UC Irvine

UC Irvine Previously Published Works

Title

Paradoxical response to sedative/hypnotics in patients with Self-injurious behavior and stereotypy

Permalink

<https://escholarship.org/uc/item/2xd083wh>

Journal

Journal of Developmental and Physical Disabilities, 4(4)

ISSN

1056-263X

Authors

Sandman, CA
Barron, JL

Publication Date

1992-12-01

DOI

10.1007/BF01047433

Copyright Information

This work is made available under the terms of a Creative Commons Attribution License, available at

<https://creativecommons.org/licenses/by/4.0/>

Peer reviewed

Paradoxical Response to Sedative/Hypnotics in Patients With Self-Injurious Behavior and Stereotypy

Curt A. Sandman^{1,3} and Jennifer L. Barron^{2,4}

Paradoxical response to sedative medication has been reported previously among patients with Self-injurious (SIB) and Stereotypic (ST) Behavior (Barron and Sandman, 1983, 1985). The prevalence of this marker was examined in 648 consecutive developmentally delayed patients tested in the EEG laboratory. Several analyses compared response to sedative/hypnotics, assessment of the EEG, and behavioral profiles from the most recent annual comprehensive behavioral/medical evaluation (CDER). The presence of SIB and ST were significantly related to paradoxical response. The EEG was not related to paradoxical response, but had fewer epileptic foci in frequent or severe SIB and/or ST.

KEY WORDS: paradoxical; response; sedative/hypnotics; self-injurious behavior; stereotypy.

INTRODUCTION

Self-injurious behavior (SIB) occurs among 40% of institutionalized psychotic and autistic children (Green, 1967; Shodell and Reiter, 1968) and between 7-19% of mentally retarded individuals (MacKay *et al.*, 1974; Maisto *et al.*, 1978; Schroeder *et al.*, 1978). Aversive stimulation has been modestly effective in reducing moderate and high-intensity or life-threatening SIB (Romanczyk and Goren, 1975). However, SIB re-emerges when the patient is withdrawn from these treatment environments (Lovaas and Simmons, 1969; Romanczyk and Goren, 1975).

¹State Developmental Research Institutes.

²Fairview Developmental Center, 2501 Harbor Blvd., Box 5A, Costa Mesa, California 92626.

³Department of Psychiatry, University of California, Irvine, California 92664.

⁴Department of Pediatrics, University of California, Irvine, California 92664.

Table I. Description of the Patients in the Paradoxical Response Study

Modal prevalence	
Sex	Males = 348 Females = 300
Age (years)	31.6 $\pm$ 8.5
Length of institutionalization (years)	22.9 $\pm$ 7.1
Level of mental retardation	Profound/severe
Degree of cerebral palsy	Mild/moderate
Degree of hearing loss	None/mild
Degree of vision loss	Moderate
Number of psychotropic drugs	Zero/one
Level of aggression	Verbal/not physical
Frequency of sib	Monthly/3 times year
Severity of sib	No injury
Evidence of depression	Minimal
Frequency of stereotypy	Daily/response to stress
Level of hyperactivity	Controlled
Frequency of temper tantrums	Monthly
Response to sedative/hypnotics	Light sleep
EEG Abnormalities	Slightly abnormal

Note: Capitals reflect most prevalent rating and lower case reflects next relevant rating.

Previous studies suggested that paradoxical responding to sedative/hypnotic drugs in patients with self-injurious behavior (SIB) and stereotypy (ST) may be a marker of endogenous opiate dysfunction (Barron and Sandman, 1983, 1985). Patients with SIB and/or ST remained awake and either were resistive, combative, restless, uncooperative, or abusive after administration of sedative/hypnotics. Although the direct mechanism underlying this behavior is not evident from these data, this behavior may be valuable as an index of subgroups of patients with opiate dysregulation.

The present study was conducted to extend previous studies of the relationship between SIB, ST, and paradoxical response in a large sample of patients. In addition relationships were included among SIB, other behaviors and neurological status.

METHOD

Subjects

From a population of 1240 patients, 648 with reliable data for response to sedative/hypnotics and measures of the EEG were included. The general characteristics of the sample are presented in Table I. In this

Table II. Rating Scale for the EEG

1	NORMAL Essentially normal. No Abnormality seen. Within normal limits
2	ABNORMAL Generalized epileptic discharges
3	SLIGHTLY ABNORMAL Mild, diffuse slow wave disorder
4	MILDLY ABNORMAL Excessive or diffuse slowing, generalized slowing, poor organization
5	MODERATELY ABNORMAL Generalized or diffuse cerebral involvement or dysfunction, active epileptic discharges
6	MARKEDLY ABNORMAL Extremely or very active epileptic discharges
7	GROSSLY ABNORMAL Extremely active and severe epileptic discharges bisynchronous and multi-focal

population, 36.5% of the patients exhibited SIB at least yearly. SIB occurred daily in 8.4% of the patients and weekly in 10.2%. Some form of ST was observed in 52.2% of the patients.

Procedure

A consecutive series of patients was followed through the EEG laboratory. Patients receiving sedative/hypnotics for performance of the EEG were rated for level of sedation. Ratings were observations made upon arrival at the EEG clinic with the following scale; 1 = light sleep, 2 = wake/sleep, 3 = awake/nervous, 4 = awake/resistive (Barron and Sandman, 1983). Dosage levels were not manipulated parametrically but followed the general rules governing clinical practice. Typically, patients were administered the sedative in their residence and were brought to the clinic with postural support. Staff physicians determined probable effective dosage based on weight and history. Although an attempt was made to consider dose/behavior relationships, it was not possible to do so in a reliable manner.

The rating system for the EEG was supervised by a neurologist and is presented in Table II. Blind ratings were made from paper tracings and the degree of abnormality generally reflected the presence of epileptic foci. Other patient behavior was obtained from the most recent Client Development Evaluation Report (CDER) which is completed for each patient annually. Aggression, depression, ST, SIB, hyperactivity, and temper tantrums

Fig. 1. Level of paradoxical response to sedative/hypnotics (low number indicates sedation) in patients who are SIB and ST ($2.29 \pm .002$ SEM); SIB only ($1.89 \pm .001$ SEM) or neither SIB nor ST ($1.85 \pm .001$ SEM).

were rated on a 4- or 5-point scale with the lowest number (1) representing the most severe or frequent rating. Levels of mental retardation, cerebral palsy, hearing and visual impairment were rated with *highest* numbers representing the most severe or frequent occurrence.

RESULTS

Analysis of Variance

Previous findings were re-examined by comparison of paradoxical response with a 2 (presence of SIB vs. no SIB) $\times$ 2 (presence of ST vs. no ST) analysis of variance. A main effect of SIB ($F(1,591) = 6.54$, $p < .01$) and ST ($F(1,591) = 6.50$, $p < .01$) and their interaction ($F(1,591) = 4.64$, $p < .03$) replicated two earlier studies (Barron and Sandman, 1983, 1985) with much smaller samples. As illustrated in

Fig. 2. Paradoxical response in patients with high levels of SIB and/or ST (not related to environmental factors) in patients with SIB and ST ($2.4 \pm .002$ SEM), SIB only ($1.8 \pm .001$ SEM), ST only ($1.9 \pm .002$ SEM) or neither behavior ($1.8 \pm .002$ SEM).

Fig. 1, the SIB + ST group had the highest incidence of paradoxical responding. Because age was significantly related to SIB and ST, a subsequent analysis was computed with age as a covariate. The results were virtually identical except that level of significance was slightly lower for the main effects but greater for the interaction ($F(1,590) = 5.51$, $p < .01$).

A subsequent ANOVA included only patients with high frequency SIB and ST that was judged by clinical staff to be unrelated to environmental influence. Thus, patients were excluded if they exhibited frequent, environmentally-induced (stress) SIB and ST or very infrequent SIB or ST. With age as covariate, the interaction of SIB and ST on paradoxical responding was highly significant ($F(1,490) = 8.58$, $p < .001$). As illustrated in Fig. 2, the order of the effects were consistent with the previous analysis.

Table III. Correlations Among Patient Characteristics Including Paradoxical Response and EEG with SIB and ST

	Age	SIB severity	SIB frequency	ST frequency
Age		-.19*	-.15*	-.11*
Sex		.02	.01	.07
Length of institutional		.07	.04	-.08
Level of mental retardation ^a		.04	-.01	-.07
CP ^a		.23*	.23*	.24*
Hearing ^a		-.07	.04	-.02
Vision ^a		-.03	.01	-.04
Number of psychotropics		-.17*	-.14*	.08
Level of aggression ^b		.15*	.38*	.09
Evidence of depression ^b		.11*	.06	.04
Stereotypy ^b		.25*	.23*	N/A
Hyperactivity ^b		.24*	.24*	.16*
Frequency of temper tantrums		.43*	.46*	.13*
Response to sedatives ^b		.17*	-.14*	-.15*
EEG Abnormalities ^a		.27*	.28	.27*

*Note. $r = .011$

^a Highest rating indicates most abnormal.

^b Lowest rating indicates most abnormal.

Correlational and Factor Analysis

Correlations between patient characteristics and SIB severity and frequency are presented in Table III. Severity of SIB was correlated 0.82 ($p < .0001$) with frequency. Increases in both frequency ($r = -0.14$, $p < .01$) and severity ($r = -0.17$, $p < .01$) of SIB were significantly correlated with greater incidence of paradoxical responses to sedative/hypnotic medication. Both SIB severity and frequency were related to less severe neurological abnormalities detected in the EEG ($r = 0.27$ and 0.28 , respectively). It is apparent that a large number of variables were statistically (all < 0.01) related to both SIB severity and frequency.

Several other findings were of interest. First, because frequency and severity of SIB were highly related, variables that discriminated these behaviors were determined. Depression was significantly ($p < .01$) related to severity but not frequency of SIB. Conversely, aggression was related to SIB frequency but only marginally to SIB severity. Both severity and frequency of SIB were highly related to frequency of temper tantrums. There was no relationship between sensory loss and ST with hearing loss ($r = -.02$) or visual loss ($r = -.04$). The relationship between paradoxical response and EEG was at the chance level ($r = -.07$).

A Kaiser normalized, factor analysis was computed on a subset of 10 variables of interest with complete data for 648 patients. The variables were age, sex, level MR, number psychotropics, frequency of SIB, severity of SIB, ST, hyperactivity, paradoxical response, and EEG. (The correlational values in this sample remained unchanged). The Principal Components solution was constrained to three factors. The first factor accounted for 24% of the variance and reflected the communalities among severity and frequency of SIB, frequency of ST, the EEG, age, and presence of paradoxical responding (direction of these relations are evident in Table III). The second factor accounted for another 13% of the variance and illustrated the relationship among age, level of MR, and dependence on psychotropics. The third factor explained 11% of the variance and reflected the relationship between hyperactivity and ST.

DISCUSSION

The purpose of this study was to examine the relationship among SIB, ST, and response to sedative/hypnotics. Neurological status of patients with SIB and ST was determined by evaluation of the EEG during sedation. In addition, several demographic variables and behavioral profiles were related to SIB and ST. Reliable relationships were found among SIB, ST and paradoxical responding to sedative/hypnotics replicating earlier findings with smaller samples of patients selected for a higher prevalence of paradoxical excitement (Barron and Sandman, 1983, 1985). Both frequency and severity of SIB were significantly ($p < .01$) related to the degree of paradoxical response. These variables, plus ratings of the EEG and age, congregated on the first factor of a Principal Component solution. Factorial modelling, suggested that the *presence* and *rate* of SIB and ST, predicted paradoxical excitement. Level of significance was slightly greater when only higher frequency patients were entered into the model.

It remains a curious finding, now repeated four times (Barron and Sandman, 1983, 1985; Sandman *et al.*, 1990), that paradoxical responding is most prevalent in patients with both SIB and ST. It has been argued

that SIB and ST are related, but that SIB is the most maladaptive or regressed expression on a behavioral continuum (Barron and Sandman, 1983; Cataldo and Harris, 1982). This argument implies that co-occurrence of SIB and ST should be rare, but both often are exhibited by patients. Further, paradoxical excitement is highly prevalent only in patients with both SIB and ST (see Figs. 1 and 2), and patients with both SIB and ST have the highest B-endorphin levels (Sandman *et al.*, 1990). These data suggest that there may be three distinct groups of patients manifesting SIB and/or ST and that the biological mechanisms responsible for the expression of symptoms may be distinct.

The relationship of neurological status to behavior was measured by the level of epileptic abnormality of the EEG. Increasing epileptic abnormality was related to absence of both SIB and ST and there was no relationship between EEG and paradoxical response. It has been suggested that SIB and ST are seizures without recognizable EEG signs (Gedye, 1989). Alternatively, occurrences of epilepsy and SIB or ST may be mutually exclusive. Careful trials with anticonvulsants (see Langee, 1989) in patients with ST and SIB may be warranted even though anecdotal reports indicate they may be ineffective.

Finally, these results can be compared with earlier demographic studies of SIB. The prevalence of daily SIB in institutionalized populations (8.4%) though slightly lower than the Ross (1972) survey of 12%, is within the range of other investigators (Maisto *et al.*, 1978; Schroeder *et al.*, 1974; Smeets, 1971). The estimate of SIB occurring at least three times within a year in 36.5% of our institutionalized population is difficult to compare with previous studies because of differences in the method and criteria of reporting. Sex, level of retardation (though our range was restricted), and length of hospitalization were not related to SIB or ST (see Schroeder *et al.*, 1978). SIB was more frequent in older patients, in patients receiving psychotropic medications, and correlated with aggression, temper tantrums, ST, and hyperactivity. Depression was related to severity but not frequency of SIB (see also Pirodsky *et al.*, 1985). The profile of behaviors was similar for ST, except for the relationship with aggression.

This study confirmed previous relationships among SIB, ST, and paradoxical response to sedative/hypnotics (Barron and Sandman, 1983, 1985; Sandman *et al.*, 1990). Speculations (Barron and Sandman, 1983, 1985) connecting this response with the opiate system have received tentative support from direct studies of the opiate system in SIB (Gillberg *et al.*, 1985; Sandman *et al.*, 1990; Wiezman *et al.*, 1984). The ability of opiate blockers to attenuate SIB and perhaps ST (Barrett *et al.*, 1989; Campbell *et al.*, 1988; Herman *et al.*, 1987; Richardson and Zaleski, 1983; Sandyk, 1985; Sandman *et al.*, 1983; Sandman, Barron, and Colman, 1990; Sandman, Barron,

Crinella, and Donnelly, 1987) supports the role of the opiates in this syndrome. Future studies of paradoxical responding will determine whether it is a marker of specific neurochemical and perhaps opiate dysregulation in SIB.

ACKNOWLEDGMENTS

The invaluable support of Francis Crinella, Director, SDRI, Hugh Kohler, Director and Lou Sarrao, Clinical Director, Fairview Hospital, is gratefully acknowledged. The assistance of Betty Kelley and Eileen Brennen is appreciated. Supported in part by grant number R01-MH41446 from NIMH (CAS).

REFERENCES

- Adamson, W. C., Nellis, B. P., Runge, C., Cleland, C., and Killian, E. (1958). Use of tranquilizers for mentally deficient patients. *J. Dis. Child.* 96: 154-164.
- Barrett R. P., Feinstein C., and Hole W. T. (1989). Effects of Naloxone and Naltrexone on Self-Injury: A double blind, placebo-controlled analysis. *Am. J. Ment. Retard.* 93: 644-651.
- Barron, J. L., and Sandman, C. A. (1985). Paradoxical excitement to sedative-hypnotics in mentally retarded clients. *Am. J. Ment. Def.* 2: 124-129.
- Barron, J. L., and Sandman, C. A. (1983). Relationship of sedative-hypnotic response to self-injurious behavior and stereotypy in mentally retarded clients. *Am. J. Ment. Def.* 88-2: 177-186.
- Campbell, M., Adams, P., Small, A. M., Tesch, L. M., and Currens, E. L. (1988). Naltrexone in infantile autism. *Psychopharmacol. Bull.* 24: 135-139.
- Campbell, M. C., Overall, J. E., Small, A. M., Sokol, M. S., Spencer, E. K., Adams, P., Foltz, R. L., Monti, K. M., Perry, R., Nobler, M., and Roberts, E. (1989). Naltrexone in autistic children: An acute open dose range tolerance trial. *J. Am. Acad. Child. Adol. Psychiatry* 28: 200-206.
- Cataldo, M. F., and Harris, J. (1982). The biological basis for self-injury in the mentally retarded. *Anal. Intervent. Devel. Dis.* 2: 21-39.
- Deuth, S. I. (1989). Rationale for the administration of opiate antagonists in treating infantile autism. *Am. J. Ment. Retard.* 631-635.
- Gedye, A. (1989). Extreme self-injury attributed to frontal lobe seizures. *Am. J. Ment. Retard.* 94: 20-26.
- Gillberg, C., Terenius, and Lonneholm, G. (1985). Endorphin activity in childhood psychosis. *Arch. Gen. Psychiatry* 42: 780-783.
- Green, A. H. (1967). Self-mutilation in schizophrenic children. *Arch. Gen. Psychiatry* 17: 234-244.
- Herman, B. H., Hammock, M. K., Arthur-Smith, A., Egan, J., Chatoor, I., Werner, and A., Zelnik, N. (1987). Naltrexone decreases self-injurious behavior. *Ann. Neurol.* 22: 550-552.
- Langee, H. R. (1989). A retrospective study of mentally retarded patients with behavioral disorders who were treated with carbamazepine. *Am. J. Ment. Retard.* 93: 640-643.
- Loovas, O. I., and Simmons, J. Q. (1969). Manipulation of self-destructive behavior in three retarded children. *J. Appl. Behav. Anal.* 2: 143-157.
- Maisto, C. R., Baumeister A. A., and Maisto A. A. (1978). An analysis of the variables related to self-injurious behavior among institutionalized retarded persons. *J. Ment. Def. Res.* 22: 27-35.

- Pirodsky, D. M., Gibbs, J. L., Hesse, R. A., Heish, M. C., Krause, R. B., and Rodriquez, W. H. (1985). Use of dexamethasone suppression test to detect depressive disorders of mentally retarded individuals. *Am. Ment. Def.* 90: 245-252.
- Richardson, J. S., and Zaleski, W. A. (1983). Naloxone and self-mutilation. *Biol. Psychiatry* 18: 99-101.
- Romanczyk, R. G., and Goren E. R. (1975). Severe self-injurious behavior: The problem of clinical control. *J. Consult. Clink. Psychol.* 43: 730-739.
- Ross, D. L., Klykylo, W. M., and Hitzemann, R. (1986). Reduction of elevated CSF beta-endorphin by fenfluramine in infantile autism. *Pediat. Neurol.* 3: 83-86.
- Ross, R. T. (1972). Behavior correlates of levels of intelligence. *Am. J. Ment. Def.* 76: 545-549.
- Sandman, C. A., Barron, J. L., Crinella, F. M., and Donnelly, J. F. (1987). Influence of naloxone on brain and behavior of a self-injurious woman. *Biol. Psychiatry* 22: 99-906.
- Sandman, C. A., Barron, J. L., and Colman, H. (1990). An orally administered opiate blocker, Naltrexone attenuates self-injurious behavior. *Am. J. Ment. Retard.* 95: 93-102.
- Sandman, C. A., Barron, J. L., Chicx-DeMet, A., and DeMet, E. (990). Plasma B-endorphin levels in patients with self-injurious behavior and stereotypy. *Am. J. Ment. Retard.* 7: 84-92.
- Sandman, C. A., Datta, P., Barron, J. L., Hoehler, F., Williams, C., and Swanson, J. (1983). Naloxone attenuates self-abusive behavior in developmentally disabled clients. *Appl. Res. Ment. Retard.* 4: 5-11.
- Sandyk R. (1985). Naloxone abolished self-injuring in a mentally retarded child. *Ann. Neurol.* 17: 520.
- Schroeder, S. R., Schroeder, C. S., Smith, B., and Dalldorf, J. (1978). Prevalence of self-injurious behavior in a large state facility for the retarded. A three-year follow-up study. *J. Aut. Child. Schiz.* 8: 261.
- Shodell, M., and Reiter H. (1968). Self-mutilative behavior in verbal and non-verbal schizophrenic children. *Arch. Gen. Psychiatry* 19: 453-455.
- Smeets, P. M. (1971). Some characteristics of mental defectives displaying self-mutilative behaviors. *Train. School Bull.* 68: 131-135.
- Weizman, R., Weizman, A., Tyano, S., Szekeley, B. A., and Sarne, Y. H. (1984). Humoral-endorphin blood levels in autistic, schizophrenic and healthy subjects. *Psychopharmacology* 82: 368-370.