

20. Youdim MBH, Yehuda S, Ben-Shachar D, et al: Behavioral and brain biochemical changes in iron deficient rats: The involvement of iron and dopamine receptor function. In Pollitt E, Leibel RL (eds): *Iron Deficiency: Brain Biochemistry and Behavior*. New York, Raven, 1982, pp 39–56
21. Young IR, Hall AS, Pallis CA, et al: Nuclear magnetic resonance imaging of the brain in multiple sclerosis. *Lancet* 2:1063–1066, 1981

## Naltrexone Decreases Self-Injurious Behavior

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The effect of naltrexone (0.5, 1.0, 1.5, and 2.0 mg/kg) on the frequency of self-injurious behavior (SIB) was investigated in three male adolescents. The frequency of total SIB was reduced significantly in all three subjects; dose-dependent decreases (at 0.5, 1.0, and 1.5 mg/kg) in SIB frequency were observed in the two mentally retarded subjects. These data suggest a role for opioid peptides in SIB.

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Self-injurious behavior (SIB) is a severe behavioral problem. Enhanced brain opioid activity may underlie SIB [1–3], especially given the evidence linking opioids and antinociception [4, 5]. In normal individuals, pain-producing behavior stops quickly. In self-injurious individuals, SIB may not induce pain, since these individuals may be in an opioid analgesic state. Accordingly, there may be little motivation to terminate SIB.

The aim of the present study was to evaluate the acute effects of the opioid receptor antagonist, naltrexone, on the frequency of SIB in three self-injurious

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male adolescents. We chose to test only this small sample because the three subjects were uniformly extremely self-injurious (greater than 35 SIB attempts per 5 minutes).

### Materials and Methods

#### Subjects

Our subjects were three males who had demonstrated 35 to 200 self-injurious attempts within a 5-minute period, and had a history of SIB for at least 5 years. Subject A. T. was a 10-year-old with severe SIB since the age of 2, profound mental retardation and infantile autism. Subject R. B. was a 17-year-old with severe SIB since the age of 7, phenylketonuria, profound mental retardation, and autistic behavior. Subject L. K. was a 17-year-old with Tourette's syndrome and normal intelligence who has displayed increasing SIB over the past 5 years. Informed consent was obtained as appropriate.

Using the criteria of the Diagnostic and Statistical Manual of Mental Disorders (1980) (DSM III) [6], two psychiatrists evaluated each subject. Each subject had a normal karyotype and was negative for conventional metabolic SIB disorders such as Lesch-Nyhan syndrome (uric acid levels were normal). Cranial computed tomographic scans and electroencephalograms were normal, and there was no evidence of seizures. Baseline heart rate, electrocardiograms, blood pressure, and axillary temperature were all normal. All drugs were discontinued at least 30 days prior to the investigation.

#### Drugs

The drug administered was naltrexone HCl (Trexan, Du Pont of Wilmington, DE). Fifty-milligram tablets were divided into quarters to approximate the appropriate mg/kg doses. A matched tablet was used as a placebo.

#### Procedure

Subjects were given the drug in increasing doses, and at least two baseline sessions preceded the drug sequence. Both A. T. and L. K. were tested on the placebo or the drug once per week (on the same day of the week). A. T. was tested as follows: placebo; placebo; 0.5, 1.0, 1.5, and 2.0 mg/kg of naltrexone; placebo. L. K.'s sequence was the same, except that the final placebo was omitted (the subject refused to participate). Because of time constraints, R. B. was tested on the placebo or the drug for two days, followed by two no-drug days. R. B.'s drug sequence was placebo; 0.5, 1.0, and 1.5 mg/kg of naltrexone; placebo. Data obtained on R. B.'s first drug day are presented in all figures.

An experimental self-injury test was used to evaluate the effects of naltrexone on SIB frequency. In this test, the frequency of a number of different types of SIB was quantitated for 5 minutes (five consecutive 1-minute trials, each separated by a 1-minute rest period, were summed to yield a single 5-minute total SIB score). The total SIB score included the frequency of facial, head, and body hits, and self-biting. SIBs were counted using hand-held tally counters. At least three raters observed the subject in the test situation or on videotape. All environmental conditions were held constant. All methods of SIB self-restraint (e.g., helmets) were removed approximately 10 minutes before testing. For R. B.,

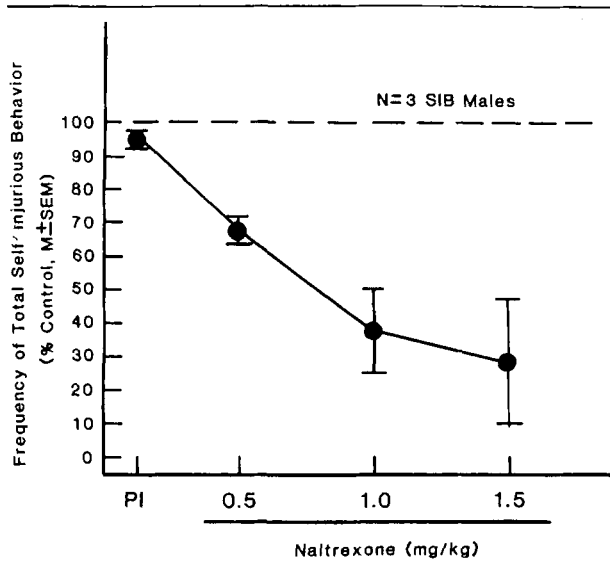


Fig 1. Mean frequency of total self-injurious behavior (SIB) for three male subjects after placebo (P1) or naltrexone (0.5, 1.0, and 1.5 mg/kg) administration. Each test period was 5 minutes in duration. Types of SIBs included head and facial hits, facial gouging, self-biting, and other SIB responses such as hand-to-leg hits and chin-to-shoulder hits.

SIB tests were conducted 1 hour (see Figs 1 and 2), and 4 hours after drug administration. Since the behavioral effects of the drug appeared to be comparable for the two time points, and since peak concentrations of naltrexone occur by 2 hours following administration [7], SIB testing of subjects A. T. and L. K. was conducted 2 hours following naltrexone administration. A neurologist, masked for the drugs used, examined each subject approximately 3 hours following drug administration.

Since this was the first time that naltrexone had been used in children, the Food and Drug Administration did not permit a double-blind design. However, by videotaping and coding each test session and using raters who were naive to the drug-test sequence, we were able to obtain drug-blind ratings for each session. Behavior was rated by three individuals, at least two of whom were blind to the drug. For each of the three subjects, interrater reliabilities were  $r \geq +0.96$ ,  $p < 0.001$ .

#### Statistical Analysis

BMDP statistical software (UCLA, CA) was used to examine appropriate one-way repeated measures analysis of variance (ANOVA). Dependent Student *t* tests (two-tailed) were used when overall *F*s (ANOVA) were statistically significant ( $p < 0.05$ ).

#### Results

Figure 1 depicts the dose-dependent decreases in frequency of total SIB induced by naltrexone for all three subjects ( $F[3, 6] = 7.52$ ,  $p < 0.05$ ; first placebo = 95.5% of baseline frequency of SIB, 0.5 mg/kg = 68.1%, 1.0 mg/kg = 38.1%, and 1.5 mg/kg = 29.0%). Compared to the first placebo trial (P1), even

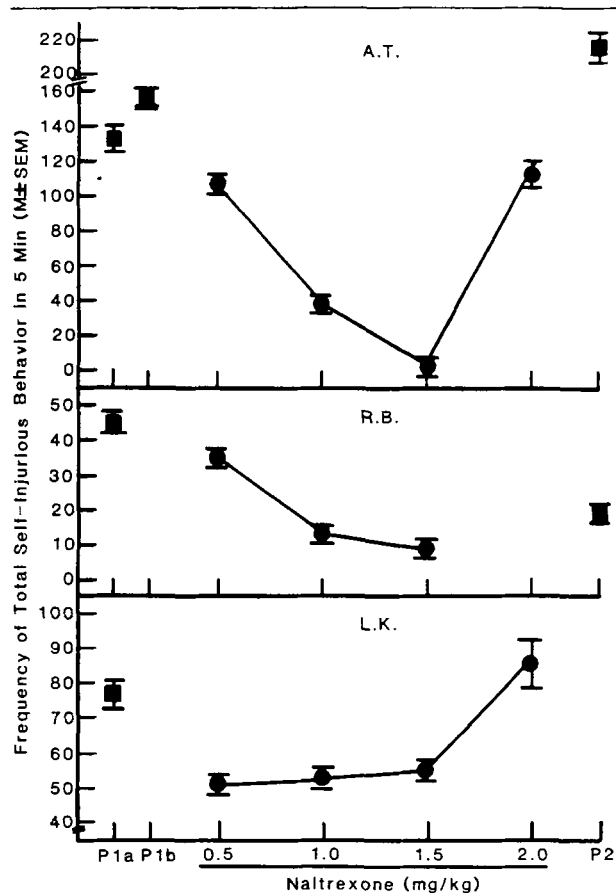


Fig 2. Frequency of total self-injurious behavior (SIB) for each of the three male subjects after placebo (P1a, P1b, and P2) or naltrexone (0.5, 1.0, 1.5, and 2.0 mg/kg) administration. Data are averaged (mean  $\pm$  SEM) for the three raters who scored the behavior. Other procedural details are provided in the caption to Figure 1.

the lowest dose (0.5 mg/kg) produced significant decreases in the frequency of SIB [ $t(2) = 8.39$ ,  $p < 0.05$ ]. Variance among subjects increased between the 0.5 and the 1.5 mg/kg doses (Fig 1) because of differences in the dose-response profiles of each subject (Fig 2). The small variance at each data point in Figure 2 reflects the exceptionally high interrater agreement in scoring SIB. Naltrexone induced decreases in total SIB for each subject. These effects were most dramatic for A. T., the most self-injurious subject, who showed a 50-fold decrease in total SIB frequency from the placebo to the 1.5 mg/kg dose. For R. B., data for day 2 of testing were similar to the dose-dependent decreases in SIB obtained on day 1 (Fig 2). L. K. was the least responsive to the drug (maximum decrease of 33% from baseline frequency of SIB). Figure 2 suggests an inverted U-shaped dose-response curve: the highest dose of naltrexone tested (2.0 mg/kg) had less of an effect (A. T.) or no effect (L. K.) on SIB frequency in comparison with the lower doses.

For A. T., SIB frequencies for all placebo trials in-

cluding predrug trials ( $134 \pm 7$  and  $156 \pm 2$  SIBs per 5 minutes) and the postdrug trials ( $217 \pm 8$ ) were higher than any of the naltrexone scores, and an increase in SIB frequency appeared to occur following the naltrexone sequence (Fig 2). However, for R. B., SIB scores for postdrug placebo trials ( $19 \pm 2$ ) were significantly lower than predrug placebo scores ( $46 \pm 2$ ) [Fig 2,  $t(2) = 11.09$ ,  $p < 0.01$ ]. The reason for the latter finding is not clear, but the possibility of a drug carryover effect exists. For example, for R. B., the postdrug placebo trial took place 72 hours after 2.0 mg/kg of naltrexone, while the interval was one week for A. T. Further evidence for a drug carryover effect is the observation that baseline SIB frequencies for R. B. were between 32 to 55 responses, values closer to the predrug trial frequencies than to the postdrug SIB frequencies (Fig 2).

### Discussion

Naloxone, a short-acting opioid receptor antagonist, has been shown to reduce SIB frequency [8, 9, but see 10], and naltrexone, a long-acting opioid antagonist, has been found to have similar inhibitory effects in this study [preliminary results in 1–3, 11]. Moreover, SIB children appear to have higher concentrations of certain opioid peptides in their cerebrospinal fluid compared to normal children [12]. This constitutes pharmacological and biochemical evidence for the opioid SIB hypothesis.

Thus, the results of the present investigation provide evidence for the potential therapeutic usefulness of an opioid receptor antagonist in the treatment of SIB. Additional testing using double-blind controlled trials and a larger group of subjects is needed. Based upon the pharmacology of naltrexone, these data indicate a role of brain opioid peptides in SIB. More specifically,  $\mu$  opioid receptors in brain are implicated, since both naltrexone and naloxone have higher affinity for  $\mu$  than  $\delta$  or  $\kappa$  opioid receptors [see 5, 13]. The lowest dose of naltrexone used here (0.5 mg/kg) corresponds to the dose needed to block completely  $\mu$ -type brain opioid receptors in human brain as measured by positron emission tomography [14].

Although all three subjects showed decreases in SIB frequency with naltrexone, there were important individual differences. The most severe SIB subject (A. T.) showed the largest decrease in SIB frequency, with 1.5 mg/kg of naltrexone reducing SIB approximately 50-fold in comparison with placebo levels. A much smaller effect (30% decrease) was observed in L. K. It is possible that there may be different subgroups of SIB individuals reflecting different biochemical etiologies. A high dose of naltrexone (2.0 mg/kg) was tested in two of the subjects (A. T. and L. K.), and surprisingly, failed to decrease SIB frequency. One explanation is that at these high doses, naltrexone may

bind in a nonspecific fashion with nonopioid receptors that compete with the opioid receptor blockade achieved with lower doses of naltrexone.

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### References

1. Herman BH, Hammock MK, Egan J, et al. Naltrexone induces dose-dependent decreases in self-injurious behavior. *Soc Neurosci Abstracts* 1985;11:468
2. Herman BH, Hammock MK, Arthur-Smith A, et al. A biochemical role for opioid peptides in self-injurious behavior. In *Scientific Proceedings of the 33rd Annual Meeting of the American Academy of Child and Adolescent Psychiatry*, Los Angeles, CA, 1986:29
3. Zelnik N, Herman BH, Hammock MK, et al. Role of opioid peptides in self-injurious behavior. *Soc Neurosci Abstracts*, 1986;12:412
4. Adams SE. Naloxone reversal of analgesia produced by brain stimulation in the human. *Pain* 1976;2:161–166
5. Herman BH, Leslie F, Goldstein A. Behavioral effects and *in vivo* degradation of intraventricularly administered dynorphin-(1-13) and D-Ala<sup>2</sup>-dynorphin-(1-11) in rats. *Life Sci* 1980; 27:883–892
6. American Psychiatric Association: *Diagnostic and Statistical Manual of Mental Disorders*, 3rd ed. Washington DC: APA, 1980
7. Verebey K. The clinical pharmacology of naltrexone: pharmacology and pharmacodynamics. In: Willette RE, Barnett G, eds. *Naltrexone: NIDA research monograph* 28. 1980:147–158
8. Gillman MA, Sandyk R. Opiatergic and dopaminergic function and Lesch-Nyhan syndrome. *Am J Psychiatry* 1985;142:1226
9. Sandman CA, Datta FC, Barron J, et al. Naloxone attenuates self-abusive behavior in developmentally disabled clients. *Appl Res Ment Retard* 1983;4:5–11
10. Richardson JS, Zaleski NA. Naloxone and self-mutilation. *Biol Psychiatry* 1983;18:99–101
11. Bernstein GA. Effects of naltrexone on self-injurious behavior: a case study. Paper presented at the 32nd meeting of the American Academy of Child Psychiatry, Proceedings for Papers and New Research Posters, San Antonio, TX, 1985
12. Gillberg C, Terenius L, Lunnerholm G. Endorphin activity in childhood psychosis. *Arch Gen Psychiatry* 1985;42:780–783
13. Chavkin C, James IF, Goldstein A. Dynorphin is a specific endogenous ligand of the *kappa* opioid receptor. *Science* 1982; 215:413–415
14. Frost JJ. Effects of drugs on opiate receptors. Paper presented at the Johns Hopkins Medical Institutions Conference on *Imaging of Living Brain Chemistry: Neuroreceptors*, Baltimore, MD, Apr 1986