received fluoxetine or CBT alone improved from 59 to 36 and 60 to 42, respectively, while the placebo group improved from 61 to 42. The percentage of patients that returned a positive CGI score was greater in the fluoxetine and combination groups at 61% and 71%, respectively, compared to the placebo and CBT groups, at only 35% and 34%, respectively. Overall, the researchers concluded that fluoxetine was effective for treating MDD in adolescents, but that it was more effective if used in combination with CBT. Conversely, CBT alone was not as effective in treating MDD and was not significantly different from the placebo. This study also used the CDRS-R to assess suicidality throughout the trial, with 27% of the participants expressing some suicidal ideation at baseline. By the conclusion of the trial, those expressing suicidality had fallen to approximately 9%. While suicidal ideation as a whole had decreased, the number of adverse events involving suicidal ideation was higher among patients receiving fluoxetine, with 15 of the 216 compared to 9 of the 223 who did not receive any fluoxetine. In total, seven (1.6%) of the patients attempted suicide, but fortunately none were successful. The study concluded that: (1) the risks of suicidal ideation did not outweigh the benefits of fluoxetine for the treatment of MDD in adolescents, (2) the SSRI was effective in its treatment, (3) the combination treatment of fluoxetine and CBT was the most effective for treating depression, and (4) fluoxetine did not significantly increase suicidal ideation [29].

In 2002, a trial studied fluoxetine's use in patients diagnosed with MDD, between 8 and 18 years of age, in a 9-week double-blind, placebo-controlled trial, focusing on CGI and CDRS-R as primary outcomes [30]. In total, 219 patients received fluoxetine at 10mg/day for the first week, and 20 mg/day for the following 8 weeks. Approximately 41% of the fluoxetine group achieved remission in their symptoms, compared to 21% in the placebo group. None of the fluoxetine-treated patients expressed any worsening of depression or suicidal ideation. These results were similar to a 1997 study, conducted by the same lead investigators, that assessed 96 patients with non-psychotic major depression between 7 and 17 years of age, in an 8 week, double-blind, placebo-controlled trial. These patients received 20 mg of fluoxetine a day, and utilized the same CGI and CDRS-R as the primary outcomes. Fluoxetine was reported to be superior to the placebo group, with 31% of the treatment group achieving symptom remission, compared to 23% in the placebo group. Again, no patients in either group experienced increased suicidal ideation. Both of these studies highlighted the effectiveness of fluoxetine, as well as the low risk for suicidal ideation in adolescents with MDD, which agrees with evidence from further trials and meta-analyses [30–32].

Obtaining similar results, the Treatment of SSRI Resistant Depression in Adolescents (TORDIA) trial was conducted between 2000 and 2006, at six US academic and community clinics [14,33–36]. In total, 334 patients, between 12 and 18 years of age, with a primary diagnosis of MDD, and not responding to a 2-month treatment with an SSRI, were included. The study was designed to test the efficacy of antidepressants in treatment-resistant depression in adolescents, and included interventions where patients would receive either (1) a different SSRI (fluoxetine, citalopram, or paroxetine), (2) venlafaxine, (3) a different SSRI and CBT, or 4) venlafaxine and CBT. The primary outcomes were based on a CGI score of 2 or less, as well as a 50% or greater decrease in CDRS-R. The results revealed that those who switched to a different medication with CBT had a higher response rate

of 54.8%, compared to those who switched to a different medication only (40.5%). The Suicide Ideation Questionnaire—Jr was used to access suicidality in the participants. No significant differences between the treatment groups were reported. The number of adverse events involving suicidal ideation were higher in this study compared to other trials, such as TADS. However, this was attributed to having a higher portion of patients with suicidality at baseline. The authors concluded that adolescents who did not respond to the initial SSRI treatment for MDD, who then switched to a different SSRI or venlafaxine with CBT, achieved higher positive clinical outcomes than with a medication switch alone. Additionally, neither switch led to increased suicidal ideation [14].

Compared to other SSRIs, fluoxetine showed a lower relative risk (RR) of suicidal ideation as demonstrated in a meta-analysis of 24 pediatric trials, including 23 placebo-controlled clinical trials and the aforementioned TADS trial [37]. This analysis was conducted in 2006 and included 4582 patients, 18 years of age or younger, with a diagnosis of MDD, obsessive–compulsive disorder, attention deficit hyperactivity disorder, generalized anxiety disorder, and/or social anxiety disorder. The majority of the trials were conducted in the late 1990s and ranged between 4 and 16 weeks long, testing nine different antidepressants, including; fluoxetine, paroxetine, citalopram, sertraline, venlafaxine, mirtazapine, fluvoxamine, bupropion, and nefazodone. The analysis used suicide-related adverse events (SREs), with suicidal ideation and behavior as their primary outcome, with possible suicidal behavior and ideation as secondary. Fortunately, there were no successful suicides in any of these trials. Four of the twenty-four trials did not report any SREs, while the TADS trial reported a statistically significant number of patients expressing suicidality in the treatment group, with an RR of 4.62; with eight other trials reporting an RR of 2 or greater. Overall, the RR of the SSRIs tested was 1.66, compared to all antidepressants, which was 1.95. Fluoxetine had one of the lowest RRs of the SSRIs tested at 1.53 in the four MDD trials, and 1.52 when considering all of the trials. This was comparable to citalopram, which had a risk of 1.37, and was only included in two MDD trials. Paroxetine also conversely had a higher RR of 2.65 amongst all of the trials. Paroxetine had the highest RR in an individual trial at 6.62, in terms of either primary or secondary outcomes [37]. This is similar to results seen in a systematic review that singled out paroxetine as having a higher suicidal ideation risk [38]. Overall, this meta-analysis concluded that there is a moderately high risk of suicidality in adolescents when using antidepressants. This varies from antidepressant to antidepressant; however, the researchers could not determine superiority solely based on this meta-analysis. Similar results were seen in large-scale meta-analyses for adult patients on SSRIs and other antidepressants, with no significant difference reported, although the risk for suicidal ideation was still present [12,24,39].

2.2. Paroxetine

Paroxetine was introduced by GlaxoSmithKline in 1992 under the brand name Paxil. In 2001, a double-blind, multicenter study was conducted over an 8-week period, comparing the efficacy of paroxetine to imipramine (a TCA), as well as a placebo. In total, 275 patients, between 12 and 18 years of age, who were diagnosed with MDD based on the DSM-IV criteria, and with a depressive episode lasting at least 8 weeks, participated [40]. The patients received either paroxetine (20 mg/day up to 40 mg/day by week 8, if necessary), imipramine (50 mg/day titrated up by 50 mg each week until a 200 mg/day dosage was reached), or a placebo. The primary outcomes were based on a Hamilton Rating Scale for Depression (HRSD) score of less than or equal to 8, or a 50% or greater reduction in baseline HRSD. The secondary outcomes included a CGI score of 1 or 2, indicating great improvement. The results demonstrated that paroxetine was significantly more effective than imipramine and the placebo, with 66.7% of the paroxetine group reaching one or both

primary outcomes, compared to 58.5% in the imipramine group and 55.2% in the placebo group, respectively. Additionally, 65.5% of patients who received paroxetine reported a CGI score of 1 or 2, compared to only 52.1% and 48.3% in the imipramine and placebo groups, respectively. Withdrawal rates for this study were high among all groups, with 28% in the paroxetine group, 24% in the placebo group, and 40% in the imipramine group. Of the adverse events reported, the most common were cardiovascular complications. In the imipramine group, 31.5% of those who withdrew cited this as the reasoning, compared to only 9.7% in the paroxetine group. Suicidality was not a major adverse event seen in any of the groups, with only two patients in the paroxetine group expressing suicidal ideation and one patient in the imipramine group. The researchers suggested that neither of these were a result of the antidepressant treatment. This study supported paroxetine as an effective treatment in adolescents with MDD, with some concerns surrounding adverse events pertaining to cardiovascular complications, and minimal concerns surrounding suicidal ideation [40].

Paroxetine has also been studied in adults for increasing suicidality, with results suggesting a genetic component. The Geneva Outpatient Depression Study (GODS) included 131 patients, between 18 and 65 years of age, suffering from moderate-to-severe depression [41]. Requiring a score of 25 or higher on the Montgomery–Asberg Depression Rating Scale (MADRS) was a part of the inclusion criteria. MADRS was also used to determine the effectiveness of the antidepressant throughout the study and to determine if a patient's treatment should continue to the next step. The patients received paroxetine (20 mg/day) with an increase to the next step if a 25% decrease in their baseline MADRS was not observed. Step 2 was an increase to 30mg/day. If a baseline improvement of 40% was not observed by week 4, the patient would be moved up to Step 3, receiving either 40 mg/day, 30 mg/day augmented with lithium (dosed to target blood lithium levels of 0.6–0.8 mEq/L), or 150 mg/day of venlafaxine. Furthermore, if a 50% improvement was not seen by week 6, the patient would be moved to Step 4 and receive either paroxetine (40 mg/day augmented with lithium dosed to the same target blood lithium level) or 300 mg/day of venlafaxine. Lastly, for the remaining 12 weeks of the study, the patients who were not responding well enough would be moved to Steps 5–7, whereby every 4 weeks they would first receive clomipramine (150 mg/day in Step 5), the addition of lithium (Step 6), and triiodothyronine (37.5 mg/day in Step 7). In total, 49 of the 131 patients experienced an increase in suicidal ideation. Patients who continued to later-step therapy and were switched from paroxetine to a different antidepressant, were associated with higher rates of TESI with an odds ratio (OR) of 1.11. The researcher also investigated the potential genetic component by studying 10 different genes, with the strongest evidence being linked to FKBP5. Specifically, the genotype rs1360780 TT of FKBP5, which encodes for protein subsensitivity to the glucocorticoid receptor. This led the researchers to suggest a connection between suicidality and dysregulation of the hypothalamic–pituitary–adrenal axis. Carriers of the minor T allele were at a higher risk of increasing suicidal ideation, regardless of drug, compared to those homozygous for the C allele. These were similar results to the TORDIA study, which suggested a connection between the FKBP5 gene and suicidal ideation in adolescents [42]. While suicidal ideation was increased in some patients in all groups, the study showed an overall decrease in suicidality amongst all patients; these were similar to results to those seen in other adult trials for paroxetine where suicidal ideation was measured [43]. In general, it was reported that antidepressants are beneficial for treating suicidal ideation in patients, but a poor or low response may lead to an increase in suicidal ideation. Additionally, paroxetine showed less association to an increase in suicidal ideation, but genetics may play a notable role [41].

Table 1. Trials testing SSRIs that had suicidal ideation as an outcome or reported adverse event.

Drug	Trial	Meta Analysis	Number of Participants	Included Those Under 18	Percentage Reporting SI at Beginning	Percentage Reporting SI at Conclusion	RR of SI	Ref.
Fluoxetine	TADS	no	439	yes	27.33/21.81 *a	11.79/14.44 *a	4.62	[29]
	Fluoxetine for acute treatment of depression in children and adolescents	no	219	yes	none	None	n/a	[30]
	A double-blind, randomized, placebo-controlled trial of fluoxetine in children and adolescents with depression	no	96	yes	none	none	n/a	[30]
Paroxetine	Efficacy of Paroxetine in the Treatment of Adolescent Major Depression	no	275	yes	n/a	5.38%	n/a	[40]
	GODS	no	131	no	n/a	n/a	1.11 *b	[41]
Sertraline	Efficacy of Sertraline in the Treatment of Children and Adolescents with Major Depressive Disorder	no	376	yes	n/a	n/a	2.65	[44]
	A Comparison of Cognitive-Behavioral Therapy, Sertraline, and Their Combination for Adolescent Depression	no	73	yes	n/a	11.1	n/a	[45]
Citalopram	STAR *D	no	4041	no	53	14.8	n/a	[46]
Escitalopram	Efficacy and safety of bupropion hydrochloride extended-release versus escitalopram oxalate in Chinese patients with major depressive disorder: Results from a randomized, double-blind, non-inferiority trial	no	534	no	n/a	3.5 *c	n/a	[47]
Fluvoxamine	Fluvoxamine versus fluoxetine in major depressive episode: a double-blind randomized comparison	no	184	no	4.7 *d	1.6 *d	n/a	[48]
Fluoxetine, Paroxetine, Citalopram	TORDIA	no	334	no	42.8	31.6	n/a	[14]
Fluoxetine, Citalopram, Fluvoxamine, Sertraline, Paroxetine	Suicidality in Pediatric Patients Treated With Antidepressant Drugs	yes	4582	yes	n/a	n/a	1.66 *e	[37]

*a: The first percentage represents the group that received fluoxetine with CBT, the second percentage is those who received only fluoxetine. *b: The RR of the other antidepressants (venlafaxine, clomipramine, or nefazodone) developing SI. *c: % of participants that had worsening emotional blunting that may lead to suicidal ideation. *d: The mean of Beck's SSI score in the fluvoxamine-treated group. *e: The RR of all SSRIs included.

2.3. Sertraline

Sertraline (Zoloft) from Pfizer was first introduced to the market in 1991. In a study from December 1999 to May 2001, 367 patients, between 6 and 17 years of age, with a diagnosis of moderate MDD, were tested for their response to either sertraline at a flexible

dosage of 50 mg/day to 200 mg/day, or a matching placebo tablet, for 10 weeks [44]. The study was conducted as a randomized control trial at 53 different sites in the USA, India, Costa Rica, Canada, and Mexico. An improvement in the patient's CDRS-R score was used as the primary outcome, as well as any reported adverse events. The results highlighted a significant improvement in CDRS-R scores in the sertraline group compared to the placebo. A mean change of −30.24 in the sertraline group, compared to −25.83 in the placebo group, was observed. Additionally, 69% of the sertraline patients had a 40% decrease in CDRS-R scores, compared to 59% for those on the placebo. The investigators also concluded there was no statistically significant difference in suicidality between the groups. Of the adverse events, two suicide attempts were reported in both groups, with one patient on sertraline experiencing suicidal ideation; although this was attributed to teasing by peers. The study concluded that sertraline was an effective safe treatment for MDD in children and adolescents. Additionally, the risk of suicidality was not significantly different between the treatment and placebo groups, but it was suggested that all patients with MDD be assessed for suicidality when starting any antidepressant [44].

Between July 2000 and December 2002, a study was conducted in Australia comparing the efficacy and safety of sertraline, CBT, or a combination of CBT and sertraline, in adolescents, over a 12-week period [45]. In total, 73 patients between 12 and 18 years of age, with a diagnosis of MDD, DD, or a depressive disorder not otherwise specified, participated in the trial. The patients received 25 mg/day of sertraline for 1 week that could be titrated up to 100 mg/day by the study's conclusion if needed, as well as titrated down to 12.5 mg/day, if needed as a result of adverse events. The diagnosis of depression was the primary outcome with a goal of complete regression, and all other outcomes, including suicidal ideation, were secondary. The results revealed that patients who received only CBT were at significantly lower odds of depressive disorder post treatment (12 weeks), with 86% responding to acute treatment with CBT compared to 46% of those receiving just sertraline. However, a follow-up conducted after 6 months found that the change in the proportion of patients that were depressed was not significantly different in any of the groups during that time. There was also no significant difference between any of the groups for patients that achieved full remission, although the group receiving the combination had the highest proportion at follow-up with 60%. The Suicidal Ideation Questionnaire-Junior score was used to access suicidal ideation throughout the trial. In all groups, the scores were reduced post treatment and at follow-up. Adverse events involving suicidal ideation did occur in five patients who received sertraline—one in the combination group and four who received only sertraline—although all had reported suicidality at pre-treatment and none had to be taken off the medication. There was no new emergence of suicidal ideation in any patient during the study or at follow-up in any treatment group. Overall, the study concluded that all three treatment options were effective at reducing depression. Additionally, no clear additional benefits were observed for the combination of CBT and sertraline. Furthermore, suicidal ideation did not emerge in any patients who received sertraline [45].

2.4. Citalopram and Escitalopram

From July 2001 to April 2004, the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial was conducted to find the most effective treatment for patients with non-psychotic MDD [46]. In total, 4041 outpatients, between 18 and 75 years of age, who scored at least a 14 on the 17-item HRSD, participated in the trial. The patients were treated with citalopram 10–60 mg/day for 12 to 14 weeks. The patients used the HRSD to track their depression severity as the primary outcome at baseline, as well as using the Quick Inventory of Depressive Symptomatology—Self Rated (QID-SR) to track their suicidal ideation. A remission of depressive symptoms, defined as an HRSD score less than

or equal to 7, was seen in 27.5% of patients. Suicidal ideation was reported at baseline in 1909 patients (53%); however, by the conclusion of the trial, 74% of those patients achieved an improvement over their baseline score, 22% remained the same, and 4% had worse scores. Initial improvements in QID-SR scores were seen in 57% of those who reported suicidal ideation at baseline by their first treatment visit. Comparatively, of the 1721 patients who reported no suicidal ideation at baseline, 115 (7%) reported TESI by the first treatment visit, although the majority had returned to their baseline of no suicidal ideation by the conclusion of the study. Suicidal ideation emerged at later points in the trial in 67 patients, with 5% of those who did not report any suicidal ideation at baseline, or at the first treatment session, experiencing suicidal ideation by at the conclusion of the trial. The researchers concluded that citalopram is more likely to improve suicidal ideation in those presenting at baseline, than it is to worsen it. Additionally, when suicidal ideation did emerge, it was suggested that this may be due to the fluctuating suicidal thoughts of this high-risk population with MDD [46].

The chiral form of citalopram, escitalopram, was studied in a 2019 randomized, double-blind, active-controlled, non-inferiority trial in China where it was compared to bupropion [47]. In total, 534 patients, at least 18 years of age, who had experienced depressive episodes for four or more weeks, and with HRSD scores of 20 or greater, participated in the 8-week trial. The participants were randomly assigned to receive either bupropion (150 mg/day for 1 week titrated up to 300 mg/day thereafter) or escitalopram (10–20 mg/day based on response). The primary outcome was based on a reduction in HRSD scores; however, the MADRS was used to measure emotional blunting, described as the inability to feel and is thought to increase suicidal ideation in patients either as a residual symptom or an adverse event. The results concluded that bupropion and escitalopram were non-inferior to one another, with response rates of 69.6% for bupropion, and 72.9% for escitalopram. Similarly, the results concluded there was no statistically significant difference between the two for emotional blunting, with the bupropion group decreasing by 1.83 on average, and the escitalopram group decreasing by 2.04. With no difference in emotional blunting, the investigators concluded there was no difference in similar behaviors, such as suicidal ideation, between the two drugs [47].

2.5. Fluvoxamine

The results from a trial published in 2003 compared fluvoxamine to fluoxetine for safety and effectiveness in outpatients with MDD. The trial was a randomized, double-blind, fixed-dose, parallel-group study, consisting of 184 patients between 18 and 70 years of age [48]. The patients were included if they scored 17 or greater on the HRSD, with a mean change in scores being the primary outcome. Suicidal ideation was used as a secondary outcome and was measured using Beck's scale for suicide ideation. Patients were randomized to receive either 100 mg/day of fluvoxamine or 20 mg/day of fluoxetine, for 6 weeks, following a 7-day placebo run-in period. The results reported a mean change of 22.3 to 10.0 in the fluvoxamine group, and 22.2 to 11.3 in the fluoxetine group, with no statistically or clinically significant differences between the groups at any point. The mean score on Beck's scale for suicide ideation fell throughout the trial in both groups, from 4.7 to 1.6 in the fluvoxamine group and from 5.4 to 2.1 in the fluoxetine group. In total, there were four serious adverse reactions in the groups, including two suicide attempts from patients taking fluoxetine, although one was unrelated to the treatment and the cause of the other was unclear, although the treatment regimen was considered as a possibility. Overall, the trial concluded that fluvoxamine was at least as effective as fluoxetine in treating MDD, and it may have a better safety profile for adverse events [48].

3. Conclusions

Over the past thirty years, since the introduction of fluoxetine, numerous efficacy and safety trials of it and other SSRIs have been conducted (Table 1). In the years leading up to and since the FDA's decision to place a black box warning for SSRI use for pediatric patients, the focus has shifted to their safety in this specific patient population. This is in-line with multiple adult trials reporting limited evidence of TESI developing, and that those who do develop TESI are typically younger adults, suggesting an age-specific component is at play. Meta-analyses have shown that there is a risk of suicidal ideation in general with SSRI use in adolescents. However, the risk of SSRIs is not significantly different from other antidepressants, and the effectiveness of SSRIs is also equal to or greater than others, such as TCAs. Therapy duration may also play a role, as TESI has been reported in greater numbers in the beginning weeks of trials, and many cases resolve with continued treatment duration, suggesting the first few weeks of therapy may carry a higher risk. A genetic component has also been hypothesized, as the TORDIA trial and the GOD study reported an association between the FKBP5 gene and suicidal ideation developing or worsening with SSRI treatment. Specifically, patients who are homozygous for the recessive T allele for the FKBP5 gene are at a higher risk for suicidal ideation, due to how it affects the protein sensitivity at the glucocorticoid receptor and the effect that it has on the hypothalamic–pituitary–adrenal axis [41]. Patients who have baseline suicidal ideation have been observed to benefit from SSRI treatment, as seen in adult trials. In addition, average suicidal ideation decreased amongst pediatric patient groups in certain trials using SSRIs [49,50]. Lastly, those who experience no response to SSRI treatment may still respond to other SSRIs or antidepressants, with the addition of CBT to lessen their suicidal ideation. In general, pediatric patients with MDD are an at-risk population for suicidal ideation, whether they are left untreated or while taking an SSRI, and even more so if they have a comorbid condition, such as bipolar disorder [51–53]. The risk is present to some degree, although SSRIs specifically may not be the answer to lowering this risk. In conclusion, any patient, but especially pediatric patients, with MDD should be assessed for suicidality before starting and while on an SSRI or any antidepressant, as currently there is no conclusive approach to determining risk. We acknowledge that a limitation in this work is that it is a narrative review and neither a clinical study nor a meta-analysis. Additionally, as the data search was conducted in mid-2023, more recent studies (albeit very limited) [54] have not been included. This latter point highlights both the need for further studies on SSRIs and suicidal ideation as well as a general cautionary warning on their blanket usage amongst adolescents.

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