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Use of the opioid receptor antagonist – naltrexone in the treatment of non-suicidal self-injury

Hanna Karakuła-Juchnowicz[1], Agnieszka Banaszek[2], Dariusz Juchnowicz[3]

[1] I Department of Psychiatry, Psychotherapy and Early Intervention, Medical University of Lublin
[2] Student Scientific Club at the I Department of Psychiatry, Psychotherapy and Early Intervention, Medical University of Lublin
[3] Department of Psychiatric Nursing, Medical University of Lublin

Summary

Aim. The aim of the study was to review the existing research, conducted on animal and human models, regarding the possibility of using low doses of naltrexone (LDN) in treatment of non-suicidal self-injury (NSSI).

Method. The available Polish– and English-language literature on NSSI was reviewed. Relevant studies were identified through an electronic search of PubMed/MEDLINE and Google Scholar databases using the following keywords: non-suicidal self-injury, NSSI, naltrexone, LDN, self-injury, self-harm, and time descriptors 1982–2022. The review was based on information reported in original papers, review articles and case reports. The quality of the article was assessed using the six-point Scale for the Assessment of Narrative Review Articles (SANRA).

Results. Studies conducted on animal models show that use of LDN can prevent habitual self-injury. As far as the possibility of clinical use of LDN in treatment of NSSI is concerned, results of a relatively small number of studies conducted so far confirm the efficacy of using naltrexone 25–50 mg/day to decrease or eliminate self-injurious behaviors in NSSI patients.

Conclusions. The use of LDN in treatment of NSSI seems to be a promising clinical option, whose efficacy, however, needs to be corroborated in a larger number of randomized placebo-controlled clinical trials.

Key words: non-suicidal self-injury, self-injurious behavior, naltrexone

Introduction

Non-suicidal self-injury (NSSI) is a form of self-destructive behavior, frequently observed in patients with mental disorders, which poses a serious threat to the health

and sometimes even the lives of those people and considerably reduces their quality of life. The topic of NSSI has given rise to numerous controversies and disputes among specialists. In the past, NSSI was often viewed as transient behavior, an element of youthful rebellion typical of adolescence [1]. Today, the disorder is very common among the developmental age population, especially adolescents. The lifetime prevalence of NSSI is approximately 15% to 20%, with the trend increasing from year to year [1–4]. The search for pharmacological treatment options for NSSI is highly justified on clinical grounds, especially that it has been reported that at least 5% of the people who self-injure, commit suicide [5, 6].

The goal of the present paper was to review previous animal and human studies on the possibility of using low doses of naltrexone (LDN) in the treatment of NSSI.

Method

Publically available Polish – and English-language literature on NSSI was reviewed by searching the PubMed/MEDLINE and Google Scholar databases using the following keywords: non-suicidal self-injury, NSSI, naltrexone, LDN, self-injury, self-harm, and the time descriptors 1982–2022. The review was based on information contained in original papers, review articles and case reports. The six-item SANRA scale (Scale for the Assessment of Narrative Review Articles) and a seven-point checklist were used to maintain the quality of the narrative review. The use of SANRA allows the structure of the article to be maintained by including the following components: an explanation of the importance of the review and a statement of its aims, a description of the literature search, a reference to key statements, scientific reasoning and the presentation of relevant and appropriate data on the article's endpoints. By using a seven-point checklist, it is possible to evaluate the article as a narrative review, identifying the purpose and implications for further research or clinical practice. In addition, it allows for the identification of key questions about the paper, the literature search process and its quality [7, 8].

Results

For the sake of clarity, the article has been divided into the following subsections: Definition of non-suicidal self-injury (NSSI), Hypotheses of the development of NSSI, Hypothesis of NSSI addiction associated with opioid system dysfunction (a. diminished levels of endogenous opioids, b. elevated levels of endogenous opioids), Pharmacological treatment of NSSI using opioid receptor antagonists (a. NSSI therapy using LDN in the *rhesus* macaque (*Macaca mulatta*), b. treatment of NSSI in humans with LDN use, including case reports of LDN use and randomized trials with LDN use).

Definition of non-suicidal self-injury

There are two basic types of self-injury: suicidal self-injury (SSI) and non-suicidal self-injury (NSSI), the latter of which is the subject of the present paper [9]. The basic criterion that distinguishes these two categories is the presence of the desire to die. People who attempt suicide, according to the WHO definition, deliberately want to end their lives. In legal terms, suicidal death is the result of a direct or indirect act or neglect on the part of the victim, who is fully aware of the consequences of his actions [9].

NSSI is defined differently by many authors. Favazza [2] considers self-injury to be an act of intentional and direct destruction or alteration of one's own body tissues without a conscious intent to die, which is severe enough to cause damage [10]. Gratz [11] adds to this definition by saying that the act is repeated and the victim is aware of the desire to hurt themselves and the consequences that this behavior brings [10]. Babiker and Arnold [12] characterize NSSI as deliberate infliction of pain or injury on one's own body that is not intended to lead to death [6, 10]. It is worth noting that not every act of inflicting pain on oneself results in the damage of one's own tissues [13]. It must also be underlined that NSSI is not the same as socially and culturally accepted forms of body tissue modification, such as piercing or tattooing, or religiously motivated body injury [6, 10, 14].

NSSI can range from relatively mild acts, such as scratching the skin, interfering with wound healing, or pulling one's hair, to severe acts, such as cutting or burning the skin, or punching oneself [6, 9, 10, 12]. Wounds are most commonly inflicted with a knife, needle, razor blade or another sharp object on the forearm area (dorsal side) and the front surface of the thighs. Self-inflicted wounds can become deeper and more numerous; they may bleed and leave a characteristic pattern of scars that are about 1–2 cm apart [11, 15]. Other acts of NSSI include pricking with a needle or a sharp pointed knife, burning the skin with a cigarette end, or rubbing an elastic band against the skin to create a burn [9, 11, 13, 16].

Mental disorders such as borderline personality disorder (BPD) should also be considered in the differential diagnosis of NSSI [11]. NSSI used to be considered a symptom of this personality disorder for a very long time, even though people with eating disorders or substance addiction also often exhibit such behaviors [4, 17].

Hypotheses of the development of NSSI

There are various hypotheses regarding the reasons why people engage in self-injurious behaviors (SIB). They range from psychodynamic models (the hostility reduction hypothesis, or the anxiety hypothesis) [18], through models related to neurotransmitters (dopaminergic, serotonergic and opioidergic models) [19], to behavioral models (positive reinforcement, which may result from self-punishment and may put one in a pleasant and relaxed state, draw the attention of selected people or be

an expression of anger; and negative reinforcement, which results from the regulation of affect and reducing negative emotions and disturbing thoughts, including suicidal thoughts) [18, 19].

Behavioral addiction can be defined as continuing a given behavior despite its obviously adverse consequences, as an effect of a loss of control [18]. This type of addiction is quite widespread and has many features in common with substance addiction. Behavioral addictions and substance addictions also have a common neurobiological and genetic background (tolerance, withdrawal symptoms, relapses) [3, 6, 12, 14, 17, 20]. Impaired functioning of the dopaminergic system and the stress-related hypothalamic-pituitary-adrenal (HPA) axis may contribute to the formation of NSSI addiction.

Among the many hypotheses concerning the psychological, environmental as well as neurobiological causes of NSSI addiction, there is a hypothesis that connects it with dysfunctions of the endogenous opioid system [12, 16, 19–22].

Hypothesis of NSSI addiction associated with opioid system dysfunction

Increased release of endogenous opioids (mainly beta-endorphins) has been observed following stressful events [20]. For example, chronic stress in mice can lead to the development of opioid dependence, while prolonged injuring increases met-enkephalin levels [23]. Studies also confirm that all these systems are interconnected since both beta-endorphins and adrenocorticotropic hormone (ACTH), related to the HPA axis, come from a common precursor – pro-opiomelanocortin (POMC) [20, 24].

It is also worth noting that, according to some studies, dysfunctions of the serotonin and dopaminergic systems are more often associated with suicidal behavior, while impairments of the opioid system play an essential role in non-suicidal SIB [9, 20, 22]. Analyzing the results of research on this hypothesis, one can assume that the endogenous opioid system plays a considerable role in relieving mental pain in persons exhibiting non-suicidal SIB. The increased levels of endogenous opioids in the body of a person who engages in NSSI may result in the development of tolerance and then dependence on these substances in susceptible individuals [17, 22, 25].

During an act of self-injury, endogenous opioids are released, mainly those that cause analgesia and reduce stress levels. It has been speculated that the opioid system is also involved in the elimination of mental pain [19, 22, 26, 27]. It has also been suggested that people who self-injure may have lower levels of endogenous opioids, which results in a greater tolerance to pain and allows them to engage in NSSI behaviors habitually [17, 20].

The proposed opioid system dysfunctions associated with NSSI include two states:

a) diminished levels of endogenous opioids

A higher level of pain tolerance in people who self-injure has been observed in many studies. Stanley et al. [22] found that the resting levels of beta-endorphins

and enkephalins in the cerebrospinal fluid were reduced in people engaging in NSSI compared to the control group [17, 20, 22, 24]. Moreover, numerous authors have found diminished levels of endogenous opioids in peripheral tissues and the cerebrospinal fluid of patients suffering from mental disorders of which self-injury is symptomatic, such as autism spectrum disorders, BPD, Lesch-Nyhan syndrome, Prader-Willi syndrome, fragile X syndrome, or Cornelia de Lange syndrome. There are also studies which demonstrate that patients with eating disorders, both bulimia and anorexia nervosa, also fall within this group [11, 19, 22, 26]. Often, opioid deficiency is an effect of a childhood trauma, such as abuse, neglect, or loss [19]. Opioid levels may also be genetically determined [21, 26, 28].

The endogenous opioids beta-endorphin and met-enkephalin are antagonists of mu – and delta-opioid receptors, respectively. They take part in the perception of physical pain and so-called stress-induced analgesia [21, 27, 28]. There are also studies that have observed changes in mu-opioid neurotransmission in response to an experimentally-induced negative affective state [22]. Since the mechanisms involved in NSSI are related to the opioid system, these behaviors can be viewed as addictive ones [16, 17, 21, 25]. When a person is exposed to chronic stress, the response of their opioid system to acute stress may be impaired. Severe physical or psychological trauma, in turn, may result in a chronic deficiency of endogenous opioids or habituation to their high levels in the body. Such patients may need elevated concentrations of endogenous opioids to restore balance to their body, and they can achieve this by engaging in NSSI.

b) Elevated levels of endogenous opioids

According to the pain hypothesis, the opioid system in people who self-injure malfunctions by secreting excessive amounts of opioids. The increased concentration of these substances in the body leads to an increase in the pain threshold, thus weakening or completely eliminating the perception of pain stimuli. Self-injury raises the level of endogenous opioids, restoring in this way homeostasis and an appropriate level of perception of body sensations [15, 17, 21, 22].

Another hypothesis assumes that the biological basis of self-injury is a secondary increase in the concentration of enkephalins, caused by an individual's life experiences [19, 21, 28, 29]. As an effect of overstimulation of the opioid system, the increased tolerance to the release of opioids into the body enhances the need to constantly maintain higher than normal levels of these substances, which may result in the development of dependence.

There are also studies which indicate that mu-opioid receptors take part in suppressing stress reactions to threatening and harmful stimuli and separating the infant from the mother [19, 21, 28]. There are theories which hold that the increase in negative emotions before NSSI is analogous to the withdrawal symptoms experienced by people addicted to drugs. It has also been shown that people engaging in NSSI and

those addicted to drugs have a similar age of onset and that both types of behavior are compulsive and provide relief [3, 17, 20].

Pharmacological treatment of NSSI using opioid receptor antagonists

In connection with the mechanism of the development of dependence on NSSI described above, attempts have been made to develop an effective form of pharmacotherapy for this condition, which could be used to support the therapeutic interventions in patients who habitually self-injure.

Given the fact that the endogenous opioid system can be viewed as playing a crucial role in habitual NSSI, the use of an opioid receptor antagonist may be therapeutically justified. The use of opioid receptor antagonists reduces the effect of endogenous opioids on mu and delta receptors, which are involved in the process of pain perception in NSSI, and can thus suppress these behaviors [30, 31]. Following the discovery of the involvement of endogenous opioids in the dependence on NSSI, attempts have been made to treat these self-destructive behaviors pharmacologically using opioid antagonists, whose activity opposes the action of the endogenous opioids secreted during self-injury [19, 29–32].

An ideal drug of this type should have good tolerability, an efficacy leading to a reduction in the severity of NSSI, and therapeutic benefits that should be maintained after discontinuation of the drug. Unfortunately, there is no drug yet that meets these criteria, but the use of opioid antagonists seems to be a promising approach [30, 31, 33]. Opioid receptor antagonists are substances which block one or more types of opioid receptors in the CNS or the peripheral nervous system. Opioid receptors are G protein-coupled transmembrane proteins which, when stimulated by an opioid, initiate signal transduction in the cell. There are three types of opioid receptors – mu, delta and kappa. Stimulation of mu receptors leads to respiratory depression, analgesia and euphoria. The highest concentrations of mu receptors are found in the smooth muscles of the bronchi and in the digestive tract. Delta and kappa receptors have a strong analgesic effect; delta receptors also modulate the activity of mu receptors, while kappa receptors are involved in the formation of states such as hallucinations, dissociation or dysphoria [33, 34].

Centrally acting opioid receptor antagonists, which competitively block opioid receptors, are potent inhibitors with an increased affinity for the mu receptor [30, 31, 33, 34]. Mu receptor antagonism stimulates the respiratory center, increases alertness, causes mydriasis and interrupts the states of analgesia and euphoria – an effect that is crucial in the treatment of NSSI. Peripherally acting opioid receptor antagonists do not easily cross the blood–brain barrier, but they do strongly block peripheral mu receptors, which may lead to an acute pain crisis [19, 22, 33, 34].

The best-studied opioid antagonists are naloxone and naltrexone, both of which are used in the pharmacotherapy of NSSI [30, 31, 35, 36]. Naloxone is a pure opioid

receptor antagonist, available in intravenous, intramuscular and intranasal formulations [33–35]. It is used in the treatment of opioid overdose and in the reversal of respiratory depression associated with opioid abuse. It has no pharmacological effect itself. There is no risk of developing tolerance or dependence. Naloxone is metabolized in the liver and excreted in the urine [35].

Naltrexone is a semi-synthetic, long-acting specific opioid antagonist with slight agonist activity at kappa opioid receptors in the brain and spinal cord and very weak agonist activity at delta receptors [36]. It competitively binds to receptors in both the CNS and the peripheral nervous system, blocking the access of opioids to these receptors. In Poland, naltrexone is available in oral formulations [36], while naloxone is available in injectable formulations [35]; both drugs are absorbed very quickly [35, 36]. Naltrexone undergoes first-pass metabolism in the liver, independently of cytochrome P450 enzymes, to form its active metabolite [33, 34]. It is used in alcohol and opioid abuse disorders as maintenance treatment [33, 36]. It does not cause physical or psychological dependence, and patients do not develop tolerance to its effects [36]. It is metabolized in the liver to active and inactive metabolites and, similarly to naloxone, is excreted in the urine [33–36].

a) NSSI therapy using LDN in the *rhesus* macaque *(Macaca mulatta)*

To more thoroughly investigate the phenomenon of addiction to self-injury, studies were conducted in primates who engaged in NSSI behaviors and the results were discussed in the context of the hypotheses put forward for humans who self-injure [19]. Humans and *rhesus* macaques have similar life expectancy, social structure, level of cognitive processes, brain–body volume ratio, and manual dexterity [37]. As they grow up, macaques go through similar stages of development as humans do [19]. All of these features suggest that models based on these animals can provide reliable information on human behavior, including NSSI.

The endogenous opioid system is involved in NSSI behaviors, as evidenced, for example, by reports of reduced pain sensitivity during NSSI episodes and the fact that endogenous opioid levels are altered in individuals engaging in NSSI [19, 29]. *Rhesus* monkeys that engage in non-suicidal behavior preferentially self-injure those body areas that may be associated with analgesia acupuncture. A similar relationship has been found in people with NSSI [19, 37]. Analgesia induced during acupuncture in humans is explained in terms of the action of the opioid system, especially met-enkephalin; monkeys also exhibit acupuncture-induced analgesia [19, 37]. These findings suggest that monkeys that engage in NSSI may be doing so to self-stimulate. Baseline opioid activity in the periphery and CNS was also tested in the investigated primates. Following self-injury, the monkeys had reduced blood plasma levels of beta-endorphin and cerebrospinal fluid levels of met-enkephalin [19, 29, 37].

These findings are consistent with research on the levels of endogenous opioids in individuals with NSSI, and provide further support for the hypothesis that addiction to NSSI is caused by endogenous opioid dependence [19, 37]. There

are many similarities between NSSI in humans and *rhesus* monkeys. The most important of them are the forms of SIB – biting, hitting, scratching the skin; the only exceptions are cutting and burning the skin. In both humans and monkeys, self-harm behaviors appear spontaneously, without being induced, usually during puberty. Both monkeys and humans self-injure to varying degrees. Self-injury in monkeys may require veterinary treatment, and in humans – medical care or hospitalization [29, 37].

In the case of *rhesus* macaques which engaged in NSSI, the use of naltrexone as an opioid receptor antagonist brought promising results [29]. By stimulating the endogenous opioid system, NSSI produces feelings of relaxation and euphoria, which can lead to the development of an addiction. Additionally, these behaviors are often ritual or stereotyped [29, 37]. In studies conducted on macaques, naltrexone reduced the induction of analgesia and euphoria by NSSI via blocking opioid receptors [33, 38, 39]. The drug decreased the occurrence of SIB. In a study by Kempf et al. [29], seven out of eight macaques responded positively to treatment with extended-release naltrexone administered at a dose of 20 mg/kg. In the group of the seven macaques included in the analysis, a decrease in the frequency of self-injury was observed in six (86%) subjects. Among the monkeys which responded positively to naltrexone treatment, half showed a 50% reduction in the frequency of NSSI.

The positive effects of the therapy were maintained throughout a two-week follow-up period which started 110–200 days after the last injection of naltrexone [29]. Extended-release naltrexone was well tolerated by the macaques, with no injection site reactions or adverse drug reactions observed. Body mass remained stable throughout the study [19, 29, 37].

b) Treatment of NSSI in humans with LDN use

In cases of moderate to severe NSSI in humans, therapeutic modalities such as behavioral and psychopharmacological interventions are helpful to some extent only [30, 31]. Different classes of drugs have been studied in the treatment of NSSI, with antipsychotics likely being the most commonly used medication [30, 31]. Attempts at treating NSSI pharmacologically with the use of opioid antagonists have been made for many years now. An extra advantage of opioid antagonist therapy is the fact that no significant side effects have been observed during the studies.

Case reports of LDN use

The first case of using an opioid antagonist in the treatment of BPD was reported in 1997 [38, 40]. The patient, who was additionally treated for recurrent depression and alcohol dependence after severe trauma, repeatedly self-injured herself in order to reduce tension. Addition of naltrexone 50mg/day to previously ineffective pharma-

cological treatment resulted in a reduction in compulsive NSSI, alcohol craving, and relapse rate of the harmful behaviors [41].

In 2000, a case was reported of a woman with BPD who responded to the addition of naltrexone to her pharmacological treatment with a reduction in NSSI symptoms [42].

Griengl et al. [43] described the case of a man who engaged in severe NSSI by injecting inflammatory substances, such as urine, into his skin and muscles as a reaction to a diagnosis of dysthymia. Naltrexone 50 mg/day was successfully used as an adjunctive treatment to previous, largely futile, attempts at treating the disorder with valproic acid, levomepromazine, sertraline, doxepin, and risperidone. In this case, the patient ceased to engage in NSSI and the abstinence was maintained over 32 weeks of follow-up.

A case of a three-year-old boy who displayed self-injury behavior unresponsive to behavioral intervention has also been described. The initial symptom was head banging, which then evolved into repetitive ear slapping, which resulted in bleeding fissures behind the ears; the boy also bit his arms. Treatment with 12.5 mg/day (0.98 mg/kg/day) naltrexone was started. After two weeks, self-injury behavior was observed to have worsened to the point where a wound had developed on the boy's left arm which required pediatric intervention, and the boy became more irritable. It was decided to increase the dose of naltrexone, under close monitoring, to 25 mg/day (1.97 mg/kg/day), and the NSSI gradually improved over the next month [44].

Another case was that of a 50-year-old woman who, after taking naltrexone, stopped compulsively scratching her skin, which had earlier led to chronic dermatitis. After using the drug, the frequency of self-injury decreased and the inflammation of the skin subsided [45].

In 2011, a case was reported of a 32-year-old woman who had been admitted to hospital more than 50 times over an 8-year period, mostly due to severe cutting behavior which posed a serious risk to her health. She was diagnosed with recurrent major depressive disorder superimposed on BPD, with transient psychotic episodes. The patient was treated with 25 mg/day of naltrexone, titrated up to 50 mg after 1 month. A reduction of symptoms was observed after five months of continuous treatment with naltrexone, with only one episode of superficial cutting in the six-month follow-up period [46].

In 2022, a case of an eight-year-old boy diagnosed with seizure disorder with moderate intellectual disability was described. The boy presented with complaints of biting on hands, forearms and lips. The self-biting episodes were severe and progressively worsening, and the child also exhibited episodes of head banging. Treatment with oxcarbazepine (600 mg/day) was followed by naltrexone, initially at a dose of 12.5 mg/day, increased to 25 mg/day after 10 days. The child showed a significant improvement in the frequency and severity of self-biting and head

banging during treatment. His mental state did not deteriorate afterwards. The results of liver function tests performed as part of the follow-up were also within the normal range [47].

Randomized trials with LDN use

A cohort of five patients with BPD was followed in a three-week study. The patients received naltrexone starting from week two of the study. The results showed a decrease in the intensity of self-injurious thoughts compared to the period after discontinuation of opioid antagonist treatment. All patients exhibited SIB at the beginning of the study, and only one person self-injured while receiving naltrexone. The patients were treated with naltrexone for only one week, followed by a one-week post-treatment period, in which all five patients experienced a relapse of symptoms [48]. This shows that the period of active intervention may have been too short to determine the efficacy of the drug.

Another study was conducted in a group of seven patients who experienced analgesia and reduced dysphoria during NSSI [49]. In that study, the subjects received oral naltrexone at a dose of 50 mg/day, and the mean follow-up period was 10 weeks. Six of the seven patients ceased to engage in NSSI completely while on naltrexone, and all seven showed a reduction in the number of NSSI acts. Four out of the seven patients attempted NSSI, and all patients reported recession of analgesia with simultaneous reduction of dysphoria. After interruption of naltrexone treatment, two patients experienced a rapid recurrence of NSSI [49].

Discussion

The results of animal model studies and findings from clinical trials indicate that low doses of naltrexone, from 12.5 mg/day to 50 mg/day, may exert a beneficial therapeutic effect in the treatment of NSSI. The numerous theories that explain engagement in NSSI lead to the conclusion that self-injury behavior is very complex. Often, the choice of adequate treatment for an individual patient seems difficult; however, the growing number of studies in which opioid receptor antagonists, such as naltrexone, have been successfully used to treat NSSI raises hopes of finding an effective treatment for this condition in some patients.

Opioid receptor antagonists compete with endogenous opioids for binding sites, but do not activate opioid receptors, as a result of which they counteract the reinforcement of self-aggressive behaviors, thus allowing to reduce the severity of NSSI or even completely eliminate it.

It should also be emphasized that they have relatively few dangerous or burdensome side effects. Naltrexone may cause gastrointestinal irritation symptoms such as diarrhea, abdominal cramps, nausea and vomiting, and in some studies it has been observed to cause clinically insignificant increases in blood pressure [50].

There are limited data on naltrexone overdose in humans. Cases of hepatitis and hepatic dysfunction have been observed. The use of naltrexone may give rise to a periodic asymptomatic increase in the activity of hepatic transaminases [50]. There have been reports of depression, suicidal ideation and suicide attempts. Patients should be monitored for those symptoms [51].

The conclusions are limited primarily by the small number of clinical trials and their character. Most reports are case studies, and few are well-design randomized double-blind studies. In addition, these investigations were conducted in small groups of patients, from one to seven, and the follow-up period was relatively short.

The ultimate efficacy of LDN, their therapeutic value in short-term and long-term therapy, and their long-term safety need to be confirmed in further studies, especially randomized placebo-controlled studies conducted in larger cohorts.

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Address: Agnieszka Banaszek
Student Scientific Club at the I Department of Psychiatry, Psychotherapy and Early Intervention
Medical University of Lublin
e-mail: banaszek.agnieszka14@gmail.com