ADVERSE EFFECTS OF DISULFIRAM AND PATIENT COMPLIANCE
T.N.Srinivasan, T.R.Suresh Vasanth Jayaram

ABSTRACT
Use of Disulfiram under supervision in well-motivated alcoholics is effective in reducing relapse rates. Several adverse effects, some of them life-threatening, have been reported due to the drug. An awareness of the adverse effects is useful to keep a follow up and sustain patient compliance with the drug. This study of 158 out patients on daily oral disulfiram revealed that though many patients report unpleasant effects most of them could not be distinguished from symptoms of alcoholism present before taking disulfiram and hence cannot be considered as adverse effects of the drug. The actual adverse symptoms were also mild and could be easily managed and were infrequent and not the common cause for poor patient compliance. The study suggests that Disulfiram with its low toxicity can be offered to patients without too much reservation.

Keywords: Disulfiram - adverse effects - patient compliance.

INTRODUCTION
Alcoholism is a major growing health problem all over the world. Disulfiram (DSM) is being used in the treatment of alcoholism, since its introduction for this purpose in 1948. Use of this drug under supervision has been documented to be effective and useful even in long-term for well-motivated patients (Ojehagen et al 1991). Even if it does not prevent relapses completely, it does reduce relapse rate and the patients are in sobriety for longer periods than those who are not on treatment (Kristensen, 1992).

Alcoholics often stop taking DSM voluntarily for reasons only partly known. Their compliance with oral DSM is a troublesome clinical problem. They are known to report a high number of adverse effects (AE) when treated with DSM (or even placebo) (Christensen et al 1984) and it is expected that some of them may use the AE as an argument for stopping the drug (Brewer et al,1992). Fear about possible AE can inhibit the clinician also from continuing therapy. Adverse effects of DSM have often been reported in the form of case reports. Borup et al (1992) studied 93 patients on 600 - 800 mgms of DSM twice a week for at least a year and found a low incidence of AE. Poulson et al (1992) have comprehensively reviewed the AE featuring in the Adverse Drug Reaction reports to the Danish Committee on Adverse Drug Relations during the period 1968-1991 and the reports to the WHO collaborating centre for International Drug monitoring (numbering 1,131) collected from a number of national centres around the world. They noted occurrence of AE at an intermediate frequency of 1 per 200-2000 treatment years. Most adverse reactions were of intermediate severity and they found no indications that DSM treatment imposes a deleterious health impact. Only liver damage described as a result of DSM could be life-threatening, with a mortality rate of about 1:25000 patients per year. Other AE of DSM are not life threatening. Poulsen et al (1992) have also noted that majority of AE, especially that of liver and peripheral nerves are not easily distinguished from manifestations of alcohol abuse.

The use of DSM is increasing in India with increasing facilities for treatment of alcoholism. It would be of benefit to be aware of the profile of AE that could be seen in Indian patients to help the clinicians in the follow up of the patients. This study attempts to answer this issue. It is a cross-sectional study of patients of alcoholism on outpatients treatment with DSM. The study evaluated only the clinically verifiable signs and symptoms and did not involve laboratory investigations as a routine. The profile of AE reported, their relationship to duration of treatment and compliance was studied. The doubt whether the adverse symptoms reported by patient could be preexisting before starting DSM therapy and could be related to prior alcoholism rather than the drug was explored. The results are presented to highlight the clinical safety of DSM and its relevance to treatment of alcoholism.

MATERIAL AND METHODS:
Out patients who were under treatment of the authors for alcoholism (ICD-10 diagnosis WHO, 1992)
was the population from which the study group was selected. 158 consecutive patients who had attended the clinic for followup and disulfiram therapy in 1994 formed the study group. All these patients had earlier been detoxified as inpatients. They were started on DSM only if the level of hepatic enzymes Alanine Amino transferase (ALAT) and Aspartate aminotransferase (ASAT) in the serum were normal. Patients who had other disorders like tuberculosis, diabetes mellitus and required concurrent medication were not studied.

The patients were given Tablet Disulfiram (Torrent Laboratories) 250mgms per day every day in a week to be taken in the morning with breakfast. The drug intake was supervised by wife/parents. Patients were reviewed once in 10 days during the first month after starting the drug and later at monthly intervals. Any symptom which the patient and / or the family reported as having developed after starting on DSM was noted as an "Adverse Effect" to DSM to begin with notwithstanding the subsequent enquiry showing that the symptom was present even before taking DSM. In addition, a check-list of 36 symptoms reported as AE to DSM was made based on descriptions by Poulsen et al (1992) and standard pharmacology test books. Each patient was enquired if he had any of the AE on the check list in addition to the spontaneously reported ones. As mentioned earlier, only the clinical evaluation of AE were done. Laboratory investigations were restricted to estimation of serum hepatic enzymes ALAT and ASAT in those with gastrointestinal symptoms.

Following the above enquiry, the relationship of onset of AE to starting DSM therapy was queried to identify those instances where the symptoms were present before taking DSM. The total duration of treatment, whether there was discontinuity in the treatment (a continuous period of more than one week without drug was considered as a discontinuation), the reasons for such discontinuity and occurrence of relapse after such discontinuation were also recorded.

RESULTS:

All the 158 patients were male and, excepting three, were married. All of them were literate with at least primary level education and living within the city of Madras and its suburbs. 65 of the 158 patients reported AE with 30 having a single AE and others having 2 or more symptoms, totalling 137 instances of AE. When comparing patients on continuous and discontinuous treatment nearly equal proportion of them i.e. 28 out of 75 and 37 out of 83 respectively, reported adverse effects. But the number of symptoms experienced were more in those on regular treatment (totalling 84 symptoms, averaging 3 per patient) which is twice that reported by those taking discontinuous treatment (53 symptoms averaging 1.4 per patient). Overall the commonest symptoms were (number of patients in parentheses) tiredness (31), Gastrointestinal including anorexia, nausea, vomiting, abdominal pain, bloating of stomach, constipation, diarrhoea and jaundice (23), peripheral neuritis (13) and non-psychotic psychiatric symptoms like anxiety, depression (12). Other common AE were drowsiness (9), sleep disturbance (7), Psychosis (7) and confusion (4). Infrequently reported symptoms were dizziness, headache and tremors (2 each) and one case of irritability, ideas of reference, reduced libido, loss of visual acuity, irritation in the eyes and odd taste in the mouth. Liver enzymes in the 23 patients with gastrointestinal symptoms were normal. 50 of the 65 patients experienced some or all of the AE before starting to take DSM accounting for 85 out of 137 instances of AE. Hence only these 85 instances could be considered as actual adverse effect of DSM. The proportion of patients having the symptoms in the pre-DSM period also were as follows: Tiredness (20/31), Gastrointestinal symptoms (20/25), peripheral neuritis (7/13), anxiety/depression (6/12) drowsiness (3/9), psychosis (7/7) sleep disturbance (5/7) and confusion (2/4). Of the remaining symptoms loss of libido, odd taste in the mouth and irritation in the eyes were experienced only after taking DSM. Hence only the symptom of drowsiness, with least doubt, occurred more often after taking disulfiram.

On examining the relationship of duration of treatment to AE, irrespective of whether there were periods of non-compliance, no association was discovered. 35 of 80 patients on less than 6 months of treatment and 30 of 78 patients on more than 6 months of treatment reported AE. This lack of difference persisted when the groups were subdivided into those receiving treat-
DISULFIRAM COMPLIANCE

ment for one month or less, 1 to 3 months and 4 to 36 months. To make the observation more meaningful only those patients on continuous treatment were analysed (N-83, totalling 621 months of treatment). There was no difference in frequency of AE in patients of either groups (28 of 59 on less than 6 months treatment and 9 of 24 on longer treatment had AE). The time of onset of the frequently occurring symptoms were looked into. The symptoms of gastrointestinal tract (15 to 23), anxiety/depression (8 of 12) and drowsiness (8 to 9) occurred more often in those on less than 6 months treatment. (The same trend was seen in patients on less than 3 months treatment) 6 of 7 cases of psychosis occurred after 6 months of treatment. Symptoms like tiredness (15 of 31), peripheral neuritis (7 of 13), sleep disturbance (4 of 7) and confusion (2 of 4) occurred equally in both treatment-duration groups.

The reasons of discontinuation of treatment were analysed. 75 of the 158 patients had discontinued taking DSM at least once. Only 6 of them gave the 'AE' of DSM as the reason for stopping the drug. Others often stopped the drug because they felt that they could manage without the drug or wanted to drink again. 52 of the 75 experienced a relapse into alcohol abuse on stopping the drug but all of them were willing to continue the treatment subsequently.

DISCUSSION:

The study suggests, on initial analysis that alcoholics frequently experience adverse effects due to disulfiram. But further examination of the time of onset of symptoms revealed that majority of them were present before taking the drug and hence cannot be considered as an adverse effect of DSM. The reason for such fallacious reporting could be that under the influence of alcohol the symptoms were either not troublesome or ignored but were brought to focus during sobriety with disulfiram. It is also possible that in some cases the symptoms could have become more severe due to DSM. Only the symptoms of drowsiness and that too in a small number was reported more often after starting the drug. All the actual AE were mild in nature and did not require any vigorous treatment or discontinuation of disulfiram. No instances of hepatic dysfunction was seen, probably because of careful selection of DSM of cases before starting DSM. Anyway, no longterm ill-effects of DSM on liver have been reported (Borup et al. 1992).

The adverse symptoms that occured early in the treatment with DSM were the gastrointestinal ones, anxiety/depression and drowsiness. As already noted only drowsiness could be related with any confidence to DSM rather than predrug alcoholism. The frequency of drowsiness decreased with continued treatment indicating that it is a short-term AE of the drug. The complaint was managed by administering the drug at bed time instead of in the morning.

A latency in the time of onset of AE to DSM was reported for different organ systems (Poulsen et al. 1994) . Skin Reactions peak after 2 weeks, hepatitis at 2 months and neurological symptoms increase with duration of therapy. In this study, to begin with, no skin or hepatic AE were noted. The neurological symptoms of peripheral neuritis and confusion was equally prevalent irrespective of duration of treatment. Psychosis in almost all the cases emerged in those patients on long duration of treatment. As all these patients had psychosis before the Disulfiram treatment it could possibly indicate an aggravating effect of the drug, if it is not a relapse of the illness in its natural course. Disulfiram was continued in these patients along with antipsychotic measures as they were able to understand the risk of ingesting alcohol while taking DSM.

Adverse effects of a drug could understandably cause poor patient compliance. So it was interesting to note in our study that though 75 out of 158 patients had discontinued treatment at least once, only 6 of them blamed the adverse effects of DSM for their non-compliance. Moreover it was seen that patients on regular treatment had more number of adverse symptoms thereby showing that AE of the drug had no relation to poor drug compliance. This observation is similar to that of Liskow et al (1990) who found that only 20% of their 345 patients gave as reason for stopping DSM and none of the 210 patients who discontinued DSM under treatment by Borup et al (1992) blamed the AE of the drug. This suggests that the AE of DSM are not too disturbing especially when weighed against the risks of relapse of alcoholism. Proper reassurance and management would help patients maintain treatment compliance.
The study indicated that the AE of Disulfiram are infrequent and mild. The frequent attribution of symptoms existing even before taking the drug to the drug confounds evaluation of adverse effects to Disulfiram. This has to be taken into account in studying the adverse effects of the drug. Most importantly AE are found not to contribute to poor compliance. Hence, as Brewer et al. (1992) pointed out, with this relative low toxicity of the drug especially compared with toxicity of alcohol, Disulfiram could be safely offered to a wide range of patients with alcohol problems rather than being thought of as a last resort.

REFERENCES

Borup, C., Kaiser, A and Jenson E (1992) Long-term Antabuse treatment tolerance and reasons for withdrawal. Acta Psychiatrica Scandinavica, Supplementum 369, 86, 47-49.

Brewer, C., Hardt, F and Petersen, E.N. (1992). Acta Psychiatrica Scandinavica, Supplementum 369, 86, 72.

Christensen, J.K, Roasted, P and Vang, U.H (1984) Side effects after disulfiram. Comparison of disulfiram and placebo in a double-blind multicentre study. Acta Psychiatrica Scandinavica 69, 265-273.

Kristensen, H (1992). Long-term Antabuse treatment of alcohol-dependent patients. Acta Psychiatrica Scandinavica, 86, 41-45.

Liskow, B., Powell B. and Peters, E.C., (1990) Alcoholics attitude towards and experiences with disulfiram. American Journal of Drug Alcohol Abuse, 16, 147 - 160.

Ojehagen, A., Skjærring, A and Berglund M (1991) Long-term use of aversive drugs in outpatient alcohol treatment. Acta Psychiatrica Scandinavica 84, 185 - 190.

Poulsen, H.E., Loft, S., Andersen J.R and Andersen, M (1992) Disulfiram therapy - adverse drug reactions and interactions. Acta Psychiatrica Scandinavica, Supplementum 369, 86, 59-66.

World Health Organisation (1992) The ICD-10 classification of mental and behavioural disorders. GENEVA, WHO.