Psychotropic drugs for the treatment of non-suicidal self-injury in children and adolescents: a systematic review and meta-analysis

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Abstract

Non-suicidal self-injury (NSSI) in children and adolescents is a frequent phenomenon. NSSI at any time is a significant predictor of future NSSI but also, and more importantly, for suicide attempts. Less evidence is available for the impact, or more specifically, the therapeutic effect of psychotropic drugs on the emergence of NSSI in this population. The phenomenon is clinically highly relevant since adolescent psychiatric inpatients are often affected by NSSI and most of them are treated with psychotropic drugs. While previous reviews on NSSI comprised suicidal self-injury (SSI), this review aims at elucidating the potential impact of psychotropic drugs on the emergence of specifically NSSI in children and adolescents. Systematic searches of articles indexed electronically in PubMed, Embase and PsycInfo were conducted (PROSPERO CRD42020209505). Studies included in the quantitative synthesis were evaluated using the SIGN level of evidence rating. Meta-analyses were performed using RevMan (Version 5.4). 2227 records were identified through database searches. Two additional records were identified manually. In total, seven studies were included in qualitative and four studies in quantitative analyses. In a meta-analysis, selective serotonin reuptake inhibitors (SSRIs) were compared vs. control medication (placebo or serotonin-norepinephrine reuptake inhibitor) and here, no statistically significant difference between the groups could be observed regarding the frequency of NSSI events (Risk Ratio (RR) = 1.07, 95% confidence interval (CI) 0.60–1.91, $p = 0.82$, $I^2 = 12\%$). Evidence regarding the association of SSRI use and NSSI among children and adolescents is sparse and the impact of psychotropic drugs in general on NSSI rates in this population should be addressed in future clinical and observational studies.

Keywords Non-suicidal self-injury · NSSI · Self-harm · Psychotropic drugs · Psychopharmacology · SSRI · Children · Adolescents

Introduction

Non-suicidal self-injury (NSSI) is defined as the deliberate, socially not-accepted, self-inflicted destruction of the own body tissue without suicidal intent [1]. It comprises behaviors such as cutting, burning, biting, punching, and scratching skin [1].

Children and mainly adolescents are frequently affected by NSSI [2]. Recent studies revealed a high overall NSSI (defined according to DSM-V criteria [3]) prevalence in community samples of adolescents (6.7–7.6%), with significantly more girls (11.1–11.7%) than boys (2.3–2.9%) meeting the diagnostic criteria [4, 5]. Adolescents with self-injurious behavior show increased hospitalization rates and it is estimated that up to 70% off all adolescent psychiatric inpatients engage in NSSI [6].

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Comorbid NSSI is most frequently associated with mood disorders and borderline personality disorders, but also anxiety disorders, posttraumatic stress disorders, attention deficit hyperactivity disorder (ADHD), substance abuse and especially eating disorders [1, 7]. Meta-analytic evidence suggests that women are more likely to report a history of NSSI and are more likely to use NSSI methods (e.g., cutting) compared to men, but for other patterns (e.g., punching) no significant differences are described in the literature [8]. Importantly, NSSI in adolescents is a significant predictor of future NSSI but also for suicide ideation and suicide attempts [9–12].

Established risk factors for NSSI among adolescents are childhood abuse or maltreatment, separated parents, a parent with a history of mental illness, unemployment, somatic complaints, mood disorders, aggression, anxiety, alexithymia, low self-confidence, self-abasement, desperation, dissociative experiences and family neglect or attachment problems [1].

A variety of psychological models are available that approach both the motives and influencing factors of NSSI and offer psychotherapeutic treatment options. In one of the main models from Nock and Prinstein [13, 14], named the four-function model of NSSI [1], inter- and intrapersonal motives and positive and negative consequences play a decisive role. Intrapersonal functions (66–81%), and especially those concerning emotion regulation were most frequently reported by individuals who engage in NSSI (63–78%), whereas interpersonal functions (e.g., expressing distress) were less frequently reported (33–56%) [15].

From a neurobiological perspective, abnormalities in the hypothalamic-pituitary-adrenocortical (HPA) axis, as well as dysfunctions in the serotonergic and dopaminergic neurotransmission and the endogenous opioid system are presumed to be implicated in the development of NSSI in adolescents [16, 17]. While a variety of potential drug targets to treat NSSI are known and adolescent psychiatric inpatients are often treated with psychotropic drugs [18], current guidelines do not report the level of evidence on the association of psychotropic drugs and their impact on the emergence of NSSI in adolescents [1, 19, 20]. Regarding self-harm (SH), a potential increase in suicidal thoughts and behaviors due to antidepressant treatment interventions in adolescents (as addressed in the US Food and Drug Administration (FDA) black box warning in 2004) was again presumed in a report from the FDA in 2018 [21].

Furthermore, there are inconsistencies in national guidelines in the categorization of NSSI resulting in differing concepts. The concept of SH is a broad category, often comprising suicidal self-injury (SSI), suicide attempts and NSSI [22]. Previous reviews evaluating treatment options of self-injurious behavior included either SH in adults and adolescents [22, 23] or NSSI in adolescents [24, 25] and reported the absence of evidence for effective pharmacological interventions to improve SH or NSSI. A recent review on SH among adolescents outlined the widespread but not empirically supported use of polypharmacy in adolescents with suicide attempts and/or NSSI [23]. In national (on NSSI) [1] and international guidelines (on SH) [19, 20] a lack of available studies regarding pharmacological treatment of NSSI was reported.

Thus, even though NSSI is a widespread phenomenon among adolescents, clinicians might be uncertain about effective and safe pharmacological treatment option for adolescents affected by NSSI or for adolescents with a high-risk for the emergence of NSSI. This systematic review and meta-analysis aimed to elucidating the overall impact of psychotropic drugs on the frequency of NSSI in children and adolescents to investigate potential both beneficial and detrimental medication effects on NSSI (defined according to DSM-V criteria [3]) in this population.

Methods

This systematic review was pre-registered on PROSPERO (CRD42020209505). Systematic searches were conducted of articles indexed electronically in PubMed, Embase and PsycInfo using the search terms: "Self injur* OR self harm* AND children OR adolescent* OR young* AND benzodiazepin* OR tranquil* OR antidepress* OR SSRI* OR antipsychotic* OR neuroleptic* OR mood stabil* OR anticonvuls* OR stimulan* OR opioid receptor antagonist* OR psychopharm*" (search period 01/1970 to 04/10/2020).

The abstracts and titles of articles identified through electronic searches were reviewed independently by two authors (VE, SC). Both English and non-English articles were considered for inclusion following translation. Articles assessed for eligibility, the full-texts were screened again independently by two authors (VE and SC), conflicts were resolved by a third (AH).

Study types considered eligible for inclusion were studies that reported information on the frequency of NSSI for children and adolescents treated with psychotropic drugs in observational studies or randomized controlled trials (RCT) or non-randomized controlled trials.

Studies were included if they reported the frequency of NSSI in children and adolescents (< 18 years) among psychotropic drug users and non-users or using a different drug or placebo (between-subject or within-subject analyses). The frequency of reported NSSI was defined as primary outcome. Of note, the outcome measure diverges from the original protocol and due to a lack of available studies, meaningful meta-regression analyses were not feasible.

Consistent with the definition of NSSI according to DSM-V, we excluded studies examining populations with

developmental or intellectual disabilities or with psychotic disorders. We also excluded studies without a control group, studies including participants aged 18 or older, studies including participants diagnosed with autism-spectrum or other neurodevelopmental disorders.

Studies included in quantitative synthesis were evaluated using the Scottish Intercollegiate Guidelines Network (SIGN) level of evidence rating [26]. Meta-analyses were conducted using RevMan (Version 5.4) [27]. Risk ratios (RR) were used as effect size for the primary outcome.

We assessed heterogeneity using the I^2 statistic, a measure that does not depend on the number of studies in the meta-analysis and hence has greater power to detect heterogeneity when the number of studies is small. Heterogeneity was assessed using the I^2 statistic, providing an estimate of the variability due to heterogeneity rather than chance, with > 50% suggesting possible heterogeneity and > 75% suggesting high heterogeneity. As the expected levels of heterogeneity were high, a random-effects model was used throughout. Significance was set at $\alpha < 0.05$.

Results

2227 records were identified through PubMed, Embase and PsycInfo database searches. Two additional records were identified by manually screening the reference list of recent topic-related reviews [28, 29]. After duplicates were removed, 1737 records were reviewed on title/abstract level (see Fig. 1) [28]. 144 articles were assessed for eligibility and the full-texts were screened again. 137 full-text articles were excluded with reasons (see Supplementary Table 1).

In total, seven studies were included in our qualitative synthesis (see Table 1; data extraction performed independently by two authors, VE and EW) [29–35]. From these seven studies, four RCTs [29, 31–33] investigated selective

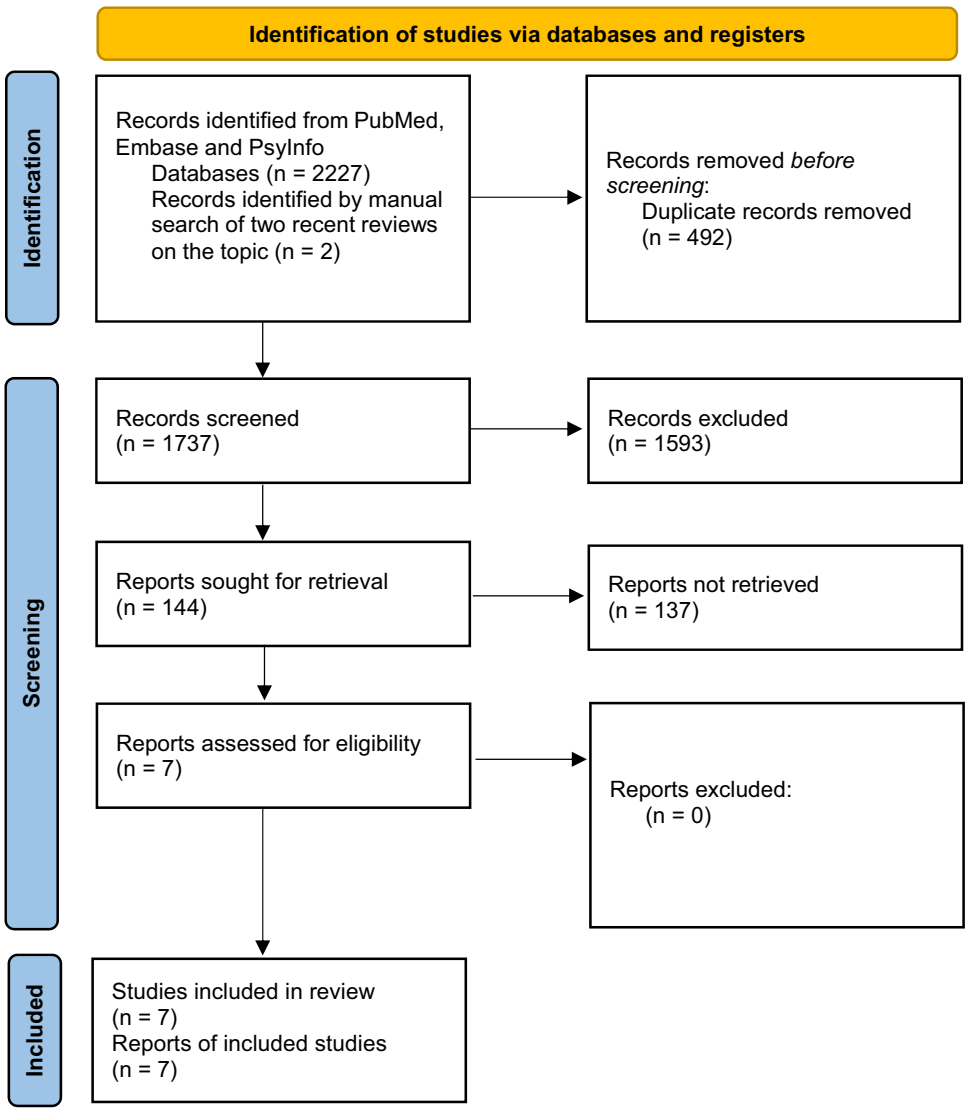

Fig. 1 PRISMA 2020 Flow Diagram. *Abbreviations: n* number. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. (2021) The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 372:n71. https://doi.org/10.1136/bmj.n71

Table 1 Studies included in qualitative synthesis

Author, Year	Sample size	Diagnosis	Age (mean, SD)	Gender (M:F ratio)	Duration of illness (mean, SD)	Study design	Intervention	NSSI primary or secondary outcome	Results	Overall sign level of evidence rating
Brent, 2009*	*N* = 334	Major depressive disorder (DSM-IV)	12–18 (15,9; 1,6)	30:70	22,5 months (SD 20,31)	RCT	SSRI (N 168) vs. Venlafaxine (N 166)	Secondary outcome	No significant difference	+
	N = 334	Major depressive disorder (DSM-IV)	12–18 (15,9; 1,6)	30:70	22,5 months (SD 20,31)	Non randomized, open label "add-on treatment"	Benzodiazepine (N 10) vs. no add-on medication (N 324)	Secondary outcome	More NSSI in Benzodiazepine group (N 4) vs. no add-on medication (N 27)	
Findling, 2013	*N* = 312	Major depressive disorder (DSM-IV)	12–17 (14,63; 1,56)	41:59	16,07 months (SD 16,39)	RCT	Escitalopram (N 155) vs placebo (N 157)	Primary outcome	No significant difference	+
Melvin, 2019	*N* = 59	Social phobia or specific phobia or generalized anxiety disorder or separation anxiety disorder or panic disorder	10–16,5 (13,59; 1,08)	54:46	At least 4 weeks	RCT	Fluoxetine (N 21) vs. placebo (N 20) vs. none (N 18)	Primary outcome	Less NSSI in Fluoxetine group (N 0) vs. the other groups (N 2, 6)	–
Pozzi, 2019	*N* = 2532	Unknown, drug of interest using adolescents	13- 17	Unknown	Unknown	Historical cohort study	Methylphenidate vs. lisdexamfetamine vs. atomoxetine vs. amphetamine	Primary outcome	Reported odds ratios for methylphenidate (1,7) and lisdexamphetamine (1,31) were better than for atomoxetine (2,56) and amphetamine (5.17)	

Table 1 (continued)

Author, Year	Sample size	Diagnosis	Age (mean, SD)	Gender (M:F ratio)	Duration of illness (mean, SD)	Study design	Intervention	NSSI primary or secondary outcome	Results	Overall sign level of evidence rating
Shamseddeen, 2019*	$N=334$	Major depressive disorder (DSM-IV)	12–18 (15,9; 1,6)	30:70	22,5 months (SD 20,31)	Non randomized, open label "add-on treatment"	Trazodon (N 33) vs. another sleep medication (N 25) vs. no add-on medication (N 276)	Secondary outcome	More NSSI in Trazodone group (N 5) vs. no add-on medication (N 15) vs. other sleeping medication (N 0)	
Libal, 2005	$N=16$	Mood disorder or anxiety disorder or disorder of personality development	13;10 – 17;11 (15,3)	0:100	Unknown	Retrospective case series	Ziprasidone (N 8) vs. another antipsychotic drug (N 8)	Primary outcome	Decrease in the rate of self-injurious events per day in the ziprasidone group (47.3%) and the control group (17.8%)	
Walkup, 2008	$N=488$	Separation or generalized anxiety disorder or social phobia (DSM-IV)	7–17 (10,7; 2,8)	50.4:49.6	Unknown	RCT	Sertraline + CBT (N 140) vs. Sertraline (N 133) vs. CBT (N 139) vs. Placebo (N 76)	Primary outcome	No significant difference for Sertraline vs. Placebo and Sertraline vs. CBT	+

*Information came from the original TORDIA paper (same sample) for Brent et al. [36] and Shamseddeen et al. [37]. Abbreviations: *CBT* cognitive behavioral therapy, *DSM* diagnostic and statistical manual of mental disorders, *f* female, *m* male, *N* number, *NSSI* non-suicidal self-injury, *RCT* randomized controlled trial, *SD* standard deviation, *SIGN* Scottish Intercollegiate Guidelines Network, *SSRI* selective serotonin reuptake inhibitor

serotonin reuptake inhibitors (SSRIs) as a class of antidepressants and were included in quantitative analyses with a total $N=1193$. All of them reported events of NSSI in a SSRI-treated group (30 events in $N=617$; 4.86%) vs. a control group (33 events in $N=576$; 5.73%) among adolescents with depressive or anxiety disorders. Studies were included in quantitative analyses after performing a SIGN level of evidence rating [26] (see below). Three studies [29, 31, 32] were rated as 1 + according to SIGN (well-conducted RCTs with a low risk of bias) [26]. One study was rated as 1- [33] (RCT with a high risk of bias) (see Table 1).

Qualitative analyses

Apart from the RCTs included in the quantitative analyses (see below), three other studies [30, 34, 35] and one secondary analysis of a RCT (Brent et al. 2009 [31]) were identified. The pharmacological interventions investigated were to heterogenous to be included in the quantitative analyses (see Table 1).

In the study from Brent et al. 2009 [31], a secondary analysis of a non-randomized, open-label "add-on treatment" with a benzodiazepine (clonazepam or lorazepam) ($N=10$) vs. no add-on medication ($N=324$) reported an increased rate of NSSI in the benzodiazepine group ($N=4$ vs. $N=27$) compared to the group without respective add-on medication. Benzodiazepine treatment was associated with a higher rate of NSSI among depressive adolescents, but the number of participants was small, participants were not randomly assigned, and NSSI was not the primary outcome.

In the study from Shamseddeen 2019 [35], a secondary analysis from the TORDIA study from Brent et al. [31, 36], a non-randomized, open-label "add-on treatment" with trazodone ($N=33$) was compared vs. other "sleeping medication" (diphenhydramine, zaleplon, zolpidem) ($N=25$) and vs. no add-on medication ($N=276$). Higher rates of NSSI in the trazodone group (5 events in $N=33$) compared to no add-on medication (15 events in $N=276$) and to other "sleeping medication" (0 events in $N=25$) were reported.

Two of the included studies were retrospective [30, 34]. The study from Libal et al. 2005 [30], was a retrospective case series ($N=16$) and compared ziprasidone ($N=8$) vs. another antipsychotic drug (chlorprothixen or olanzapine or promethazine or risperidone) ($N=8$). It showed a reduction of NSSI per day among female adolescent high-risk inpatients diagnosed with mood disorders, anxiety disorders or disorders of personality development treated with ziprasidone or other antipsychotics. More specifically, it showed a decrease in the rate of self-injurious events per day in the ziprasidone group (47%) and a lower symptom reduction in the control group (17.8%).

A comparative analysis of the US Food and Drug Administration adverse event reporting system database from Pozzi et al. 2019 [34] investigated the side effects (including NSSI) of methylphenidate compared to lisdexamphetamine, atomoxetine and amphetamine in children (6–12 years) and adolescents (13–17 years). For adolescents, odds ratios (OR) were reported for methylphenidate, lisdexamphetamine, atomoxetine and amphetamine. All drugs of interests were reported with significant reporting odds ratios (RORs) for self-injury, except for lisdexamphetamine, in adolescents. For adolescents affected by ADHD, in line with these results, the authors report an increased risk for self-injury under therapy with stimulants, methylphenidate (ROR: 1.70; lower boundary of the 95% 2-sided confidence interval (LB): 1.28) and lisdexamphetamine (ROR: 1.31; LB: 0.72) were significantly better than both atomoxetine (ROR: 2.56; LB 2.02) and amphetamine (ROR: 5.17; LB: 2.24).

Quantitative analysis

Four studies, all RCTs reporting events of NSSI in a SSRI-treated cohort vs. a control group were included in quantitative analyses [29, 31–33]. A meta-analysis showed no statistically significant difference between NSSI rates between the two groups (Risk Ratio (RR) = 1.07, 95% confidence interval (CI) 0.60–1.91, $p=0.82$). Heterogeneity between studies was low ($I^2=12\%$). (see Fig. 2). In a sensitivity analysis, where specifically SSRI were compared to placebo with regard to difference in NSSI rates, results remained non-significant (RR = 1.10, 95% CI 0.50–2.45, $p=0.81$) (see Fig. 3).

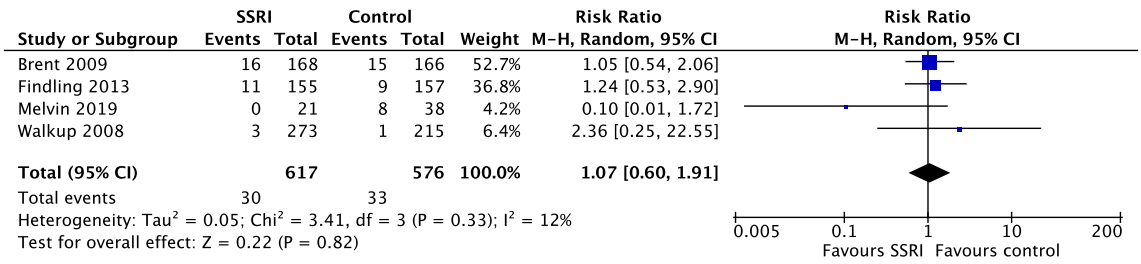

Fig. 2 NSSI rates (RR) SSRI vs. control medication. *Abbreviations: CI* confidence interval, *M–H* Mantel–Haenszel, *RR* relative risk, *SSRI* selective serotonin reuptake inhibitor

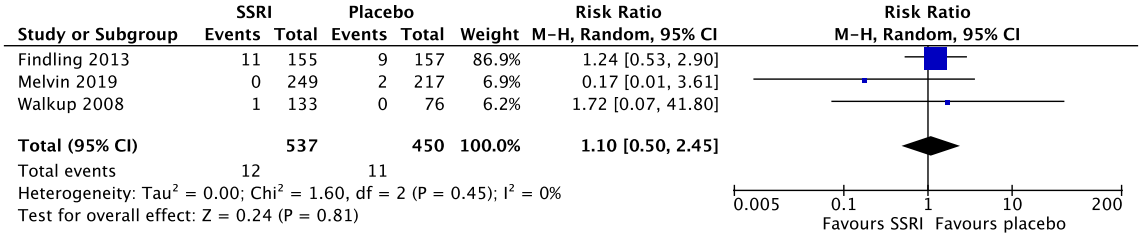

Fig. 3 NSSI rates (RR) SSRI vs. placebo. For this sensitivity analyses, the study from Brent et al. was excluded [31], since no placebo arm was available in this study. Furthermore, the CBT only arm from the study of Melvin et al. was excluded from this analysis and only the two arms were CBT + placebo and CBT + fluoxetine were included. With regard to the study from Walkup et al., the CBT arm and the CBT + sertraline arm were excluded. Thus for this analysis, CBT was only present in both of the selected arms from the study from Melvin et al. *Abbreviations: CI* confidence interval, *M–H* Mantel–Haenszel, *RR* relative risk, *SSRI* selective serotonin reuptake inhibitor

Discussion

The aim of this systematic review and meta-analysis was to identify the available evidence of the impact of psychotropic drugs on NSSI in children and adolescents. Our meta-analysis showed no statistically significant differences of SSRI vs control (medication or placebo) on the emergence of NSSI in adolescents. Three studies (Brent et al., Findling et al., Walkup et al.; [29, 31, 32]) were rated as 1 + according to SIGN [26]. One study was rated as 1- (Melvin et al. [33]). Two secondary analyses of the TORDIA study from Brent et al. 2009 [31, 35, 36] reported an increase in NSSI rates among depressive adolescents treated with benzodiazepines or trazodone. One study [34] showed an increase of NSSI among adolescents with ADHD treated with stimulants (methylphenidate, lisdexamfetamine, atomoxetine, amphetamine) with the highest risk for atomoxetine and amphetamine. Since ADHD itself is a risk factor for NSSI, at least the relative risks of the different stimulants appear to be relevant. The only study investigating the potential impact of antipsychotics on NSSI in adolescents was a small retrospective chart-review showing a reduction of NSSI in a small sample of high-risk females [30]. As a limitation, it must be noted that all study participants received non-manualized psychotherapy (and other non-antipsychotic co-medication). Second, the study had a retrospective design and a small sample size.

The available evidence regarding the impact of psychotropic drugs on the emergence and frequency of NSSI in adolescents is sparse. For adults, little empirical evidence regarding psychopharmacological effects on NSSI is available for at least some drug classes: SSRIs, atypical antipsychotics, SNRIs, opioids and opioid antagonists [24]. As suggested shown by our systematic review, the evidence regarding the association of SSRI and NSSI in children and adolescents is sparse and the impact of psychotropic drugs in general on NSSI rates in this population should be further investigated in the context of observational studies and clinical trials. No conclusion can be drawn yet from our negative meta-analytic evidence comprising only few studies of rather low quality. Nevertheless, single reports showed an increased frequency of NSSI among adolescents in association with specific psychotropic drugs (benzodiazepines, trazodone, and stimulants) [31, 34, 35]. Less evidence is available for the impact antipsychotics on NSSI [30]. Moreover, we were not able to detect studies with other psychotropic drugs (mood-stabilizers, anticonvulsants, or opioid receptor antagonists) investigating the relationship between treatment and NSSI in adolescents.

In line with these results, the consensus-based German guideline of NSSI in children and adolescents published in 2016 [1]—to our knowledge the only guideline worldwide specifically approaching NSSI among children and adolescents reported an absence of available studies regarding pharmacological treatment of NSSI. This statement reflects other international guidelines, such as the practice guideline for the management of deliberate self-harm from the Royal Australian and New Zealand College of Psychiatrists [19] or the National Institute for Health and Care Excellence (NICE) guideline for self-harm [20]. As in the German guideline, the NICE guideline emphasized the need to offer psychological, pharmacological and psychosocial interventions for any underlying or associated condition (e.g. depression) [20].

As suggested by our meta-analysis, SSRIs, the pharmacological first-line treatment option for depressive adolescents [38–40], a group which is most often affected by NSSI [1], appear to have little impact on the frequency of NSSI among adolescents. In line with treatment guidelines for depressive adolescents [38–40] and guidelines for the treatment of NSSI among adolescents [1, 19, 20], SSRIs appear to be the treatment of choice for depressive adolescents affected by NSSI, since they are beneficial for the underlying or associated condition (depression) [38–40] and do not appear to increase NSSI rates.

ADHD itself is a risk factor and often an underlying condition of NSSI. Choosing a treatment option for an

adolescent with ADHD affected by NSSI might be clinically challenging, since an increased risk for NSSI was previously assumed for all stimulants, with increasing risk rates from lisdexamphetamine to methylphenidate, atomoxetine and amphetamine. Considering the most recent treatment guideline for ADHD in adolescents [41], methylphenidate seems to be the pharmacological treatment of choice for adolescents with ADHD being affected by NSSI. For antipsychotic agents, these were shown to be beneficial in some adults with personality disorders affected by NSSI [42], whereas for adolescents, evidence is sparse.

Hence, our results must be interpreted with caution. It must be considered that the meta-analysis was to a great extent influenced by the results of two studies [31, 32] and the results of the remaining studies were negligible. Furthermore, selection bias due to the small number of cases and the inclusion of mostly non-randomized studies must be considered [43]. However, we decided to present all detected sources of evidence to give a complete picture. As further limitation, psychotherapy interventions, that have been extensively reviewed elsewhere [44], were not within the scope of our analysis. The PICO framework was not used, since we applied a broad search algorithm and focused mainly on assembling the evidence in a qualitative review, especially since our patient group cannot be defined precisely due to the focus on behavioral phenomenons (such as NSSI).

In summary, according to our meta-analysis, SSRIs seem to have no substantial impact on the incidence of NSSI in adolescents with depressive or anxiety disorders. Our meta-analytic finding does not strengthen the proposed relationship between self-harming behavior and psychotropic drugs in adolescent patients as addressed in the FDA warnings and reports from 2004 and 2018 [21]. Of note, NSSI might occur in association with other psychotropic drugs (e.g. benzodiazepines, trazodone, and stimulants). Nevertheless, our review is in line with national and international treatment guidelines, highlighting that no effective pharmacological treatment option for NSSI in adolescents is currently available. Thus, there is an urgent need for more studies to foster the evidence for the pharmacological treatment of NSSI in adolescents and the (potentially negative) impact of psychotropic drugs on the emergence of NSSI in adolescents. This is from particular importance since in child and adolescence psychiatry off-label prescription of psychotropic agents is based on research evidence derived from adult populations [45]. However, taking into consideration several possible psychosocial moderators or cofounders of NSSI in children and adolescents [13, 14], the extent of the pharmacological impact on NSSI is still elusive and must be investigated in future large-scale trials.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00406-022-01385-w.

Declarations

Conflict of interest Vincent Eggart, Sebastian Cordier, and Elias Wagner reported no conflict of interest. Alkomiet Hasan has been invited to scientific meetings by Lundbeck, Janssen, and Pfizer, and he received paid speakerships from Desitin, Janssen, Otsuka, and Lundbeck. He was member of Roche, Otsuka, Lundbeck, and Janssen advisory boards.

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