Psychopharmacologia (Berl.) 15, 144—152 (1969)

The Behavioral Effects of Nicotinamide Adenine Dinucleotide in Chronic Schizophrenia*

HERBERT MELTZER**, RICHARD SHADER, and LESTER GRINSPOON

Department of Psychiatry, The University of Chicago, Chicago, Illinois and Massachusetts Mental Health Center, Boston and Harvard University, Department of Psychiatry, Boston, Massachusetts

Received November 12, 1968
Final Version: March 24, 1969

Summary. Two grams of NAD were administered orally to ten chronic schizophrenic patients for twenty-one days. Five of the patients were also receiving thioridazine. There was no gross clinical improvement noted in any of the patients despite the fact that related experiments suggested that the NAD was absorbed. In those patients who were not also receiving phenothiazines there was a distinct tendency towards increased hostility, aggressiveness and irritability beginning one week after the initiation of NAD treatment and lasting for nearly two weeks after the NAD was discontinued.

Key-Words: Niacin — Nicotinamide Adenine Dinucleotide — Schizophrenia — Phenothiazines — Psychopharmacology.

Introduction

The use of nicotinamide adenine dinucleotide (NAD) and the precursors of its nicotinamide moiety, nicotinamide and nicotinic acid, as treatment modalities for acute and chronic schizophrenia have been of considerable interest in the last decade. HOFFER and OSMOND have found a significant reduction in the requirement for readmission to mental hospitals of acute schizophrenic patients who have received nicotinamide or nicotinic acid along with other treatments such as electroconvulsive therapy, insulin subcoma and supportive psychotherapy (HOFFER *et al.*, 1957). Repeated follow-up studies by these authors, including five and ten year periods, have continued to show the usefulness of these drugs in reducing the need for rehospitalization (HOFFER, 1962; HOFFER and OSMOND, 1965). These studies of effects of nicotinamide and the acid on acute schizophrenics have been criticized on the grounds of inadequate statistical treatment, discrepencies between control and test groups,

* This study was supported by U. S. Public Health Service Grant No. 5-P01-MH-12556-02 and a grant from the Otho S. A. Sprague Foundation.

** Present address: Department of Psychiatry, University of Chicago, 950 East 59th Street, Chicago, Illinois 60637.

and the choice of criteria for differences between control and test groups (EIDUSON *et al.*, 1964; MELTZER, 1966). No effect of nicotinamide or nicotinic acid on chronic schizophrenic patients was found by HOFFER or other investigators (HOFFER, 1965; ASHBY *et al.*, 1960). Recently HOFFER has claimed large doses of NAD produced extremely rapid and significant improvement even in chronic schizophrenic patients (HOFFER, 1966). The first published efforts to replicate these studies showed no positive clinical effect of NAD on chronic schizophrenic patients (KLINE, 1967; GALLANT *et al.*, 1966; NICHOLS *et al.*, 1967).

The study reported here undertook to assess the effects of NAD on ten male chronic schizophrenic patients who had been intensively studied for a two year period. In addition, possible clinical interaction between NAD and a phenothiazine, thioridazine, was investigated because of previous reports of possible synergistic action between the tranquilizing or sedative properties of chlorpromazine and reserpine, and nicotinamide, in man and animals (BURTON *et al.*, 1960; KORNETSKY, 1963).

Methods

Subjects and Experimental Design

The patients who participated in this investigation were ten male chronic schizophrenic patients who were being treated and studied at the Clinical Research Center of the Massachusetts Mental Health Center. All were single, between the ages of twenty and thirty-five, in good physical health and good nutritional status, and all had been hospitalized for at least five years prior to the present study. Following their transfer to the Clinical Research Center from a nearby State Hospital all patients received capsules containing placebo for three months, after which five were randomly assigned to continue on placebo and five were designated to receive thioridazine orally. The nursing and medical staff, except for one of the authors (L. G.), were blind to the nature of the medication each subject received.

After about two years of the above regimen, the current study was begun. All patients began to receive, in addition to the project capsules, tablets which contained either NAD or placebo. Group A patients who had been receiving and continued to receive inactive capsules, received tablets which contained inert filler for the first week, 2.0 g NAD during the next three weeks, and inert filller for the final three weeks of the study. Group B patients who had been receiving and continued to receive thioridazine 400—800 mg/per day, in addition received inactive tablets the first three weeks of this study, 2.0 g of NAD during weeks four-to-six, and inactive tablets the last three weeks of this study.

Absorption of NAD

In order to prevent destruction of NAD in the stomach, the tablets were coated with five thin layers of shellac. The U.S.P. tests for enteric coating were performed; the shellac-coated tablets withstood hydrochloric acid at pH 1.7 for one hour and then disintegrated within forty-five minutes at pH 7.5.

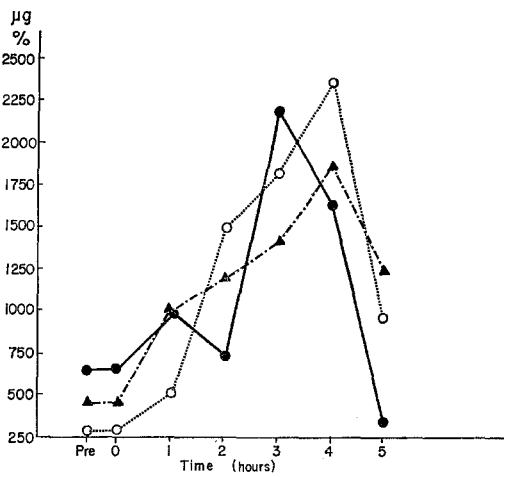

Fig. 1. Blood level of nicotinamide adenine dinucleotide.
Each plot represents a different subject. Determination according to the LOWRY *et al.* modification of the method of KAPLAN *et al.* (LOWRY *et al.*, 1957; KAPLAN *et al.*, 1951)

The biological activity of the NAD in the tablet after compounding and coating was determined by grinding the finished tablet and assaying NAD spectrophotometrically (KAPLAN *et al.*, 1951; LOWRY *et al.*, 1957). Since the NAD in the coated tablet was found to be 85—90% active as a co-factor in the dehydrogenation reaction, each tablet was considered to contain approximately 200 mg of NAD.

To determine if the enteric coating was effective *in vivo*, 1.0 g of the NAD in tablet form was given to three normal volunteers. Blood levels of NAD were obtained prior to drug administration and hourly during the next eight hours using the methods cited above. A three-to-five fold increase in NAD and NADH was noted in three-to-four hours; by six hours, blood NAD and NADH levels had returned to baseline levels (Fig. 1 and 2).

Psychiatric Evaluation

1. Inpatient Multidimensional Psychiatric Scale (IMPS)

As part of the ongoing longitudinal research each patient was rated weekly with the IMPS (LORR *et al.*, 1962) by each of two trained raters who were blind to the nature of the medication the patients were receiving. For the purpose of this report the scores used were the weekly averages

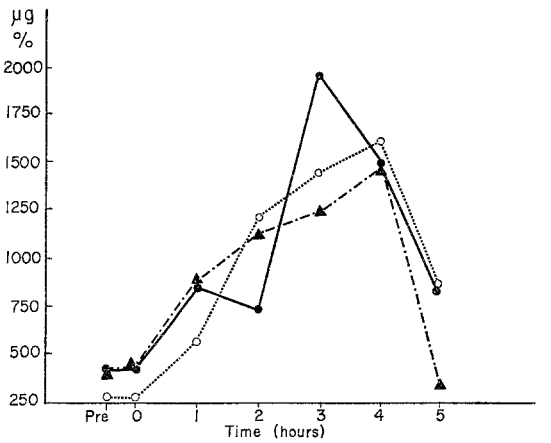

Fig. 2. Blood level of nicotinamide adenin dinucleotide, reduced

of the two raters for each patient. Means were obtained for each patient for each three week period. We have focused on the Hostile Belligerence Subscale and on a second order factor or cluster of subscales called Schizophrenic Disorganization. Hostile Belligerence reflects Verbal Hostility, Contempt, Hostile Attitudes, Irritability, Blaming of Others, Bitterness, Complaints, and Suspiciousness. The Schizophrenic Disorganization cluster is derived by combining the subscales: Conceptual Disorganization, Retardation and Apathy, Disorientation, and Motor Disturbances.

2. Behavioral Disturbance Index (BDI)

Each patient was also rated on a modified form of the BDI, a 54-item scale which reflects the degree to which a patient's behavior, thinking processes, and effect are disturbed (FRAMO and ADLERSTEIN, 1961). Our use of this scale has been previously reported (COHLER *et al.*, 1966). For the purpose of this report daily individual patient ratings done by members of the nursing staff were averaged into weekly mean total BDI scores for each patient and were then averaged for each three week period.

3. Observations by Psychiatrists and Nursing Staff

The two ward psychiatrists saw the patients daily and made an evaluation of global clinical status every two weeks during the study. During each eight hour nursing shift, reports were made by nursing staff of each patient's general condition as well as any unusual behavior.

Results and Data Analysis

Behavioral Changes

In order to evaluate the effects of NAD, with and without thioridazine, data was arranged into three phases: a three week pre-NAD period; a three week NAD period; and a three week post-drug period. The ratings for each patient on each of the variables (BDI total scores, IMPS—Schizophrenic Disorganization Cluster, and IMPS—Hostile Belligerence Subscale) for each of these phases were then used to obtain group mean scores for each variable for the two treatment groups during each period. One patient in Group A (the non-thioridazine group) was so destructive and potentially homicidal that he was given large amounts of supplementary chlorpromazine prior to and during this study. Since he cannot properly be considered a placebo patient, the data gathered on him during this study were not included in these analyses.

The data for the four patients in Group A and the five patients in Group B are summarized in the Table.

Table. *Behavioral Ratings in all Phases of the Drug Study*

	Pre-NAD	NAD	Post-NAD
Mean BDI Total Scores			
Group A ($N = 12$)	33.17 (12.09)	37.30 (12.28)	36.93 (11.39)
Group B ($N = 15$)	23.91 (13.98)	24.25 (12.37)	32.43 (18.43)
Mean Hostile Belligerence Ratings			
Group A ($N = 12$)	17.58 (3.36)	20.08 (7.12)	21.24 (3.99)[a]
Group B ($N = 15$)	11.19 (8.00)	9.33 (9.32)	9.00 (9.19)
Schizophrenic Disorganization Cluster Ratings			
Group A ($N = 12$)	66.17 (32.40)	64.56 (27.71)	69.21 (23.06)
Group B ($N = 15$)	35.95 (29.74)	39.99 (34.18)	46.50 (37.92)

(Standard deviation).

[a] Significantly different from pre-NAD rating at the 0.05 level of confidence.

Group A patients showed an increase in their Behavioral Disturbance Index ratings and Hostile Belligerence ratings, indicating a deterioration in those aspects of their behavior which these indices reflect, when the NAD period is compared with the pre-drug period. This deterioration tended to persist into the immediate post-drug period. Data not shown in the table indicated that three weeks after the NAD was stopped the patients in Group A returned to their pre-drug level of functioning. All of the Group A patients showed a worsening of their BDI total scores during the NAD period as compared to the pre-drug period. Two of the Group A patients showed very large increases in the Hostile Belligerence Subscale in the NAD phase as compared to the pre-drug phase while two showed essentially no change. Group B patients did show some slight improvement when receiving NAD as noted by the modest decrease in the Hostile Belligerence Subscale ratings in the NAD phase as compared to the pre-NAD phase. The BDI ratings were essentially unchanged in the Group B patients while on NAD but increased in four of five Group B patients after NAD was discontinued and inert tablets substituted. Schizophrenic Disorganization Cluster scores showed negligible changes with NAD for Groups A and B but four of five Group B patients also had increased ratings for Schizophrenic Disorganization in the post-NAD period.

In order to evaluate the statistical significance of the observed changes these data were tested with two-tailed *t*-tests by comparing group ratings in the NAD and post-NAD period with the corresponding ratings in the pre-NAD period. None of the changes in group means during the NAD period achieved statistical significance at the 0.05 level of confidence. The increased Hostile Belligerence ratings of the Group A patients post-NAD was significantly different from the pre-drug ratings at the 0.05 level of confidence. However, the small size of the sample makes the actual clinical significance of this finding uncertain. This was the only such comparison which was statistically significant.

Comment

In none of our ten patients, six of whom were also receiving large amounts of phenothiazines, was there any dramatic clinical improvement, such as HOFFER has reported in many of his subjects (HOFFER, 1966), The explanation of the difference between HOFFER's results and the four investigations, including the present one, which have failed to replicate his study is not readily apparent. Our preliminary studies on the coating, absorbability and biological activity indicate that the dose of NAD used in this study (two grams per day for twenty-one days) was as large or larger than the amount used in the favorable study (one-two grams

per day for as little as three days). All of the patients in both groups, though chronically psychotic, had, during the two year period which preceded this study, experienced distinct changes in their clinical state in response to changes in phenothiazine medication, psychotherapy or other factors. Thus, this was a population of patients whose illness was not so fixed or unalterable that one could have little expectation of improvement from even the most efficacious of therapies. For example, the mean weekly BDI scores for Group B patients prior to being started on thioridazine was 28.94 $\pm$ S.D. 13.40 but after eight weeks of drug treatment, it had dropped to 15.43 $\pm$ S.D. 4.70. It was consistently possible with the Group B patients to show on a blind basis, clinical change after discontinuing or renewing treatment with thioridazine (Grinspoon *et al.*, 1968). The Group A patients had a small variance in their behavior ratings but they did manifest clinical change. For example, BDI scores for the Group A patients showed a consistent, if slight drop, during the first three months of hospitalization. The lack of improvement in Group A and Group B patients while receiving NAD does constitute a failure to replicate Hoffer's finding of very rapid response to NAD in even very chronic patients (Hoffer, 1966) but it has not been determined if the drug would be of value in acute patients or in chronic patients, after a longer period of administration.

Instead of the hoped for clinical improvement, our studies indicate a tendency for the group of patients who received NAD without thioridazine (Group A) to show a worsening in their clinical state. This was evident in clinical observation by the psychiatric staff who noted that the patients in Group A became more angry, negativistic, belligerent and irritable. It was also reflected in the total BDI ratings and the Hostile Belligerence syndrome of the IMPS but these changes were not statistically significant except for the Hostile Belligerence ratings in the post-NAD period. The disturbances in the Group A patients were similar in character to other disturbances of these same patients during various phases of their two year stay on the research ward. What was striking was their simultaneous occurrence, albeit to varying extents, in all the four patients who received NAD without also receiving a phenothiazine and their gradual subsidence after NAD was stopped and the patients were returned to placebo medication.

None of the other studies which have involved the administration of NAD to chronic schizophrenics have reported comparable data but it might well have been overlooked if the focus was on clinical improvement. In fact, one of the rating scales used by Kline *et al.*, the Rockland Rating Scale, indicates that six out of nine of their patients given NAD showed some increase in hostility, three moderately severe, while two showed significant lessening of their hostility (Kline *et al.*, 1967). The hostility

factor in the Brief Psychiatric Rating Scale which was also used in this study showed no such change. Only three of the ten controls showed any increase in hostility, only one of which was moderately severe.

The Group B patients who received thioridazine prior to and along with NAD became somewhat more behaviorally disturbed but not cognitively disturbed during the NAD treatment period but not to the same extent that the Group A patients did. However, the Group B patients showed no increase in hostility or aggressiveness. This would suggest that there are no profound synergistic actions of NAD and phenothiazines.

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Dr. Herbert Meltzer
The University of Chicago
950 East 59th Street
Chicago, Ill. 60637, U.S.A.