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Naltrexone Improves Learning and Attention in Self-injurious Individuals with Developmental Disabilities

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In the primary study, 10 patients were enrolled in a 10-week double-blind evaluation of the effectiveness of naltrexone in reducing self-injurious behavior (SIB) in adults with developmental disabilities. Within this study, the effects of naltrexone on acquisition of a paired associates task were investigated. The effects of three doses of naltrexone (0.5, 1.0, and 2.0 mg/kg orally) were tested on separate weeks. Learning evaluations were conducted on Wednesday of each week. Naltrexone improved measures of independence and attention, and decreased trial rate.

KEY WORDS: naltrexone; self-injury; β-endorphin; opiate-antagonist; learning; memory; sedation.

INTRODUCTION

The impact of opiate blockers holds demonstrated promise for the amelioration of self-injurious behavior (SIB) in persons with developmental disabilities and/or autism (Barrett *et al.,* 1989; Barron and Sandman, 1984; Bernstein *et al.,* 1987; Campbell *et al.,* 1987; Davidson *et al.,* 1983; Herman *et al.,* 1987; Kars *et al.,* 1990; Richardson and Zaleski, 1983; Sandman *et al.,* 1983, 1990b; Sandyke, 1985). Little is known, however, about the effects of this class of agents on attention and learning. Self-injury is most commonly associated with severe learning impairment and a deleterious effect of

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naltrexone on learning could outweigh its positive impact in the amelioration of maladaptive behavior. Individuals with autism or mental retardation who are self-injurious may be particularly sensitive to the cognitive effects of opiate-blockers because disregulation of opioid systems has been implicated in their pathology. Indeed, SIB patients with developmental disabilities have elevated plasma (Sandman, 1988; Sandman *et al.,* 1990) and cerebral spinal fluid (Gillberg and Terenius, 1985) opioid peptides.

Pharmacological therapy presents a challenge in persons with developmental disabilities because the causes of their neurological impairments are complex. The behavioral manifestations among this population are usually due to deficits in multiple receptor systems within the nervous system. The treatment strategy is complicated by recent evidence that early developmental stress, such as hypoxia, may result in unique pharmacokinetics and paradoxical responses to some medications (Barron and Sandman, 1985; Sandman and Kastin, 1990). Ideal treatment for self injury in individuals with developmental disabilities would enhance rather than depress cognitive features related to learning, such as attention, compliance, and memory.

Early research with pituitary hormones and their analogues indicated the potential to develop therapies that enhance memory in the developmentally disabled population. Administration of non-steroidal fragments of ACTH (a pituitary hormone) improved performance in rats (Sandman *et al.,* 1972) and healthy adults (Sandman *et al.,* 1977; Ward *et al.,* 1979), and held promise for individuals with developmental disabilities. In three early studies (Sandman *et al.,* 1976, 1980; Walker and Sandman, 1979), administration of ACTH and its analogues to individuals with developmental disabilities improved memory, learning and performance of work-related tasks. These results, though statistically significant, had only a marginal clinical impact.

Although ACTH fragments have not been developed into clinical therapies for improving cognitive functioning among the developmentally disabled, mechanisms of their action provide clues for alternative therapies. ACTH is co-released with the endogenous opiate (opioid) peptide beta-endorphin from the anterior pituitary. These two peptides are cleaved from the same precursor molecule pro-opiomelanocortin (POMC), and are found in projections from the hypothalamus to central brain areas. Many studies have suggested that these molecules have reciprocal actions (Hrdina and Singhal, 1981; Sandman and Kastin, 1981).

In contrast to ACTH analogues, morphine (an opiate agonist to the mu receptor) (Castellano, 1975) and beta-endorphin (the endogenous mu receptor agonist) (Izquierdo and Dias, 1980; Izquierdo and McGaugh, 1985) impair learning and memory probably because they exert inhibitor effects upon central processes. Blocking the action of opioid peptides on the brain with opiate antagonists may have similar effects as ACTH frag-

ments. However, because opiate blockers like naltrexone have longer lasting effects ($t^1/^2$ = 12.9 hr for naltrexone's primary active metabolite and a 50 mg dose blocks opiate receptors for up to 48 hr) (McEvoy, 1990), these drugs may be more effective.

Opiate blockers have memory enhancing properties in addition to their efficacy for the treatment of SIB (Barrett *et al.,* 1989; Bernstein *et al.,* 1987; Campbell *et al.,* 1988; Herman *et al.,* 1987; Kars *et al.,* 1990; Ryan *et al.,* 1989; Sandman *et al.,* 1983, 1990; Taylor *et al.,* 1991). Opiate blockers have been reported to improve both learning acquisition and retention in animals (Aigner and Mishkin, 1988; Flood *et al.,* 1987; Gallagher and Kapp, 1978; Gallagher *et al.,* 1983). They also appear to facilitate arousal necessary for learning in two ways. First, they remove the tonic inhibitory influences of opioids upon adrenergic and dopaminergic tone (Izquierdo *et al.,* 1980; Izquierdo and Gradients, 1980; McGaugh *et al.,* 1988). Second, they decrease inhibitory effects of opiate peptides on acetylcholinergic neurons and increase their firing rate in the septohippocampal region of the brain (Botticelli and Wurtman, 1981, 1982).

Apparently the memory enhancing effects observed in animals have not been as pronounced in humans (Cohen *et al.,* 1983; Morley *et al.,* 1980). There are several explanations for these results. Animal studies have shown that memory enhancement by naltrexone follows an inverted U-shaped curve (McGaugh *et al.,* 1988) and it has been suggested that dose response curves may be idiosyncratic in primates (Aigner *et al.,* 1988). Also, the studies in humans have used doses of naloxone (a short acting injectable opiate blocker similar to naltrexone), producing both agonist (at low dose) and antagonist (at high dose) properties (Morley *et al.,* 1980). Therefore, negative results may be due to selecting large doses on the negative end of the dose response curve producing agonist as opposed to antagonist effects. Generally positive effects in humans have been observed in several patient groups. Opiate blockers improved memory consolidation in alzheimer's patients (Reisberg *et al.,* 1983), enhanced event related potentials (ERP), normalized reaction times, and eliminated hallucinations antecedent to SIB in a subject of normal intelligence (Sandman *et al.,* 1987). In a self-injurious man with autism, treatment with naltrexone led to improvements in paired associates learning (Taylor *et al.,* 1991).

All of the above point to the potential for improved learning in individuals with developmental disabilities treated with opiate blockers. Changes in intellectual functioning, however, are difficult to detect in this non-verbal population with severely depressed learning baselines. Drug induced impairment or enhancement in intellectual functioning can be sensitively measured only by tasks requiring acquisition of new behavior (Novelly *et al.,* 1986). Performance on repeated acquisition tasks has re-

cently been proven sensitive to drug effects on individuals with developmental disabilities (Hackenberg *et al.,* 1989). The modified paired associate learning task used in this study was specifically designed to provide repeated, non-cumulative measure of the acquisition of new behavior. New, but similar, association problems were presented as learning progressed across sessions with some following placebo and others following active medication.

METHODS

Subjects

Ten residents of Fairview Developmental Center were selected for treatment with naltrexone based on chronic histories of severe and frequent self-injury. Informed consent was obtained from guardians or legal conservators. Characteristics of participants are presented in Table I.

Procedures

Three doses of naltrexone (0.5, 1.0, 2.0 mg/kg administered orally) were compared with placebo in a 10-week double-blind randomized ABACADA design. The procedures are outlined in Fig. 1. The study began

Table I. Subject Characteristics, SIB Typology and Frequency[a]

			Self-injurious behavior	
IQ	Sex	Age	Typology	Baseline Frequency
8	M	27	Hits leg and arm, Pulls hair	215.3/hr
13	F	32	Bites wrist	2.5% of time
8	M	36	Bangs and punches head	49.93/hr
20	M	26	Slaps head/face	429.18/hr
10	M	37	Bites hand/arm	6.45% of time
12	M	33	Punches head	116.42/hr
58	M	23	Bites hand	1.10% of time
15	F	38	Hits arms, bangs head	30.32/hr
25	F	43	Bangs head, Pulls own hair	1.52/hr
19	F	14	Slap head, bite arm, scratches self	4839.63/hr

[a]Note. Frequency counts are in hits per hour for single impact behaviors, such as head banging or slapping, and total percent of time the behavior is displayed for duration behaviors such as biting.

with two weeks of open placebo (baseline) followed by a seven week double blind phase and ended with one week of open placebo. The blind phase consisted of three active treatment weeks and four placebo weeks. The same treatment was given at 8:00 am on Monday and Wednesday of each week. Thus, each subject received two exposures to the active treatment within a week. Order of drug administration was randomized and at least one placebo week separated active treatments.

The subjects were videotaped six times a day, four days per week for five minute intervals. At least twenty-five minutes separated each interval. Three intervals were recorded in the morning between 9:00 and 11:30 am,

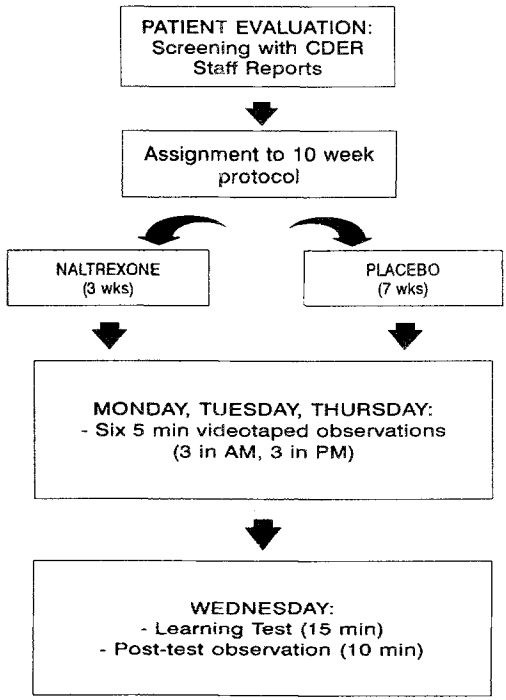

Fig. 1. The process of enrolling subjects in a ten week protocol began with survey of California Developmental Evaluation Report (CDER, a database of developmental assessments for clients under care of state developmental services) and staff reports. Subjects selected for treatment with naltrexone were enrolled in a ten week double blind naltrexone trial. Two hours of videotaped observation was distributed across Monday, Tuesday, and Thursday with six random observations per day. The test occurred on Wednesday followed by a 10-min observation session.

and another three intervals between 1:00 and 4:00 pm. The patients also were videotaped during and for ten minutes after the learning task. A single rater, blind to the order of drug administration, scored the videotapes with the aid of an interactive computer program (Hetrick *et al.*, 1991). After the computer program accepted a client's name, a display analogous to a ten key pad appeared on the screen with specific behaviors named over each key. While watching the videotape the scorer pressed a key corresponding to a specific behavior when it occurred. That behavioral event and time was stored in a database for computation of behavioral frequencies. No alterations in the subjects' normal daily schedules were imposed except for the learning measures described below.

Cognitive ability was measured using a modification of a paired associate learning test (PALT) (Swanson and Kinsbourne, 1980) as presented in Fig. 2. The task required the subject to make an association between an object and one of several spatial locations (trays). Training was conducted at the same time and in an identical setting on Wednesday of each week. The subjects were given an edible reinforcer upon entering the session to reinforce initial participation in the experiment. Another reinforcer was delivered upon completing the session to reinforce attendance and effort spent on the task. Each learning session began by seating the subject at a table in front of two identical trays. When a new object was presented, the examiner verbally instructed and then demonstrated which tray to place it in. This was followed by a single trial which began with a query from the examiner: "See the ball . . . what box does the ball go in?" If the subjects failed to respond after a four-second delay they were given verbal prompts (such as repeating the question "Which box does the ball go in?"), and if they failed to respond after another four second interval, physical prompts (gently guiding the subject's hand toward the box while verbally confirming "The ball goes here") were provided on the first trial. Incorrect trials were corrected by the examiner demonstrating correct placement while verbally instructing, "No, the ball goes right there." Correct trials were followed by verbal ("That's very good") and/or physical (pat on the back, hand clapping) reinforcement. When a subject correctly placed an object without assistance on three consecutive trials, another object was introduced with another corresponding tray location.

A subject was required to reach a criterion of three consecutive correct unassisted trials for each new object. Once the criterion was met for a new object, the object was entered into a random sequence of presentation with all previously learned objects until three trials on each had been completed. If a subject made three consecutive errors with a previously learned item, retraining to criterion was repeated for that item. When the subject placed an object in an incorrect tray the trial was scored as an

error. When the subject placed it in the designated location the trial was scored as correct whether the response occurred independently or following prompting and guidance. Thus, items were considered correct even if as-

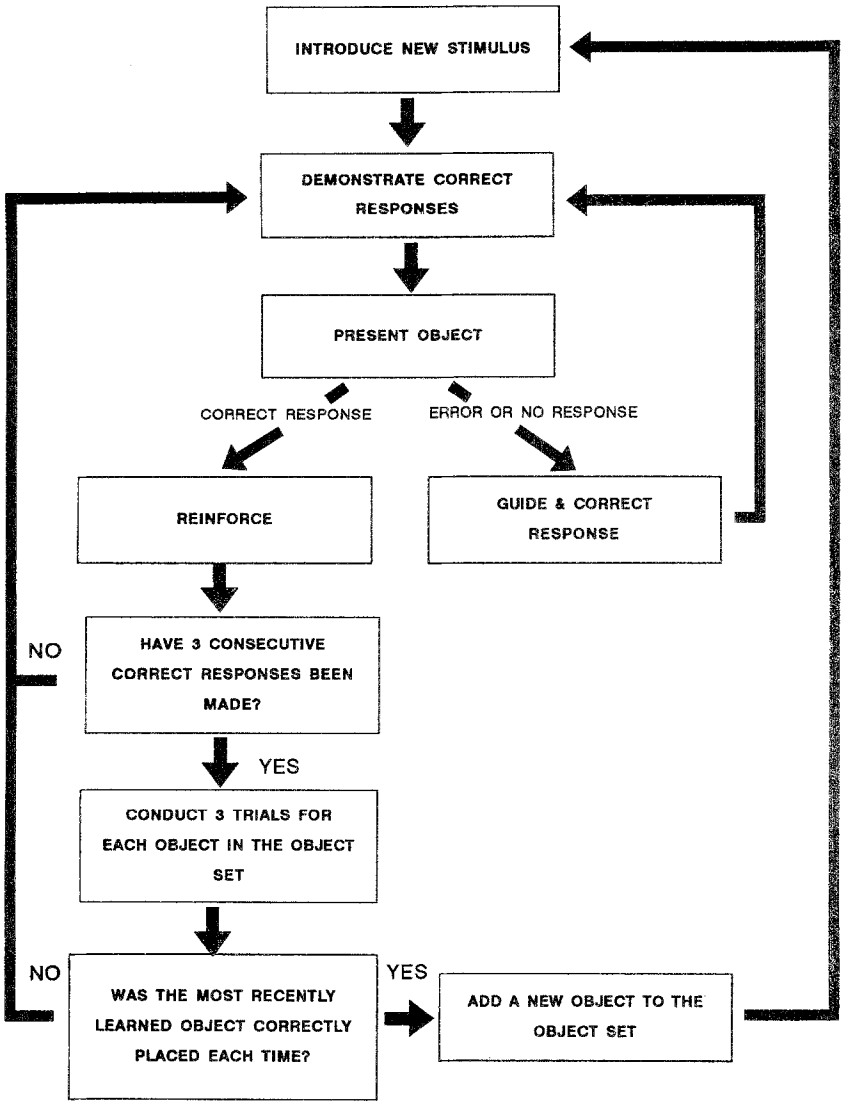

Fig. 2. The learning procedures began by introducing an object to a learning set. When correct response was demonstrated reliably (three correct responses in a row) the subject was challenged with three trials each of the learned objects. If correct on three trials with the most recent object then procedures were resumed from the top of the chart. If incorrect then the most recent object was retrained.

sistance was needed, but once an object was released in an incorrect box the trial was scored as incorrect.

Two trays were used when sorting two objects; three trays were used with three objects and four trays were used with four objects. Thereafter, the number of tray locations was kept constant at four while the number of objects increased without limit. Each session lasted 15 min unless terminated by the patient through three failures to respond to verbal request or prompts on a trial, or other behaviors such as moving away from the table or pushing away the trays. Data were collected for duration, number of trials completed, trials per minute, number of correct placements, percent correct and number of prompts used per session. At least two tests were given during baseline and data from the first test were excluded from analysis.

RESULTS

Length of sessions increased significantly after treatment with naltrexone. ANOVA with orthogonal analysis indicated a linear effect of drug dose on the duration of testing session ($F = 7.58$, $P = 0.02$; see Fig. 3). Duration ranged from 6.4 min during baseline to 12.1 min at the 2.0 mg/kg dose. A matched t-test revealed that the increase at the 2.0 mg/kg dose was significant ($t = 2.70$, $P = 0.01$).

A significant negative linear effect (see Fig. 4) indicated that increasing drug dose decreased the percentage of trials needing verbal and/or physical prompts ($F = 8.93$, $P = 0.02$). There was a slight non-significant

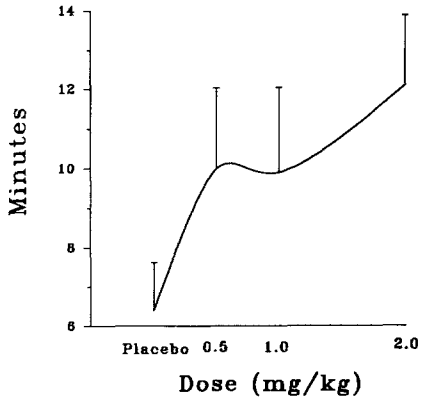

Fig. 3. The average duration of testing sessions at each dose of naltrexone (0, 0.5, 1.0, and 2.0 mg/kg). Error bars above the curve indicate one standard deviation.

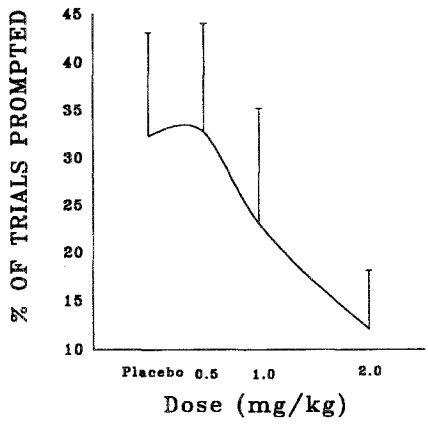

Fig. 4. The average percentage of prompted trials at each dose of naltrexone (0, 0.5, 1.0, 2.0 mg/kg). Error bars above the curve indicate one standard deviation.

increase at the 0.5 mg/kg dose but the percent of prompted trials was reduced from baseline at the 1.0 mg/kg dose and lower still at the 2.0 mg/kg dose.

Trial rate decreased linearly ($F = 8.85$, $P = 0.02$, see Fig. 5) as a function of dose. Trial rate ranged from 2.20 (SD = 0.92) trials per minute at baseline to 1.5 (SD = 2.1) trials per minute at the 2.0 mg/kg dose.

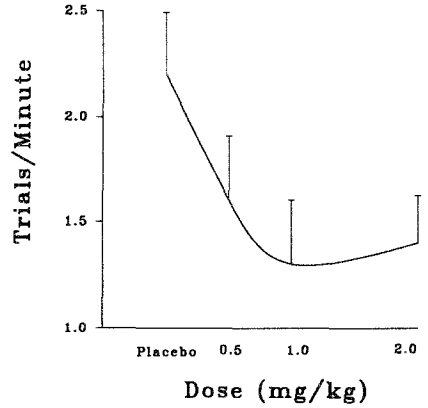

Fig. 5. The average trial rate (trials/minute) for each dose of naltrexone (0, 0.5, 1.0, 2.0 mg/kg given orally). Error bars above the curve indicate one deviation.

The total number of trials increased non-significantly from 12.6 (sd = 6.93) at baseline to 19.13 (sd = 14.15) across all doses. The range of trials completed by subjects was from 0 to 49. Total number of correct responses increased from 9 (sd = 4.73) at baseline to 12.27 (sd = 9.32) but this change was not reliable. The number of correct trials ranged from 0 to 30.

Baseline accuracy was 69.86% ± 21.00% correct and accuracy did not vary significantly across drug doses. Accuracy across active treatment was 66.00% ± 22.25%. Frequency of SIB was negatively correlated with accuracy (% correct) on the learning test ($R = 0.74$, $P < 0.05$ using Pearson Product). Further analysis revealed no correlation between the percent of change in SIB and any change in learning measures across drug weeks.

DISCUSSION

Treatment with naltrexone had significant dose-related effects on three parameters of learning performance among these 10 self-injurious clients with developmental disabilities. At the dose of naltrexone increased, the toleration, and thus the duration, of training sessions increased. This effect was observed at all three doses (Fig. 3). The largest effect was at a 2.0 mg/kg dose. Retrospective inspection of videotaped sessions suggested that there was an increase in attention and ability to remain focussed on the task following treatment with naltrexone. All clients participated in training for 15 min unless they exhibited behavior that met criteria for terminating the session (e.g., distraction, destructiveness, non-compliance). Clearly, as the dose of naltrexone increased the ability of the clients to focus on the task increased, perhaps due to an increased level of arousal.

The second learning measure influenced by naltrexone was the number of prompts required for the client to solve the problem. Prompting is a sign that the subject is not able to solve the problem independently and requires experimenter assistance. Treatment with the highest dose (2.0 mg/kg) of naltrexone resulted in threefold fewer prompted trials (Fig. 4). This dramatic effect reflects the fact that the subjects solved problems with greater independence following treatment with naltrexone. Development of independence may reflect a loss of inhibition due to changes in central arousal levels. Because order of treatment was balanced, none of these effects were related to practice or exposure to the procedures.

The third feature influenced by naltrexone was the rate of trial presentation. Trial rate reflected the speed of problem solving so that higher numbers indicated that clients performed more rapidly. All doses of naltrexone resulted in approximately 25% fewer trials per minute than

baseline performance. It is not immediately obvious why naltrexone resulted in slower performance. Although it is possible that naltrexone produced psychomotor slowing, other studies have found no such effects (Sandman *et al.,* 1990; Herman *et al.,* 1987). It is plausible that trial rate decreased because of the greater independence of the clients. That is, the rate may have decreased as they worked alone to solve the problems at their own pace.

The correspondence between frequency of SIB and lower accuracy on the learning test during baseline suggested dependence between these two behavioral domains. If they were related, it would be expected that they would co-vary during treatment with naltrexone. However, there was no relationship between any measures of SIB and learning during treatment with naltrexone. Further, since naltrexone influenced both domains of behavior, the absence of a correlation suggests that naltrexone has multiple independent effects, as reported previously for other behaviorally active peptides (Kastin *et al.,* 1981).

Improvements in attention and independence indicate that learning was facilitated in a manner similar to that seen in animals treated with naltrexone (Aigner *et al.,* 1988; Flood *et al.,* 1987; Gallagher *et al.,* 1978, 1983). The positive effects of opiate blockers have been attributed to increased arousal and removal of inhibition in central processes (Botticelli *et al.,* 1981, 1982; Izquierdo and Diaz, 1980; Izquierdo and Gradients, 1980; McGaugh *et al.,* 1988). In a similar manner, in the present study, naltrexone treatment led to removal of inhibition and an increased level of arousal that improved attention and independence with individuals who were developmentally disabled. Elevated endorphins or supersensitive receptors due to general opioid disregulation would be expected to impair learning ability in these subjects, and treatment with naltrexone would remove inhibition and restore normal arousal patterns.

This profile of effects after treatment with naltrexone is fairly consistent with previous results in the developmental disabilities with a companion treatment. Earlier studies (Sandman *et al.,* 1976, 1980; Walker and Sandman, 1979) and a recent study (Buitelaar *et al.,* 1990) have showed improvements in behavior, including learning and curiosity. Similar effects of mu receptor opiate blockers and ACTH analogues can be expected because these systems are co-localized in the POMC molecule, are co-released and have reciprocal physiological and cognitive effects (Hrdina and Singhal, 1981; Sandman and Kastin, 1981). Thus, blocking beta-endorphins may provide similar effects as administration of ACTH. In fact, many of the overall effects of opiate blockers on cognition match those of ACTH, including electrophysiological measures (Arnsten *et al.,* 1983; Sandman *et al.,* 1987) and facilitation of learning (Aigner and Mishkin, 1988; Flood *et*

al., 1987; Gallagher *et al.,* 1978, 1983; Izquierdo and McGaugh, 1985; Sandman *et al.,* 1972, 1980; Walker *et al.,* 1979; Ward *et al.,* 1979). However, due to its relatively long half-life and extended biological activity, naltrexone has the potential to exceed the ACTH analogues in biological effect and clinical significance.

These data suggest that treatment with naltrexone may improve learning in self-injurious individuals with developmental disabilities. Such individuals may be particularly sensitive to naltrexone because they may suffer from putative opioid disregulation. Treatment with an opiate blocker may effectively normalize neurochemical patterns in these individuals and improve adaptive behavior. Naltrexone attenuates SIB in this population, but the present results suggest that it also may have positive effects on cognition, and these effects appear to be independent of its effects on SIB. Although the effects on cognition with naltrexone are similar to those with ACTH/MSH analogues, because of their long acting nature, opiate blockers may have greater therapeutic value.

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