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Naloxone in Chronic Schizophrenia

Abstract. *The specific narcotic antagonist naloxone (0.4 milligram) was given intravenously to seven chronic schizophrenics who reported that they had very frequent auditory hallucinations. Saline solution was used as a placebo. The coded study did not reveal any effect of naloxone on hallucinations or on global psychopathology.*

The recent discovery of endogenously produced opioid peptides (*1*) called endorphins has been followed by the hypothesis that these substances may be implicated in the pathophysiology of schizophrenia (*2*). This hypothesis is supported by the following findings: (i) An endorphin has elevated levels in the cerebrospinal fluid (CSF) of schizophrenics (*3*). (ii) These levels decrease to normal when the patients improve clinically (*3*). (iii) A specific opiate antagonist (naloxone, 0.4 mg, given intravenously) reverses schizophrenic hallucinations (*2*). The main purpose of our study was to verify the therapeutic effect of naloxone in schizophrenic hallucinations.

Seven hospital patients (six females and one male) meeting the standard diagnostic criteria for schizophrenia (*4*) were the subjects. All patients reported having very frequent auditory hallucinations; six of them hallucinated continuously. The age range was 24 to 50 years, the duration of illness was 4 to 30 years. Four patients were diagnosed as paranoid, and three were diagnosed as undifferentiated schizophrenia. All patients were receiving antipsychotic medication before and during the experimental period.

Two psychiatrists using a modified Brief Psychiatric Rating Scale (*5*) (BPRS) interviewed the patients. All interviews were videotaped. Three such interviews occurred within the week preceding the start of the experiment. The patients were then given an intravenous injection of either 0.4 mg of naloxone or of a placebo (0.9 percent saline). The BPRS interviews were held immediately before each injection and then at 5 minutes, 30 minutes, 1 hour, 2 hours, 3 hours, 4 hours, and 24 hours after the injection. Each patient received at least one injection of naloxone and one of placebo. The injections were given 24 to 72 hours apart, at the same time of day, in a semirandomized order. Coded procedures were observed throughout the experiment. The results of the first two injections are displayed in Figs. 1 and 2. No average difference between naloxone and placebo was seen. Two patients reported a decrease of hallucinations after having been given placebo. However, two other patients showed a slight reduction of hallucinations after naloxone, without any response to placebo. To test the stability of these findings, one of these "responders" was given an additional injection of 0.4 mg of naloxone without any effect.

The other "responder," however, again improved after an additional injection of naloxone (0.4 mg). This patient subsequently received five injections of placebo, three injections of 0.8 mg of naloxone, and one injection of 1.2 mg of naloxone, in a semirandomized order. The results do not demonstrate any systematic difference between the effects of naloxone and placebo. We therefore conclude that the slight reduction of hallucinations in this patient after the first two injections of naloxone was a function either of chance or of a placebo effect.

In view of the fact that we failed to see any effect of naloxone, we hypothesized that our drug might have deteriorated in storage. We have therefore tested its potency in rats and found that it did have the expected antagonist action (*6*).

We conclude that the report (*2*) of reversal of schizophrenic hallucinations by naxolone cannot be replicated. Although our patient sample was similar to that described in (*2*) in average age and duration of illness, some other differences between the patient sets may have contributed to the divergent results. In contradistinction to Gunn *et al.* (*2*), we have used coded procedures, and

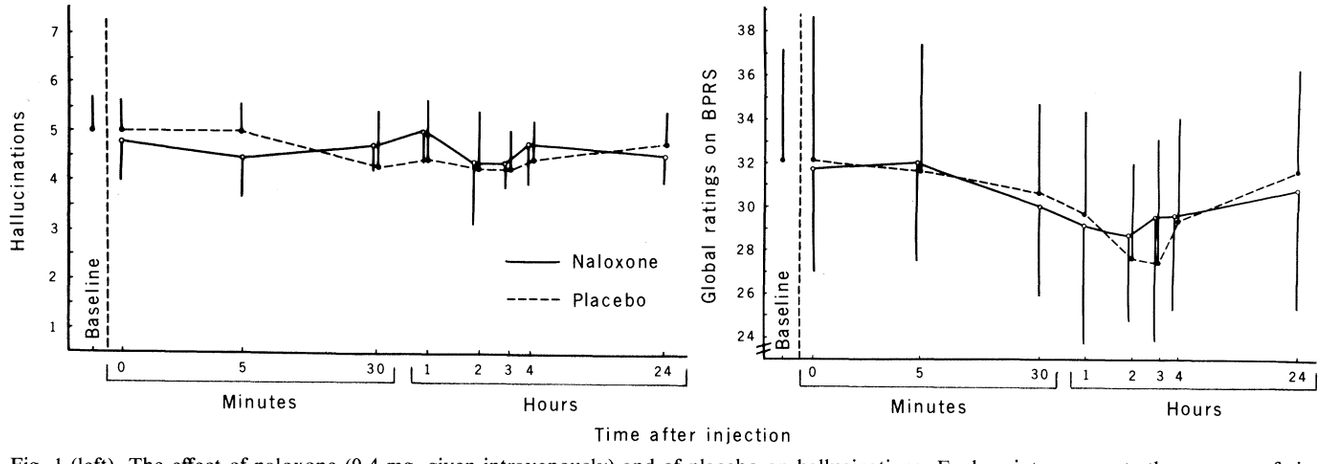

Fig. 1 (left). The effect of naloxone (0.4 mg, given intravenously) and of placebo on hallucinations. Each point represents the average of six patients. (One patient is not included because she did not hallucinate continuously during the baseline assessments.) The baseline measure represents the average of three interviews held in a period of 1 week. The vertical lines represent standard deviations. The scale for hallucinations ranges between 1 (absent) and 7 (extremely severe). Fig. 2 (right). The effect of naloxone (0.4 mg, given intravenously) and of placebo on the global modified BPRS score (excluding the score item "hallucinatory behavior"). Each point represents the average of the seven patients. The vertical lines are standard deviations. The minimal global score (no psychopathology) is 15; the maximum is 105.

we have tested the stability of positive "responses" by repeating the injections. We believe that the differences in methodology between the two studies could fully account for our failure to replicate.

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6. Twelve rats received intraperitoneal injections of morphine sulfate in doses of either 10, 20, or 30 mg per kilogram. All doses produced catalepsy. Naloxone (0.4 mg, given intravenously) immediately blocked the catalepsy; the duration of naloxone effect ranged between 10 and 30 minutes, depending on the dose of morphine. Injection of saline aroused the animals, but the duration of this effect did not exceed 10 seconds.
7. We thank Mary Ginther for technical assistance.

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Vestibular Stimulation Influence on Motor Development in Infants

Abstract. *Preambulatory, normal human infants were exposed to sessions of mild semicircular canal stimulation on 2 days per week for 4 weeks. The gross motor ability of each child was assessed before and after the 4-week period. The vestibular stimulation effected a significant improvement in gross motor skills.*

Physical and occupational therapists working with developmentally delayed children have advocated the use of various forms of vestibular stimulation in their therapy programs (*1*). Vestibular dysfunction has been related to slow development of motor skills and learning disorders (*2*), but little evidence exists to support the claims of beneficial effects of vestibular stimulation. In one study, premature infants were exposed to daily sessions of sinusoidal vestibular stimulation, beginning on the fifth day after birth, and showed improved scores on tests involving auditory and visual responses, motor development, and maturation at 36 weeks of age (*3*). In a second study, we exposed three preambulatory children (one normal and two with Down's syndrome) to ten sessions of semicircular canal stimulation in 2 weeks. Motor skills test scores were markedly improved compared with those of four control subjects (*4*). We hypothesized that exposure to vestibular stimulation influences motor development in infants.

Twenty-six normal, preambulatory infants between 3 and 13 months of age, with a mean age of 7 months, were examined for level of motor performance on reflex and motor skills tests. The reflex test was developed by Chee (*5*) from existing tests (*6*). For each child examined, the elicited reflex was first determined to be normal or abnormal for his or her age and then scored from 1 (abnormal) to 4 (normal). Seventeen reflexes were examined, with a maximum possible score of 68. The motor skills test, developed by Kantner (*7*) from existing tests (*8*), allows an observer to quantitatively evaluate motor skills of the infant successively in five areas of increasing difficulty: prone and supine position, sitting, creeping, standing, and walking. Each area was subdivided into three to seven tasks, with each task further subdivided into five levels of difficulty. One point was scored for accomplishment of one level of each task. The maximum possible score on the motor skills test was 150. In both tests, a low score reflects immature motor ability and a high score more mature motor ability.

Tests were administered during the pretreatment week by a physical therapist (F. C. or J. K.) and each infant's performance was scored independently by two observers, both of whom were physical therapists experienced with young children. Correlation between observers, with pre- and posttreatment scores combined, was 0.90 for the reflex test and 0.98 for the motor skills test. Infants' scores were rank-ordered on the basis of the sum of the pretreatment mean scores on both tests, and infants were assigned as matched pairs to either the treatment (N = 13) or the control group (N = 13). To control for handling effects, the control group was subdivided into control handled (CH) (N = 6) and control nonhandled groups (CNH) (N = 7).

Each infant assigned to the treatment group received 16 sessions of semicircular canal stimulation during the 4 weeks after the pretreatment week. Two sessions, separated by 30 minutes, were given on each of 2 days of every week. The session days were separated alternately by 1 and 4 days. A session consisted of ten spins in a rotating chair. One of the investigators held the infant in his lap while he sat in the rotating chair in a dark room. Each spin consisted of a rapid (1- to 3-second) angular acceleration, a 1-minute period of constant velocity rotation at 100 deg/sec (16.7 rev/min), followed by an impulsive stop in less than 1 second. The infant was held in an upright sitting position during two spins, one clockwise (CW) and one counterclockwise (CCW), with his head tilted forward at about 30°, which placed the horizontal semicircular canals in the horizontal plane. The infant was shifted to a side-lying position to place one anterior and the opposite posterior semicircular canal in the horizontal plane during four spins, two CW and two CCW, alternating directions. The side-lying position was then reversed during four spins, two CW and two CCW, alternating direc-

Table 1. Mean scores on the reflex and motor skills tests before and after adjustment with the covariate; T, treatment group (N = 13); CH, control handled group (N = 7); CNH, control nonhandled group (N = 6); S.D., standard deviation.

Group	Pretreatment	Posttreatment		
	Unadjusted (mean ± S.D.)	Adjusted (mean)	Unadjusted (mean ± S.D.)	Adjusted (mean)
		Reflex test		
T	50.54 ± 11.87		62.54 ± 5.64	63.03
CH	55.83 ± 8.68	51.52	58.00 ± 9.73	55.83
CNH	49.64 ± 10.54		53.93 ± 7.76	54.87
		Motor skills test		
T	59.00 ± 34.84		86.38 ± 35.66	85.95
CH	68.17 ± 32.49	58.56	77.83 ± 35.10	68.40
CNH	49.50 ± 33.30		60.50 ± 39.94	69.39