Naltrexone for the treatment of self-injurious behaviour

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Self-injurious behaviour (SIB), or self-mutilation (SM), is a potentially dangerous and anxiety-provoking condition. SM was recognised as early as the 5th century BC, there are some variations in definition, and Favazza described SM as "deliberate, direct destruction or alteration of body tissue without conscious suicidal intent".[1,2] It can present in various forms including head-banging, self-cutting, self-choking, self-biting, self-scratching, hair pulling, hand mouthing and many others.[3] The extreme forms described were eye enucleation and castration.[1]

SIB can be a manifestation of a wide variety of psychiatric disorders including intellectual and developmental disability (IDD),[4] schizophrenia,[1] borderline personality disorder,[5-8] pervasive developmental disorder,[9] stereotypic movement disorder[10] and Tourette disorder.[11,12] It is also quite commonly found in people with specific genetic conditions or syndromes such as fragile X syndrome, Prader–Willi syndrome, Cornelia de Lange syndrome, Smith–Magenis syndrome and Lesh–Nyhan syndrome.[13-16] SIB is seen more frequently in individuals with communication deficits, restrictive adaptive skills, and severe or profound intellectual disability (ID).[17-19]

The prevalence of SIB varies depending on the methods and criteria used; for example, a community survey of SIB among developmentally disabled children and adolescents done by Griffin found that 2.6%, of the students exhibited at least one type of SIB during the preceding 12 months. [20] The studies have found higher incidences of SIB (27.7- 50%) in children with comorbid autism. Risk factors for SIBs included lower chronological age, associated perinatal conditions, a higher level of autism and greater impairment in self-care skills.[21]

Untreated SIB has a major effect on various domains of quality of life, including self-care, vocational opportunities, social involvement and learning experiences.[22,23] Untreated SIB can also lead to an increase in the rate of institutionalisation[24] and multiple medical issues, including death.[25]

Self-injurious behaviour in those with intellectual and developmental disability is often a complex and chronic condition that is challenging to treat. Treatment depends on the examination of the causal contributors including a behavioural analysis and consideration of the aetiology of SIB and other risk factors. In those who are non-verbal this includes full medical examination, including examination under anaesthetic for 'silent' causes of pain. A comprehensive psychotherapeutic treatment plan may include various behavioural interventions such as social skills training[26] and reinforcement-based strategies to increase more appropri-

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ate behaviours.[3] Extinction and punishment-based strategies, for example, aversive procedures,[2,3,27-30] have been used especially for people with intellectual disabilities and extreme self-injury. Some aversive treatments need ethical review to be appropriate to consider the impact of self-jury versus the impact of treatment.[2,23]

Pharmacological interventions are commonly used alone or with behaviour therapies. Antipsychotic medications are the most frequently used.[31-35] Other medications which have been used in treatment of SIB include selective serotonin reuptake inhibitors,[35-37] lithium,[35,38] tricyclic antidepressants,[39] beta-blockers (propranolol and pindolol),[40-42] tryptophan,[43] L-dopa,[14,44] buspirone,[45,46] clozapine,[47] clonidine,[35,48] guanfacine,[40] monoamine oxidase inhibitor inhibitors[40] and the opioid antagonists (naloxone and naltrexone). Naloxone and naltrexone have drawn attention due to positive results in severe cases of SIB unresponsive to multiple modalities of treatments.[3,9,10,24,49-65] In a very severe refractory case of SIB, psychosurgery, including cingulotomy and limbic leucotomy, decreased the severity and frequency of SIB in an adolescent boy with Tourette disorder after the failure of other treatments.[12]

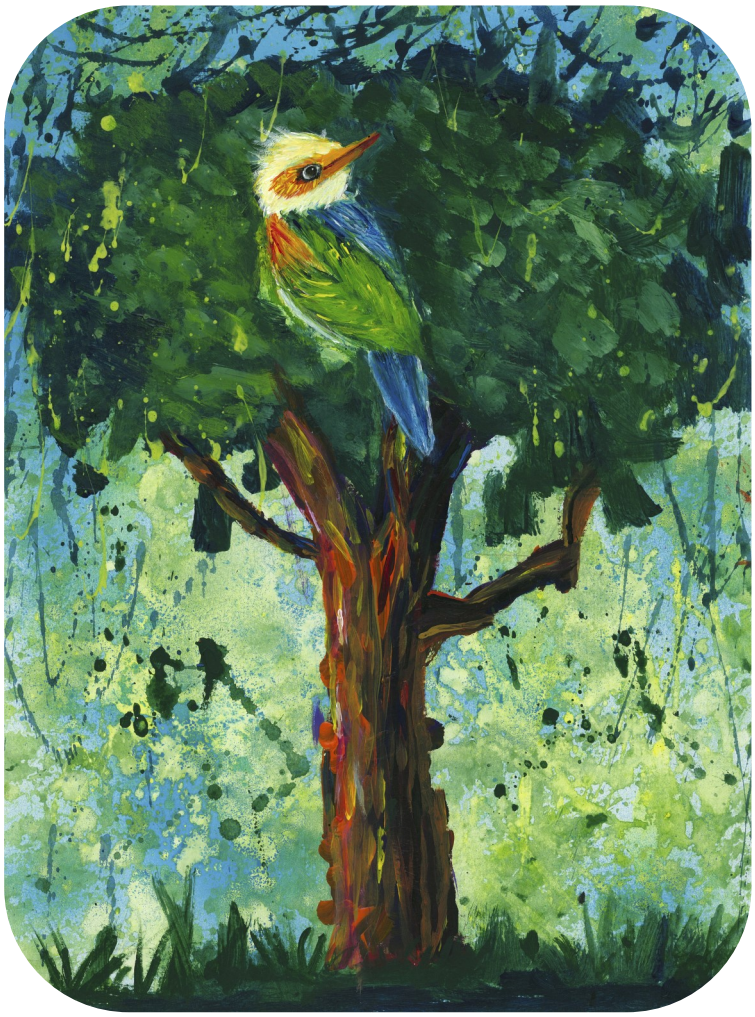
What is naltrexone?

Naltrexone is a specific, competitive, long-acting, non-addictive oral opiate antagonist that highly binds to the mu-receptor, followed by kappa and delta receptors, thus hindering the activity of opiates.[8,66] Although naltrexone was first synthesised in 1963 and was approved for medical use in the United States in 1984,[67] it was not reported in the literature as a treatment for SIB until 1985.[51]

Pharmacology and pharmacodynamics

After absorption from the gastrointestinal tract, naltrexone is extensively metabolised in the liver.[66] It has a major active metabolite (6-β-naltrexol) which may also have weak opioid antagonist activity.[66] Peak plasma concentrations of naltrexone and 6-β-naltrexol occur about 1 hour after oral dose. The elimination half-life of oral naltrexone is about four hours, and of 6-β-naltrexol is about 13 hours.[66] However, Verebey et al. reported a possible prolonged pharmacological effect (24–96 hours) which may be secondary to the slow release of tissue-bound naltrexone and partial reabsorption by the kidney.[68]

The side effects reported with naltrexone include increased or decreased appetite, oedema, toothache, ejaculatory difficulties, reduced potency, depression and suicidal ideation.[66] Reversible hepatotoxicity has been reported after the use of higher doses (e.g.



300 mg/day or more) for extended periods.[66,67] Naltrexone is contraindicated in patients who have been treated with opioid analgesic for a painful condition as naltrexone will decrease analgesia.[69] Naltrexone is also contraindicated in acute hepatitis, liver failure or with elevation of liver enzymes (>3 times). Dose reduction may be required with mild renal impairment but naltrexone should be avoided if impairment is severe as risk of hepatotoxicity may be increased.[70] There has been safety testing in children down to the age of 2-3 years.[10 71]

Clinical use

In Australia, naltrexone hydrochloride (ReVia) requires an authority prescription and is only available under the Pharmaceutical Benefits Scheme[72] for alcohol dependence. However, naltrexone has been used effectively for other clinical conditions, for example, opioid dependence, obesity, ASD,[10,51] SIB that is unresponsive to pharmacological and behaviour treatments,[24,51,73] and pathological gambling.[74]Naltrexone may improve hyperactivity and restlessness in children with Autism[55]. Interestingly naltrexone is used as modified release preparation in the management of obesity in patients with BMI of 30 kg/m2 or greater with antidepressant Bupropion along with exercise and dietary modification.[66] There is also some evidence of improvement in dissociation and SIB in borderline per-

sonality disorder.[8,51,66,75,76] Naltrexone is preferred over naloxone due to its high potency, ease of oral administration and longer duration of action.[51,66] As naltrexone is a potent opioid blocker naltrexone should not be given prior to surgery where opioids may utilized for pain relief. The effects of naltrexone are still present up to 3 days after ceasing to take.

Physically the naltrexone tablets are bitter tasting which can be a problem for some children. The taste can be masked by using a product called GLOUP which can help lubricate the throat and help the tablet slide down. Commercial flavorings from a Compounding Chemist can be added to a solution of the dispersed tablet in water. The tablets can be dispersed in 20ml and takes up to 2 minutes to dissolve and also Compounding Pharmacies will make up bespoke mixtures. Recent literature supports the use of naltrexone in adults with SIB.[24,73] However, there is a lack of up-to-date evidence to guide naltrexone safety and efficacy for SIB in children and adolescents (the most recent review was done in 2004 in the 7–67-year age group).

Previous reviews evaluating the safety and efficacy of naltrexone

Buzan et al.[51] performed the first published literature review for the use of an opiate antagonist for recurrent SIB. They included 31 case reports with a total of 98 patients (5–67 years) and reported a dose-dependent improvement up to 1.5 mg/kg/day. Of these 98 patients, 89 were developmentally disabled or autistic.[51] No hepatic or significant adverse effects were noted in SIB patients.[51]

Symons et al. conducted the first quantitative synthesis of peer-reviewed literature from 1983 to 2003 on the efficacy of naltrexone treatment on SIB. The review included 27 research articles involving 86 subjects (7–67 years) with 85% of them double-blind, 9% open-label and 6% single-blind studies. SIB reduced in 80% of subjects, and in 47% of subjects, SIB reduced by 50% or greater. The most common dose evaluated was 50 mg (1 mg/kg).[24]

A systematic review by Roy et al. in 2015 evaluated the efficacy of opioid antagonists for SIB in adults with ID. They included ten RCTs with a total of 124 participants (91 males, 33 females). Eight of the 10 studies reported a reduction in the frequency of SIB, and 61 of the 124 participants showed statistically significant improvements. The naltrexone dose varied from 0.25 mg/kg/day to 2 mg/kg/day, and 9% of the participants reported minor side effects including nausea, tiredness, sedation, loss of appetite, weight loss and mild liver abnormalities.[50]

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Some individual studies in children and adolescents:

The Bernstein et al. study was the first documented single-case trial using naloxone and oral naltrexone, in an 18-year-old intellectually impaired adolescent. Oral naltrexone reduced SIB by 33%. The reduction in SIB persisted despite no further naltrexone treatment.[65] The study by Barrett et al. was the first double blind placebo controlled (DBPC) study, which showed positive effects on SIB even with smaller doses of naltrexone (at doses of up to 50 mg/day) after an initial increase of SIB with naloxone. [52]

Walters et al. investigated naltrexone in a 14-year-old autistic and IDD boy (DBPC). Results indicated a marked decrease in SIB and increase in social relatedness.[53]

Benjamin et al. found naltrexone useful for severe SIB of a nine-year-old boy with IDD and Prader–Willi syndrome. The combined treatment of naltrexone with a behavioural intervention yielded marked improvement in weight control, skin picking and oppositional behaviour. The associated weight loss raised the hypothesis that obesity may be related to excessive endorphins and that opioid antagonists may therefore have a role in treating obesity.[58]

Johnson et al. compared the effects of behavioural treatment and naltrexone to reduce the SIB of a 7-year-old boy with severe IDD and autistic disorder, and found that the combined use of naltrexone, splint-fading, differential reinforcement, and a brief hand restraint was effective in reducing severe SIB to zero.[57]

In conclusion, although the research is limited in the child and adolescent population, due to the relatively benign side-effect profile of naltrexone and the reported benefits in the previous studies, clinicians may consider this as an option for severe, refractory SIB. Such consideration would require rigorous assessment and treatment of medical and psychiatric comorbidities, and exhaustion of other treatment modalities, including behavioural treatments. Clear documentation of any off-label use is recommended, including noting the limitations of the current evidence and a record of informed consent obtained from the patient or caregiver

after explanation of the purpose, side effects, risks and benefits of naltrexone treatment.[77]

Note: This brief report is derived from a comprehensive literature review by Vinita Bansal, which is available on request.

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