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A DOUBLE BLIND COMPARATIVE STUDY OF USEFULNESS OF DIPHENOXYLATE AND PROPOXYPHENE NAPSYLATE IN THE WITHDRAWAL TREATMENT OF OPIUM ADDICTS

GURMEET SINGH[1], M.B.B.S., M.R.C. Psych., D.P.M. (Lond.), Dip. Psych. (McGill), Dip. Am. Board of Psych. and Neurology,
JASWANT SINGH SACHDEVA[2], M.B.B.S., M.D.
ASHWANI KUMAR[3], M.D.

At present probably the most popular and effective method to alleviate the withdrawal symptoms in narcotic addicts is the substitution of the stronger narcotics by methadone which because of its milder addictiveness can be more easily and rapidly withdrawn (Weiland and Chambers, 1970). However, methadone itself is an addictive drug, its abuse liability being enhanced by the fact that it can also be used by injection and its comparatively low cost. Further, since it is no longer available in the Indian market a search must be made for a safe and effective substitute. There are two drugs that hold promise in this regard.

Fraser and Isbell (1961) studied the addiction liability of diphenoxylate, a congener of Pethidine. They concluded that its abuse liability was less than that of morphine and comparable to codeine. Subsequently, Goodman (1968) reported the use of diphenoxylate in withdrawal of twenty narcotic addicts using a total dose of 260 mg. over five and a half days. He concluded that it resulted in allaying the usual severe symptoms of withdrawal but found it necessary to use barbiturate and phenothiazines or glutethimide to control the symptoms of anxiety in these subjects. More recently Glatt *et al.* (1970) found the combination of Diphenoxylate with Heminevrin to be quite effective in the treatment of the withdrawal abstinence syndrome in a series of 88 narcotic (including 70 heroin) addicts.

The analgesic, propoxyphene napsylate has also been used in a manner similar to methadone in the detoxification or maintenance of narcotic addicts. Because of its higher toxicity and low potency, it is considered to have a lower abuse potential than other opiate substitutes. In the treatment of addicts, this drug has been administered in oral doses ranging from 400 mg. to 1600 mg. per day—the higher doses often producing untoward side-effects like convulsions, dysphoria and toxic psychosis Recently Jasinsky *et al.* (1977) carried out studies to assess the morphine—like activity of propoxyphene napsylate as well as the more potent propoxyphene hydrochloride. According to their assessments, propoxyphene hydrocloride was approximately 1/24th as potent, and propoxyphene napsylate 1/49th as potent as morphine in suppressing the abstinence syndrome. In another paper, Tennant *et al* (1977) have also reported on the use of propoxyphene napsylate in daily dose of 1000, 1000, 800, 500, 300, and 0 mg on consecutive days in the detoxification of narcotic (heroin) addicts under double-blind conditions using placebo in identical capsules, and found good results and patient acceptance similar to that of methadone.

1. Professor and Head
2. Assistant Professor
3. P. G. Student
Department of Psychiatry, Government Medical College, Patiala.

In view of these reports it was considered worthwhile to assess the value of these two drugs in the treatment of withdrawal symptoms in opium addicts in a controlled double-blind study.

MATERIAL AND METHOD

One hundred and five consecutive patients with a diagnosis of opium addiction who were admitted to the Psychiatry Ward of Rajendra Hospital, Patiala during the period 1980, 1981 and 1982 for detoxification were taken up for the study. The patients with multiple addictions or other gross psychiatric illnesses were excluded. After taking a detailed psychiatric history and medical examination, their present level of opium or narcotic intake was calculated in terms of Morphine. The study was conducted in two phases. In the first phase, withdrawal was undertaken using the low dose regimen and in the second phase using the high dose regimen. In each phase of the sudy, subjects were randomly allocated to two treatment groups A and B. Group A receiving Diphenoxylate and Group B receiving Dextropropoxyphene. The total daily dose to be administered, of either experimental drug, was calculated for each patient according to the present level of daily Morphine consumption e.g. in low dose regimen, the patients consuming upto 250 mg of morphine daily were given 20 mg of Diphenoxylate if in group A or 400 mg. of Propoxyphene Napsylate if in Group B; those consuming between 250 to 500 mg. received 30 mg. of diphenoxylate or 600 mg of propoxyphene and those consuming more than 500 mg. received 40 mg of diphenoxylate or 800 mg. of propoxyphene. In the high dose regimen the respective daily doses were doubled i.e. the dose of diphenoxylate was between 40 to 80 mg. and of propoxyphene between 800 to 1600 mg. daily in divided doses. The drugs were administered by nurses on double blind basis in identical capsules—each capsule containing either 5 mg. of diphenoxylate or 100 mg. of propoxyphene. No other medicines were given except mild hypnotics (for example Diazepam or Nitrazepam) at bed time.

The procedure adopted for withdrawal was the same as reported earlier by Singh and Lal (1975-76) in which the blocking dose of the drugs was adjusted upward or downward in first 48 hours but thereafter maintained at the same level, for ten days and then suddenly withdrawn on 11th day to be replaced by the same number of identical looking placebos. In a few cases the initial calculated dose had to be adjusted because of the fact that the patient did not give an accurate estimate of amount of narcotic being consumed by him or because of varying potency of the opium available in the market. The patients were observed on placebos for three days and for next two days without the placebo. All the patients were assessed daily for presence of any abstinence symptom which were duly recorded in their case-sheets. As 15 patients out of 105 (14%) dropped out during the course of study or attempted to smuggle in drugs clandestinely or were suspected to be taking narcotics during the treatment period and hence were removed from the study. Thus this report is based on an analysis of 90 patients who completed the full 15 days treatment programme.

RESULT AND DISCUSSION

As is evident from Table I all the patients in the present sudy were males between the age of 20 years to 58 years with a mean of 33.4 years. A vast majority were married and farmers or farm labourers. Interestingly there were more literates i.e. primary or upto matric educated in contrast to illiterates as expected

TABLE I—*Demographic Characteristics of Total Sample*

		Group A (Diphenoxylate) (N=46)	Group B (Dextropropoxyphene) (N=44)
Age	Range	22—58 years	20—55 years
	Mean	32.9 years	33.8 years
Marital Status	Married	36	44
	Unmarried	8	0
	Divorced	2	0
Occupation	Farmers/Farm-Labourers	36	30
	Drivers	2	4
	Tech.	4	4
	Business	2	4
	Student	2	2
Religion	Sikh	36	34
	Hindu	8	10
	Muslim	2	0
Education	Illiterate	12	20
	Primary	18	12
	Matric	12	6
	Above Matric	4	6

from the population norms for this community. Table II shows the type and amount of narcotic drugs used by the subjects. Thus in respect of all major demographic variables and the type and amount of narcotic drugs used in the two experimental groups were very similar.

TABLE II—*Amount of daily opiate consumption of total sample*

		Group A	Group B
Oral Opium	Range	1.5 to 10 gm.	1.5 to 10 gm.
	Mean	6 gm.	4.8 gm.
Intravenous-Morphine	Range	30 to 300 mgm.	90 to 500 mgm.
	Mean	190 mgm.	295 mgm.

Table III and IV pertain to findings in the low dose treatment group. Table III shows that the stabilising daily dose of diphenoxylate, ranging between 20 to 40 mg. with a mean of 31.6 mg. and that of dextropropoxyphene was from 400 to 800 mg. with a mean of 709.1 mg. Table IV shows the withdrawal symptoms reported during the treatment with a low dose regimen. Although practically all the

TABLE III—*Stabilizing daily dose (L. D. Group)*

	Group A	Group B
Range	20 to 40 mg.	400 to 800 mg.
Mean	31.6 mg.	709.1 mg.

TABLE IV—*Withdrawal Symptoms Reported During Treatment (L. D. Group)*

	Group A (N=22)	Group B (N=24)	Significance
1. Body aches & pains	22 (100.0%)	24 (100.0%)	N. S.
Mild	14 (63.6%)	14 (58.3%)	
Severe	8 (36.4%)	10 (41.7%)	
2. Insomnia	16 (72.7%)	24 (100.0%)	($p<0.05$)
3. Rhinorrhoea/sneezing	14 (63.6%)	16 (66.6%)	N. S.
4. Diarrhoea	2 (9.1%)	10 (41.6%)	($p<0.1$)
5. Nervousness/tremors	2 (9.1%)	4 (16.6%)	N. S.
6. Nausea/retching	0 (0.0%)	4 (16.6%)	($p<0.1$)
7. Anorexia	4 (18.2%)	4 (16.6%)	N. S.
8. Lacrymation	4 (18.2%)	2 (8.3%)	N. S.

patients complained of body aches and pains these were mild in majority (60.9%) of cases with a mean duration of about 3.7 ± 1.5 days. It is interesting that the sleep disturbance was not apparently related to the physical pains as Insomnia was complained of by only 72.7 per cent patients on Diphenoxylate as against the complaints of body aches by all the patients. There was no significant difference in relation to complaints of rhinorrhoea and sneezing, nervousness, tremors, lacrymation and anorexia, between the two experimental drug groups except that Diphenoxylate was found better in controlling diarrhoea. There were no reported side effects with either of the drugs on this dose.

Table V and VI pertain to findings in the high dose treatment group. Table V shows that the stabilising daily dose of Diphenoxylate was between 40 to 60 mg with a mean of 56.6 mg. and that of Dextropropoxyphene was 800 to 1200 mg. with a mean of 1120 mg. By and large, on the high dose schedule the period of narcotic withdrawal was characterised by good cooperation and lack of daily petty complaints by the patients as witnessed in the low dose schedule. The complaint of bodyaches and pains were reported by only 28.3% of all patients and were mild in all cases not requiring any drug treatment apart from reassurance. Complaints of insomnia were also markedly less with this high dose regimen (only 13.3% patients) and none of the patients reported diarrhoea, nausea, retching or anorexia with either of the drugs. Complaints of Rhinorrhoea/sneezing, nervousness were reduced with high dose of both the drugs. Only two side effects were encountered on the high dose trial viz.—constipation was reported by one patient on Diphenoxylate while

TABLE V—*Stabilizing daily dose (H. D. Group)*

	Group A	Group B
Range	40-60 mg.	800-1200 mg.
Mean	56.6 mg.	1120 mg.

TABLE VI—*Withdrawal Symptoms reported during treatment (N. D. Group)*

	Group A (N=24)	Group B (N=2)	Significance
1. Body aches & Pains	4 (16.6%)	8 (40.0%)	N. S.
Mild	4 (16.6%)	8 (40.0%)	N. S.
Severe	0	0	—
2. Insomnia	4 (16.6%)	8 (10.0%)	N. S.
3. Rhinorrhoea/sneezing	4 (16.6%)	4 (20.0%)	N. S.
4. Diarrhoea	0 (0.0%)	0 (0.0%)	—
5. Nervousness/Tremors	2 (8. %)	0 (0.0%)	N. S.
6. Nausea/retching	0 (0.0%)	0 (0.0%)	—
7. Anorexia	0 (0.0%)	0 (0.0%)	—
8. Lacrymation	2 (8.3%)	4 (20.0%)	N. S.
Side Effects reported			
	Constipation 1	Giddi ess 2	

2 persons on Propoxyphene complained of giddiness. These were both mild and did not necessitate discontinuation of the treatment.

CONCLUSIONS

The present study is an attempt to assess the efficacy and safety of use of Diphenoxylate and Dextropropoxyphene in the withdrawal of Narcotic addicts. In view of the reports of serious side effects like convulsions and toxic psychosis on high dose (i.e. upto 1600 mg. of Dextropropoxyphene) of these drugs by Glatt *et al.* (1970) and Jasinski *et al.* (1977) it was decided to carry out the study in two phases. First one using dose ranging between 400 to 800 mg. and in the absence of any adverse effect we then went on to the second phase using dose range between 800 to 1600 mg. daily. The results of the present study demonstrate that both Diphenoxylate and Propoxyphene are both useful in alleviating the symptoms of opiate withdrawal quite effectively. With low dose regimen their less effectiveness is almost the same as of Methadone (Lal and Singh 1975-76). Diphenoxylate appears to be slightly superior to Propoxyphene napsylate and being a cheap and easily available compound, with little abuse potential, is an ideal drug for detoxification of narcotic addicts in our Country. No adverse effects of any kind were reported on low dose schedule whereas on high dose regimen, giddiness and constipation were the only minor adverse effects reported. There was no case of any serious reaction like convulsion or toxic psychosis as reported earlier. This study again confirms the efficacy and safety of the technique of giving full blocking dose of the drug for 10 days followed by sudden withdrawal in the treatment of Opiate addicts.

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