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PHARMACOLOGICAL SUPPORT TREATMENT OF NON-SUICIDAL SELF-INJURIES AMONG CHILDREN AND ADOLESCENTS: A NARRATIVE REVIEW

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Authors' contribution
A. Study design/planning
B. Data collection/entry
C. Data analysis/statistics
D. Data interpretation
E. Preparation of manuscript
F. Literature analysis/search
G. Funds collection

Summary

Non-suicidal self-injuries (NSSI) constitute a significant problem among children and adolescents, especially during the global burden of mental disorders worldwide. Moreover, such behaviors are perceived as a risk factor for the suicidal behaviors occurrence in the future. Thus, it would appear necessary to search for effective forms of their treatment. A pharmacological approach may play a supportive role. This study is a narrative review summarizing scientific reports on possible pharmacological support treatment of NSSI among children and adolescents. Internet scientific bases were searched for literature, including original research, review articles and case reports. There are many possible pharmacological interventions that may reduce the incidence of self-harm behaviors. Antihistamines and neuroleptics can be used successfully in the acute phase. In turn, second-generation antipsychotics and potentially naltrexone seem to be the most effective in long-term treatment. Although psychotherapy is the basic form of NSSI treatment, a psychopharmacological approach may play an essential role in reducing the incidence of self-harm behaviors. Nevertheless, the use of psychotropic medications is prohibited in most cases and may be limited due to their side effects. Moreover, there is a need to validate their efficiency in next studies to gather strong evidences concerning their widespread use.

Keywords: non-suicidal self-injuries, psychopharmacotherapy, adolescents, mental health, children

Introduction

The global burden of mental disorders among adolescents has become a significant problem for healthcare systems worldwide. An important issue in this context are Non-Suicidal Self-Injuries (NSSI). According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) and International Classification of Diseases 11th revision (ICD-11), they are defined as socially unacceptable, direct, repetitive and intentional damage to one's own body, without suicidal intent [1-3]. They are expressed in various forms, ranging from relatively mild (e.g. superficial cuts in the epidermis), to relatively severe (e.g. incised wounds requiring surgical debridement). NSSI also includes, among others: cutting, burning the skin, scratching wounds, scratching the epidermis itself to break its continuity, or punching oneself [4]. It is estimated that the lifetime prevalence of NSSI among adolescents is about 22%, but emerging data showed an increasing trend of these behaviors in the last

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few years, making it a significant challenge for mental health around the world [5,6]. Moreover, the percentage of such behaviors among adolescents hospitalized due to mental disorders is much higher and even reaches 70-80% [7,8]. In addition, these behaviors are perceived as an independent risk factor for the occurrence of suicidal behaviors in the future [9]. Thus, it seems necessary for clinicians to search for effective forms of their treatment. To date, no drug has been approved by the U.S. Food and Drug Administration (FDA) as a possible pharmacological intervention for NSSI. However, several groups of medications have been investigated to assess their effectiveness in reducing the incidence of NSSI.

Aim of the work

The aim of this review was to present possible pharmacological interventions to reduce the incidence of NSSI, both in short- and long-term perspectives. The authors assume that this work will help clinicians take appropriate therapeutic actions and constitute a rationale for future professional and unified recommendations.

Methods

This is a narrative review summarizing scientific reports from 1980 to 2023 on possible pharmacological support treatment of NSSI among children and adolescents. Internet scientific databases, Google Scholar, Medline, PubMed and Science Direct, were searched for references by two independent authors throughout December 2023 and January 2024, using the following keywords and their combinations: "agitation", "antipsychotics", "benzodiazepines", "clonidine", "drugs", "histamine receptor antagonists", "medications", "mood stabilizers", "naltrexone", "non-suicidal self-injury", "NSSI", "pharmacotherapy", "self-harm", "self-injurious behavior", "self-mutilation", and "self-wounding". Original research, review articles and case reports were included, based on the authors' research and clinical experience. Finally, 69 scientific papers were cited. For the quality assessment of this narrative review of the scientific literature, the Scale for the Assessment of Narrative Review Articles (SANRA) was used [10].

Literature review results

Short-term treatment of NSSI

Benzodiazepines (BZDs)

The ad hoc use of short-acting BZDs, positive allosteric modulators of γ-aminobutyric acid (GABA) binding through the $GABA_A$ receptor, might seem reliable in urgently reducing the incidence of NSSI due to their anxiolytic and sedative effect. However, results of the TORDIA trial indicated that the adjunctive use of BZDs can be associated with a higher rate of both suicidal and NSSI adverse events, which can be explained by cognitive effects of BZDs and paradoxical reactions, leading to psychomotor agitation, increased risk-taking, disinhibition and, rebound anxiety. It is worth noting that this relationship should be interpreted cautiously, because of the small number of patients included in the study group and without randomization [11]. Nevertheless, several other studies pointed out that augmentation of BZDs may aggravate suicidal behaviors [12,13]. All in all, the use of BZDs may be justified in individual cases, after considering the balance of potential benefits and losses associated with including them in the treatment regimen [14]. Additionally, their long-term use is limited by a potential addictive effect which may lead to substance-use disorder development. Moreover, particular attention should be paid when using BZDs in subjects with chronic respiratory diseases resulting in reduced respiratory drive, due to the risk of respiratory depression.

Histamine-1 receptor (H_1) antagonists

Hydroxyzine

Hydroxyzine, a first-generation H_1 antagonist, is widely used to reduce nervous tension, anxiety and to facilitate falling asleep [15]. Most likely, it acts through the inhibition of the activity of centers in the subcortical layer of the central nervous system – this anxiolytic-sedative effect may be useful in reducing the number of NSSIs undertaken ad hoc, especially among adolescents with anxiety symptoms and psychomotor agitation. It is worth noting that augmentation of hydroxyzine can be associated with the lowering of the seizure threshold, especially among younger children. Moreover, the use of hydroxyzine may have an impact on QT interval prolongation. The anticholinergic potential and associated side effects may also limit its use in some patients [16].

Diphenhydramine (DPH)

DPH, another H_1 receptor antagonist, is also widely used in psychiatric inpatient units and emergency departments to reduce symptoms of agitation among children and adolescents [17]. Thus, its use to reduce the incidence of NSSI in the short term may be adequate. However, a double-blind, placebo-controlled study showed no difference between DPH and placebo in behavioral change [18]. Nevertheless, as Hoffmann et al. noted, the favorable safety profile of DPH and the rare incidence of adverse effects (similar to those observed during augmentation of hydroxyzine) are the main factors that make DPH a commonly prescribed drug among clinicians in moderate agitation [19]. According to the Consensus Statement of the American Association for Emergency Psychiatry, the use of DPH should be considered for younger children and youth with anxiety symptoms, not secondary to delirium, intoxication, or withdrawal [20].

Antipsychotics

In states of psychomotor agitation and intense anxiety, the use of such first-generation neuroleptics as haloperidol, promethazine, chlorpromazine, levomepromazine and zuclopenthixol may be useful to reduce tension in a short time because of their sedative effect [14,19,21]. Low doses of second-generation antipsychotics (SGAs), such as quetiapine, olanzapine or risperidone, especially in immediate-release form, are also used in practice [22].

Clonidine

Clonidine is a non-selective alpha-2 adrenergic agonist, that interferes with noradrenergic neurotransmission in the central nervous system. Alpha-2a receptors are highly prevalent in the prefrontal cortex and mediate impulsivity rise. Alpha-2c receptors are present in the locus coeruleus and their arousal is responsible for sedative effect. Taking into account the non-selectivity of clonidine towards particular subtypes of alpha-2 receptors, its use may be beneficial in the reduction of the incidence of NSSI in the short term [23].

The ad hoc use of clonidine in agitation treatment can be perceived as an alternative for neuroleptics in the case of any contraindications. Additionally, its use may be also justified in concomitant autism spectrum disorder, attention deficit hyperactivity disorder, tics disorder and post-traumatic stress disorder [20,24]. Moreover, in the Philipsen et al. study, orally administered doses of clonidine (75 and 100 μg), among adult patients with borderline personality disorder, were found to be effective in decreasing the urge to commit self-injurious behaviors [25]. During the augmentation of clonidine, it is essential to monitor for hypotension and bradycardia, thus giving BZDs or antipsychotics is not recommended due to the additive depressant effect on the cardiovascular system. The dosing regimen of the above-mentioned medications is presented in Table 1.

Table 1. Chosen psychotropic medications in the temporary treatment of agitation

Name of the drug	Single dosage	Peak effect in minutes	Maximum daily dose	References
Lorazepam	p.o., i.m., i.v.: 0.05-0.1 mg/kg or 0.5-2 mg	i.m., i.v.: 10 p.o.: 60-120	< 12 y.o.: 4 mg > 12 y.o.: 6-8 mg	[19,20,22]
Hydroxyzine	p.o., i.m.: < 6 y.o.: 0.6 mg/kg 6-12 y.o.: 12.5-25.0 mg > 12 y.o.: as adults	p.o.: 120 i.m.: 120	< 6 y.o.: 50 mg > 6 y.o.: 50-100 mg > 12 y.o.: as adults	[26-28]
Diphenhydramine	p.o., i.m.: 1mg/kg or 12.5-50 mg	p.o.: 120-240 i.m.: 120	< 12 y.o.: 50-100 mg > 12 y.o.: 100-200 mg	[19,22]
Clonidine	p.o.: 0.05-0.1 mg	30-60	27.0-40.5 kg: 0.2 mg/day 40.5-45 kg: 0.3 mg/day >45 kg: 0.4 mg/day	[20,22]
Haloperidol	p.o., i.m.: 0.05-0.1 mg/kg or 0.5-5 mg	p.o.: 120 i.m: 15-30	children: 5 mg adolescents: 15 mg	[19,22]
Chlorpromazine	p.o., i.m.: 0.55 mg/kg or 12.5-60 mg (i.m. dose should be ½ of p.o. dose)	p.o.: 30-60 i.m.: 15	< 5 y.o.: 40 mg > 5 y.o.: 75 mg	[19,20,22]
Olanzapine	p.o., i.m.: 0.1 mg/kg or 2.5-10.0 mg (i.m. dose should be from ¼ to ½ of p.o. dose)	i.m.: 15-45 p.o.: 240-480	> 12 y.o.: 20 mg	[19,20,22]
Quetiapine	p.o.: 1.0-1.5 mg/kg or 25-50 mg	30	> 12 y.o.: 600-800 mg	[22]
Risperidone	p.o.: 0.025-0.05 mg/kg or 0.25-1.0 mg	60-120	< 12 y.o.: 1-2 mg > 12 y.o.: 2-4 mg	[22,29]

Chronic pharmacological support treatment of NSSI

Selective Serotonin Reuptake Inhibitors (SSRIs) and Serotonin and Noradrenaline Reuptake Inhibitors (SNRIs)

In a meta-analysis conducted by Eggart et al. [30], SSRIs were compared with control medication (placebo or SNRIs), and no statistically significant difference between the groups was observed in terms of the reduction of frequency of NSSI undertaken. However, the authors made a point that the number of studies included in this meta-analysis and their quality are insufficient to draw clear conclusions [30]. Nevertheless, in accordance with several national guidelines, the use of SSRIs should be considered as a first-line treatment for depression or anxiety disorders with concomitant NSSI events among children and adolescents, because their use is beneficial in the treatment of the underlying disorders and does not increase the risk of NSSI events [14,31].

Markovitz and Wagner study, performed on subjects diagnosed with borderline personality disorder, reported promising results of the venlafaxine use in reducing NSSI frequency [32]. Nevertheless, the next studies with controlled design should take place to confirm these findings.

Antipsychotics

A series of case reports suggests that impaired dopaminergic transmission, associated with dopamine 1 (D1) receptors, may partially contribute to the occurrence of NSSI – the use of such neuroleptics like zuclopenthixol or flupentixol, and their antagonism towards the mentioned D1 receptors, may be effective in reducing the incidence of self-harm [33].

On the other hand, the role of SGAs was also emphasized. Their affinity for serotonin (5-HT) receptor families (particularly to 5-HT_2) may be responsible for their efficacy in diminishing aggressive behaviors [34]. Moreover, their mood-stabilizing properties may be also useful in reducing the incidence of NSSI. In the Libal et al. study [35], the use of ziprasidone, with a dose range of 40-80 mg/day, was associated with a decrease in the rate of self-injurious events among adolescents. Furthermore, ziprasidone was found to be more effective than alternate neuroleptic medication. However, this was a non-randomized case-control design study. Additionally, the duration of treatment wasn't emphasized [35]. In the randomized control trial performed by Nickel et al., after 8 weeks of aripiprazole use at a dose of 15 mg/day, there was also a decrease in NSSI incidence compared with the placebo group observed [36]. Another series of case reports indicated that adjunctive use of quetiapine (titrated to 150-200 mg a day) may reduce self-harm behavior incidence among adolescents with a major depressive disorder [37]. The possible effect of risperidone, especially among subjects with intellectual disability, was also emphasized in the context of NSSI [38]. Augmentation of low doses of olanzapine was also found to be effective [39]. In turn, Hammock et al. suggested that the use of clozapine (in a dose of 200 mg a day) can be reliable in resistant cases, non-responsive to all other behavioral and psychopharmacological interventions [40].

Despite numerous scientific reports indicating the effectiveness of neuroleptics in reducing the frequency of NSSI, their side effects should not be forgotten. Particular caution should be paid when using first-generation antipsychotic drugs due to the risk of extrapyramidal symptoms and hyperprolactinemia [41]. Furthermore, in the case of SGAs, metabolic repercussions in terms of carbohydrate and lipid metabolism should be also taken into account [42]. Therefore, these side effects may limit their augmentation.

Non-neuroleptic mood stabilizers (MS)

Considering features of developing borderline personality disorder (BPD) are often observed among children and adolescents who undertake NSSI acts, it seems reliable to include mood stabilizers (MS) into the treatment scheme. Their possible effect on subcortical limbic structures may lead to a behavioral disorder decrease. No drug has been approved for the treatment of this disorder by the FDA yet. Cochrane meta-analysis results showed little to even no effect of applied psychopharmacotherapy on symptom severity in the course of BPD [43]. Another Cochrane systematic review, conducted by Witt et al., whose aim was to assess the effect of a pharmacological approach for self-harm incidence reduction among adults, revealed no difference for MS compared with placebo for repetition of self-injuries [44]. Nevertheless, their off-label use in practice is still observed because of the possible reduction of impulsiveness and agitation among youth in the long term. Apart from the above-mentioned antipsychotics, there are also antiepileptic drugs and lithium. According to UK National Institute for Health and Care Excellence (NICE) guidelines, these medications should be considered as the next lines of support treatment in BPD, just behind SGAs [45].

Antiepileptic drugs

In the context of NSSI, several studies were performed to assess the effectiveness of antiepileptic drugs and their mood-stabilizing properties on self-injury incidence. Promising results were observed in the case of valproic acid, carbamazepine and lamotrigine [46-48]. However, no next studies were conducted to confirm these results.

Moreover, some scientific reports suggest that anticonvulsants may escalate suicidal ideation [49]. Hence, their inclusion into the treatment regimen should be cautious and results from a positive balance of possible gains and losses in a selected group of patients (with bipolar or schizoaffective disorder; high impulsivity or emotional instability).

Lithium

Hayes et al. indicated that adult patients diagnosed with bipolar disorder and taking lithium had lower rates of self-harm and unintentional injury [50]. However, there is a lack of research assessing the impact of lithium on the NSSI incidence decrease in youth, especially among those with traits of abnormally developing personality – to the best of our knowledge, only Masters et. al indicated a decrease in self-harm behavior among adolescents treated with lithium carbonate [51]. Surprisingly, a recent randomized clinical trial, conducted by Katz et al., revealed that the addition of lithium didn't reduce the incidence of suicide-related events, including NSSI [52]. These findings seem to disrupt the current paradigm regarding the antisuicidal effect of lithium, but these results should be interpreted with great caution [53]. Therefore, its use is empirical and should be limited to the cases where bipolar disorder or schizoaffective disorder is an essential diagnosis. It should be also noted that chronic treatment with lithium requires an appropriate level of compliance with the doctor's recommendations (strict dosing regimen, periodic measurement of serum lithium concentration, thyroid or renal parameters), which may be challenging among emotionally unstable adolescents in an outpatient setting. Moreover, side effects of lithium, including hypothyroidism and tubulointerstitial nephropathy, limit its wide use among children and adolescents.

Naltrexone (NTX)

Disruptions in the endogenous opioid system play an important role in the pathogenesis of NSSI. Moreover, NSSI may be perceived as a form of behavioral addiction for several reasons:

- both non-suicidal and suicidal behaviors can be a form of psychological pain relief associated with endogenous opioid release (especially β-endorphin), which has addictive potential [54,55];
- during the act of self-harm, there is an activation of dopaminergic pathways which results in dopamine "high" [56].

Hence, the use of an opioid receptor antagonist may potentially provide therapeutic benefits in reducing the number of acts of NSSI undertaken. NTX appears to be such a drug – it is a long-acting reversible competitive opioid antagonist, with the highest affinity for μ-opioid receptors [57]. To a lesser extent, it is also an antagonist of δ and κ opioid receptors. It has its active metabolite, 6-beta-naltrexone, arising as a result of extensive first-pass metabolism in the liver [58]. It has been already used in the treatment of both substance (including alcohol) and behavioral addictions, with satisfactory results [59,60]. Several case reports on children with neurodevelopment disorders indicated that chronic use of graduated titrated low doses of NTX, 12.5-50 mg per day, may effectively reduce the frequency of self-injurious behaviors [61,62]. Similar findings were observed in open-label trials, however, the number of patients included in the study group was relatively small in these studies, and they were performed on adult subjects [63,64]. To the best of our knowledge, only one study, performed by Campbell et al., evaluated the effect of NTX on the reduction of self-aggressiveness among children diagnosed with an autism spectrum disorder. These symptoms were only slightly reduced, but it seems that the size of the study group and the overall design of the study are insufficient to make binding conclusions [65]. Studies on a larger scale, exploring the efficiency, tolerability, and safety of NTX chronic use among children and adolescents, are needed. Furthermore, a practical and unified algorithm for dosing and the duration of NTX therapy would be useful for clinicians.

Other agents

Another study suggested that the use of a long-acting opioid antagonist, buprenorphine (doses 0.5-6.0 mg per day), may be reliable in the reduction of NSSI incidence [66]. N-acetylcysteine (NAC) has been found to be effective in trichotillomania, excoriation disorder, onychophagia and onychotillomania [67]. Particular attention has been also given to topiramate: several studies indicated its efficiency in such disorders as trichotillomania, excoriation disorder and NSSI [68]. However, a recent case report revealed that the use of topiramate may be associated with drug-induced suicidal ideation [69].

All in all, these studies should be considered as a rationale for future studies that will evaluate the impact of these medications on NSSI incidence reduction, especially on larger groups of subjects.

Conclusions

Although psychotherapeutic interventions, aimed primarily at developing emotional regulation skills, are the basic form of treatment for NSSI, the pharmacological approach, both in the short and long term, may play a supportive role in this process. There is a plethora of possible psychotropic medications used to decrease NSSI incidence in a short time, including antihistamines and neuroleptics. On the other hand, SGAs and potentially naltrexone seem to be effective in long-term treatment. However, it is important to remember that the application of most of these drugs involves their off-label use among children and adolescents. Moreover, further research with a controlled design or longitudinal follow-up is needed to evaluate properly the efficacy of agents in the NSSI repetition reduction and find strong evidence supporting their widespread use. It should also not be forgotten that in each case, the inclusion of a potential drug in the therapeutic treatment should result in a positive balance of therapeutic benefits and losses (mainly caused by side effects of psychotropic agents).

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