

EVALUATION OF DISULFIRAM IN THE TREATMENT OF ALCOHOLISM¹

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SUMMARY

Seventy five male patients with the diagnosis of alcohol dependence syndrome were given disulfiram and an alcohol challenge was administered to all of them. They were kept on maintenance dose of the drug and followed up for six months, note being made of their improvement on several parameters, viz. the number of drinking episodes, the severity of reaction suffered, the side effects experienced etc. Twenty one patients were considered as drop outs and four were abstinent without the aid of the drug. 54 % of the fifty patients who continued taking the drug showed good to moderate improvement. 42% had one or more drinking episode while consuming the tablets. Older patients, and those brought by relatives and friends did better than the others. Results are discussed.

Alcoholics and alcohol related problems continue to pose a formidable and recurrent challenge to the psychiatrist (Gallant *et al.*, 1973). These constitute a drain on the community resources. During the past 25 years we have acquired extensive experience in the management of alcoholism (Bagadia *et al.*, 1970; 1975, 1979).

Disulfiram, introduced abroad in 1948 (Hald & Jacobson), has since earned a reputation as a valuable aid in maintaining abstinence (Costello, 1975; Armor *et al.*, 1976). Lundwall & Backland (1971) have critically reviewed the various studies and have indicated the factors crucial in determining the final outcome. Since the drug was introduced in our country only recently, we decided to evaluate its efficacy in the setting of a general hospital.

MATERIAL AND METHODS

Patients fulfilling the ICD-9 criteria of Alcohol dependence syndrome (WHO 1978), after initial screening in the O.P.D., were admitted in the hospital for evaluation.

After detoxification, they were subjected to a detailed physical, psychiatric and laboratory examination to exclude serious myocardial or hepatic diseases an active psychosis or organic brain syndrome (Barrera *et al.*, 1950). The involvement of a relative was considered mandatory as he was to be responsible for the daily administration of tablets, accompanying the patient to the hospital on follow-up visits and providing aid in the event of an emergency. Both were explained in full detail the symptoms and signs of an alcohol disulfiram reaction. They were also informed of the possibility of a fatal end, and the treatment to be met out in case a reaction should take place. Each patient was given a card giving the details of the reaction and the management and they were urged to carry it constantly on their person. A written informed consent was then obtained from the patient as well as the relative. Patients without readily available relatives were not accepted.

The patients were started on disulfiram

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(250 mg.) in a standard regime of 4, 3, 2 and 1 tablet on four successive days (Glud, 1949). All the patients were given a challenge, utilizing 40-50% v/v whisky, at the rate of 30 ml. to be drunk every half hour, till an unpleasant reaction was experienced or a maximum quantity of 90 ml. was consumed.

Alternative regimes of loading were practised, however, in order to cut short the hospital stay. Thus 14 patients received a loading dose of 6 tablets on the first day and 6 on the second day, the challenge being given on the third day. Another 48 patients received the loading dose in a single day; 6 tablets on the morning of admission and 4 in the evening, the challenge being given on the morning of the second day i.e. within 24 hours of admission. After successful challenge the patient was discharged on a maintenance dose of 250 mg. or 500 mg. per day.

Regular follow-up at weekly to fortnightly intervals for a minimum period of six months was expected for completion of the study (Davies *et al.*, 1956). Efforts were made to investigate the possible factor for the failure to report for a single follow-up after discharge, which was recorded in some cases. No satisfactory answer, however, was available. It was therefore considered that these patients had received inadequate treatment and were not included in any further analysis.

In the absence of any objective and unambiguous criteria of assessing improvement in an alcoholic (Vallance, 1965), we modified a global improvement scale devised by Mindler (1959) and revised by Bagadia *et al.* (1979). The state of health at the time of admission was assessed, on the basis of the clinical evaluation supported by data obtained from a relative who was residing with the patient. A 4-point scale was utilised to measure the improvement in the different parameters of physical health, psychological adjustments with self and at

the inter-personal level and the relation to work. Since it was inconceivable for a patient to simultaneously consume alcohol and Disulfiram without experiencing a reaction, drinking pattern was not considered as a satisfactory parameter. Instead, the patient was requested to give a subjective evaluation of his preoccupation with alcohol and its use and the reduction in the urge that this represented was added as a fifth parameter. To ensure reliability, the same research worker interviewed the patient and his relative on every subsequent follow-up visit.

<i>Assessment Schedule</i>			
	<i>Parameters</i>		<i>Score</i>
1. Physical	0-3
2. Emotional	0-3
3. Interpersonal	0-3
4. Work	0-3
5. Reduction in urge	0-3
			Total Score
Good Improvement	12-15
Moderate Improvement		..	8-11
Mild/No Improvement	0-7

Sample of the Study :

TABLE I. *Characteristics of the sample (N=75)*

<i>Age (in yrs.) :</i>			
21-30 20
31-40 36
41-50 15
51-60 4
<i>Problem of Drinking (in yrs.) :</i>			
1 8
1-2 14
2-5 36
5 17

TABLE 2.

Severity of Reaction :

Severity	N=75		
Nil	1
Mild	24
Moderate	42
Severe	8

The reaction started within 15-20 minutes of alcohol ingestion and initially comprised of flushing of the face and neck, and mild tachycardia. Minutes later there was an appreciable fall in the blood pressure, the patient complained of giddiness and throbbing headache and difficulty in breathing due to the congestion of the nasal mucosa. They found it necessary to lie down when the systolic blood pressure rapidly dropped to below 40-50 mm of mercury and the diastolic was often not recordable. There was concomitant nausea and most of the patients either vomitted or had empty retching depending on the contents of their stomach. By about an hour, they were thoroughly miserable and sick and requested that something be done to relieve the distress. Probably due to the selection criteria, there was no serious cardiac or respiratory involvement and no resuscitative measures were found necessary. All of them responded to simple standard treatment of Inj. Ascorbic acid 100 mg. I.V. Inj. Diphenhydramine 2 ml. I.M. or I.V. and in the more severe cases Inj. Hydrocortisone succinate 50 mg. I.V. (Kalimowsky and Hippus, 1969). Complete recovery took place within 3-4 hours. Thus, the alcohol challenge, carefully administered to a select population, is a relatively safe procedure.

RESULTS AND DISCUSSION

Out of a total of 75 patients taken up for the study, 21 did not report even once after discharge and were considered as drop

outs. 4 did not take the drug but were abstinent at the end of the 6 month period. This probably constitutes the spontaneously remitting group of alcoholics. Armor *et al.* (1976) indicate that in some studies this figure may be as high as 50%. The results of the remaining 50 are presented below.

TABLE 3.

Improvement	N=50		%
Good	..	10	20
Moderate	..	17	34
Relapse	..	23	46

Of the 27 who showed good to moderate improvement only 13 were completely abstinent for the trial period of 6 months. The other 14 had one or two very brief episodes of drinking when they experienced a reaction. These episodes, however, in no way caused any major set-back in their overall improvement testifying to the fact that improvement in an alcoholic is not synonymous with the degree of abstinence alone.

Lundwall and Baekland (1971) have pointed out that the difference in the methodology of various studies virtually excludes inter-study comparisons. Reports of improvement range from 19-83% depending on a) the characteristics of the population included; b) the criteria of assessment utilized and c) the presence or absence of a control group. Also, with the increasing passage of time, both the novelty of the treatment and the improvement rates tend to decrease. Wallerstein (1957), in one of the few satisfactory studies, has reported an improvement of 50% as against 26% in the controls. More recently, Armor *et al.* (1976) have reported an overall abstinence rate of 25% for six months, for all varieties of treatment modalities.

Of the 23 patients who relapsed, 17 did so in the first month of starting treatment. This is in agreement with the findings of Baekland *et al.* (1971) and probably suggests that more energetic and comprehensive treatment approach in the early period might diminish the relapse rate.

IMPROVEMENT AND DEMOGRAPHIC VARIABLES

TABLE 4.

Improvement and Age :

Age	Total N=50	Improved N=27	Relapsed N=23
21—40 ..	41	19	22
41—60 ..	9	8	1

$X^2=5.38$, d.f.=1, $p<0.05$ $p<.01$

The older age group is seen to do significantly better than those below 40 years of age. Baekland *et al.* (1971) too have documented similar findings. In addition, a better social class and stability appears to point to a better prognosis (Gregson and Taylor, 1977). All our patients in business and profession improved, but the number is probably too small (only six) to be significant. Similarly, the married group does better than the single, though the contribution of the age variable to this finding cannot be discounted.

IMPROVEMENT AND DURATION OF DRINKING

We were unable to replicate the findings of Baekland *et al.* (1971) that a longer duration of drinking favours a better prognosis. In fact, we found that the previous abstinence pattern, previous treatment taken, or a history of withdrawal symptoms in the past or present are poor indicators of a good prognosis.

IMPROVEMENT AND MOTIVATION

TABLE 5.

Motivation	Total N=50	Improved N=27	Relapsed N=23
Self motivated & employer	23	10	13
Relatives & Friends ..	27	17	10

$X^2=1.90$, d.f.=1, N.S. N.S.

Lundwall and Baekland (1971) emphasize the importance of self motivation in determining the final outcome. However, it is far easier to assess the motivation of relatives and friends than that of an alcoholic himself. It is not surprising that with disulfiram it is the social pressure that is important in deciding whether the patient would consume the drug and remain abstinent. The work of Garrein *et al.* (1973) suggests that mere willingness to take the drug does not indicate an above average motivation. A supervised and frequent administration on an out-patient basis produces satisfactory results, probably through subtle reinforcement for consumption of the tablet and diminishing of social isolation. It is possible that the relatives of those of our patients who improved fulfilled this function.

IMPROVEMENT AND MENTAL STATUS

We failed to confirm the findings of Bowman *et al.* (1951) that depressed patients do badly on disulfiram since 5 out of 9 depressed patients improved. Nor could we replicate Lundwall and Baekland's (1971) findings that blackouts are an indicator of poor prognosis, as a majority of the patients showed a satisfactory response. In fact, the crucial factor appears to be the adequacy of treatment.

As Kissin and Gross (1970) have pointed out, a judicious combination of tranquilizers, antidepressants and disulfiram is the best psychopharmacological

programme currently available, in the treatment of this condition. Hence, a careful screening of patients for detecting an underlying depression and energetic treatment of the same would, perhaps, diminish the relapse rate.

SIDE EFFECTS

TABLE 6.

Skin Reaction ..	3	Impotence ..	1
Anorexia ..	5	Acute OSB ..	1
Sleep Disturbance	4	Mixed Psychosis ..	1
Fatigue Dizziness	2	Functional Psychosis	1
Restlessness ..	1		

Except for the skin reactions, which consisted of transient papular and vesicular eruptions, and 3 cases of psychotic episodes, none of the other side effects could be attributed solely to the drug. All of them disappeared with continued medication. Lidson and Straton (1967) state the incidence of Disulfiram psychosis to be between 2-20%. They have located a total of 52 cases in the English literature and have classified the reactions into 3 broad groups viz. acute delirium, mixed psychosis, and purely functional psychosis. Gottesfeld *et al.* (1951) described the psychodynamic constellation which constitutes a positive risk for developing adverse psychiatric reactions. Kree and Razani (1974) feel that these episodes respond poorly to antipsychotic medication.

6% of our patients suffered these episodes after almost 2-3 weeks of commencing therapy, and recovered completely within 2-3 days of omission of the drug. Two of them had unstable neurotic personalities and the third had consumed alcohol a few days previously, experiencing a moderately severe reaction. Unfortunately, none of these patients continued on treatment, hence subsequent follow up was not possible.

DRINKING EPISODES WHILE ON DISULFIRAM

TABLE 7

	Patients	No. of Episodes
Improved ..	14	24
Relapsed ..	7	8

42% of our patients, while consuming disulfiram, experimented with alcohol outside the hospital setting, all of them thereby experiencing a moderate to severe reaction. This is a surprising finding, since considering the general educational level and social class of our patients, we had felt that giving all of them a challenge would forewarn the patients and prevent such experimentation. Hoff (1968) claims that the administration of a challenge makes no difference to the outcome. Kitson (1977) too emphasizes that the anxiety in regard to developing a reaction is only one of several factors which determine compliance. Thimann (1951) and Hayman (1965), on the other hand, emphasize the necessity of the patient experiencing at least one reaction to bolster his motivation and to ensure safety.

The longer the duration of disulfiram therapy, the greater are the chances of a patient having a reaction. This is borne out by our figures. Thus, the anxious physician who discontinues Disulfiram after the first such episode is only depriving the patient of a possible chance of recovery. Billet (1964) has shown that the anxiety of the physician about the safety of the treatment procedure is negatively correlated with a positive therapeutic outcome.

The question of duration of therapy with disulfiram is a controversial affair. As the 'Rand Report' (Armor *et al.*, 1976) has pointed out, a return to controlled drinking is the rule rather than an exception in recovered alcoholics. However, till such time that the characteristics of the controlled drinker are available, it is practical to advise

total abstinence on an indefinite basis. Disulfiram appears to be an useful aid in achieving this goal. It may be worthwhile to explore the feasibility of a long-acting depot preparation for this purpose.

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