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Effect of different neuroleptics in tardive dyskinesia and parkinsonism

A video-controlled multicenter study with chlorprothixene, perphenazine, haloperidol and haloperidol + biperiden

Nordic Dyskinesia Study Group

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Abstract. Thirty-three chronic psychiatric patients with tardive dyskinesia (TD) were included in a video-controlled multicenter study of the effect of chlorprothixene, perphenazine, haloperidol and haloperidol + biperiden in TD and parkinsonism. The drugs were given in a cross-over design in randomized order in dosages equipotent to the earlier neuroleptic treatment and administered for periods of 6 months with 6-week placebo periods before and after. A total of 55 treatment periods were completed; only seven patients were able to go through all three treatment phases (= 96 weeks). Perphenazine (20.5 mg/day), haloperidol (5.5 mg/day), and haloperidol (11 mg/day) + biperiden (7 mg/day) induced a moderate suppression of TD and at the same time produced a corresponding aggravation in parkinsonism. Chlorprothixene (142 mg/day) had only a slight TD reducing effect and did not change parkinsonism. Thus the TD suppressing effect was inversely related to the parkinsonian-inducing effect of the neuroleptics. Following withdrawal of the drugs, TD increased in some cases and decreased in others compared to the pretreatment level. No significant correlation was found between the intensity of the withdrawal TD and either drugs or preceding parkinsonism or TD suppression. Only in a subgroup of seven patients who consecutively received all three neuroleptics, perphenazine, but not haloperidol and chlorprothixene, produced a post-treatment aggravation which was correlated to the parkinsonsim and TD suppression during treatment. Independent of the neuroleptic given, the TD intensity increased significantly from the first to the third placebo period. This suggests that drug holidays are inappropriate to prevent TD induction/aggravation.

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In the treatment and prevention of tardive dyskinesia (TD) two of the most essential problems are: 1) whether the TD-suppressing effect of neuroleptic drugs is secondary to a parkinsonian-inducing effect or can be obtained without concomitant parkinsonism, and 2) whether some neuroleptics are more liable than others to induce TD.

Neuroleptic drugs of various kinds can suppress TD, powerful dopamine receptor-blocking neuroleptics like haloperidol and pimozide being more effective than weaker dopamine antagonists like thioridazine and clozapine (Kazamatsuri et al. 1972; Claveria et al. 1975; Gerlach and Simmelsgaard 1978; Simpson 1979). However, in most studies, neuroleptics induce parkinsonism together with the TD suppression (Claveria 1975; Gerlach and Simmelsgaard 1978; Pollak et al. 1985). Only a few studies suggest that some selective dopamine antagonists have an antihyperkinetic effect without an obligatory increase in parkinsonism (Bedard et al. 1978; Casey et al. 1979).

The TD-inducing potential of neuroleptic drugs may be measured as the relative TD aggravation seen after withdrawal of the neuroleptic drug: post-treatment score – pretreatment score = TD aggravation. In monkeys this TD withdrawal aggravation was found to be related to a preceding TD suppression (Gunne and Bařany 1979): the TD aggravation following a challenge dose of haloperidol (0.05 mg/kg), which gave marked parkinsonism and TD suppression, was more intensive and prolonged than the reaction to thioridazine (1 mg/kg), which only caused a par-

tial TD suppression. Similar results were found in a clinical study: the TD aggravation after an initial thioridazine treatment (267.5 mg/day) was significantly less than after a second treatment period with haloperidol (5.25 mg/day) which caused parkinsonism and suppressed TD to a significantly higher degree than thioridazine (Gerlach and Simmelsgaard 1978). These observations suggest that strong antidopaminergic neuroleptics such as haloperidol may have a greater tendency to induce TD than weaker antidopaminergic neuroleptics like thioridazine. However, in the clinical study mentioned above, there was no randomization of the drugs and the treatment periods were only of 4 weeks duration. Therefore, more studies are needed on this subject.

With this background it was decided to evaluate (1) the TD-suppressing and parkinsonian-inducing effect of three different neuroleptics, chlorprothixene, perphenazine and haloperidol (with and without an anticholinergic drug, biperiden), (2) the potential TD aggravation after withdrawal of these treatments, and (3) the effect on psychiatric variables of these drugs in a Nordic multicenter study using chronic psychiatric TD patients, randomized drug administration, 24-week treatment periods, and video assessment of the movement abnormalities.

Materials and methods

Patient selection. Psychiatric patients with TD, from seven psychiatric hospitals, were included in the study provided they fulfilled the following criteria: informed consent from patient or relatives; age above 20 years; duration of neuroleptic treatment at least 2 years; a TD total score of at least 2 (rating scale, see later) during previous neuroleptic treatment. Excluded were patients with severe somatic or neurological diseases, alcohol or drug abuse or severe psychotic symptoms (the patients should not be unduly troubled by their psychosis during placebo treatment).

Design and medication. The study was planned as a crossover design in which each patient would receive treatment with chlorprothixene, haloperidol and perphenazine (three of the seven participating clinics used haloperidol + biperiden instead of perphenazine) in randomized order. Each treatment period of 6 months was preceded and followed by 6 weeks placebo. Due to the long duration of this study (96 weeks), it was anticipated and accepted that a substantial proportion of the patients might be unable to complete all treatment periods.

The drugs were administered as tablets, and the dose was chosen to be equivalent to the dose of the neuroleptic given before the trial (for dose equivalents, see Davis 1976). For the test drugs, the following dose relationships were used: haloperidol 1 mg/perphenazine 4 mg/chlorprothixene 25 mg. During the treatment it was allowed to make small dose adjustments in order to accomplish a satisfying antipsychotic effect. No attempt was made to abolish the involuntary movements.

Evaluation. TD and parkinsonian symptoms were recorded on videotape every 2nd week in the placebo periods and every 8th week during the active treatment periods. All investigators were carefully instructed in performing these recordings according to a standardized examination procedure which included sitting, standing, walking, distraction by conversation and performing voluntary movements of non-affected muscle groups such as writing (the detailed instructions can be obtained from the authors). All the videotapes were later randomly sequenced and blindly scored by the same two raters using the Sct. Hans Rating Scale for Extrapyramidal Side Effects (Gerlach and Korsgaard 1983). Only rigidity and salivation were scored non-blind during the video-recordings and spoken into the microphone. Scores ranges from 0–6 (absent–severe) for each item. The interrater reliability was 0.91.

The psychiatric condition was assessed by means of 18 items from the Comprehensive Psychiatric Rating Scale (CPRS) (Åsberg et al. 1978) aimed to measure schizophrenic and depressive symptoms. Side effects (except TD and parkinsonism) were assessed by a specific side effect check list. These assessments were performed before and at week 8 and 12 in each active treatment period and were carried out by a person uninformed about the medication given.

Statistical analysis. The potential differences between the different groups with respect to the demographic data and the final drug doses were analyzed by Students *t*-test. The treatment effects within the same patient group over time were tested by a paired *t*-test, while differences between groups were analyzed by an analysis of variance followed by a *t*-test. Correlations were evaluated by Spearman rank correlation test.

Results

Demographic data of patient groups. Forty-four TD patients passed the pretreatment placebo period and entered the first treatment phase. Eleven dropped out, six due to aggravation of the psychosis (one on chlorprothixene, one on perphenazine, four on placebo) and five unrelated to the medication. The remaining 33 patients (27 schizophrenics, two manic depressive, two chronic paranoid psychotics and two alcohol dementia) completed the treatment with active test drug and subsequent placebo of phase I.

Two of the seven participating clinics (with a total of seven patients) stopped the study after phase I. Twenty-six patients continued into phase II, where 11 dropped out, four due to psychotic exacerbation (one on chlorprothixene, one on haloperidol, and two on placebo), the rest for non-medicational reasons. Fifteen patients completed phase II. Only three clinics with 11 patients continued into phase III. Four patients dropped out; one due to a psychotic exacerbation (chlorprothixene), three for non-medicational reasons. Thus, only seven patients went through the whole 96-week study period, and a total of 55 treatment phases were finished.

Eighteen patients completed a treatment period with chlorprothixene, 19 with haloperidol, 12 with perphenazine and six with haloperidol + biperiden. The sex, age, duration of illness, of neuroleptic treatment and of TD are shown in Table 1. It can be seen that the patients were relatively old and long-term treated. There were no significant differences between the four groups with respect to the variables mentioned.

Seven patients were treated with all three neuroleptics in three consecutive phases. They were analyzed separately. The demographic data of these seven patients are also

Table 1. Demographic patient data

	All patients	Patient subgroups treated with				
		Chlorprothixene	Haloperidol	Perphenazine	hal + bip	chl-per-hal
Number of patients	33	18	19	12	6	7
Sex (male/female)	18/15	10/8	9/10	3/9	4/2	0/7
Age[a]	66 (46–80)	66 (48–80)	66 (48–79)	66 (47–79)	60 (48–72)	60 (50–74)
Duration of illness[a]	27 (6–56)	24 (6–50)	31 (7–53)	24 (6–56)	26 (10–50)	18 (9–30)
Duration of neuroleptic treatment[a]	20 (2–32)	17 (2–30)	22 (9–32)	17 (6–30)	18 (3–30)	16 (9–23)
Duration of tardive dyskinesia[a]	5 (1–20)	8 (1–20)	8 (2–17)	5 (2–12)	9 (38–15)	6 (2–12)

Abbrevations: hal haloperidol; *bip* biperiden; *chl* chlorprothixene; *per* perphenazine

[a] Expressed as means with range in brackets

shown in Table 1 (chl-per-hal). They were all females, but otherwise there were no significant differences between this subgroup and the rest of the patient material.

General observation of TD and parkinsonism. At the end of the pretreatment placebo period, 32 of the 33 patients had oral TD (chewing and/or tongue movements). Fourteen had dyskinesias in the extremities, three of the trunk, one of the head and one in the face [patients with questionable TD symptoms (score 1) are not included]. At the same time, 28 patients had parkinsonian symptoms (at least one item scored 2). All 28 had hypokinesia (reduced facial expression, bradykinesia, reduced arm swing, and parkinsonian gait), 11 had rigidity, and seven tremor. There was no correlation between parkinsonian score and total TD score during placebo treatment ($r=0.17$). Seven patients showed slight motor akathisia.

Dosage. The final mean dose of chlorprothixene was 142 mg/day (range 25–300), of perphenazine 20.5 mg/day (6–72), of haloperidol 5.5 mg/day (1–16), and of haloperidol 11 mg/day (2–24) + biperiden 7 mg/day (2–12). For chlorprothixene, haloperidol and haloperidol + biperiden the doses were relatively stable throughout the study periods, while some adjustments occurred during perphenazine treatment (Fig. 1).

No antiparkinsonian medications were used except for the haloperidol-biperiden period. Nine patients received diazepam 5–15 mg/day, three continuously during the whole study, four only in the placebo periods, and two periodically during treatment with chlorprothixene and perphenazine.

TD-suppressing effect. Compared with the respective pretreatment values, the mean total TD score was slightly reduced during treatment with chlorprothixene ($P<0.1$, $N=18$) and haloperidol (11 mg/day) + biperiden (7 mg/day) ($P<0.1$, $N=6$), and moderately reduced during perphenazine ($P<0.01$, $N=12$) and haloperidol ($P<0.001$, $N=19$) (see Fig. 1). The TD score during treatment with both perphenazine and haloperidol was significantly lower than during treatment with chlorprothixene ($P<0.05$), while no difference could be found between perphenazine and haloperidol.

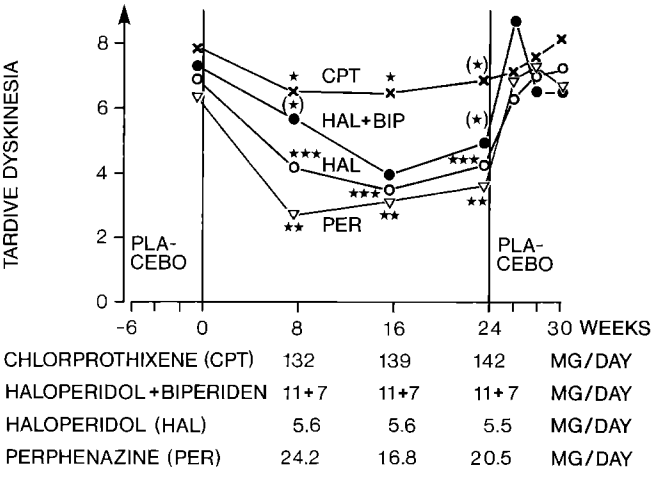

Fig 1. Mean tardive dyskinesia scores before, during, and after treatment with chlorprothixene ($N=18$), haloperidol + biperiden ($N=6$), haloperidol ($N=19$), and perphenazine ($N=12$). Mean doses of drugs given at week 8, 16, and 24 are shown below. (*) $0.05<P<0.1$; * $P<0.05$; ** $P<0.01$; *** $P<0.001$ compared with pretreatment placebo scores

Parkinsonian-inducing effect. Compared with the respective pretreatment scores, the mean total parkinsonian score increased significantly during treatment with perphenazine as well as haloperidol ($P<0.01$) (Fig. 2). There was no significant correlation between the pretreatment parkinsonism and the parkinsonism increase during treatment. Chlorprothixene and haloperidol + biperiden did not change the parkinsonian score significantly. Measured by global evaluation, but not by total score, the parkinsonism was more pronounced during treatment with perphenazine and haloperidol than during treatment with chlorprothixene ($P<0.05$).

As can be seen from Figs. 1 and 2, there appears to be an inverse relationship between the TD-suppressing effect and the parkinsonian-inducing effect of the neuroleptics studied. Chlorprothixene had only slight or no effect on TD and parkinsonism, while perphenazine and haloperidol increased mean parkinsonian score corresponding to the decrease in mean TD score. A correlation analysis revealed that for the total number of treatments ($N=55$) a significant

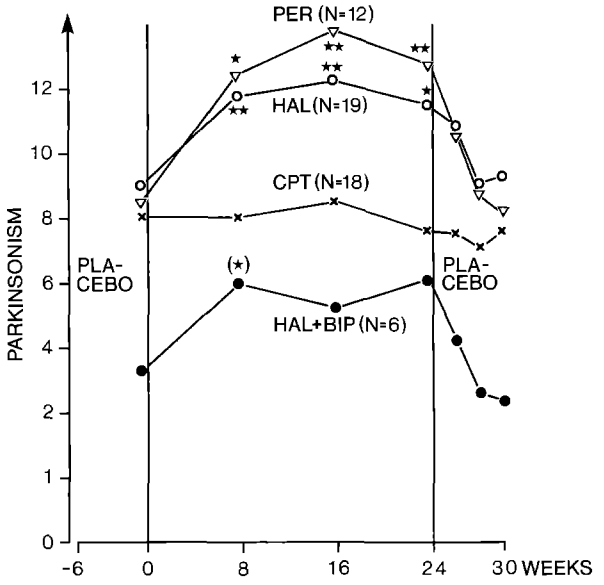

Fig. 2. Mean parkinsonian scores before, during, and following treatment with perphenazine (*PER*), haloperidol (*HAL*), chlorprothixene (*CPT*), and haloperidol + biperiden (*BIP*). For drug doses and *P* signs, see Fig. 2

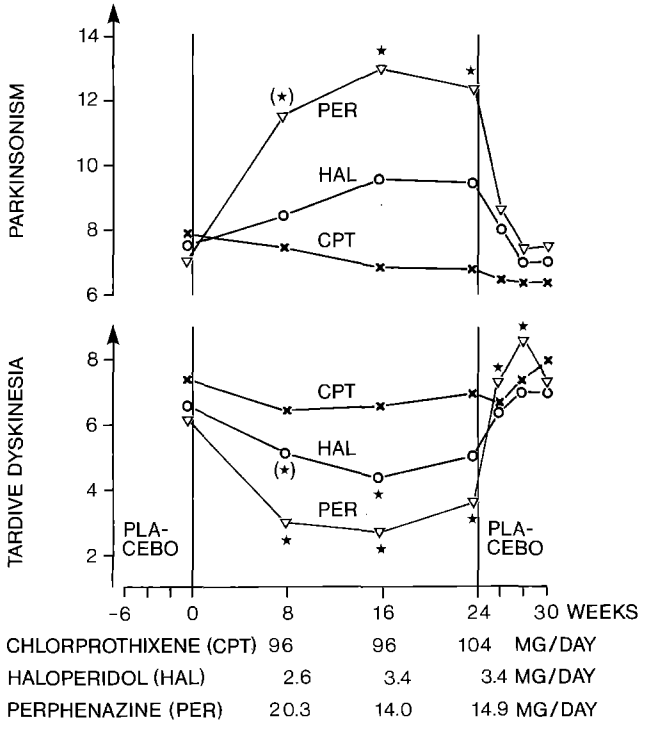

Fig. 3. Mean tardive dyskinesia and parkinsonian scores before, during, and following treatment with perphenazine, haloperidol, and chlorprothixene in a subgroup of seven patients who completed all three treatment periods. Mean doses are given below. (*) $0.05 < P < 0.1$; $*P < 0.05$ compared with pretreatment placebo scores

correlation exists between the parkinsonism increase and the TD decrease ($P < 0.05$).

The TD changes after withdrawal of the drugs. The potential TD-inducing effect of the different treatments was evaluated by comparing the TD scores before and after treatment: Post-treatment score − pretreatment score = TD aggravation, where the post-treatment score is defined as the mean of the scores at week 2, 4, and 6 after withdrawal, and pretreatment score as the last score before treatment.

Table 2. Distribution of treatment conditions according to post-treatment changes in TD score compared to pretreatment TD score and type of neuroleptic given

TD changes	Chlorpro-thixene	Halo-peridol	Perphen-azine	Halo-peridol + bi-periden	Total
Aggravation (Score increase ≧2)	4	8	6	3	21
No changes (<2)	8	4	4	3	19
Improvement (Score decrease ≧2)	6	7	2	0	15

As can be seen from Fig. 1, there was no significant difference between the post- and pretreatment mean TD scores in relation to the four different treatments, i.e. no significant TD aggravation was found for the material as a whole. However, clear individual changes occurred; aggravation, improvement and no change were seen. Table 2 shows the number of treatment conditions which were followed by a TD aggravation (score increased ≧2), no change (score changed less than 2), and TD improvement (score decreased ≧2) compared to pretreatment score. It can be seen that TD aggravation as well as TD improvement occurred in all four treatment subgroups, and no significant differences were found. A total of 21 treatments gave TD aggravation, while 15 gave improvement.

The relationship between withdrawal TD and TD-suppression/parkinsonism induced *during* treatment was also analyzed. No correlation was found. Among the 21 treatment conditions which were followed by a TD withdrawal aggravation, 16 had a preceding TD suppression and 13 parkinsonism aggravation. Among the 15 treatments with TD improvements after withdrawal, 14 had preceding TD suppression and 11 parkinsonism aggravation (no significant difference). Of 23 treatments with both TD suppression and parkinsonism, nine developed TD aggravation, 11 TD improvement, while three showed no changes after withdrawal. These figures clearly indicate that no correlation exists between antihyperkinetic and parkinsonian effects on the one hand, and TD withdrawal aggravation on the other.

A slightly different result emerged from an evaluation of the subgroup of seven patients who received all three neuroleptic drugs in three separate treatment periods. The TD suppression and parkinsonism induced (Fig. 3) corresponded to what was found for the material as a whole (Figs. 1 and 2). In this group, however, a statistically significant TD aggravation occurred after withdrawal of perphenazine (14.9 mg/day). The pretreatment TD score of 6.2 increased to max 8.7 ($P < 0.02$), mean 7.8 ($P < 0.05$) after treatment. Furthermore, a correlation analysis revealed a significant correlation between the TD aggravation and the preceding TD suppression ($P < 0.05$) and parkinsonism ($P < 0.05$) induced by perphenazine. No TD aggravation

was seen after chlorprothixene (104 mg/day) and haloperidol (3.4 mg/day). However, for haloperidol a correlation was found between the TD change (pretreatment − post-treatment max score) and the max TD suppression during treatment ($P<0.05$), but not between TD change and parkinsonism.

Effect of consecutive drug-free periods on withdrawal TD. In order to evaluate the effect of repeated drug-free periods (drug holidays) on withdrawal TD, we have analyzed the 15 patients who, independently of the neuroleptics given, completed three consecutive placebo periods (pretreatment placebo, phase I placebo and phase II placebo). As can be seen from Fig. 4, there was an increase in mean TD score from one to the next placebo period. From the first to the third placebo period, the increase was significant. Figure 4 also illustrates that the TD scores after withdrawal of a neuroleptic drug tend to reach a maximum at week 4 (see also Fig. 1).

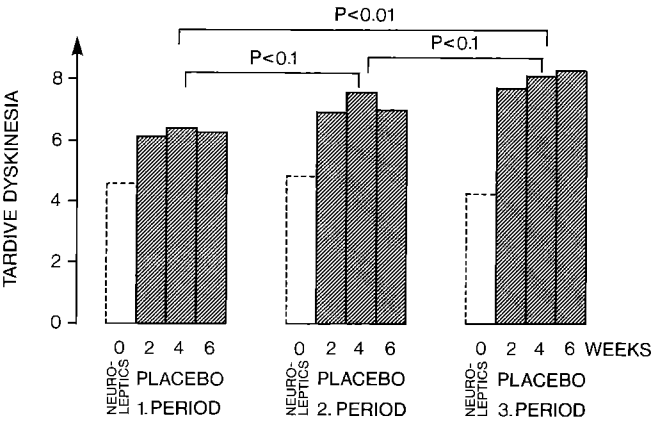

Fig. 4. Mean tardive dyskinesia scores during three consecutive placebo periods following neuroleptic treatment for at least 24 weeks. *Neuroleptics* given before the placebo periods represent a mixture of different neuroleptics ($N=15$)

Effect on mental functions. A total of 11 patients dropped out due to psychotic exacerbation, six during placebo, three during chlorprothixene, one during perphenazine and one during haloperidol. Otherwise, only slight and clinically insignificant alterations occurred in the psychotic state of the patients during the four treatments applied in this study. During treatment with perphenazine, chlorprothixene, haloperidol, haloperidol + biperiden the mean total CPRS score (18 items) decreased from 23.3 to 23.0, from 19.8 to 15.8, from 19.5 to 14.6, and from 8.7 to 6.8, respectively (nonsignificant in all cases). At the end of the treatment period, the total score in the perphenazine-treated patients was higher than the corresponding scores following haloperidol ($P<0.05$) and chlorprothixene ($P<0.1$). Among the single items, "reduced sleep" score was higher during perphenazine than during chlorprothixene (1.39 versus 0.39, $P<0.05$). Otherwise, no significant differences were found.

Side effects. All side effects were scored to be of mild to moderate degree, and caused in no cases discontinuation of the treatment. No significant differences were observed in side effect index (number of patients multiplied by the severity of symptoms), but there was a tendency towards a greater increase in autonomic symptoms during treatment with chlorprothixene (from 18 to 37) than during haloperidol (from 23 to 24) and perphenazine (from 22 to 27).

Discussion

Relationship between TD suppression and parkinsonism. The present study suggests that in elderly long-term treated psychiatric patients, neuroleptic-induced TD suppression is inversely related to concomitantly-induced parkinsonism. This was seen in the patient material as a whole and in the subgroup of seven patients who received all three neuroleptic treatments. Other studies also indicate that TD suppression occurs together with parkinsonism (see Introduction). This inverse relationship implies that parkinsonian bradykinesia may be the primary factor underlying the antihyperkinetic effect of neuroleptic drugs, although sedation and improvement in the psychotic state may also contribute in individual cases. The assumption that antihyperkinetic effect is secondary to parkinsonism is in accordance with the observation that anticholinergic treatment reduces parkinsonism as well as aggravates TD (Gerlach and Thorsen 1975; Gerlach and Simmelsgaard 1978). In addition, a TD follow-up study showing that over time TD decreases while parkinsonism increases, supports this view (Casey et al. 1986).

A clinical study with the selective D-2 receptor antagonist sulpiride has suggested that antihyperkinetic effects may be obtained without an obligatory increase in parkinsonism (Casey et al. 1979). This antihyperkinetic effect may, however, be related to the induction of minimal or subclinical parkinsonism, which may escape simple observation. Therefore, it is necessary with further studies to assess whether certain neuroleptics like sulpiride have selective antihyperkinetic effects without inducing parkinsonism. It should be added that a recent study (Pollak et al. 1985) has shown that another benzamide, tiapride, has an antihyperkinetic effect, which appears to be related to the parkinsonism induced.

The TD-inducing effect of neuroleptics. The TD withdrawal aggravation (post-treatment TD − pretreatment TD) is supposed to be the best index of the TD-inducing capacity of neuroleptic drugs. In monkeys, strong antidopaminergic drugs like haloperidol and fluphenazine, which induce acute dystonia and parkinsonism and suppress TD, cause more intensive and prolonged TD aggravation than weaker neuroleptics like clozapine and thioridazine, which produce only slight acute extrapyramidal symptoms (Gunne and Bárány 1979). These monkey observations are in agreement with the traditional hypothesis of dopamine receptor supersensitivity as the main pathophysiological factor underlying TD: the greater dopamine receptor blockade, the greater dopamine receptor supersensitivity (Christensen et al. 1976; Hyttel 1977). This TD rebound aggravation model has, however, never been tested systematically in patients.

In the present study, no consistent TD rebound aggravation was found in the overall group. TD improvement occurred nearly as often as TD aggravation. No significant differences with respect to withdrawal TD were found between the different neuroleptics, and no correlation could be found between aggravation of parkinsonism/TD suppression on one side and the TD alterations following withdrawal on the other. This means that at least for the patient population and the drugs examined in this study, the inten-

sity of withdrawal TD is unrelated to the neuroleptic drug given or the preceding parkinsonism/TD suppression.

However, in the seven women who received all three drugs, TD aggravation was found after perphenazine, an aggravation which appeared to be correlated to the preceding parkinsonism and TD suppression. This might be coincidental, but it cannot be excluded that a subgroup of TD patients are especially vulnerable, so that a marked parkinsonism and TD suppression may be followed by TD deterioration above the pretreatment level. Therefore, although the exact mechanism of action is unknown, it might be advisable to avoid induction of parkinsonism and other acute extrapyramidal syndromes as such side effects in some cases may increase the risk of later TD. A prospective epidemological study showing that those patients who develop acute extrapyramidal symptoms are also those who develop TD supports this view (Kane 1986).

The exact pathophysiology of TD is still unknown. However, recent observations suggest that the traditional dopamine supersensitivity theory is insufficient, and that other mechanisms are involved, especially a direct blocking effect of neuroleptics on subgroups of dopamine receptors (Gerlach et al. 1986) and a decreased activity in certain GABAergic striatonigral neurons (Gunne et al. 1984; Scheel-Krüger and Arnt 1985). In addition, the possibility of a noradrenergic hyperactivity should be mentioned (Jeste et al. 1986). The present findings of varying TD response after neuroleptic treatment are in favour of such a heterogeneous pathophysiology of TD rather than a simple dopamine supersensitivity.

Drug holidays (drug-free periods in long-term treatment) have been proposed as a measure to reduce the risk of TD development/aggravation. This study, however, indicates that repeated discontinuations aggravate TD, independently of the neuroleptics given. This observation is in agreement with other related findings. Thus it has been found that intermittent neuroleptic treatment causes the same behavioral supersensitivity and dopamine receptor increase as continuous treatment (Koller 1984; Belmaker et al. 1985), and retrospective clinical studies have suggested that interruption of neuroleptic treatment may not reduce and may even increase the incidence of TD (Degkwitz et al. 1967; Jeste et al. 1979). The present study is the first prospective confirmation of these observations. The mechanisms underlying such an aggravation are unknown, but it might just be an unspecific disturbance or increased vulnerability leading to aggravation of motor dysfunctions. In any event, the best procedure to avoid a TD induction/aggravation appears to gradually reduce the neuroleptic treatment over a long period of time (Casey and Gerlach 1984).

Mental functions. The patients in this study were old chronic institutionalized individuals selected in such a way that no serious mental alteration should occur. Therefore, it was not surprising that only minimal changes occurred in the psychic state during and following the different treatments. Three patients dropped out during chlorprothixene treatment, one during perphenazine and one during haloperidol. Otherwise only clinical insignificant changes occurred.

The observation of an equal antipsychotic effect of the different neuroleptics used in this study suggests that, in most chronic psychotic patients, anti-psychotic treatment can be performed with high-dose neuroleptics such as chlorprothixene with a limited risk of inducing parkinsonism and other acute extrapyramidal symptoms. Furthermore, available evidence indicates that such treatment implies the lowest risk of eliciting TD in the long run.

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