Review Article

A narrative review of advances in pharmacotherapy for depression and suicidal behavior in youth within the era of heightened social media

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Background and Objective: While social media has connected its users worldwide to share information and beliefs, the impact of increased access and exposure to digital platforms on the mental health of our children has raised concerns. The pandemic has also had a significant impact on pediatric mental health compounded by isolation, lack of exercise and increased exposure to mobile devices. Pediatric depression, suicide and non-suicidal self-injurious behaviors have significantly increased during the pandemic and there will be long-term effects of these mental health conditions into their adulthood. Unfortunately, there have been no significant advances in depression treatment for children and adolescents although off-label uses of newer antidepressants and second generation antipsychotics have increased. This paper examines the latest evidence on pharmacological treatments explored and applied in children and adolescents for depression, suicidal tendencies, and non-suicidal self-injurious behavior. Agents such as lithium and clozapine have anti-suicidal properties but their use in pediatrics are limited by their adverse effects and monitoring requirements. Second generation antipsychotics (SGAs) and N-acetylcysteine (NAC) have shown promise for reducing non-suicidal self-injurious behaviors. In addition to pharmacotherapy, psychotherapy should always be combined for enhanced benefit in the treatment of depression, suicidality and non-suicidal self-injurious behavior. Clinicians, educators and family should be aware of primary and secondary suicide prevention strategies to protect our most vulnerable youths.

Methods: A literature review was conducted using the PubMed (National Library of Medicine) database and Google Scholar for studies that were published during January 1, 2000 to August 1, 2022. Specific English-language articles that focused on treatment of depression, suicide and self-injurious behavior in youths were selected for inclusion. Articles that solely included adults (≥18 years) were excluded from this literature review.

Key Content and Findings: Psychotherapy remains first line for treatment of depression, suicide and self-injurious behavior. Pharmacotherapy can be combined for enhanced benefit, especially in those who do not respond to psychotherapy and/or those who are at imminent self-harm. Agents such as lithium and clozapine have anti-suicidal properties but their use in pediatrics are limited by their adverse effects and monitoring requirements. SGAs and NAC have shown promise for reducing non-suicidal self-injuries (NSSIs).

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Conclusions: Clinicians, educators and family should be aware of primary and secondary suicide prevention strategies to protect our most vulnerable youths.

Keywords: Pediatric; depression; suicide; self-injurious behavior; social media

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Introduction

In an era where social media is heavily contributing to the increased prevalence of mental health disorders among children and adolescents, it is important for clinicians to be aware of the heightened risk of developing mood and anxiety-related disorders in this vulnerable patient population. Healthcare providers need to understand the influence of social media on our youth and how social media may increase the risk of depression, suicide attempts and non-suicidal self-injuries (NSSIs). The purpose of this article is to provide a focused literature review, elucidating advancements in behavioral and pharmacological treatment modalities for the treatment of depression, NSSI, and suicide in children and adolescents growing up in an era of heightened social media presence.

The emergence of social media

Social media is an ever-evolving communication tool where users of these platforms create biographical profiles that allows them to easily connect and engage with friends and strangers, as well as share and exchange information, ideas, photos, and more. The rise of social media has been directly associated with the 21st century's technological revolution, where the advancement and accessibility of smart devices has been rising at unpresented rates (1). Given the conveniently portable nature of smart devices, owners can remain constantly connected to the digital world (2). Consequently, this has ushered in a new era where social media has become extensively integrated into the daily lives of most Americans. In 2005, Pew Research Center found that only 5% of Americans were active on at least one social media platform. As of 2020, that percentage has markedly increased to 72% (3). Simultaneously, younger generations are having an increasing presence on social media platforms, with a recent study finding that approximately 90% of children and adolescents reported having an active social media account (4).

It has been suggested that the "fear of missing out (FoMO)" is a driving factor for both the increased social media activity and consequent mental health implications in today's youth (5). Contextually, FoMO has been described as "a pervasive apprehension that others might be having rewarding experiences from which one is absent" (6). To mitigate these fears, individuals turn to social media platforms in order to be continually connected and aware of what others are doing, in the hopes that these online interactions will provide a means to increase their own social engagement (5,6). Given the human brain continues to develop and mature until early to mid-20's, it has been suggested that children and adolescents may be particularly susceptible to the negative impact of frequent social media use by fostering feelings of exclusion and loneliness (7).

Although social media involvement may transiently fulfill a young adult's desire to stay connected, it also has the potential to invoke and exacerbate feelings of loneliness, inadequacy, and low self-esteem. A growing body of evidence has associated frequent (>7 hours/day) social media use with negative mental health implications, including increased risk of depression, suicide attempts, and NSSI (8,9).

Mental health in children and adolescents

In the United States, there are approximately 73 million children aged 0 to 17 years old, representing 22% of the population (10). The 2016–2020 data of 174,551 children from the National Survey of Children's Health, depicted several alarming trends in the prevalence of mental health disorders. Of note, between the years 2016 and 2020, there was a 27% increase in the prevalence of depression, with 3.1% in 2016 to 4.0% in 2020. Anxiety also increased significantly from 7.1% to 9.2%, which reflects a 29% increase from 2016 to 2020. These prevalence rates represent 2.4 million children diagnosed with depression and 5.6 million with anxiety disorders in 2020 (11). In two national surveys of youth in grades 8 to 12 (n=506,820), the study investigators found that those who spent more time

on new media such as social media or electronic devices, were more likely to report mental health issues compared to those who were engaged in non-screen activities (e.g., in-person social interaction, sports/exercise, homework, print media, attending religious activities) (12). Moreover, COVID-19 has undoubtedly impacted children and adolescent physical and social well-being, which resulted in negative implications for their overall mental health. In 2021, the American Academy of Pediatrics, American Academy of Pediatrics, American Academy of Child and Adolescent Psychiatry and Children's Hospital Association declared a National State of Emergency in Children's Mental Health. They attributed the rise in suicides and increases in emergency department mental health visits due to COVID-19 related stress, ongoing racial justice struggles and loss of primary and/or secondary caregivers during the pandemic (13).

The presentation of major depression in children up to age 7 may differ compared to adolescents and adults (14). Rather than verbal expressions of depression, children may have sleep complaints, physical ailments such as gastrointestinal issues, and irritability/crying episodes (15). Children 8 years and older may have presentation similar to adolescents and adults with symptoms required for diagnosis of major depressive disorders (MDDs) that include depressed mood, anhedonia, changes in appetite, changes in sleep, lack of energy, decreased concentration, thoughts of worthlessness or guilt, psychomotor retardation/agitation and suicidal thoughts/ideation/behaviors. Five or more symptoms must be present for at least the same two weeks (with at least one of the symptoms being either depressed mood or anhedonia) with significant social and occupational dysfunction (15). Presentation of children may depend on the maturity of the child and their ability to verbally express their emotions. It is also important to recognize that other psychiatric and medical conditions may influence not only prognosis but treatment response, remission and recovery of major depression (16). In 2016, the US Preventive Services Task Force (USPSTF) reaffirmed their endorsement of screenings of all adolescents aged 12 to 18 years for major depression in settings where appropriate follow-up is available (17). Unfortunately, there remain gaps in screening due to lack of availability of primary care, COVID-19 pandemic, and disparities in care among marginalized groups (18).

NSSI is defined as maladaptive behavior where a person intentionally self-inflects bodily damage without the intent of dying by suicide (19). The average prevalence of NSSI behavior in adolescents has increased within the past decade. Results from a 2014 survey found a 17.7% lifetime prevalence of NSSI among adolescents, which has since increased to 27.6% as of 2021 (20). NSSI has been associated with a variety of mental illnesses including depression, anxiety, and eating disorders (21). Therefore, it stands to reason that the increasing rate of depression and anxiety disorders associated with the rise of social media simultaneously increases a young adult's risk of NSSI. Additionally, NSSI has been found to be a strong predictor of future suicide attempts, as well as dying by suicide (22). Therefore, it is critical to effectively treat NSSIs in order to mitigate suicidal events.

By definition, suicide is "death caused by injuring oneself with the intent to die" (23). In 2020, suicide was the second leading cause of death for people ages 10–14 and 25–34 (24). Nonmodifiable risk factors for suicide among children and adolescents aged 5 to 19 years old include male gender, age 12–19 years old, personal history of suicide attempts, suicidal behavior, any NSSI, physical and/or sexual abuse, lesbian, gay bisexual, transgender, queer (LGBTQ) sexual orientation, being witness to violence, or family history of psychiatric illness or suicide (25). According to the 2019 Youth Risk Behaviors Survey, 8.9% of 9th through 12th graders reported making at least one suicide attempt in the past 12 months. Female students attempted suicide almost twice as often as male students (11% *vs.* 6.6%). Multiple race/minority students had higher rate of suicide attempts compared to White students who required treatment (26). In a survey study of 120,617 adolescents (ages 11–19 years), female to male transgender and non-binary adolescents had the highest rate of suicide attempts (50.8% and 41.8%, respectively) (27). In a qualitative study using the National Violent Death Reporting System (NVDRS), the most frequent method of suicides among children aged 5 to 11 years during 2013 to 2017 was hanging or suffocation (78.4%), followed by firearms (18.7%) (28). Thematic analysis revealed four themes that precipitated the 134 suicides: (I) family-related problems (39.8%), (II) school or peer-related problems (35.6%), (III) mental health and suicide-related concerns (31.4%), and (IV) trauma (27.1%).

Influence of media on children and adolescent mental health

The accessibility of technology enables vulnerable children and adolescents to either communicate plans for suicide or be exposed to various methods for suicide. Cyberbullying has been linked to suicidality and suicide attempts; in one

Table 1 The search strategy summary

Items	Specification
Date of search	June–August 2022
Databases and other sources searched	PubMed (National Library of Medicine), Google Scholar, secondary references from initial sources
Search terms used	"social network, youth, young adult, fear of missing out, non-suicidal self-injury, psychotherapy, depress*, MDD, suicid*, selective serotonin reuptake inhibitor, SSRIs, antipsychotics, naltrexone, N-acetylcysteine"
Timeframe	January 1, 2000–August 1, 2022
Inclusion and exclusion criteria	Inclusion: all English language, peer-reviewed
	Exclusion: studies in adults only
Selection process	Two investigators conducted the searches for the three sections (depression, suicide, NSSI) and applied inclusion and exclusion criteria using time frame and population restriction
Additional considerations	NSSI, depression and suicide

MDD, major depressive disorder; SSRIs, selective serotonin reuptake inhibitors; NSSI, non-suicidal self-injury.

study, 9.5% of those who made suicide attempts reported school bullying, 14.7% reported cyberbullying and 21.1% reported being a victim of both types of bullying (29). A meta-analysis of the impact of cyberbullying on self-harm or suicidal behaviors showed that those who experienced cybervictimization were twice as likely to self-harm and exhibit suicidal behaviors, attempt suicide and have suicidal thoughts (30). A systematic review revealed that events leading to perceived low relational evaluation (e.g., social rejection) and psychological pain (resulting in social rejection, low popularity, and peer victimization) have been associated with self-injurious thoughts and behaviors (SITBs) among adolescents. The authors found that there was a negative association between popularity and SITBs (P<0.001), and strong evidence for the relationship between social rejection and SITBs, and parental rejection and suicidal ideation (SI) (P<0.001). Parental acceptance was a protective factor for passive SI in boys. There was also a strong relationship between peer victimization (i.e., bullying) and SI (P<0.01) and increased suicide attempts [pooled odds ratio (OR) =2.14; 95% confidence interval (CI): 1.73–2.65], suggesting increased peer victimization and increased SI and suicide attempts among adolescents (31).

The Netflix series, "*13 Reasons Why*", was a source of much controversy upon its, release in March 31, 2017. The show, which depicts the aftermath of a high school student's suicide, has been extensively debated in regards to its potential for sensationalizing and glamorizing suicide, thereby potentially causing suicide contagion. Suicide contagion is the exposure to suicide or suicidal behaviors that can result in an increase in similar behaviors (32). In one study, the overall suicide rate among 10 to 17 years old increased significantly in the month immediately after the release of "*13 Reasons Why*" [incidence rate ratio (IRR) =1.29; 95% CI: 1.09–1.53] (33). The authors also forecasted increased observed suicide rates in the month after release and in two subsequent months, relative to corresponding forecasted rates. These associations, interestingly, were restricted to boys. Among 18 to 29 years old and 30 to 64 years old, there was no significant change in suicide trends after the show's release. Younger audience may be more vulnerable to profiles of individuals who died by suicide (34). We present this article in accordance with the Narrative Review reporting checklist (available at https://pm.amegroups.com/article/view/10.21037/pm-23-23/rc).

Methods

For pharmacotherapy options for depressive disorders, suicide and NSSI, a literature review was conducted using the PubMed (National Library of Medicine) database and Google Scholar for studies that were published during January 1, 2000 to August 1, 2022. The following key words were used: "social network, youth, young adult, fear of missing out, non-suicidal self-injury, psychotherapy, depress*, MDD, suicid*, selective serotonin reuptake inhibitor, SSRIs, antipsychotics, naltrexone, N-acetylcysteine". Inclusion criteria for articles included: English language and peer-reviewed (*Table 1*).

Secondary review of references from selected articles

was also used to identify additional studies related to NSSI, depression and suicide. Articles that solely included adults (≥18 years) were excluded from this literature review.

Depressive disorders

Antidepressants, especially selective serotonin reuptake inhibitors (SSRIs), remain first-line monotherapy for treatment of depression and other related disorders (i.e., anxiety disorders, obsessive-compulsive disorder, post-traumatic stress disorder) in children and adolescents (35). Currently, there are seven antidepressants that have been approved for use in children and adolescents (*Table 2*). While there are limited number of antidepressants that have been approved for use in children and adolescents, other antidepressants are often used off-label for adult indications. In addition to fluoxetine, sertraline, fluvoxamine, escitalopram, non-SSRIs duloxetine, clomipramine and desipramine have also been approved for use in children and adolescents (38). Duloxetine is not approved for use in major depression; rather its pediatric indications are for generalized anxiety disorder and fibromyalgia (39). SSRIs remain first line due to their tolerability, dosing convenience and minimal of drug-drug interactions. Second generation antipsychotics (SGAs), such as aripiprazole and quetiapine have also been approved for use in major depression as augmentation strategies but they have not yet been approved for use in pediatric population. Rather, they are approved for use in schizophrenia, bipolar disorder (mania, depression, maintenance), and irritability associated with autistic disorder in children and adolescents and are often used off-label for depression augmentation (*Table 3*). The SGAs are also used on an off-label basis for numerous other disorders such as Tourette's syndrome and chronic tic disorders in children and adolescents. Bupropion has also been used off-label for children and

Table 2 FDA indications for adults, children and adolescents for antidepressants (36,37)

Generic (trade)	FDA indications for adult	Indications for children/adolescents
Selective serotonin reuptake inhibitors		
Fluoxetine (Fluoxetine, Prozac, Prozac Weekly, Sarafem)	Prozac: MDD, bulimia nervosa, OCD, panic disorder	Children: ≥8 years (MDD), ≥7 years (OCD)†
	Sarafem: PMDD	
Sertraline (Zoloft)	MDD, OCD, SAD, panic disorder, PTSD, PMDD (continuous or luteal dosing)	Children: ≥6 years (OCD)†
Paroxetine (Paxil, Paxil CR)	MDD, panic disorder, OCD, SAD, GAD, PTSD	–
Fluvoxamine (Luvox)	OCD	Children: ≥8 years (OCD)†
Citalopram (Celexa)	Major depression	
Escitalopram (Lexapro)	Major depression, GAD, SAD	Children: ≥12 years (MDD)†
Serotonin norepinephrine reuptake inhibitors		
Desvenlafaxine (Pristiq)	Depression	–
Levomilnacipran (Fetzima)	Depression	–
Duloxetine (Cymbalta)	Depression, diabetic peripheral neuropathy	Children/adolescents: ≥7 years (GAD)†
		Adolescents: ≥13 years (fibromyalgia)†
		Children/adolescents: ≥7 years (MDD)
Venlafaxine (Effexor)	Depression, GAD, SAD	Children/adolescents: ≥7 years (MDD)
		Children/adolescents: ≥6 years (GAD)
		Children/adolescents: ≥8 years (SAD)

Table 2 (*continued*)

Table 2 (*continued*)

Generic (trade)	FDA indications for adult	Indications for children/adolescents
Atypical antidepressants		
Bupropion (Wellbutrin, Wellbutrin SR, Wellbutrin XL, Aplenzin)	Depression, tobacco cessation, seasonal affective disorder (XL)	Children and adolescents: ≥6 years (MDD)
		Adolescents: (tobacco cessation)
		Children and adolescents: ≥6 years (ADHD)
Mirtazapine (Remeron)	Depression	Children and adolescents (MDD)
Trazodone (Desyrel)	Depression	Children 6–12 years and adolescents (MDD)
Vortioxetine (Trintellix)	Depression	–
Vilazodone (Viibryd)	Depression	Children 6–12 years and adolescents (MDD)
Esketamine (Spravato) (CIII)	Treatment-resistant depression in conjunction with an oral antidepressant	–
	Treatment of depressive symptoms in patients with acute suicidal ideation or behavior in conjunction with an oral antidepressant	
Select tricyclic antidepressants		
Amitriptyline (Elavil)	Relief of depression symptoms	Children: ≥9 years (MDD)
		Adolescents: MDD
		Children and adolescents: 10–17 years (migraine prophylaxis)
		Children: 6–10 years (nocturnal enuresis)
Clomipramine (Anafranil)	OCD	Children: ≥10 years (OCD)[†]
		Children and adolescents: (treatment of behavioral symptoms associated with autistic disorder)
Doxepin (Sinequan)	Depression, pruritus (topical form)	Children 6–12 years and adolescents: MDD and or anxiety, including psychotic depressive disorders with associated anxiety
Desipramine (Norpramin)	MDD	Adolescents (MDD)[†]
		Children 6–12 years (MDD)
		Children 6 years and older (nocturnal enuresis)
		Children: 5 years and older (ADHD)

[†], FDA-approved. FDA, Food and Drug Administration; MDD, major depressive disorder; OCD, obsessive compulsive disorder; PMDD, premenstrual dysphoric disorder; SAD, social anxiety disorder; PTSD, posttraumatic stress disorder; GAD, generalized anxiety disorder; SR, sustained-release; XL, extended-release; ADHD, attention-deficit hyperactivity disorder.

adolescents with depression due to its effectiveness in attention-deficit hyperactivity disorder (ADHD) (40). Tricyclic antidepressant utilization is limited due to side effects [e.g., increased diastolic blood pressure (BP)], as well as the inconvenience of obtaining a mandatory baseline electrocardiogram in children and adolescents.

A systematic review and network meta-analysis of antidepressants, psychotherapies and combination of medication and psychotherapy for children and adolescents with depressive disorders was conducted (41). Efficacy was defined as depressive symptoms as measured by mean overall change scores from baseline to treatment

Table 3 Second generation antipsychotics pediatric indications (36,37)

Generic (trade)	Schizophrenia	Bipolar disorder	Other indications
Aripiprazole (Abilify)	Adolescents	Children and adolescents ≥10 years	Irritability associated with autistic disorder: children and adolescents 5–17 years
			Off-label: moderate to severe tics associated with Tourette's/chronic tic disorders: children and adolescents 7–17 years
			Moderate to severe disruptive behaviors associated with oppositional defiant disorder or other disruptive behavioral disorders: children 5–12 years
Risperidone (Risperdal)	Adolescents Off-label: children 8–12 years	Children and adolescents 10–17 years	Irritability associated with autistic disorder (children and adolescents 5–17 years)
Quetiapine (Seroquel)	Adolescents	Children and adolescents ≥10 years	–
Paliperidone (Invega)	Children and adolescents 12 years and older	–	–
Lurasidone (Latuda)	Adolescents	Children and adolescents ≥10 years	–
Brexpiprazole (Rexulti)	Adolescents	–	–
Olanzapine (Zyprexa)	Adolescents ≥13 years	Adolescents	Off-label (IM and oral): children 6–12 years and older for acute agitation associated with schizophrenia or bipolar mania
		Children and adolescents: ≥10 years (adjunct treatment of depressive episodes associated with bipolar I disorder in combination with fluoxetine)	
Asenapine (Saphris)	–	Children and adolescents: ≥10 years	–

IM, intramuscular.

completion on standardized depressive symptom scales) and acceptability (all-cause discontinuation measured by proportion of patients who withdrew from the study for any reason). Outcomes were measured at 8 weeks as close as possible. The authors retrieved 71 randomized controlled trials (RCTs) representing 9,510 patients of articles published between 1986–2018.

The authors found that fluoxetine plus cognitive behavioral therapy (CBT) [standardized mean difference (SMD) =–0.73; 95% CI: –1.39 to –0.07] was more effective than CBT alone (SMD =–0.78; 95% CI: –1.55 to –0.01) and psychodynamic therapy (SMD =–1.14; 95% CI: –2.20 to –0.08) (41). Only interpersonal therapy (IPT) was more effective than all psychological controls.

The findings above confirm previously published landmark studies [Treatment for Adolescents With Depression Study (TADS) and Treatment of Resistant Depression in Adolescents (TORDIA)]. Based upon the TADS study, combination of fluoxetine plus CBT was superior to placebo after acute treatment and reduced suicidal thinking (42). In the TORDIA study, combination of CBT and pharmacotherapy had more favorable cost/benefit ratio for treating adolescent depression than other modalities (43). There is evidence that treating adolescent depression effectively may reduce suicide risk later in adults (44). Of the psychotherapy options, CBT, family therapy, exercise and spirituality have shown benefit in adolescents with MDDs (45,46). Family-based IPT have been shown to be additionally effective for reducing depression in children (45,46).

American Psychiatric Association and American Academy of Child and Adolescent Psychiatry recommend engaging parents and guardians in the monitoring stage when beginning an antidepressant (47). Providers should educate them to call the child's physician immediately if the child has new or more frequent thoughts of suicide,

self-destructive behavior, signs of increased anxiety/panic, agitation, aggressiveness, impulsivity, insomnia or irritability, new or increased restlessness, extreme bouts of elation or energy, or fast or pressured speech.

Self-injurious behavior

Behavioral interventions

Although CBT tends to be the gold standard for behavioral interventions for depression and anxiety-related disorders, two RCTs found that CBT in conjunction with a SSRI did not result in a reduction of NSSI frequency in adolescents (42,48). Conversely, dialectical behavior therapy (DBT) has the strongest evidence supporting its efficacy in reducing the frequency of NSSI in adolescence. One RCT found that at the one-year follow-up visit, DBT was significantly superior to enhanced usual care (EUC), with a reported mean of 14.8 episodes of NSSI in the EUC group compared to a mean of 5.5 episodes in the DBT group (49). The benefits of DBT are further highlighted by a recent RCT where adolescents with a history of self-harm received either DBT or individual and group supportive therapy (IGST) on a weekly basis. Findings at the one-year follow-up visit suggested DBT was associated with significantly higher rates of absence of self-harm (51.2%) compared to the IGST group (32.2%) (50).

Pharmacological interventions

There are currently no pharmacological interventions that have Food and Drug Administration (FDA) approval for the treatment of NSSI. Therefore, this section will review the evidence behind medication used off-label for this indication (*Table 4*).

In contrast to the treatment of depression and anxiety, antidepressants actually have the least amount of evidence supporting its efficacy in minimizing NSSI frequency. Yet, SSRIs remain one of the most prescribed classes of psychotropics for children and adolescents diagnosed with NSSI, given these self-injurious behaviors often co-occur in the context of MDD or anxiety-related disorders (51,59). To our knowledge, there have been no clinical trials to date that have investigated SSRIs and their potential role in reducing NSSI frequency among children and adolescents. However, one case report found fluoxetine significantly decreased NSSI frequency in an adolescent with an intellectual disability (52). Moreover, there have been 2 RCTs that found SSRIs combined with CBT do not offer any additional therapeutic benefits compared to SSRI monotherapy (48,51). For these reasons, antidepressant monotherapy may not be the optimal pharmacological regimen for the treatment of NSSI.

Conversely, several studies support SGAs having potential benefits in decreasing NSSI episodes in children and adolescents. A recent case report found clozapine therapy to be associated with markedly lower rates of NSSI-related behaviors compared to placebo (55). However, the significant metabolic side effects coupled with the inconvenient lab monitoring, significantly limits widespread use of clozapine for NSSI treatment. To address this issue, both a retrospective chart review and RCT investigated the efficacy of weight-neutral SGAs, ziprasidone and aripiprazole, respectively. Ziprasidone was found to decrease the frequency of NSSI by ~47%, while aripiprazole resulted in a staggering 92% reduction in NSSI episodes (53,54). As such, aripiprazole monotherapy or in combination with a SSRI may be good treatment options for children and adolescents given the minimal adverse effects compared to other SGAs.

Similar to antidepressants, opioid antagonists have minimal to no high-quality clinical trials supporting its use in adolescents with NSSI. However, naltrexone is still used as an intervention, owning to its mechanism of blocking increased activity of endogenous opioids that result from self-injurious behaviors, as well as its minimal side effect profile. To date, two single-subject placebo-controlled cross-over case studies and one case report have demonstrated the benefits of opioid antagonists (naltrexone and naloxone) in mitigating NSSI behaviors in adolescents with intellectual disabilities (56,57,60). As a result, opioid antagonists are reasonable treatment options in NSSI as monotherapy or in conjunction with an alternative medication treatment.

One of the most well-tolerated and readily accessible treatment options is the over-the-counter nutritional supplement, N-acetylcysteine (NAC). It is theorized that two likely mechanisms are involved in NAC's treatment potential for NSSI. First, NAC is a precursor to an antioxidant in the central nervous system, which is believed to induce neuroprotective effects. Second, NAC is a dopamine and glutamate receptor modulator, thereby enabling it to potentially interfere with the transient reward pathways associated with NSSI behaviors (61). The potential role of NAC in the treatment of NSSI is further underscored by an 8-week open-label, which found a significant reduction in both NSSI frequency and depressive

Table 4 Clinical trials evaluating pharmacological Interventions for adolescents with NSSI

References	Population	Study design	Intervention(s)	Results	Conclusions/limitation
SSRIs					
Asarnow *et al.* (51)	Adolescents (aged 12–18 years) with treatment-resistant MDD and history of SA and NSSI	24-week RCT (n=327)	Subjects randomized into 4 groups: (I) Switching to another SSRI (II) Switching to venlafaxine (III) Switching to another SSRI + CBT (IV) Switching to venlafaxine + CBT	No statistical difference between the 4 interventions	24-week therapy with SSRI or SNRI +/– CBT was not associated with improvement in SA or NSSI rates; however, a major limitation of the study was that it did not report mean antidepressant dose or dosing ranges
Goodyer *et al.* (48)	Adolescents (aged 11–17 years) with moderate-severe MDD and history of SI and NSSI, who did not respond to initial psychosocial intervention	12-week RCT (n=208)	Subjects randomized into 2 groups: (I) Fluoxetine monotherapy (II) Fluoxetine + routine care + CBT	~10–15% decrease in frequency of NSSI at week 12	Although there was a mild decrease in the frequency of NSSI, combination of CBT and SSRI had no additional benefits to SSRI monotherapy
			Mean fluoxetine dose =30 mg (range, 20–60 mg)	Combination of SSRI + CBT had no significant benefit over SSRI monotherapy	Limitation: the lack of a placebo control group prevents drawing conclusions regarding overall treatment effectiveness
Bass and Beltis (52)	17-year-old male with intellectual disability and NSSI, who did not respond to naltrexone (n=1)	Case report (n=1)	Fluoxetine 40 mg daily for 2 years	45–55% reduction in the frequency of NSSI over 2 years	Fluoxetine was found to cause ~50% reduction in frequency of NSSI. Future studies needed
					Limitation: one case report of a male patient with an intellectual disability (potential confounder) is not generalizable
Antipsychotics					
Libal *et al.* (53)	Female adolescents (aged 13–17 years) with documented incidents of prior self-harm	Retrospective chart review (n=16)	Subjects randomized into 2 groups: (I) Ziprasidone 40–80 mg (II) Received a different SGA	47% decrease in NSSI frequency in the ziprasidone group compared to alternative SGAs (18%)	Limitation: ziprasidone may serve as an augmenting agent for SSRI therapy
				Nearly all subjects (88%) were simultaneously being treated with an SSRI	Additionally, 16 of 18 participants were on SSRIs including fluoxetine, citalopram, paroxetine, and sertraline. Sixteen of 18 participants were on SSRIs including fluoxetine, citalopram, paroxetine and sertraline, which may be a confounder to the study
Nickel (54)	Young adults aged ≥16 years (mean: 22 years) with BPD and history of NSSI	An 8-week double-blind, placebo-controlled trial (n=52)	Subjects randomized into 2 groups: (I) Aripiprazole 15 mg daily (II) Placebo tablet	92% decrease in NSSI frequency at 8 weeks compared to placebo (73%)	Aripiprazole significantly reduced NSSI episode frequency after 8 weeks of therapy
					Limitation: sample size was relatively small and having only an 8-week study length, which may have reduced the failure rate of the intervention. Additionally, since sample size included patients with BPD, results may not be generalizable
Yang *et al.* (55)	Two females aged 15 and 18 years with MDD and concomitant NSSI (cutting forearms and thighs) who were refractory to SSRIs	Case series (n=2)	Each subject was initiated on low-dose clozapine (12.5 to 25 mg)	Each subject showed marked improvement in depressive symptoms and NSSI, which was sustained over 4 months after discharge	Low-dose clozapine monotherapy may be a treatment option with refractory depression and NSSI
					Limitation: study failed to address the long-term metabolic effects and inconvenient monitoring associated with clozapine use
Opioid antagonists & over-the-counter nutritional supplement					
Navkhare *et al.* (56)	Male aged 18 years with poor intellectual developments was admitted to a behavioral health unit for daily episodes of scratching himself and pulling out his hair. Patient was refractory to risperidone 8 mg and lithium 900 mg (8–12-week trial)	Case report (n=1)	Switched from previous psychotropic therapy to naltrexone 25 mg daily by mouth Patient was on concomitant lorazepam 2 mg daily and risperidone 2 mg daily	Total remission of NSSI was reported to have been achieved within 4 weeks of starting intervention	Naltrexone may be a good therapeutic option for stereotypic NSSI (episodic and often done in isolation) Limitation: the extent by which risperidone and/or lorazepam contributed to treatment success is unclear

Table 4 (*continued*)

Table 4 (*continued*)

References	Population	Study design	Intervention(s)	Results	Conclusions/limitation
Bernstein *et al.* (57)	Male aged 18 years with intellectual disability and severe NSSI	Double-blind placebo-controlled cross-over study (n=1)	Phase 1: naloxone 0.5–1 mg every 30 minutes over 6 hours *vs.* placebo	Naloxone was associated with a 50% reduction in NSSI frequency	Both naloxone and naltrexone demonstrated benefits in minimizing NSSI frequency
			Phase 2: naltrexone 12.5 mg daily *vs.* placebo	Naltrexone was associated with a 33% reduction in frequency	Limitation: 12.5 mg dose of naltrexone is lower than doses used in other studies that showed significant benefit with naltrexone
			Each phase took place over 15 days		
Cullen *et al.* (58)	Adolescents aged 13–21 years with NSSI	Open label pilot study (n=35)	NAC titrated from 1,200 to 3,600 mg/day (divided doses) over 8 weeks	Significant reduction in NSSI frequency at week 6 and 8, compared to baseline	Provides preliminary evidence that NAC may be an effective and safe treatment option for adolescents with NSSI

NSSI, non-suicidal self-injury; SSRIs, selective serotonin reuptake inhibitors; MDD, major depressive disorder; SA, suicide attempt; RCT, randomized controlled trial; CBT, cognitive behavioral therapy; SNRI, serotonin norepinephrine reuptake inhibitor; SI, suicidal ideation; SGA, second generation antipsychotic; BPD, borderline-personality disorder; NAC, N-acetylcysteine.

symptoms (58). However, NAC still lacks high quality-evidence given there has been no RCT studying its effect in adolescents with NSSI.

DBT has the strongest evidence supporting its role in NSSI treatment in adolescents. In conjunction with DBT, pharmacotherapy with SSRIs, SGAs, opioid antagonists, and/or NAC, are reasonable treatment modalities. Choice of pharmacotherapy should be based on the most current evidence, as well as the presence of a concomitant psychiatric illness. More importantly, patient-centered decision making, where the provider and patient discuss the risks versus benefits of the various interventions, plays an instrumental role in treatment success. Moreover, the significant lack of available robust studies supporting pharmacotherapy interventions in the treatment of NSSI affords numerous novel research opportunities in the field of child and adolescent psychiatry.

Suicide

Antidepressants, while effective in treating the symptoms of depression including suicidal thoughts and behaviors, have also been associated with increasing suicide risk in children, adolescents and young adults. In 1990, Teicher *et al.* first published a report of suicidal preoccupation with fluoxetine followed by case reports that raised questions about the etiology/pathophysiology of SI associated with antidepressants (possibly due to akathisia) (62). In June 2003, the United Kingdom issued warning about use of paroxetine in children less than 18 years old due to increased suicidality and in February 2004, the FDA Advisory Committee and Pediatric Subcommittee reviewed 15 studies in pediatric depression (63). In their investigation, they did not find any completed suicides but there was a stronger association of suicidal behavior or suicide attempts in the antidepressant-treated groups compared to placebo (64). In September 2004, the Neuro-Psychopharmacologic Advisory Committee and the Pediatric Advisory Committee concluded that there was a causal link between the newer antidepressants and suicidality among children, adolescents and young adults. As a result, on October 15, 2004, the FDA then issued an order for all pharmaceutical companies to add a "black box" warning on all antidepressants regarding this risk. In the prescribing information labeling of all antidepressants (and medications with FDA approved indication for depression), a black-box warning is included, stating that increased suicidal thinking/behavior during first 2 months of treatment may occur for children and young adults aged 18–24 years.

In the Zhou *et al.* study described above, a secondary outcome for suicidality was also analyzed as measured by reported cases of suicidal behavior or ideation (41). Venlafaxine was associated with significantly increased risk of suicidal behavior or ideation compared to placebo and other treatments (citalopram, escitalopram, fluoxetine, fluoxetine plus CBT, fluoxetine, imipramine, family therapy, desvenlafaxine, CBT and pill placebo plus CBT). CBT has been shown to reduce suicidality in adolescents in other studies (65,66).

Lu *et al.* studied the antidepressant use patterns by young adults and the suicidal behavior after the FDA warnings were released (67). The authors found that antidepressant use declined after the warnings and media coverage but the number of completed suicides per 100,000 increased after the media coverage.

There is no approved pharmacotherapy for suicidal behaviors in children and/or adolescents. Clozapine is the only medication that is FDA-indicated for suicidality and its use is limited to adults with psychosis. While off-label use of clozapine has been described in children and adolescents, the indications are predominantly related to schizophrenia, bipolar disorder or autism-spectrum disorders. The risks and benefits of using clozapine, given its adverse effect profile and monitoring requirements, need to be weighed (68). There has been at least one case report of a 15-year-old patient who developed completed atrioventricular block after a suicide attempt with clozapine (69). Lithium has also been shown to augment antidepressants as well as reduce suicidality in those with mood disorders, although there are certain limitations with its use (e.g., adverse effects, drug-drug interactions, monitoring requirements) (70,71). Currently, there is insufficient evidence to suggest that lithium should be used to reduce suicidality in unipolar depression in children and adolescents (72).

Esketamine has been studied in adults with depressive disorder and active SI with intent. While there was improvement in depressive symptoms per the Montgomery-Asberg Depression Rating Scale (MADRS) scale from baseline compared to placebo, there was no difference between groups in severity of suicidality per the Clinical Global Impression of Severity of Suicidality revised version (73). The use of esketamine in pediatrics has not been published and it is unknown whether it would have rapid antidepressant or anti-suicidal effect in this population.

In addition to pharmacotherapy options for suicide,

non-pharmacologic primary and secondary prevention strategies for youth suicide are important to protect those who are vulnerable and treat those with active suicidal behaviors (74). Universal screening has been shown to detect MDD more effectively than targeted screening based upon concerning behavior in high schools (75). Youths who screen positive for SI do not necessarily have known mental health concerns (76); therefore, they should be screened at every opportunity. The American Academy of Child and Adolescent Psychiatry recommends using the brief validated screening tool, Ask Suicide-Screening Questions (ASQ) as the first step in screening youth for suicidality (46). The Joint Commission also endorses the ASQ tool and takes 20 seconds to administer. The Columbia-Suicide Severity Rating Scale can also be used for more extensive evaluation of suicidality. Resources for screening and referral for those in crisis are provided at the end of this article. Additionally, responsible portrayal and reporting of suicides, mental illness and related disorders in the news and entertainment industry can help minimize suicide contagion. There are resources for those in the media about how they can responsibly portray suicides so that they are not sensationalized or traumatic to those exposed to the stories (34,77).

Strengths and limitations

The strengths of this narrative review are that it includes a summary of pediatric indications and evidence for non-pharmacologic and pharmacologic agents that can be used for depressive disorders, self-injurious behaviors and suicide in our youth population. The review also provides an in-depth analysis of clinical trials that investigated pharmacological interventions for adolescents who have NSSI. There are some limitations of this review that should be noted. This manuscript was not a systematic, comprehensive review of all literature on depression, suicide and NSSI in youths; therefore, there may be articles that were omitted. The literature search also included English language manuscripts that were published between January 1, 2000 through August 1, 2022 (when usage of social media was prevalent); there may have been older studies that could be relevant. It should be noted, however, that there were very few pediatric studies and the authors included not only RCTs, but case series as well. The discussion of treatments for depression was also limited to those that had evidence for use in pediatric populations and therefore, not all inclusive.

Conclusions

Primary and secondary prevention of suicides are key strategies for protecting our vulnerable youths. Similar to adults, psychotherapy combined with pharmacotherapy provides the best treatment of depression in children and adolescents. The mainstay for treating pediatric depression are SSRIs, but children and young adults must be monitored for increased suicidality at the beginning of treatment and after any dose changes. Psychotherapy should be used first line for depression, suicidality or NSSI in children and adolescents and pharmacotherapy with antidepressants should be reserved in cases when psychotherapy is ineffective or not available. While there are no specific pharmacotherapy agents approved for use in suicidality or NSSI, augmentation of antidepressants with SGAs and NAC may have additional therapeutic benefits for reducing these suicidal and self-harm behaviors.

There are several resources available for those struggling with suicide or who care for those with suicidality (78-84). These include American Foundation for Suicide Prevention, ASQ, Columbia-Suicide Severity Rating Scale, PHQ-9 modified for Adolescents (PHQ-A), Bullying Resource Center, Suicide Resource Center and the 988 Suicide & Crisis Lifeline.

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Footnote

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