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# Effectiveness of Zuclopenthixol Compared with Haloperidol in the Treatment of Behavioural Disturbances in Learning Disabled Patients

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**Background.** We compared the efficacy of two neuroleptics with different receptor profiles (zuclopenthixol and haloperidol) in learning disabled patients with behavioural disturbance. **Method.** A double-blind crossover study (2 × 8 weeks; $n = 34$), interrupted by a two-week single-blind washout period, was employed. Assessments included the Schedule for Handicaps, Behaviour, and Skills (SHBS) and Clinical Global Impression (CGI). **Results.** The SHBS score was significantly reduced for the zuclopenthixol cohort only. End-point analysis between the two drugs also showed an enhanced effect for zuclopenthixol over haloperidol. CGI scores did not reveal significant differences between the two drugs. **Conclusion.** Zuclopenthixol may be superior to haloperidol for the treatment of behavioural disturbances in mentally retarded subjects.

High-dose neuroleptics are frequently used to treat disruptive symptoms and behaviour in learning disabled subjects. The main drawbacks of this procedure have been the sedating effects of high-dose neuroleptics, and the interference with the subjects' social learning abilities (Aman & Singh, 1988, 1989; Linaker, 1990). Consequently, the selective dopamine-antagonist haloperidol has been proposed as a low-dose drug alternative to high-dose neuroleptics (Aman *et al*, 1989). Previous studies (Mlele & Wiley, 1986; Izmeth *et al*, 1988; Singh & Owino, 1992) and our clinical experience suggest that zuclopenthixol, a neuroleptic drug with antagonistic effects on several monoamine receptors, offers greater advantages than haloperidol in the treatment of learning disabled subjects with behavioural disturbance (Karsten *et al*, 1981). This hypothesis has not been subjected to double-blind assessment. This study tests this hypothesis by comparing the effectiveness and side-effects of zuclopenthixol with those of haloperidol in learning disabled patients with behavioural disorders that persist despite optimal psychosocial treatment.

## Methods

### Subjects

The patients were recruited from municipal special care units for the learning disabled in Oslo ($n = 24$) and the Central Institution for Mentally Retarded Patients at Åkershagan, Hedmark County, Norway ($n = 11$). Inclusion criteria were as follows: an ICD–10 (World Health Organization, 1992) diagnosis of F79-79 (Mental Retardation); an age of 18–60 years; and a need for psychopharmacologic intervention for psychiatric symptoms or behavioural disturbances that significantly impaired social interaction or learning, despite optimal psychosocial treatment. Exclusion criteria were as follows: drug abuse, pregnancy, or treatment with depot neuroleptics within the last three months. A sample size of 30 was estimated to provide a level of statistical significance of 0.05, given an explanatory power of 80% with the effect size expected on the Schedule for Handicaps, Behaviour, and Skills (SHBS) and Clinical Global Expression (CGI) scales.

Sixteen subjects were women (mean age 37.9 years, range 25–55), and 19 were men (mean age 35.8 years, range 24–59). Eight subjects were day-patients and 26 were in-patients. The behavioural disturbance was related to: persistent anxiety and psychomotor agitation ($n = 21$); aggression ($n = 11$); psychotic symptoms, hallucinations, or both ($n = 7$); and self-injurious behaviour ($n = 3$). Twenty-eight of the patients had been prescribed oral neuroleptics during the month before the washout.

The study was approved by the regional ethics committee and the Norwegian Drug Control Authority (Statens Legemiddelkontroll) and conducted according to the Helsinki Declaration (II). As required by law, relatives or guardians gave written informed consent for participation in the study.

Treatment of patients with learning disability is provided as part of the national health and social security system in Norway.

### Design

After a single-blind placebo washout period of two weeks, patients were randomised to *double-blind* oral zuclopenthixol or haloperidol for eight weeks in a crossover design. A two-week single-blind placebo washout period occurred between the crossover periods. The initial dose was zuclopenthixol (2 mg) or haloperidol (0.5 mg). The dose was titrated upward by 2 mg and 0.5 mg, respectively, with at least a three-day interval according to the clinical response. The final dose range was zuclopenthixol (2–20 mg) or haloperidol (0.5–5 mg). Compliance with medication intake was supervised. At the end of the first drug-trial period of eight weeks, the mean daily dosages for zuclopenthixol and haloperidol, respectively, were 5.5 and 1.56 mg. At the end of the second drug-trial period, the mean daily dosages were 5.13 and 1.23 mg, respectively. Prescriptions for anti-convulsant medication, alimemazin (for insomnia), and antibiotics or analgesics as needed were permitted. Consequently, 12 and 17 subjects took concomitant medication with zuclopenthixol and haloperidol, respectively.

### Instruments

The behaviour subscales of the SHBS and CGI were used to assess behavioural changes. Twelve SHBS items (rated from 0 = no problem to 4 = marked problems) evaluating the following abnormal behaviour were selected: (1) wandering, (2) destructiveness, (3) noisiness, (4) temper tantrums, (5) aggressive behaviour, (6) hyperactivity, (7) aberrant behaviour in public places, (8) lack of cooperation, (9) crying and moaning, (10) difficult or objectionable personal habits, (11) scattering or throwing objects, and (12) other behavioural problems. Rasch analyses have shown a one-dimensional latent structure of the SHBS behaviour subscale. The subscale is thus a valid measurement of deviant behaviour in the learning disabled (Lund, 1989). Three items were added: (13) self-injurious behaviour, (14) self-stimulation, and (15) stereotyped nagging behaviour. The ratings were based on observation of patients and interviews with nursing staff.

### Reliability of the assessments

After extensive theoretic and practical training, ten patients were rated before the study began to achieve high interrater reliability. The intraclass correlations (ICC 1.1) (Shrout & Fleiss, 1979) for the 12-item subscore of the SHBS were 0.81 and 0.80 in the two study sites, respectively. Because the interrater reliability of the CGI was lower (0.72 and 0.56), it was decided to emphasise the SHBS subscore. On single items of the SHBS, acceptable interrater reliability (ICC > 0.60) was obtained only for noisiness, aberrant behaviour in public places, and self-injurious behaviour. Drug effectiveness was measured at the beginning and the end of the two single-blind placebo washout periods, as well as after 2, 4, and 8 weeks of active drug treatment. Side-effects were assessed by a 48-item rating scale (UKU Side-Effect Rating Scale) developed by the Scandinavian Society for Psychopharmacology (Lingjærde *et al*, 1987) at the following times: inclusion into the study, the time of randomisation to active drug treatment, the end of the first drug period, the end of the second placebo period, and the end of the second drug administration.

### Statistical procedures

The differences were statistically evaluated with Wilcoxon's matched-pair, signed-rank test; the Mann–Whitney U-test; Fisher's exact probability test, and the chi-square test for dichotomous variables. Before the effects of the two active treatments were compared, the possibility of period effect and treatment-period interaction was tested. A slight, but not significant tendency for subjects to do better in the first than the second period was detected. The subjects' average response to the two treatment arms was also the same regardless of the order in which they were received. The treatment-period interaction was tested by a scatter plot of the difference between the two periods against the average of the two periods. Because no horizontal difference between the groups was observed, indicating the absence of a significant treatment-period interaction, evaluation of the treatment effects was accomplished for the two treatment periods combined.

## Results

Thirty-four patients were eligible for SHBS end-point analysis in the first drug period. (The SHBS scores of one patient for the first six weeks were lost.) One patient refused to comply (zuclopenthixol) and the condition of another on haloperidol so deteriorated that he was withdrawn after four weeks. During the second placebo period, two other patients who had been on zuclopenthixol stopped treatment after deterioration. In the second active drug period, another two patients were excluded: one on

zuclopenthixol whose relatives withdrew their permission, and one on haloperidol who violated protocol by taking 12 tablets.

End-point analysis of the reduction in total 12-item SHBS score ($n = 34$) was statistically significant only for the drug zuclopenthixol: 9.97 (s.d. 7.67) to 5.85 (s.d. 5.46); $P < 0.001$. the corresponding reduction for haloperidol was 10.10 (s.d. 7.66) to 8.28 (s.d. 7.81); $P = 0.18$. End-point analysis *between* the two drugs ($n = 31$) also showed zuclopenthixol to be more effective (9.90 (s.d. 7.70) to 5.52 (s.d. 55.07)) than haloperidol (9.60 (s.d. 7.27) to 7.58 (s.d. 6.84); $P = 0.02$). Similar results occurred when the 15-item SHBS total score was used. Of the 28 patients completing both active drug periods, zuclopenthixol reduced the mean 12-item SHBS score from 9.93 to 5.54 ($P < 0.001$), in contrast to haloperidol (9.29 to 7.50 ($P = 0.16$) (Fig. 1). Similar results were found from analysing the 15-item SHBS total score. However, on the basis of at least a 50% reduction in total SHBS score only, 16 patients on zuclopenthixol and 13 on haloperidol exhibited a response (non-significant). Patients on zuclopenthixol showed significantly larger reductions in two SHBS categories: noisiness and other behavioural problems. No statistical differences were found in response pattern between the effects of either drug by assessing: (1) total score response; (2) change in the profile of mean SHBS scores; or (3) single SHBS item response.

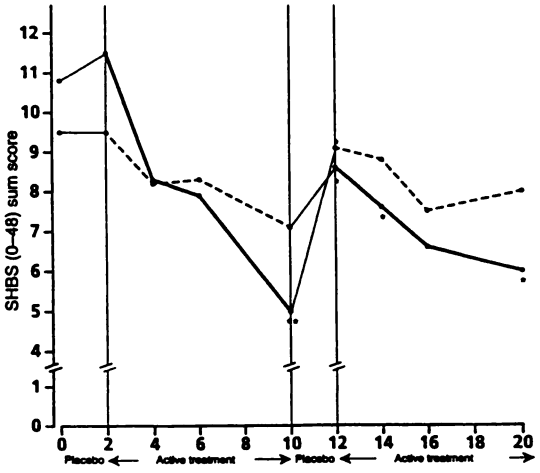


Fig. 1 Schedule of handicaps, behaviour, and skills (12-item) SHBS): total score completers. ▬, zuclopenthixol; ---, haloperidol; —, placebo.

### CGI of overall abnormality

In the first period, end-point analyses showed zuclopenthixol and haloperidol, respectively, to be associated with statistically significant reduced mean CGI scores: 3.24 to 2.69 ($P = 0.04$) and 3.44 to 2.76 ($P = 0.01$). Analyses of completers showed similar findings. In the second period, the reductions in mean CGI scores did not reach statistical significance for either of the two drugs. However, when the results from the two drug periods were pooled, both drugs showed significant improvement as defined by the reduction in CGI score from the initial score. The CGI mean scores did not reflect the observed differences in effect between the two drugs seen on the SHBS mean score reduction.

Neither the number nor the severity of side-effects differed between the two drugs. The side-effects most frequently cited were fatigue ($n = 8$) and increased duration of sleep ($n = 7$). Side-effects were considered to have some influence on the daily functioning of four patients on zuclopenthixol and three on haloperidol.

## Discussion

This is the first double-blind study comparing the effectiveness of zuclopenthixol and haloperidol in learning disabled patients with regard to behavioural disturbances. A decrease in behavioural disturbances as measured by the end-point SHBS total score was achieved in a substantial number of patients by relatively small doses of either zuclopenthixol or haloperidol. However, zuclopenthixol was more effective in reducing disturbed behaviour (SHBS score) than haloperidol, despite equal mean defined daily doses (zuclopenthixol (0.367 and 0.342 mg) haloperidol (0.472 and 0.372 mg)). Another indication of greater effectiveness was that two subjects dropped out of the study when they changed from zuclopenthixol to placebo, whereas none did so when they changed to placebo from haloperidol. The effect obtained in this study with low doses is remarkable considering the tendency to prescribe higher dosages when treating learning disabled patients (Izmeth *et al*, 1988; Aman *et al*, 1989; Singh & Owino, 1992).

The result confirms previous studies suggesting that zuclopenthixol offers advantages over other neuroleptics in the treatment of learning disabled subjects with behavioural disturbances (Karsten *et al*, 1981; Mlele & Wiley, 1986; Izmeth *et al*, 1988;

Singh & Owino, 1992). The difference in effect may be explained by the different receptor profiles of the two drugs. Haloperidol is a rather selective dopamine receptor antagonist. Zuclopenthixol has a significant antagonistic effect on other monoamine receptors also (i.e. adrenergic receptors).

The difference in effect was not detected by the CGI, possibly because the CGI focuses on overall abnormality and not behavioural dysfunction, and because of the low interrater reliability coefficients obtained for this scale. During the interrater reliability training of the clinicians before the study, the total SHBS score was considered to be the most relevant and also the most reliable outcome measure. Because the CGI is one of the most frequently used overall assessment instruments of clinical effects (Singh & Owino, 1992), the finding that this measure had lower reliability than the SHBS total score is an important one. Previous studies based on small samples may have missed true differences between drugs on the outcome measure CGI because of low interrater reliability on this instrument.

Side-effects were few, were of minor severity, and did not differ between the two drugs. The argument against the use of neuroleptics has been their tendency to cause sedation and interfere with social learning abilities. Our findings may indicate that this should not be a major problem with zuclopenthixol and haloperidol in small doses. However, the subjects' learning abilities were not formally tested.

The carry-over of treatment effect from one period to the next remains a central issue with crossover designs. Statistical analysis did not show any treatment-period interaction, and the SHBS scores increased significantly ($P<0.01$) during both placebo periods. Nevertheless, there may be some carry-over effect in the sample because the statistical tests for these interactions are not very powerful.

In conclusion, behavioural disturbances in learning disabled subjects may be treated successfully with relatively small doses of low-dose neuroleptics. Our study confirms several previous studies suggesting that zuclopenthixol is superior to other, more commonly used psychotropic medications in this respect.

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**References**

AMAN, M. G. & SINGH, N. N. (1988) Patterns of drug use, methodological considerations, measurement techniques, and future trends. In *Psychopharmacology of the Development Disabilities* (eds M. G. Aman, N. N. Singh), pp. 1–20. New York: Springer.

———, TEECHAN, C. J., WHITE, A. J., *et al* (1989) Haloperidol treatment with chronically medicated residents: dose effects on clinical behaviour and reinforcement contingencies. *American Journal of Mental Retardation*, **93**, 452–460.

IZMETH, M. G., KHAN, S. Y., KUMARAJEEWA, D. I., *et al* (1988) Zuclopenthixol decanoate in the management of behavioural disorders in mentally handicapped patients. *Pharmatherapeutica*, **5**, 217–227.

KARSTEN, D., KIVIMAEKI, T., LINNA, S.-L., *et al* (1981) Neuroleptic treatment of oligophrenic patients. *Acta Psychiatrica Scandinavica*, **64** (suppl. 294), 39–45.

LINAKER, O. (1990) Frequency of and determinants for psychotropic drug use in an institution for the mentally retarded. *British Journal of Psychiatry*, **156**, 525–530.

LINGJÆRDE, O., AHLFORS, U. G., BECH, P., *et al* (1987) The UKU Side Effect Rating Scale. A new comprehensive rating scale for psychotropic drugs and a cross-sectional study of side effects in neuroleptic-treated patients. *Acta Psychiatrica Scandinavica*, **76** (suppl. 334).

LUND, J. (1989) Measuring behaviour disorder in mental handicap. *British Journal of Psychiatry*, **155**, 379–383.

MLELE, T. J. & WILEY, Y. V. (1986) Clopenthixol decanoate in the management of aggressive mentally handicapped patients. *British Journal of Psychiatry*, **149**, 373–376.

SHROUT, P. E. & FLEISS, J. L. (1979) Intraclass correlations: uses in assessing rater reliability. *Psychological Bulletin*, **86**, 420–428.

SINGH, I. & OWINO, W. J. (1992) A double-blind comparison of zuclopenthixol tablets with placebo in the treatment of mentally handicapped in-patients with associated behavioural problems. *Journal of Intellectual Disability Research*, **36**, 541–549.

WORLD HEALTH ORGANIZATION (1992) The ICD–10 Classification of Mental and Behavioural Disorders. Geneva: WHO.

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