THE COENZYME NICOTINAMIDE ADENINE DINUCLEOTIDE (NADH) AS BIOLOGICAL ANTIDEPRESSIVE AGENT EXPERIENCE WITH 205 PATIENTS

J.G.D.Birkmayer, W.Birkmayer

Birkmayer Institute for Parkinson Therapy, Vienna, Austria

SUMMARY

The coenzyme nicotinamide adenine dinucleotide (NADH) has been used in an open label trial as medication in 205 patients sufferring from depression with various clinical symptoms. NADH was given orally, intramuscularly or intravenously. The duration of therapy ranged from 5 to 310 days. 93% of the patients exhibisted a beneficial clinical effect. An improvement up to 44 with a mean value of 11,5 was observed.

KEY WORDS

Depression, NADH, Neurotransmitter, Catechnolamines

INTRODUCTION

Depression is a neuro-psychiatric disorder which disturbs the behaviour, the physical and mental activity, the emotional effectiveness and many other features which are essential for an active life with a balanced mood. A number of studies revealed that certain neurotransmitters, in particular norepinephrine, dopamine, serotonin and their metabolites play a role in the evolving depressive symptoms (10, 11, 14, 20).

Post mortem biochemical analysis of the brain of depressive patients found changes in the neurotransmitter concentration of norepinephrine, dopamine and serotonine. They were significantly reduced in nucleus ruber, nucleus caudatus and nucleus anygdalae (19). These changes in neurotransmitter concentrations may be responsible for an intraneuronal dysfunction which may be reflected in the variety of clinical symptoms.

It has been observed that many Parkinsonian patients suffer from depressive symptoms (3, 4). There are several reports on the improvement of depression after L-DOPA medication (9, 12, 13).

When treating our Parkinsonian patients with the new medication Nicotinamide adenine dinucleotide (NADH) we observed that the depressive symptoms disappeared. This observation promted us to study the clinical effect of NADH on patients suffering from psychic depression.

METHODS

In an open label trial 205 patients sufferring from depression have been treated with the coenzyme ß-Nicotinamide adenine dinucleotide in its reduced form (*NADH*). Diagnosis and the grade of severity of the depression were established according to the depression scale of Ambrozi - Birkmayer - Neumayer (2).

NADH was given parenterally as well as orally. The parenteral form was applied either intravenously or intramuscularly. NADH (Synonymns: ßNADH, reduced DPN, ß-DPNH) was obtained from Boehringer Mannheim (Germany). For the i.m. injection 12.5 mg NADH were dissolved in 5ml 0.9 percent sodium chloride, pH 7.4, filtered through a 0.22 mcm Millipore filter and then applied.

For the i.v. application 12.5 mg NADH were dissolved in 5ml 0.9 percent sodium chloride, pH 7.4, filtered through a 0.22 mcm Millipore filter and intravenously infused in 30 minutes.

The oral form consisted of film coated tablets with 5 mg of NADH in each tablet.

RESULTS

All the patients included in this open label trial are listed in Table 1. The individuals patients have been registered by initials according to the parameters: sex, age, degree of depression before and after therapy, improvement and duration of therapy. 112 (53.6%) of the patients included in the trial were

Table I: List of patients included in the study

No	Init.	Sex	Age	Disability		Improvement	Duration of Therapy (in days)
				before	after		
001	WJ	m	81	60	30	30	14
002	AF	m	55	12	2	10	60
003	OB	m	73	70	40	30	10
004	SA	m	66	60	20	40	8
005	SL	f	75	8	4	4	150
006	PO	m	71	17	17	0	60
007	AA	f	61	14	7	7	12
008	AH	m	76	8	2	6	7
009	BM	f	66	20	10	10	7
010	BJ	f	52	13	1	12	7
011	BH	m	71	12	6	6	11
012	BA	f	71	40	20	20	8
013	BM	f	77	25	15	10	14
014	BL	f	86	18	6	12	12
015	GM	f	78	24	11	13	8
016	CL	m	77	40	10	30	20
017	EE	m	47	5	3	2	7
018	EW	m	76	70	50	20	28
019	FA	f	76	20	3	17	310
020	FR	m	61	20	20	0	90
021	GR	m	74	60	29	31	62
022	GC	f	72	18	16	2	28
023	HT	f	72	21	16	5	14
024	HM	f	75	23	10	13	35
025	HL	f	70	75	45	30	20
026	HF	m	74	66	66	0	90
027	KC	f	72	70	35	35	140
028	TM	f	57	20	9	11	10
029	KH	m	78	16	12	4	12
030	PB	m	61	60	30	30	70
031	RL	f	79	26	17	9	14
032	NK	m	78	36	15	21	14
033	NO	m	53	15	5	10	10
034	MP	f	68	21	11	10	9
035	MD	m	77	20	10	10	14
036	MK	m	62	20	6	14	77
037	MA	m	75	32	20	12	14
038	LA	f	77	5	1	4	14
039	LK	m	74	20	10	10	14
040	HF	m	60	40	8	32	90
041	HH	m	62	55	25	30	12
042	SE	m	78	24	16	8	15
043	SE	m	62	11	6	5	14
044	SF	m	86	26	21	5	9
045	SI	f	80	13	4	9	12
046	SW	m	63	50	6	44	74
047	SR	m	70	37	15	22	8
048	SA	m	64	20	5	15	18
049	VC	m	80	25	2	23	14

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050	EE	m	72	25	10	15	14
051	TM	m	61	24	5	19	10
052	NJ	m	78	40	30	10	28
053	RO	m	78	45	40	5	10
054	SL	m	75	10	8	2	10
055	BA	m	78	15	5	10	8
056	AR	f	58	9	9	0	21
057	BP	m	74	15	10	5	8
058	BH	f	83	40	20	20	8
059	BE	f	79	45	30	15	14
060	BE	f	69	30	10	20	15
061	CB	m	83	35	20	15	28
062	BE	m	71	11	14	-3	14
063	BS	f	69	40	35	5	8
064	BA'	m	69	30	15	15	14
065	BH	m	81	22	16	8	10
066	BM	f	66	29	10	19	14
067	BH	m	70	40	20	20	14
068	BR	m	76	28	18	10	14
069	BG	m	67	14	3	11	21
070	BA	f	64	35	30	5	10
071	BV	f	76	16	6	10	10
072	CA	m	51	30	15	15	10
073	CC	m	87	50	20	30	9
074	CJ	m	64	40	40	0	12
075	DE	f	55	14	9	5	15
076	DV	f	66	30	15	15	14
077	DA	f	65	40	15	25	12
078	DW	f	70	35	35	0	18
079	EG	f	75	20	15	5	7
080	EH	f	73	25	15	10	17
081	EA	f	78	4	4	0	10
082	ER	m	67	16	4	12	14
083	EW	m	84	37	25	12	14
084	EK	f	67	10	16	-6	8
085	EE	f	83	40	35	5	14
086	FJ	f	69	37	30	7	19
087	FK	m	74	35	20	15	26
088	FH	f	77	30	15	15	13
089	FW	m	81	40	30	10	15
090	FH	m	83	40	25	15	18
091	FH	m	69	26	7	19	10
092	FM	f	91	30	25	5	10
093	GH	f	71	22	17	5	14
094	GC	m	70	30	20	10	5
095	GW	m	70	12	7	5	10
096	GF	m	75	34	12	22	11
097	GG	f	77	34	13	21	15
098	KG	m	62	75	70	5	11
099	KB	f	56	11	5	6	5
100	KJ	f	80	37	23	14	22
101	KW	f	82	30	15	15	10
102	KE	f	79	30	15	15	8
103	KO	m	75	30	17	13	15

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104	KH	m	83	35	18	17	14
105	KM	f	77	33	21	12	16
106	KP	m	68	30	15	15	9
107	KG	f	71	30	10	20	11
108	KW	m	68	8	4	4	9
109	KA	f	78	12	4	8	13
110	KB	f	53	20	15	5	8
111	KM	m	80	35	20	5	8
112	KW	m	51	40	30	10	11
113	KJ	f	50	4	4	0	12
114	KJ	m	78	35	15	20	16
115	KE	f	72	8	4	4	13
116	LH	f	70	10	6	4	14
117	LK	m	75	30	20	10	14
118	LZ	f	77	44	42	2	12
119	LR	f	76	20	16	4	14
120	LA	m	77	5	1	4	14
121	MM	f	68	30	20	10	17
122	ME	f	72	34	23	11	14
123	MW	m	59	11	4	7	13
124	MG	f	70	35	20	15	34
125	MN	m	64	40	30	10	8
126	MB	m	68	16	6	10	10
127	ME	f	84	44	44	0	14
128	MR	m	67	20	10	10	8
129	MG	m	80	22	9	13	13
130	HR	m	63	22	3	19	13
131	MM	f	67	30	26	4	14
132	MW	m	42	15	15	0	45
133	NJ	f	80	6	4	2	14
134	NW	m	79	35	30	5	12
135	NJ	m	78	26	19	7	8
136	NE	f	72	11	2	9	21
137	OJ	f	71	12	5	7	17
138	OM	f	73	26	11	15	14
139	OJ	m	79	16	8	8	7
140	OT	f	78	38	28	10	12
141	OE	f	77	20	10	10	12
142	PG	m	63	24	9	15	19
143	PM	m	83	20	13	7	9
144	PV	m	83	13	10	3	8
145	PJ	m	77	42	40	2	11
146	PR	f	66	9	6	3	15
147	PB	f	76	12	9	3	14
148	PJ	m	67	32	30	2	12
149	PE	m	75	35	23	12	13
150	PN	m	76	41	26	15	9
151	RF	m	80	30	30	0	21
152	RC	f	63	34	20	14	15
153	RA	f	81	36	13	23	12
154	RX	f	72	20	15	5	11
15	RA	f	52	46	30	16	24
156	RJ	m	81	12	14	-2	16
157	RK	m	69	20	20	0	3

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158	RK	m	60	41	26	15	26
159	RE	m	58	20	15	5	10
160	SJ	m	66	36	18	18	14
161	SM	f	78	20	16	4	20
162	SK	f	77	30	7	23	60
163	SD	f	69	36	9	27	15
164	SO	m	80	25	11	14	19
165	SW	m	69	20	10	10	9
166	SL	m	77	25	5	20	10
167	SH	m	66	27	27	0	12
168	SM	f	78	35	15	20	14
169	SM	m	82	37	27	10	12
170	SM	f	56	50	15	35	103
171	SA	f	77	34	20	14	10
172	SA	m	64	6	5	1	10
173	SJ	f	76	23	19	4	19
174	SJ	m	67	30	10	20	11
175	SJ	f	76	30	25	5	19
176	SL	f	82	32	15	17	12
177	SM	f	60	30	10	20	13
178	SJ	f	72	40	14	26	9
179	SP	m	62	30	20	10	14
180	SW	f	78	28	20	8	30
181	SK	m	69	40	25	15	10
182	SJ	f	70	38	11	17	12
183	SJ	m	58	50	20	30	10
184	SR	f	73	7	4	3	10
185	SE	f	69	41	35	6	9
186	SH	f	56	32	25	7	12
187	SR	f	64	48	48	0	24
188	TJ	f	71	38	26	12	18
189	TJ	m	69	33	20	13	12
190	VH	m	73	40	24	16	17
191	VE	m	74	42	40	2	21
192	VM	f	36	30	15	15	10
193	VR	m	61	38	20	18	14
194	VK	m	64	40	10	30	20
195	VH	m	64	5	3	2	10
196	VK	m	78	9	4	5	8
197	WG	m	80	45	45	0	21
198	WP	m	74	25	15	10	12
199	WE	f	68	32	28	4	13
200	WS	f	85	40	20	20	8
201	WW	m	80	35	22	13	15
202	WR	f	64	37	14	13	14
20	WE	m	69	40	24	16	14
204	WW	f	72	9	5	4	10
205	WE	f	88	41	36	5	18
206	WJ	f	75	16	18	-2	13
207	WA	m	63	26	6	20	7
208	WC	m	78	8	4	4	20
209	ZG	m	45	30	30	0	8

15 Non responders from 209 = 7,2%

male. The descriptive statistics of all these data are summarized in Table 2. This statistics describe the distribution of the 4 parameters age, duration of therapy, disability before treatment and improvement after treatment.

Table II: Summary statistics

Variable	N	Mean	St.E.	St.D.	Min	Max.	Median
Age (y)	209	71.1	0.63	9.09	36	91	72
Duration (d)	209	19.5	1.96	28.29	3	310	14
Disability bef.	209	28.6	1.00	14.40	4	75	30
Improve-ment	209	11.5	0.62	8.95	-6	44	10

The age of the patients ranged from 36 to 91 years with a mean value of 71.1+/-9.09.

The duration of therapy lasted from 3 to 310 days with a mean value of 19.5+/-28.29 days.

The degree of depression ranged from 4 to 75 with a mean value of 28.6+/-14.40. The overall improvement of the depression was 11.5+/-8.95 with a maximum of 44.

Tables 3 and 4 relate the dependent variable improvement to the independent variables age and disability before treatment. For each combination of the categories of the two variables, two entries are displayed. The first entry is the number of patients in that cell and the second entry is the column percentage. For example, 16 of the 49 (=32.7%) patients not older than 65 show an improvement less than or equal to 5. Note that among the 209 patients there are some with disability before treatment less than 10. For these little disabled patients, it is not possible, not even theoretically, to show an improvement greater than 10. Analogously, patients with disability before treatment less than 20 cannot show an improvement greater than 20, and so forth. For this reason and because of possible correlations between the independent variables, tables 3 and 4 should be interpreted with caution.

For an accurate assessment of the real relationship between age and improvement it is necessary to subtract the effects of the disability before treatment. In doing this we grouped the patients into 2 categories: marked responders (improvement of disability greater than half the original value before therapy) and non-responders or slight responders (improvement less than or

Table III: Improvement versus age

	Age				
Impr.	≤ 65	66-70	71-75	> 75	**Row Total**
≤ 5	16 32.7%	12 29.3%	16 40.0%	25 31.6%	69 33.0%
6-10	9 18.4%	9 22.0%	7 17.5%	20 25.3%	45 21.5%
11-15	9 18.4%	8 19.5%	9 22.5%	17 21.5%	43 20.6%
16-20	6 12.2%	7 17.1%	3 7.5%	9 11.4%	25 12.0%
21-25	2 4.1%	1 2.4%	1 2.5%	5 6.3%	9 4.3%
> 26	7 14.3%	4 9.8%	4 10.0%	3 3.8%	18 8.6%
Column Total	49 23.4%	41 19.6%	40 19.1%	79 37.8%	209 100.0%

Table IV: Improvement versus disability before treatment

	Disability before treatment						
Impr.	≤ 10	11-20	21-30	31-40	41-50	> 50	**Row Total**
≤ 5	20 95.2%	21 42.0%	10 19.2%	8 13.8%	8 47.1%	2 18.2%	69 33.0%
6-10	1 4.8%	21 42.0%	14 26.9%	8 13.8%	1 5.9%		45 21.5%
11-15		7 14.0%	16 30.8%	17 29.3%	3 17.6%		43 20.6%
15-20		1 2.0%	10 19.2%	12 20.7%	1 5.9%	1 9.1%	25 12.0%
5.00			2 3.8%	7 12.1%			9 4.3%
6.00				6 10.3%	4 23.5%	8 72.7%	18 8.6%
Column Total	21 10.0%	50 23.9%	52 24.9%	58 27.8%	17 8.1%	11 5.3%	209 100.0%

equal to half the original value). To avoid classification of an improvement from 5 to 2 as marked response, we excluded the 21 patients with a disability before treatment less than or equal to 10 from further analysis. Table 5 summarizes the

Table V: Summary statistics

Variable	N	Mean	St.E.	St.D.	Min.	Max.	Median
Age (y)	188	71.2	0.66	9.10	36	91	72
Duration (d)	188	19.7	2.05	28.13	3	310	14
Disability bef.	188	31.0	0.96	13.16	11	75	30
Improvement	188	12.5	0.65	8.84	-3	44	11

distribution of the variables age, duration of therapy, disability before treatment, and improvement after treatment for the remaining 188 patients (103 male). Table 6 relates the response to age separately for various categories of disability before treatment. It turns out that younger patients (<65y) have a better chance to gain a marked improvement than older patients. The last row in table 6 is a statistical artifact due to small N and therefore does not impair this general result.

DISCUSSION

This study confirms and extends our preliminary report on the clinical benefit of NADH for patients sufferring from depression (7).

The patients included in our study suffered from depression with various forms of clinical symptoms, in all of which a disturbance in the catecholamines, dopamine, serotonine and norepinphine as well as in the metabolites, vanilin mandelicacid and 5-hydroxyindol-acetic acid levels in blood plasma have been observed (G.D. Birkmayer, unpublished results).

According to the guidelines of the Diagnostic and statistical manual of mental disorder (21) one does not distinguish different forms of depression but only the severit of the symptoms.

NADH seems to be effective with all of them. In order to elucidate the mechanism of NADH action we have to look at the biochemical events leading to depression (1). It has been claimed that the balance of neurotransmitters is disturbed and this change is responsible for the clinical symptoms of depression.

TableVI: Percentages of patients with marked improvement

	Age				
Disab.bef.	< 65	66-70	71-75	> 75	**Row Total**
11-20	8/15 53.3%	3/8 37.5%	2/11 18.2%	6/16 37.5%	19/50 38.0%
21-30	5/9 55.6%	4/12 33.3%	4/10 40.0%	6/21 28.6%	19/52 36.5%
31-40	4/11 36.4%	3/14 21.4%	2/9 22.2%	7/24 29.2%	16/58 27.6%
41-50	3/6 50.0%	0/1 0.0%	0/1 0.0%	1/9 11.1%	4/17 23.5%
> 50	1/3 33.3%	1/2 50.0%	1/4 25.0%	0/2 0.0%	3/11 27.3%

One of the approaches in the treatment of depression is the application of monoaminoxidase (MAO) inhibitors, in order to block the metabolic degradation of the catecholamines thus achieving a higher endogenous concentration. Monoaminoxidase inhibitors such as imipramine and amitryptilin as antidepressive medication (20, 8) have been used for more than 30 years. One of the drawbacks of these monoaminoxidase inhibitors is the blockage of the reuptake of neurotransmitter from the presynaptic neuron. Therefore the neurotransmitter accumulate in the synaptic cleft. This unnatural condition causes clinically side-effects. Side-effects indicate always overdosage of the drug. The philosophy of using NADH as antidepressive substance was its potential capacity to stimulate the endogenous biosynthesis of L-DOPA, dopamine, norepinephine and other catecholamines, respectively. Previous studies have shown that there is a deficit in the brain of Parkinsonian patients which seems to be responsible for at least some of the symptoms of depression (3, 4). As dopamine is synthesized from tyrosine via L-DOPA under the action of tyrosinehydroxylase this particular enzyme plays a central role for biosynthesis of dopamine and noradrenaline (17) and due to this also for psychic disorders.

In this context it has been shown that tyrosinehydroxylase is strongly reduced in Parkinsonian patients, not only in the brain, but also in the adrenal medulla (15). This enzyme has 2 cofactors, tetrahydrobiopterine and iron. Tetrahydrobiopterine was found to be reduced in the brain of Parkinsonian patients by more than 50% yielding a decreased tyrosinehydroxylase activity (16). By stimulating the biosynthesis of tetrahydrobiopterine one may achieve an activation of tyrosinehydroxylase which then leads to a higher dopamine production. Tetrahydrobiopterine is synthesized from dihydropteridine by an enzyme called dihydropteridinreductase (23). Cofactor of this enzyme is NADH. The working hypothesis was that addition of NADH will trigger tyrosinehydroxylase

activation and due to this an increase of L-DOPA and dopamine production. In a study with more than 400 patients we have shown that NADH is able to improve the symptoms of Parkinsonian patients (6). Biochemical analysis showed that the improvement of clinical symptoms was paralleled by an increase of the dopamine metabolites HVA and VMA in the urine which provides indirect evidence that NADH is increasing the endogenous dopamine production (5).

Direct support for our hypothesis have been gained from tissue culture experiments. NADH added to the culture medium increased the production of dopamine in phaeochromocytoma cells up to 6 times. Furthermore, tyrosine hydroxylase activity was stimulated by NADH to 175% (21).

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