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Paradoxical Effects of Serotonin and Opioids in Pemoline-Induced Self-Injurious Behavior

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TURNER, C., J. PANKSEPP, M. BEKKEDAL, C. BORKOWSKI, AND J. BURGDORF. *Paradoxical effects of serotonin and opioids in pemoline-induced self-injurious behavior.* PHARMACOL BIOCHEM BEHAV **63**(3) 361–366, 1999.—Self-injurious behavior (SIB) is a symptom of various psychiatric disorders with differing etiologies. Although no generally effective pharmacological treatment of SIB is available, subsets of individuals exhibiting SIB have been found to respond to opioid antagonists and selective serotonin reuptake inhibitors (SSRIs). The present study evaluated the efficacy of these two treatments in the pemoline-induced model of self-biting behavior (SBB) in rats. Using a factorial design, adult rats receiving daily pemoline at 100 mg/kg or the peanut oil vehicle were pretreated with either distilled water vehicle (1 cc/kg), naltrexone (1 mg/kg), or paroxetine (1 mg/kg). Each day, animals were rated on the severity of SBB and also periodically behavioral changes were evaluated using various other outcome measures. Paroxetine significantly increased the severity of SBB induced by pemoline, while naltrexone only marginally increased the SBB. These results were not expected and suggest that further studies into the role of serotonin agonists and antagonists are needed in evaluating this model. © 1999 Elsevier Science Inc.

Self-injurious behavior Pemoline Naltrexone Paroxetine Startle Activity Rats

SELF-INJURIOUS behavior (SIB) is a devastating clinical phenomenon, especially because consistently effective treatments are not available (61). Self-injurious behavior in humans consists of self-biting, head banging, face slapping, skin picking, and scratching. These behaviors are often found in conjunction with a variety of psychiatric disorders and genetic conditions (25), including autism (57,59), Lesch–Nyhan syndrome (3,13,31,32,38), Tourette's syndrome (18,47,52), and Cornelia de Lange syndrome (23,53).

Although the underlying neural causes of SIB remain poorly understood, imbalances in various neurotransmitter systems (61) including brain dopamine, serotonin, and opioid circuits, have been provisionally linked to the disorder. For instance, dopamine (DA) deficiencies may be related to the SIB present in Lesch–Nyhan patients (23,30). Likewise, DA deficiencies in animal models have been shown to lead to DA receptor supersensitivity that may promote SIB (22,53). Breese (7–9) has demonstrated that in rats, neonatal DA denervation with 6-hydroxydopamine (6-OHDA) can lead to SIB following the administration of L-DOPA. Furthermore, DA antagonists alleviate many of the symptoms of SIB in rat models (10,41), and there is provisional clinical data for similar effects in humans (11,21,24).

Serotonin (5-HT) has also been implicated in SIB, because some Lesch–Nyhan patients exhibit amelioration of SIB symptoms following the administration of 5-hydroxytryptophan, a precursor to 5-HT (37,38). In patients with de Lange syndrome, lowered whole blood serotonin levels are commonly present (23), whereas the ratio of 5-HT to DA metabolites is reduced in Tourette's syndrome (14). Because 5-HT has been so widely implicated in the expression of SIB, it is noteworthy that SSRIs have been reported to be beneficial for alleviating SIB in some mentally retarded populations, as well as patients with coexisting obsessive–compulsive disorder (43,44,54,60,62).

Endogenous opioids have also been implicated in such disorders because some reductions in SIB have been observed following treatment with opiate receptor antagonists in mentally retarded and autistic populations, but the efficacy has varied considerably. For instance, most studies report mentally retarded and autistic populations who exhibit SIB benefiting from naltrexone or naloxone; however, most studies have employed small samples in open trials (4–6,12,17,26,27,

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46,48,50,51,56,57). Three extensive, well-controlled studies have now failed to observe any clear overall benefits from naltrexone or naloxone treatment in these populations (15,55,58).

In sum, the causes and treatment of SIB remains a major clinical problem, and the following work was premised on the supposition that a close analysis of SIB in animal models should yield important information concerning potential therapeutic agents for the control of SIB. To this end, we employed the model described by Mueller (39–41) in which self-biting behavior (SBB), an animal model of human SIB, was monitored following repeated injections of pemoline, an indirect dopamine agonist, to adult rats.

We utilized the pemoline-induced SBB model to investigate the effects of chronic pretreatment with either paroxetine or naltrexone as possible prophylactics for the emergence of SBB in adult rats. To evaluate for other neurological changes produced by chronic pemoline as well as for issues related to behavioral specificity of treatments, a number of other behavioral measures were also employed, including an analysis of social investigatory behaviors, open-field activity, startle responses, and dopamine sensitization as monitored by amphetamine-induced locomotor activity. On the basis of clinical reports, it was expected that pretreatment with either paroxetine or naltrexone would reduce the severity of SBB. The results yielded the opposite pattern, and the results of this study warrants further experiments to delineate the role of serotonin in the expression of SBB.

METHOD

Animals

Male Sprague–Dawley rats born and bred in the animal care facility of Bowling Green State University were used. At the beginning of this work they were 6 months of age, and weighing 470–670 g. All procedures had been approved by the BGSU Animal Care and Use Committee.

Animals were housed under standard laboratory conditions with an average room temperature maintained within a range of 70–75°F, and a 12 L:12 D cycle, with lights on at 0730. Animals were housed in suspended wire mesh cages (25 × 18 × 18 cm), and food and water were available ad lib throughout the experiment. Sixty animals were evenly divided into six groups of three pretreatments (vehicle, naltrexone, and paroxetine) and two treatments (vehicle or pemoline), but one animal died.

Drugs

Pemoline (Sigma Chemical Co., St. Louis, MO) was suspended in warm peanut oil and administered subcutaneously (SC) at the nape of the neck, once daily for 8 consecutive days at a constant dose of 100 mg/kg. This paradigm is different from the most common paradigm in which animals are administered a single high-dose injection of pemoline. However, our goals were to observe changes not only in the emergence of SBB, but also in the maintenance of the behavior. Furthermore, this dose was selected because it only yields a modest level of SBB (36–38). Control animals received equivolumetric injections of the peanut oil, vehicle. Each of these two groups were divided randomly into three subgroups injected intraperitoneally (IP) with either naltrexone (1 mg/kg), paroxetine (1 mg/kg), or an equivolumetric injection of distilled water, vehicle (1 cc/kg) 1 h prior to the treatment injections. The dose of naltrexone was utilized in an attempt to reconsider King (28) who showed that high doses had no effect on SBB. However, it should be noted that low doses of naltrexone may not achieve complete opiate blockade, but may merely regulate the opiate system. Furthermore, after a thorough literature review of intersubject variance, the dose of paroxetine was decided on as the median dose used in other animal models.

To evaluate potential pemoline-induced DA sensitization, the activity inducing effects of amphetamine sulfate (1 mg/kg, IP) were contrasted to vehicle injections 1-week after the last pemoline injection in a 2-day counterbalanced design.

General Procedures

Evaluation of SBB. The pretreatment injections were given 1 h prior to the pemoline treatment. Three hours after each pemoline injection, the physical status of each animal was evaluated. Each animal was removed from its cage and carefully inspected for physical evidence of any SIB, especially biting behavior. The severity of self-injury was rated by an observer (blind to treatment conditions) on a 0–4 scale based on King (28), which is summarized in Table 1. To minimize suffering, once an animal attained a substantial rating at level 3, the pretreatment and treatment doses either skipped a day or were terminated. All subsequent behavioral tests and measures commenced 4 h after the treatment injections.

Social investigation. Two adjacent testing chambers (65 × 24 × 15 cm) made of transparent Plexiglas were placed end to end such that one end of each box faced the other box, and the opposite ends faced directly away from each other. In the center of each end was a 3.2-cm hole reinforced with a metal rim. The two holes facing each other were separated by 12 cm and were designated "social ports." Animals placed individually in the adjacent boxes could explore and interact by putting their snouts through these ports. In contrast, the ports on the other end of each chamber faced into open space and were designed the "nonsocial ports." Photoelectric cells were positioned on either side of each investigation port such that when an animal placed its snout 1.3 cm through a hole, the photobeam was broken. Duration of photobeam breaks at each of the holes were scored separately as measures of social vs. nonsocial investigation. All measures were automatically scored by a microcomputer and recorded for each 30-min test

TABLE 1
SEVERITY OF SELF-BITING BEHAVIOR

Score	Classification	Description
0	No SIB	N/A
1	Very Mild SIB	Slight edema
		Pink, and moist skin
		Involves small area
2	Mild SIB	Moderate edema
		Slight erythema
		Slightly denuded skin
		Involves medium area
		Involves multiple sites
3	Moderate SIB	Substantial edema
		Substantial erythema
		Substantial denuded skin
		Involves large area
		Minor tissue loss
4	Severe SIB	Amputation of digit
		Clear lesion(s)
		Requires euthanasia

session. The social and nonsocial port durations were statistically analyzed separately for the measure of time spent investigating each port hole, as well as together for the average time spent investigating both holes (42).

Startle testing. The startle apparatus consisted of a commercial startle response system (SR-Lab) from San Diego Instruments, San Diego, CA. The apparatus was composed of two isolation cabinets each containing one startle chamber. A pair of animals were taken from their home cages and were transferred into two separate startle chambers constructed of transparent acrylic and adjusted for the length of the animal. The chambers were 3-1/2 inches in diameter and could be adjusted up to 7-1/4 inches in length. The cabinets were wood covered plastic laminate measuring 15 × 16 × 23 inches.

One test session lasted 8 min. A test session consisted of a 2-min acclimation period followed by two repetitions of six trials: a prepulse trial, a startle trial, a prepulse inhibition trial, a prepulse inhibition trial, a startle trial, and a prepulse trial. A trial consisted of a single sound with a 30-s intermission between trials. A prepulse trial consisted of a 75-dB sound, whereas the startle trial consisted of a 100-dB sound. The prepulse inhibition trial consisted of the prepulse trial (75 dB) followed 100 ms later by the startle trial (100 dB). A microcomputer recorded the movement for each trial from the two cabinets. Startle amplitude was defined as the mean value of startle trials, whereas the response magnitude was defined as the mean value of each of the three respective trials. After a session the animals were placed back into their home cages and the isolation chambers were wiped with a damp cloth.

Open-field activities. An open field measuring 60 × 60 × 30 cm was used. Two opposing walls were transparent Plexiglas, and the other two were aluminum. The aluminum floor of the apparatus was divided into four equal quadrants by lines on the floor of the apparatus. Two behaviors were monitored visually. Overall activity was measured by the frequency of line crosses and rears. A line cross was scored when all four paws of a rat were in a new quadrant. A rear was scored when both of the front paws of a rat were simultaneously off of the floor. Animals were individually tested during a 5-min session. The field was cleaned with a damp cloth between each animal.

Amphetamine-induced activity. The animals were injected with amphetamine 30 min before exposure to the shuttleboxes. Each animal was tested in a 48 × 19 × 28-cm shuttlebox, which was divided in half by an aluminum partition with a 15 × 20 cm opening. Each of four identical test boxes was situated in a sound-attenuated chamber. Visual cues distinguished each half of the shuttlebox. The walls of the left side had 2-cm black horizontal stripes separated by the same distance, whereas the right side had the same kind of stripes oriented vertically. Both chambers had a steel rod floor. A microcomputer recorded the number of crossings from one chamber to the other via two pairs of photocells placed 5-cm lateral to the medial divider, yielding an overall measure of shuttle activity. Each test session consisted of three 5-min blocks.

Statistical analysis. Data for all behavioral measures were analyzed in a 3 × 2 (pretreatment × treatment) ANOVA. Means and SEMS are provided. The ratings of SBB were also analyzed by a Fisher LSD (protected) post hoc.

RESULTS

Evaluation of SBB

Table 1 was used in rating the observations of pemoline-induced SBB. No animal received a rating higher than a 3 probably due to the 100-mg/kg dose of pemoline, which is below the published ED_{50} for SBB. Still, pemoline did reliably produce SBB in 96.55% of the pemoline treated rats. This observed effect may be the result of the previous isolation before testing, which has been shown to shift the dose–response curve leftward in other animal models. The most common areas of SBB included the forefoot, the forearms, the hindfoot, the tail, and the abdomen. Additional behavioral observations indicated that most of the animals also exhibited stereotyped head movements and licking/biting of the cage as well as some repetitive tongue protrusions. None of the behaviors were observed in any of the animals in the three vehicle control groups, and their data are not plotted in Fig. 1.

Statistically reliable differences were seen in the severity of SBB in the pemoline group. There was a statistically reliable effect of pemoline alone, $F(1, 18) = 13.75$, $p < 0.01$. This result was also statistically greater than zero, with a significant interaction of test day and treatment, $F(7, 126) = 2.89$, $p < 0.01$. As summarized in Fig. 1, the paroxetine-pretreated animals showed the highest ratings, with clear differences being evident after day 3. The other groups did not differ significantly over the 8 days, although the naltrexone-pretreated group showed a marginal increase in SBB. There were significant interactions between day, pretreatment, and treatment, $F(1, 28) = 3.16$, $p < 0.0001$, and pretreatment and treatment, $F(2, 53) = 15.79$, $p < 0.0001$. The interaction between day and pretreatment was also significant, $F(14, 371) = 3.16$, $p < 0.0001$, with the effect of paroxetine increasing the severity of SBB across days. There were also significant main effects of day, $F(7, 371) = 18.17$, $p < 0.0001$, and of pretreatment, $F(2, 53) = 18.79$, $p < 0.0001$, with the severity of SBB differing across days and by pretreatment.

Investigation. Animals were tested in the investigation chambers, half on day 3 and the other half on day 4 of treatment, with all of the animals tested at the same time of day on both days. The effects of pretreatment and treatment on investigatory behavior were analyzed by hole (social or nonsocial) nose poking. In this measure, most of the animals spent more time at the nonsocial hole. This was opposite of our expectations, and may be attributed to the old age of our males (6 months) and the prolonged period of individual housing before the beginning of this experiment (4 months). Thus, the two holes were combined for an average time spent investi-

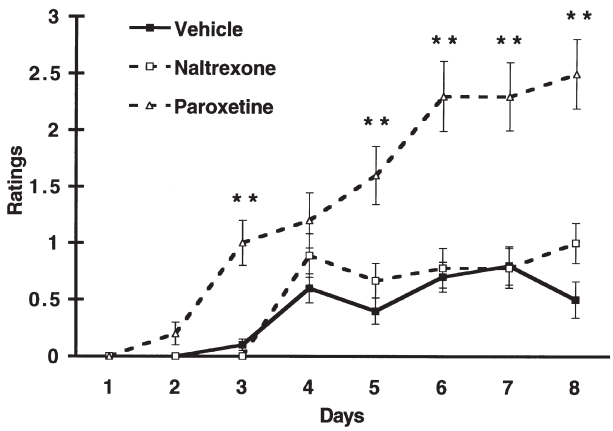

FIG. 1. Average ratings (see Table 1) for pemoline-induced self-injurious behaviors in animals pretreated with vehicle, naltrexone, and paroxetine. Values are means and SEMs. *$p < 0.05$, **$p < 0.01$.

gating both holes. As summarized in Fig. 2, pemoline clearly suppressed investigatory behavior. A significant interaction between pretreatment and treatment, $F(2, 53) = 6.31$, $p < 0.004$, was found, with naltrexone and paroxetine increasing investigatory behavior in comparison to the vehicle-treated group by 49.5 and 87.4%, respectively. No such trend was evident for animals treated with pemoline, which all showed a decrease in investigatory behavior when compared to controls.

Startle testing. The animals were tested for startle responses on days 6 and 7. The response patterns for the various types of trials were as expected, with the startle measure yielding the highest magnitude and the prepulse yielding the lowest levels. However, there were no clear significant interactions or main effects for pretreatment or treatment in this measure.

Open-field activities. The animals were tested in the open field 24 h after the last pemoline injection. As summarized in Fig. 3, there was a significant main effect of treatment on rears, $F(1, 53) = 42.74$, $p < 0.0001$, with the pemoline-treated group rearing 97.5% less than the vehicle-treated group. Furthermore, the paroxetine-pretreated, vehicle-treated group reared 28.2% more than the control group, but this trend was not statistically significant. For line crosses, there were no significant interactions or main effects for pretreatment or treatment in this measure.

Amphetamine-induced activity. The animals were tested 1 week postpemoline for sensitization by monitoring amphetamine-induced activity. There was a significant interaction between the pemoline treatment and amphetamine treatment, $F(1, 48) = 4.20$, $p < 0.05$. However, no interaction between the naltrexone, paroxetine, or vehicle pretreatments and amphetamine treatment were evident, $F(2, 48) = .18$, $p = 0.83$. The reliable interaction is summarized in Fig. 4, and was due to the fact that the pemoline-treated animals were 21% more active than the vehicle-treated animals. Although there was a significant main effect of amphetamine treatment, $F(1, 48) = 54.46$, $p < 0.0001$, reflecting a 40.4% elevation in photobeam crosses, the levels of increased activity were similar in the pemoline- and vehicle-treated animals. Because the pemoline group did not show an increase in photobeam crosses (mean = 49.8, SD = 18.15) above those of the vehicle group (mean = 50.9, SD = 17.4), we cannot conclude that the pemoline animals had been sensitized, even though their baseline activity was elevated.

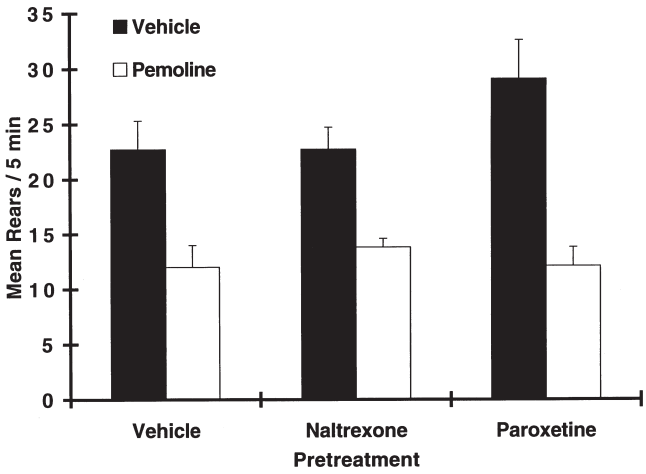

FIG. 3. Mean number of rears in the six experimental groups.

DISCUSSION

There is little evidence from prevailing clinical studies to suggest a particular drug or class to be optimally effective in the treatment of SIB. Furthermore, the lack of consistency from study to study demands the exploration of this issue. The present study does not necessarily negate or support the use of either SSRIs or naltrexone for clinical trials, but argues for the heterogeneous nature of this disorder.

In agreement with previous work (20,28,29,39–41), repeated treatment with pemoline induced clear SBB effects in the present study. In addition to mediating self-biting behavior, a variety of other behavioral changes were evident. Pemoline also decreased investigatory behaviors and rearing during the active treatment phase, and it produced a residual increase in locomotor activity following the termination of treatment. It had no effect on the magnitude of the startle response or prepulse inhibition. Contrary to expectation, neither opioid blockade with naltrexone, nor facilitation of synaptic availability of serotonin with the SSRI paroxetine, reduced

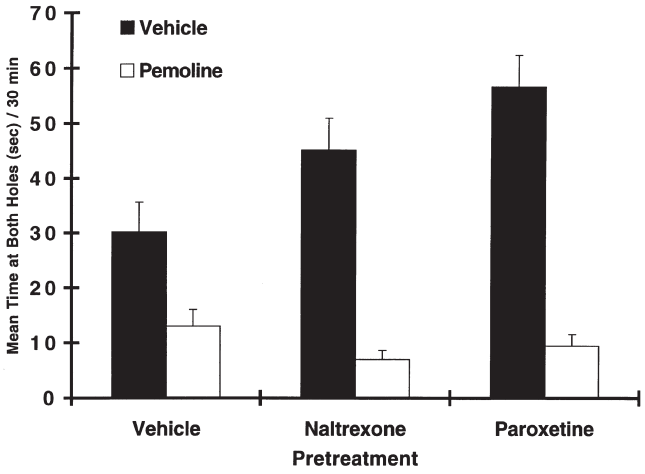

FIG. 2. Mean time at investigation ports for the various experimental groups.

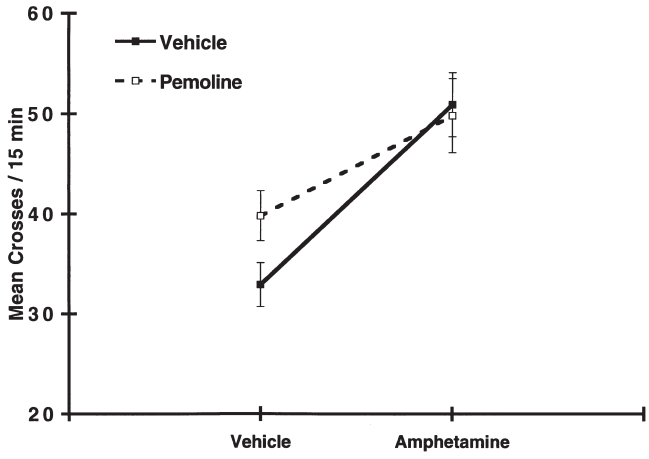

FIG. 4. Amphetamine-induced activity in the groups of animals that had previously been treated with pemoline and vehicle.

these symptoms. Indeed, on the main measure of interest, namely SBB, paroxetine significantly increased SBB, and naltrexone also marginally, albeit not statistically significant, increased the behavior.

Because the main concern of this study was the analysis of SBB, we will restrict our comments to this measure. On the basis of previous clinical results (12,17,19,27,34,35,45,46,48,49,56), our expectation had been that both opioid blockade and facilitation of serotonin would reduce SBB. The paradoxical increases observed may help explain the mixed track record of these agents in clinical populations, and is consistent with the possibility of heterogeneous underlying neural causes for SIB in clinical populations. Our preliminary evidence that high doses of naltrexone have no effect on pemoline-induced SBB agrees with King (28). This evidence also agrees with three well-controlled studies that failed to observe any beneficial effect of naltrexone in the treatment of SIB (13,55,58). The more robust changes seen with paroxetine are harder to reconcile with the existing clinical literature, and deserves special attention.

One reasonable possibility is that the paroxetine-induced increase in the synaptic availability of serotonin eventually led to serotonin receptor undersensitivity, and the gradual elevation of SBB in that group reflected such accruing receptor changes. However, in the absence of neurochemical data, that is only one of several possibilities.

The underlying reason why pemoline induces SBB remains uncertain. One possibility is that it produces a sensitization of certain brain DA systems (7,33), but our attempt to evaluate this possibility, through the evaluation of cross-sensitization to amphetamine, did not yield confirmatory data. Still, the fact that rats that have been chronically treated with pemoline are slightly more hyperactive than controls suggests that some type of long-term change in the regulation of arousability is induced by pemoline. It is possible that the neural source of that hyperactivity contributes to the development of SIB, but that possibility needs to be evaluated by future research.

In conclusion, the results of this preliminary study into the regulation of SBB demonstrated that a serotonin agonist significantly increased SBB in the pemoline model. To our knowledge, this fact has never before been demonstrated. Recent evidence has, however, shown risperidone, a 5-HT_{2c} and DA D_2 receptor antagonist, to be effective in antagonizing self-injury in a Lesch–Nyhan patient (2). Other studies have also found this antagonist to be effective in the 6-OHDA model of SBB (1,16). In light of this recent evidence and the results of this study suggesting serotonin agonists to increase the severity of SBB, future studies may wish to examine the role of risperidone in this model. If the outcome is beneficial, it will provide even more support for the use of the pemoline model as a model for Lesch–Nyhan syndrome.

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REFERENCES

1. Allen, S. M.; Davis, W. M.; Freeman, J. N.: Interaction between dopaminergic and serotonergic systems after neonatal 6-OHDA lesions. Soc. Neurosci. Abstr. 23:412; 1997.
2. Allen, S. M.; Rice, S. N.: Risperidone antagonism of self-mutilation in a Lesch–Nyhan patient. Prog. Neoropsychopharm. Biol. Psychiatry 20:793–800; 1996.
3. Anderson, L. T.; Ernst, M.: Self-injury in Lesch–Nyhan disease. J. Aut. Dev. Dis. 24:67–80; 1994.
4. Barrett, R. P.; Feinstein, C.; Hole, W. T.: Effects of naloxone and naltrexone on self-injury: A double blind placebo controlled analysis. Am. J. Ment. Retard. 93:644–651; 1989.
5. Beckwith, B. E.; Couk, D.; Schumaker, K.: Failure of naloxone to reduce self-injurious behavior in two developmentally disabled females. Appl. Res. Ment. Retard. 93:644–651; 1986.
6. Bernstein, G. A.; Hughes, J.; Mitchell, J. E.; Thompson, T.: Effects of narcotic antagonists on self-injurious behavior: A single case study. J. Am. Acad. Child Adoles. Psychiatry 26:886–889; 1987.
7. Breese, G. R.; Baumeister, A. A.; McCowan, T. J.; Emerick, S. G.; Frye, G. D.; Mueller, R. A.: Behavioral differences between neonatal and adult 6-hydroxydopamine treated rats to dopamine agonists: Relevance to neurological symptoms in clinical syndromes with reduced brain dopamine. J. Pharmacol. Exp. Ther. 231:343–354; 1984.
8. Breese, G. R.; Baumeister, A. A.; McCowan, T. J.; Emerick, S. G.; Frye, G. D.; Mueller, R. A.: Neonatal 6-hydroxydopamine treatment: Model of susceptibility for self-mutilation in Lesch–Nyhan syndrome. Pharmacol. Biochem. Behav. 21:459–461; 1984.
9. Breese, G. R.; Criswell, H. E.; Duncan, G. E.; Mueller, R. A.: Dopamine deficiency in self-injurious behavior. Psychopharmacol. Bull. 25:353–357; 1989.
10. Breese, G. R.; Mueller, R. A.: SCH-23390 antagonism of a D-2 dopamine agonist depends upon catecholaminergic neurons. Eur. J. Pharmacol. 113:109–114; 1985.
11. Burke, H. W.; Menolascino, F. J.: Haloperidol in emotionally disturbed mentally retarded individuals. Am. J. Psychiatry 124:147–149; 1968.
12. Campbell, M.; Adams, P.; Small, A.; McVeigh Tesch, L.; Curren, E. L.: Naltrexone in infantile autism. Psychopharmacol. Bull. 24:136–139; 1988.
13. Ciaranello, R. D.; Anders, T. F.; Barchas, J. D.; Berger, P. A.; Cann, H. M.: The use of 5-hydroxytryptophan in a child with Lesch–Nyhan syndrome. Child Psychiatr. Hum. Dev. 7:127–133; 1976.
14. Cohen, D. J.; Shaywitz, B. A.; Caparulo, B.; Young, J. G.; Bowers, M. B.: Chronic, multiple tics of Gilles de la Tourette's disease. CSF acid monoamine metabolites after probnecid administration. Arch. Gen Psychiatry 35:245–250; 1978.
15. Davidson, P. W.; Kleene, B. M.; Carroll, M.; Rockowitz, R. J.: Effects of naloxone on self-injurious behavior: A case study. Appl. Res. Ment. Retard. 4:1–4; 1983.
16. Davis, W. M.; Allen, S. M.; Freeman, J. N.: Pharmacological evaluation of atypical neuroleptics in the 6-OHDA rat model of Lesch–Nyhan Syndrome. Soc. Neurosci. Abstr. 23:412; 1997.
17. Deutsch, S. I.: Rationale for the administration of opiate antagonists in treating infantile autism. J. Ment. Defic. Res. 90:631–635; 1986.
18. Eisenhauer, G. L.; Woody, R. C.: Self-mutilation and Tourette's disorder. J. Child Neurol. 2:265–267; 1987.
19. Gedye, A.: Trazodone reduced aggressive and self-injurious movements in a mentally handicapped male patient with autism. J. Clin. Psychopharmacol. 11:275–276; 1991.
20. Genovese, E.; Napoli, P. A.; Bolego-Zonta, N.: Self aggressiveness: A new type of behavioral change induced by pemoline. Life Sci. 8:513–515; 1969.
21. Goldstein, M.; Anderson, L. T.; Reuben, R.; et al.: Self-mutilization in Lesch–Nyhan disease is caused by dopaminergic denervation. Lancet 1:338–339; 1985.
22. Goldstein, M.; Kuga, S.; Kusano, N.; et al.: Dopamine agonist induced self-mutilative biting behavior in monkeys with unilat-

eral ventromedial tegmental lesions of the brainstem: Possible pharmacological model for Lesch–Nyhan syndrome. Brain Res. Bull. 367:114–119; 1986.
23. Greenberg, A.; Coleman, M.: Depressed whole blood serotonin levels associated with behavioral abnormalities in the deLange syndrome. J. Ment. Defic. Res. 23:79–84; 1979.
24. Gualtieri, C. T.; Schroder, S. R.: Pharmacology for self-injurious behavior: Preliminary test of the D_1 hypothesis. Psychcopharmacol. Bull. 25:366–376; 1989.
25. Harris, J. C.: Neurobiological factors involved in self-injurious behavior. In: Luiselli, J. K.; Matson, J. L.; Singh, N. N., eds. Self-injurious behavior: Analysis, assessment and treatment. New York: Springer Verlag; 1992.
26. Herman, B. H.; Hammock, M. K.; Arthur-Smith, A. E.; Egan, J.; Chatoor, I.; Werner, A.; Zelnek, N.: Naltrexone decreases self-injurious behavior. Ann. Neurol. 22:550–552; 1987.
27. Kars, H.; Broekema, W.; Galudemans-Van Gelderen, I.; Verhoeven, W. M. A.; Van Ree, J. M.: Naltrexone attenuates self-injurious behavior in mentally retarded subjects. Biol. Psychiatry 27:741–746; 1990.
28. King, B. H.; Au, D.; Poland, R. E.: Low dose naltrexone inhibits pemoline-induced self-biting behavior in prepubertal rats. J. Child Adolesc. Psychopharmacol. 3:71–79; 1993.
29. King, B. H.; Au, D.; Poland, R. E.: Pretreatment with MK-801 inhibits pemoline-induced self-biting behavior in prepubertal rats. Dev. Neurosci. 17:47–52; 1995.
30. Kopin, I. J.: Neurotransmitters and the Lesch–Nyhan syndrome. N. Engl. J. Med. 305:1148–1149; 1981.
31. Lesch, M.; Nyhan, W. L.: A familial disorder of uric acid metabolism and CNS function. Am. J. Med. 36:561–570; 1964.
32. Lloyd, K. G.; Hornykiewicz, O.; Davidson, L.; Shannak, K.; Farley, I.; Goldstein, M.; Shibuya, M.; Kelley, W. N.; Fox, I. H.: Biochemical evidence of dysfunction of brain neurotransmitters in the Lesch–Nyhan syndrome. N. Engl. J. Med. 305:1106–1111; 1981.
33. Mailman, R. B.; Towle, A.; Schultz, D. W.; Lewis, M. H.; Breese, G. R.; DeHaven, D. H.; Krigman, M. R.: Neonatal 6-hydroxydopamine treatment of rats: Changes in dopamine (DA) receptors, striatal neurochemistry and anatomy. Soc. Neurosci. Abstr. 9:932; 1983.
34. Markowitz, P. J.; Calabrese, J. R.; Schultz, S. C.; Meltzer, H. Y.: Fluoxetine in borderline and schizotypal personality disorder. Am. J. Psychiatry 148:1964–1967; 1991.
35. Markowitz, P. J.: Effect of fluoxetine in self-injurious behavior in the developmentally disabled: A preliminary study. J. Clin. Psychopharmacol. 12:27–31; 1992.
36. Markowitz, P. J.: Longitudinal efficacy of fluoxetine and sertraline in borderline personality disorder. Presented at the International Society for the study of Personality Disorders meeting, Boston, MA, August 17, 1993.
37. Mizuno, T.; Yugari, Y.: Prophylactic effect of L-5-hydroxytryptophan on self-mutilation in the Lesch–Nyhan syndrome. Neuropediatrie 6:13–23; 1975.
38. Mizuno, T.; Yugari, Y.: Self-mutilation in Lesch–Nyhan syndrome. Lancet 1:761; 1974.
39. Mueller, K.; Hollinsworth, E.; Pettit, H.: Repeated pemoline produces self-injurious behavior in adult and weanling rats. Pharmacol. Biochem. Behav. 25:933–938; 1986.
40. Mueller, K.; Hsiao, S.: Pemoline-induced self-biting in rats and self-mutilation in the deLange syndrome. Pharmacol. Biochem. Behav. 13:627–631; 1980.
41. Mueller, K.; Nyhan, W. L.: Pharmacological control of pemoline induced self-injurious behavior in rats. Pharmacol. Biochem. Behav. 16:957–963; 1982.
42. Panksepp, J.; Nelson, E.; Bekkedal, M.: Brain systems for the mediation of social separation-distress and social reward. Ann. NY Acad. Sci. 807:78–100; 1997.
43. Patel, H.; Bruza, D.; Yeragani, V. K.: Treatment of self-abusive behavior with trazodone (Letter). Can. J. Psychiatry 33:331–332; 1988.
44. Primeau, F.; Fontaine, R.: Obsessive disorder with self-mutilation: A subgroup responsive to pharmacotherapy. Can. J. Psychiatry 7:114–117; 1978.
45. Ratey, J. J.; Sovner, R.; Mikkelsen, E.; et al.: Busipirone therapy for maladaptive behavior and anxiety in developmentally disabled persons. J. Clin. Psychiatry 50:382–384; 1989.
46. Richardson, J. S.; Zaleski, W. A.: Naloxone and self-mutilation. Biol. Psychiatry 18:99–101; 1983.
47. Robertson, M. M.: Self-injurious behavior and Tourette syndrome. Adv. Neurol. 58:105–113; 1992.
48. Roth, A. S.; Ostroff, R. B.; Hoffman, R. E.: Naltrexone as a treatment for repetitive self-injurious behavior: An open-label trial. J. Clin. Psychiatry 57:233–237; 1996.
49. Rudorfer, M. V.; Manji, H.; Potter, W. Z.: New generation antidepressants: Fluoxetine and other selective reuptake inhibitors. Hosp. Ther. 15:767–790; 1990.
50. Sandman, C. A.; Datta, P. C.; Baron, J.; Hoehler, F. K.; Williams, C.; Swenson, J. M.: Naloxone attenuates self-abusive behavior in developmentally disabled clients. Appl. Res. Ment. Retard. 4:5–11; 1983.
51. Sandyk, R.: Naloxone abolishes self-injuring in a mentally retarded child. Ann. Neurol. 17:520; 1985.
52. Shapiro, A. K.; Shapiro, E. S.; Brunn, R. D.; Sweet, R. D.: Gilles de la Tourette syndrome. New York: Raven; 1978.
53. Singh, N. N.; Pulman, R. M.: Self-injury in the deLange syndrome. J. Ment. Defic. Res. 23:79–84; 1979.
54. Swedo, S.; Leonard, H. L.; Rapoport, J. L.; et al.: A double blind comparison of clomipramine and desipramine in the treatment of trichotillomania. N. Engl. J. Med. 321:497–501; 1989.
55. Szymanski, L.; Kedesky, J.; Sulkes, S.; Cutler, A.; Stevens-Ours, P.: Naltrexone in treatment of self-injurious behavior: A clinical study. Res. Dev. Dis. 8:179–190; 1987.
56. Thompson, T.; Hackenberg, T.; Cerutti, D.; Baker, D.; Axtell, S.: Opioid antagonist effects on self-injury in adults with mental retardation: Response form and location as determinants of medication effects. Am. J. Ment. Retard. 99:85–102; 1994.
57. Walters, A. S.; Barrett, R. P.; Feinstein, C.; Mercurio, A.; Hole, W. T.: A case report of naltrexone treatment of self-injury and social withdrawal in autism. J. Auto. Dev. Dis. 20:169–176; 1990.
58. Willemsen-Swinkels, S. H. N.; Buitelaar, J. K.; Nijhof, G. J.; Van Engleland, H.: Failure of naltrexone hydrochloride to reduce self-injurious and autistic behavior in mentally retarded adults. Arch. Gen. Psychiatry 52:766–773; 1995.
59. Willemsen-Swinkels, S. H. N.; Buitelaar, J. K.; Weijnen, F. G.; Thijssen, J. H. H.; Van Engleland, H.: Plasma beta-endorphin concentrations in people with learning disability and self-injurious and/or autistic behavior. Br. J. Psychiatry 168:105–109; 1996.
60. Winchel, R. W.; Stanley, B.; Guido, J. R.; et al.: An open trial of fluoxetine for trichotillomania. In: Abstracts of the Annual Meeting of the American College of Neuropsychopharmacology, Maui, Hawaii. Nashville, TN: ACN; 1989.
61. Winchel, R. M.; Stanley, M.: Self-injurious behavior: A review of the behavior and biology of self-mutilation. Am. J. Psychiatry 148:306–317; 1991.
62. Yaryura-Tobias, J. A.; Neziroglu, F.: Compulsions, aggression and self-mutilation. J. Ortho. Psychiatry 7:114–117; 1978.