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The Dose Reduction in Schizophrenia (DORIS) study: a final report

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Abstract

Twenty-one medication-free chronic schizophrenics were randomly assigned to three treatment groups: 50% blockade of the bromocriptine growth hormone (GH) response, 100% blockade or 10 ng/ml haloperidol. Only seven of the 21 patients showed a significant improvement after 6 weeks in positive psychotic symptoms; six of the seven responders came from the 50 and 100% blockade groups, suggesting greater efficacy at lower doses. Fifty percent blockade was associated with an average daily haloperidol dose of 3.2 mg and plasma haloperidol levels below the limit of detection (< 1 ng/ml). 100% blockade was associated with a daily dose of 6.5 mg and a plasma haloperidol level of 1 ng/ml. Negative symptoms significantly improved in only four of the 21 patients, and three of these patients were from the 100% blockade group. Twenty-nine patients currently receiving 20 mg/day haloperidol were randomly assigned to three treatment groups: placebo, 100% blockade of the GH response and 10 ng/ml. Patients in the placebo group showed significant deterioration along both the positive and negative symptom dimensions. There were no significant symptom differences between the 100% blockade and the 10 ng/ml groups. The patients in the 100% blockade group had on average a daily dose reduction from 20 to 11 mg/day and a 65% reduction in the plasma haloperidol level. There was a 70% difference in the average daily dose for 100% blockade between the two study arms. The higher daily dose in the dose-reduction arm may reflect receptor up-regulation and/or other 'tolerance'-like mechanisms associated with chronic neuroleptic administration.

Keywords: Schizophrenia; Haloperidol; Dose reduction; Growth hormone; Bromocriptine; Psychosis; Positive symptoms

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1. Introduction

This communication is the final report of the Dose Reduction in Schizophrenia (DORIS) study, being conducted as a collaborative effort between the Bronx and Northport Department of Veterans Affairs Medical Centers, Mt. Sinai and SUNY at Stony Brook Schools of Medicine and the Pilgrim State Hospital. The overall purpose of the study is to explore strategies for determining the smallest possible dose of neuroleptic with the maximum therapeutic effect. In addition, the study aims to demonstrate that some very chronic patients with only partial drug responsiveness can undergo significant dose reduction with little or no loss of therapeutic benefit.

Since the classical (or typical) antipsychotic drugs exert their therapeutic effect by blockade of D_2-like dopamine receptors (Seeman et al., 1975; Creese, 1987) and since the affinity of typical neuroleptics for these receptors is known (e.g., Seeman and Van Tol, 1994), it logically follows that measures of drug uptake into the CNS could be used to titrate and adjust antipsychotic drug dosage. However, such a pharmacokinetic approach may be problematic. For example, Schlyer et al. (1992) using positron emission tomography (PET) observed that the uptake of ^{18}F-haloperidol into whole brain (measured as a percent of injected dose at 2 h) ranged from 4% in medicated schizophrenics to 6.6% in normal controls. Thus, the administration 1 mg of haloperidol will result in a brain concentration of approximately 100 nM or 30–50 times the K_D for haloperidol binding to D_2 receptors (Seeman and Van Tol, 1994). Since it is known that this dose of haloperidol will on average produce only partial receptor occupancy (see below), it follows that most of the haloperidol in the brain is sequestered at sites where it is not available for receptor binding.

Neuroleptic plasma level concentrations appear to provide a better estimate of free drug concentrations within the CNS as determined by the levels of D_2 receptor occupancy. For haloperidol, 1 ng/ml equals 2.6 nM or approximately twice the K_D concentration (Seeman and Van Tol, 1994). Using PET and ^{18}F-labelled *N*-methylspiroperidol (NMS) as the ligand, Smith et al. (1988) found that 75% striatal receptor blockade (as determined by the ratio index method) was associated with a haloperidol concentration of 1.5 ng/ml and complete receptor blockade was associated with a haloperidol concentration of 9.1 ng/ml. The expected levels of receptor occupancy are 76 and 96%, respectively. We have based these estimates of receptor occupancy on the assumption that a ratio index of 1 represents 100% receptor blockade, i.e., there is no difference in binding between the cerebellum and striatum. Wolkin et al. (1989) extended the studies of Smith et al. (1988) and confirmed that essentially complete receptor blockade is obtained at a plasma level of 10 ng/ml. In a study of normal controls, acute doses of 2 and 4 mg of haloperidol produced D_2 receptor occupancy levels of 50 and 75%, respectively, as assessed by changes in the uptake of ^{11}C-raclopride, a D_2, D_3 receptor-specific ligand (Nordstrom et al., 1992). In both subjects the plasma level was below the limit of detection (2 ng/ml). For two normal controls receiving a 7.5-mg dose of haloperidol, receptor occupancy was more than 80% and plasma haloperidol was approximately 4 ng/ml.

The level of D_2 receptor occupancy and antipsychotic response has also been assessed. Farde et al. (1992) (and Refs. therein) found that in schizophrenic patients receiving standard treatment (physicians' choice) with typical neuroleptics, the level of receptor occupancy ranged from 70 to 89% (average 78%). In patients treated with the atypical antipsychotic, clozapine, the level of D_2 receptor occupancy ranged from 38 to 63% (average 48%). All patients in this study showed significant clinical improvement with neuroleptic therapy. Baron et al. (1989) found in a group of patients with stable psychotic symptoms and receiving depot neuroleptic therapy, the level of D_2 receptor occupancy ranged from 50 to 83%. In a prospective study using raclopride treatment, Nordstrom et al. (1993) found that the maximum reduction in symptoms (measured as a change in the Brief Psychiatric Rating Scale (BPRS)) was associated with a D_2 receptor occupancy between 60 and 80%. Extrapyramidal symptoms (EPS) began to appear at 60% receptor occupancy and

were present in all patients with more than 70% receptor occupancy. A recent study of eight clinically stabilized schizophrenic outpatients demonstrated that D_2 receptor occupancies ranged from 60 to 82% (average 73%) 1 week after injection of haloperidol decanoate and ranged from 20 to 74% (average 52%) 4 weeks after injection (Nyberg et al., 1995). The investigators concluded that continuously high D_2 receptor occupancies may not be necessary to prevent relapse since the patients did not have symptom exacerbation, based on BPRS ratings, even at low D_2 receptor occupancies.

The results summarized above suggest that at least for haloperidol treatment, a combination of plasma level monitoring and measurements of receptor occupancy could be a useful adjunct to normal dosing practices and would likely lead to a reduction in the average daily dose. However, the technology to directly measure D_2 receptor occupancy (PET or SPECT) is expensive and available at only exceptional sites. As an alternative to these direct measurements, we propose an indirect measurement based on a neuroendocrine challenge technique. Stimulation of the D_2 receptors in the arcuate nucleus of the hypothalamus results in an increased secretion of growth hormone releasing factor (GRF) into the median eminence, leading to the release of GH from the anterior pituitary. This growth hormone response can be easily produced by the administration of the direct acting dopamine agonists, apomorphine (Hirschowitz et al., 1986) or bromocriptine (Hirschowitz et al., 1991). We have previously observed that the plasma haloperidol concentrations which block the growth hormone response (Hirschowitz et al., 1991) parallel those which block striatal D_2 receptor occupancy. Given the lack of variance in D_2 receptor affinity throughout the brain (Vadasz et al., 1992), and given the relative lack of variance in haloperidol concentrations throughout the brain, as determined by PET (Schlyer et al., 1992), it would appear that plasma concentrations of haloperidol that are sufficient to block the GH response will be the same concentrations that block 60 to 90% of striatal D_2 receptors as determined by PET (Wolkin et al., 1989; Coppens et al., 1991; Farde et al., 1992). The DORIS project was an attempt to confirm and extend our understanding of these relationships among the haloperidol plasma level, the GH challenge and therapeutic response.

2. Methods

2.1. Subjects

Subjects were recruited from the inpatient units of the Psychiatry Services at the Northport and Bronx VAMCs, the Mt. Sinai Medical Center, and the Pilgrim State Hospital. All subjects were between 21 and 65 years of age, had no history of recent significant substance abuse and no major medical illness. All subjects had a DSM-III-R diagnosis of schizophrenia based on a structured interview: Comprehensive Assessment of Symptoms and History (CASH; Andreasen et al., 1992). The diagnosis of schizophrenia was confirmed during the baseline period by consensus conference. None of the subjects received depot antipsychotic medications for 4 months prior to entering the study. Seventy-four subjects were entered and 50 subjects completed the inpatient protocol. Of the 24 subjects who were dropped from study, four failed to meet diagnostic criteria, three were inadvertently medicated, nine withdrew consent, and three subjects severely decompensated and/or showed adverse drug reactions during the titration phase. Five subjects were not included in the analyses because they had no growth hormone response to bromocriptine even when off medication.

Beginning with the baseline period and continuing throughout the study, assessments of psychiatric symptoms and movement abnormalities were performed by raters who completed the Positive and Negative Symptom Scale (PANSS) (Kay et al., 1987) and the Hillside Hospital modification of the Simpson Dyskinesia Scale (MSDS) (Simpson et al., 1979; Kane et al., 1988). The latter includes a detailed evaluation of extrapyramidal symptoms (EPS) and tardive dyskinesia (TD). Inter-rater reliability on all measures was maintained at >0.85.

Beginning with the baseline period, the use of

regular anticholinergic drugs was discontinued. Subjects were allowed benztropine or diphenhydramine only on a PRN basis, and the use of these agents was carefully documented. Similarly, during the dose titration phases, lorazepam was allowed on a PRN basis to treat anxiety and insomnia.

2.2. Study design

The DORIS study was composed of two study arms. At baseline, subjects were either medication-free ($n=21$) or had been stabilized on 20 mg/day haloperidol ($n=29$). In the medication-free group, six subjects were neuroleptic-naive, while the remaining 15 patients underwent a 10–14-day drug-free washout period prior to beginning haloperidol titration. Inclusion criteria required that these patients were exhibiting acute psychosis at the time of entry into the study. Thus, reduction of baseline positive symptoms was a key outcome measure among subjects in this group. Medication-free subjects were randomly assigned to one of three conditions: 50% blockade of the GH response ($n=5$), 100% blockade ($n=11$), or a dose of haloperidol that resulted in a plasma haloperidol level of 10 ng/ml ($n=7$). (Blockade was defined as no post-bromocriptine GH level greater than three times the average baseline level, a conservative a priori criterion utilized to account for normal GH fluctuations. With no express guidelines in the literature, this criterion was based on the authors' cumulative experience in investigating the GH response to bromocriptine.) Finally, based on the results described in the Introduction, it was assumed that a plasma level of 10 ng/ml would be sufficient to produce 100% striatal D_2 receptor blockade in the average patient.

Subjects who were receiving 20 mg/day haloperidol at baseline made up the other arm of the study. These subjects were typical VA patients – chronic, partial responders who were relatively low functioning in the community. Not all subjects in this arm exhibited acute psychosis at baseline; rather, some were quite stable, albeit at compromised levels of functioning. Rather than expecting significant reductions in baseline positive symptoms among these patients, a key outcome measure was dose reduction without loss of therapeutic benefit. Subjects receiving >20 mg/day haloperidol or its neuroleptic equivalent were slowly reduced to 20 mg/day and stabilized on this dose for at least 2 weeks. These subjects were randomly assigned to either 100% blockade of the GH response ($n=8$), to a 10 ng/ml plasma haloperidol level ($n=16$), or placebo ($n=6$). For most patients, assignment to the 10 ng/ml group was associated with only a modest increase or decrease from the starting haloperidol dose of 20 mg/day. For patients assigned to the 100% blockade group, the dose reduction strategy was to reduce the dose of haloperidol by 50% over a 1-week period followed by a 1-week stabilization period. A GH challenge test was performed at the end of the stabilization period. If the GH response was blocked, the dose-reduction paradigm was repeated. Once the patient escaped from blockade of the GH response, the dose was increased to the previous blockade level. The GH challenge test was repeated after a 2-week stabilization. In all patients, the GH response was reblocked. Patients were then maintained at this dose for an additional 4–6 weeks.

Overall, subjects in the 10 ng/ml plasma haloperidol and the placebo group served as comparison groups. Subjects in the 50 and 100% blockade of the GH response served as experimental groups. Baseline symptom assessments were compared to assessments made when subjects were at the desired plasma haloperidol level or at the desired percent blockade of the GH response.

In both arms of the study, dose-titration was performed in a double-blind fashion. Liquid haloperidol was given in doses suspended in water so that dose adjustment was blind to both staff and the subjects. Throughout the study, the clinical instruments, PANSS and MSDS, were administered to all subjects on a weekly basis. The GH challenge test was repeated every 2 weeks after dose adjustment. The titration phase was completed in all subjects after 8 weeks. After completing the titration phase, subjects remained in the hospital for an additional 6 weeks to complete the inpatient phase. Subjects were followed and studied for up to 1 year following the titration and stabilization phase of the study. Follow-up consisted of PANSS and MSDS ratings and haloperidol plasma levels taken at 1, 3, 6, and 12 months.

At completion of the 1-year follow-up or at the time of early termination because of symptom exacerbation, subjects received a final GH test. The data from the outpatient phase will be reported in a subsequent publication.

2.3. The bromocriptine growth hormone test (BGHT)

Beginning 24 h before the BGHT subjects were assigned to a low monoamine, caffeine-free diet and were asked to refrain from strenuous exercise. At 8:00 a.m., an indwelling intravenous catheter was inserted and maintained patent with a heparin lock. Subjects rested for 30–40 min before the first baseline sample was drawn. Baseline samples (3 ml each) were drawn at −30, −15 and 0 min. An additional 5 ml was drawn at baseline #1 for the plasma haloperidol level. At 0 time bromocriptine was administered p.o. on a per weight basis: 2.5 mg per 50 ± 12.5 kg, 3.75 mg per 75 ± 12.5 kg and 5 mg per 100 ± 12.5 kg. Blood samples (3 ml) were then obtained 60, 90, 105, 120, 135, 150, 165 and 180 min later. Samples not immediately analyzed were frozen at −70°C. Assays on frozen samples were performed within 2 weeks. Additional details for the BGHT, including GH assay specificity are found in Hirschowitz et al. (1991).

2.4. Haloperidol determination

Plasma haloperidol levels were determined by the National Psychopharmacology Laboratory (NPL) (Knoxville, TN) using the gas chromatographic method of Shvartsburd et al. (1983). The method does not measure hydroxy-haloperidol. NPL reports the CVs for haloperidol of 3.8 and 2.0% at 1 and 10 ng/ml, respectively. The limit of assay sensitivity is 0.5 ng/ml.

3. Results

3.1. Patients with a medication-free baseline

Among the patients in the 50% blockade, 100% blockade and 10 ng/ml groups, there were no differences in PANSS positive, negative, or general scores at baseline (Table 1). Within-subject percent change scores were computed by comparing baseline scores with symptom assessments made after the patients reached their desired level of blockade (50 or 100%) or plasma haloperidol level (10 ng/ml). Table 2 lists the within-subject change in PANSS and MSDS scores, as well as dose and plasma haloperidol levels. At the comparison time, which was on average 6.5 weeks after baseline assessments, the average daily dose of haloperidol for the 50% group was 3.2 mg/day (plasma haloperidol levels were undetectable), for the 100% group it was 6.5 mg/day (mean plasma level of 0.9 ng/ml), and for the 10 ng/ml group it was 14.0 mg/day (mean plasma level of 6.6 ng/ml). Kruskal-Wallis group by percent change in symptom rating ANOVAs demonstrated that despite the differences in group dose and plasma haloperidol levels, there were no significant group differences in percent change in PANSS or MSDS ratings (p-values between 0.21 and 0.97). The 50% group had a mean 14% decrease in positive symptoms compared to a 5% decrease in the 100% group, and a 2% decrease in the 10 ng/ml group.

Clinical response was also evaluated by assessing the number of patients that significantly improved, remained the same or showed significant deterioration. A ±20% change from baseline was used as the threshold for assessing improvement and deterioration (see Kane et al., 1988). Fig. 1 graphically represents the response in positive symptoms by each group. Three of the five patients in the 50% blockade group showed significant improvement while two showed significant deterioration. In the 100% blockade group, three patients improved significantly, seven showed no change, and one patient deteriorated. In the 10 ng/ml group, one patient improved, and six showed no change. The change scores for negative symptoms are shown in Fig. 2. For the 50% blockade group, none of the patients significantly improved and one deteriorated. Three of the 11 patients in the 100% blockade group significantly improved, seven showed no change, and one patient was significantly worse. For patients assigned to 10 ng/ml, one markedly improved and six showed no change. The change scores for general symptoms are shown in Fig. 3. For the 50% blockade group, two patients signifi-

Table 1
Demographic characteristics of schizophrenics and baseline scores (values are means ± SD)

Groups	Medication-free at baseline			20 mg/day at baseline		
	50%	100%	10 ng/ml	Placebo	100%	10 ng/ml
n	5	11	7	6	8	16
Age	35.4 ± 15.7	46.0 ± 9.9	39.4 ± 12.1	48.0 ± 8.9	43.1 ± 8.2	45.8 ± 8.6
Percent male	80	91	86	100	75	88
Age (years) at first hospitalization	25.3 ± 5.9	32.3 ± 9.8	23.9 ± 3.9	24.2 ± 8.5	23.2 ± 4.1	23.5 ± 4.7
Number of hospitalizations	2.5 ± 0.7	5.3 ± 3.9	7.3 ± 6.9	11.7 ± 10.9	7.8 ± 5.1	7.9 ± 3.6
Months of current hospitalization	1.2 ± 2.2	0.9 ± 0.5	0.3 ± 0.7	1.5 ± 1.9	19.0 ± 34.6	5.9 ± 15.7
Total months hospitalized	Not available	29.7 ± 36.5	21.0 ± 17.1	48.6 ± 64.1	31.1 ± 51.6	15.1 ± 104.9
Baseline values						
Dose (mg/day)	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	18.3 ± 4.1	20.0 ± 0.0	20.0 ± 0.0
Plasma level (ng/ml)	<1.0[a]	<1.0[a]	<1.0[a]	11.0 ± 9.1	6.5 ± 5.9	6.6 ± 3.8
PANSS						
Positive	19.8 ± 4.3	19.6 ± 5.0	17.3 ± 5.4	20.0 ± 4.9	19.0 ± 5.0	19.9 ± 4.6
Negative	26.0 ± 8.9	22.6 ± 6.4	24.9 ± 6.3	22.2 ± 6.5	23.6 ± 9.7	24.3 ± 7.3
General	41.8 ± 4.1	38.9 ± 8.5	37.4 ± 7.4	39.8 ± 7.6	39.5 ± 9.0	40.0 ± 6.6
MSDS						
EPS	0.4 ± 0.6	0.6 ± 0.5	0.6 ± 0.5	0.8 ± 0.8	1.5 ± 0.9	0.8 ± 0.6
TD	0.2 ± 0.5	0.6 ± 0.9	0.9 ± 0.9	1.7 ± 0.5	1.1 ± 1.1	1.3 ± 0.9

PANSS, Positive and Negative Symptoms scale; MSDS, Modified Simpson-Angus Dyskinesia scale; EPS, extrapyramidal side effects; TD, tardive dyskinesia.
[a]Plasma level was undetectable, less than 1.0 ng/ml.

Table 2
Comparison values and percent change in symptom scores (values are means ± SD)

Groups	Medication-free at baseline			20 mg/day at baseline		
	50%	100%	10 ng/ml	Placebo	100%	10 ng/ml
n	5	11	7	6	8	16
At comparison time						
Dose (mg/day)	3.2 ± 2.8	6.5 ± 5.4	14.0 ± 4.6	1.0 ± 2.2	11.1 ± 4.6	23.9 ± 7.3
Plasma level (ng/ml)	<1.0[a]	0.9 ± 1.1	6.6 ± 3.1	<1.0*	2.3 ± 2.1	10.2 ± 2.9
Percent change scores[b]						
PANSS						
Positive	−13.8 ± 34.7	−4.7 ± 22.1	−1.7 ± 20.4	19.4 ± 20.9	−7.1 ± 26.1	4.5 ± 25.4
Negative	1.8 ± 20.5	−5.4 ± 18.2	0.1 ± 22.8	21.7 ± 34.1	−7.1 ± 22.5	−1.2 ± 20.2
General	−6.2 ± 21.8	−0.7 ± 18.4	−5.5 ± 22.6	15.4 ± 20.9	−4.2 ± 16.2	−4.6 ± 13.1
MSDS						
EPS	33.3 ± 57.7	11.1 ± 33.3	−25.0 ± 50.0	−12.5 ± 25.0	−8.3 ± 95.5	−21.4 ± 42.6
TD	−33.3 ± 57.7	0.6 ± 0.9	0.9 ± 0.9	1.7 ± 0.5	1.1 ± 1.1	1.3 ± 0.9

PANSS, Positive and Negative Symptoms Scale; MSDS, Modified Simpson-Angus Dyskinesia Scale; EPS, extrapyramidal side effects; TD, tardive dyskinesia.
[a]Plasma level was undetectable, less than 1.0 ng/ml.
[b]Comparison time-baseline/baseline; negative values mean a reduction in symptom rating.

cantly improved and none deteriorated. Two of the 11 patients in the 100% blockade group deteriorated and one improved. In the 10 ng/ml group, two patients improved, one quite markedly.

3.2. *Patients on 20 mg/day haloperidol at baseline*

Twenty-nine patients with schizophrenia were stabilized on 20 mg/day haloperidol for at least 2

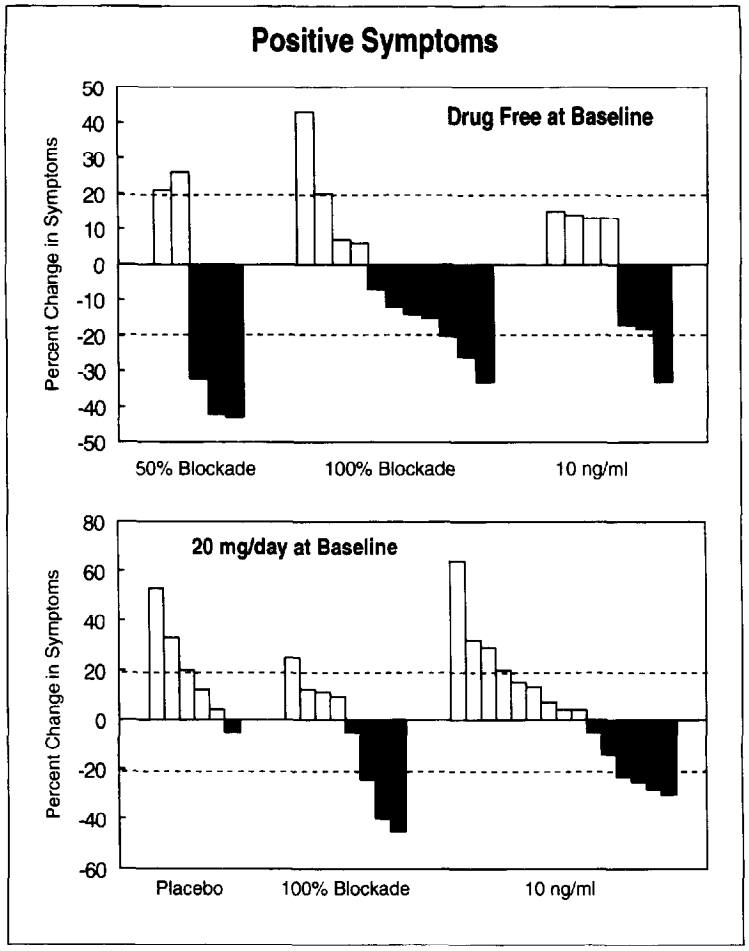

Fig. 1. Change scores in positive psychotic symptoms among various treatment groups. Subjects were either medication-free ($n=21$) or had been stabilized on 20 mg/day haloperidol ($n=29$). Medication-free subjects were assigned to the following treatment groups: 50% blockade of the GH response, 100% blockade of the GH response or 10 ng/ml plasma haloperidol. Subjects in the 20 mg/day arm were assigned to the following treatment groups: placebo, 100% blockade of the GH response or 10 ng/ml plasma haloperidol. Data presented are the change scores from baseline in the positive symptom scores of the PANSS.

weeks before random assignment into the placebo, 100% blockade, or 10 ng/ml groups. There were no significant differences between groups in terms of age, age at first hospitalization, or number of hospitalizations. At baseline there were no differences in PANSS positive, negative, or general ratings, nor were there any differences in MSDS ratings of EPS or TD between the three groups (Table 1).

The dose-reduction strategy designed to result in a 'just' 100% blockade of the GH response (see section 2) resulted in a 45% decrease in the daily dose of haloperidol (from 20.0 to 11.1 mg/day) and a 65% decrease in the plasma haloperidol level. For patients in the 10 ng/ml group, the average plasma haloperidol levels increased from 6.6 to 10.2 ng/ml. Doses were tapered down to an average of 1 mg/day (SD = 2.2 mg) in the placebo group. The average dose was not 0 mg/day because half of the subjects assigned to the placebo group decompensated before finishing the dose reduction. However, at the comparison time all placebo

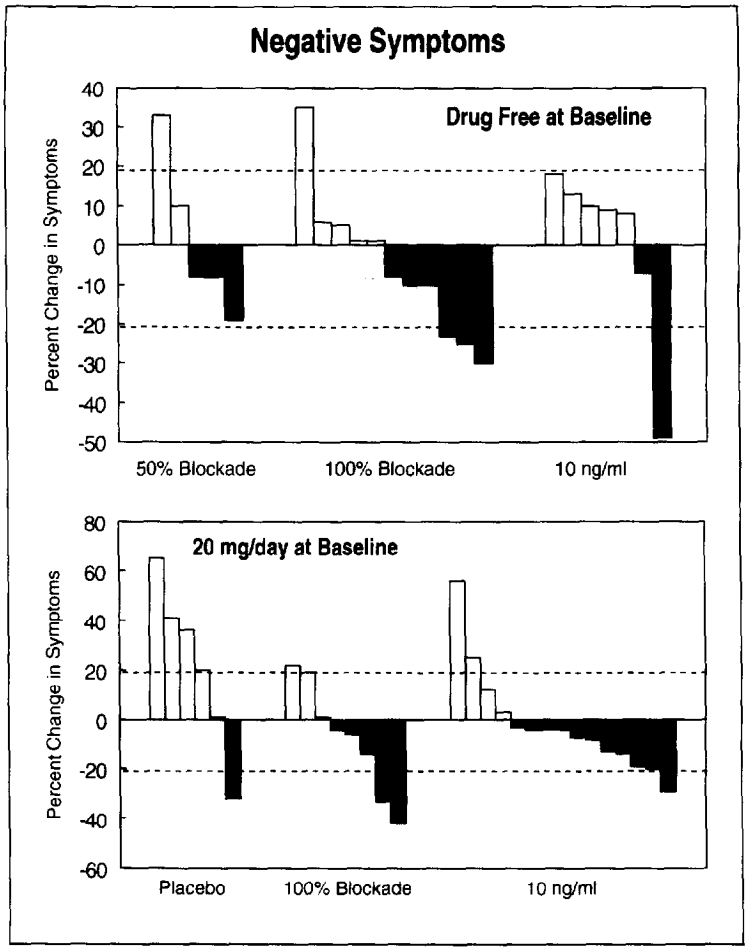

Fig. 2. Change scores in negative symptoms among various treatment groups. Subjects were either medication-free ($n=21$) or had been stabilized on 20 mg/day haloperidol ($n=29$). Medication-free subjects were assigned to the following treatment groups: 50% blockade of the GH response, 100% blockade of the GH response or 10 ng/ml plasma haloperidol. Subjects in the 20 mg/day arm were assigned to the following treatment groups: placebo, 100% blockade of the GH response or 10 ng/ml plasma haloperidol. Data presented are the change scores from baseline in the negative symptom scores of the PANSS.

patients had undetectable plasma levels of haloperidol. There were no significant differences in EPS or TD ratings between groups.

Kruskal-Wallis group by percent change in symptom rating ANOVAs were performed. The placebo group had a mean 19% increase in positive symptoms compared to a 7% decrease and a 5% increase in positive symptoms in the 100% and 10 ng/ml groups, respectively, but the difference was not significant ($\chi^2_{(2)}=2.7$, $p=0.26$). Similarly, although the placebo group had a mean 22% increase in negative symptoms compared to a 7 and 1% decrease, respectively, in the 100% and 10 ng/ml groups, the difference was not significant ($\chi^2_{(2)}=3.9, p=0.14$). However, the increase in general symptoms in the placebo patients (+15%) was significantly different from the modest decreases seen in the 100% blockade and 10 ng/ml groups ($\chi^2_{(2)}=6.0$, $p=0.05$). There were no significant differences in EPS or TD ratings between the groups.

The ±20% change in symptom ratings as a cutoff for determining response was again applied. Positive symptom change scores are shown in

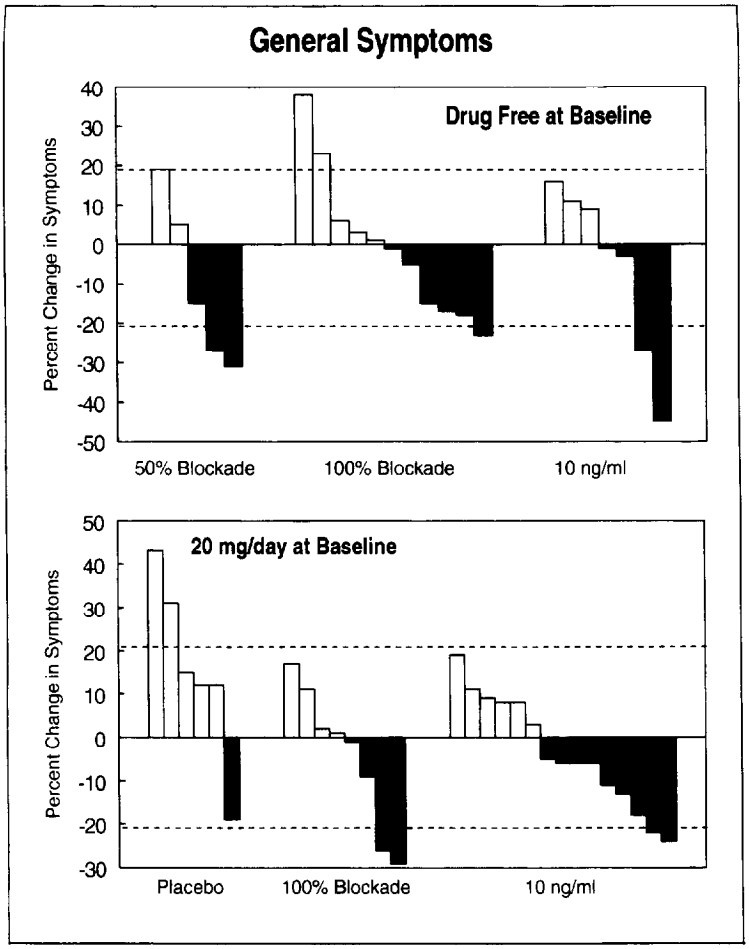

Fig. 3. Change scores in general symptoms among various treatment groups. Subjects were either medication-free ($n=21$) or had been stabilized on 20 mg/day haloperidol ($n=29$). Medication-free subjects were assigned to the following treatment groups: 50% blockade of the GH response, 100% blockade of the GH response or 10 ng/ml plasma haloperidol. Subjects in the 20 mg/day arm were assigned to the following treatment groups: placebo, 100% blockade of the GH response or 10 ng/ml plasma haloperidol. Data presented are the change scores from baseline in the general symptom scores of the PANSS.

Fig. 1. Three of the eight patients in the 100% blockade group and four of the 16 patients in the 10 ng/ml group showed a significant decrease in positive symptoms. One of the eight patients in the 100% blockade group and four of the 16 patients in the 10 ng/ml group showed significant deterioration. In the placebo group, three patients showed no change and three were significantly worse. The negative symptom change scores are shown in Fig. 2. Negative symptoms were significantly worse in four of the six placebo patients and improved in one patient. In the 100% blockade group, two of eight patients improved and one patient became significantly worse. For the 10 ng/ml group, negative symptoms improved in three of 16 patients and were worse in two patients. General symptom change scores are shown in Fig. 3. Two of the placebo patients markedly deteriorated while one improved. For the 100% blockade and 10 ng/ml groups, no subject significantly deteriorated and two subjects in each group significantly improved.

4. Discussion

In spite of increasing evidence that psychotic patients do well with low doses of antipsychotic medication (Van Putten et al., 1990; Hirschowitz et al., 1991; McEvoy et al., 1991) high doses are still widely prescribed (Reardon et al., 1989; Van Putten et al., 1990; Krakowski et al., 1993). Furthermore, non-response to antipsychotics is common (Keefe et al., 1987) and yet many of these non-responsive patients are maintained on high doses indefinitely. The practice of using such high-dose regimens "may have resulted from increasing pressure to treat patients rapidly, the increasing acuity and severity of those being hospitalized, the belief by many clinicians that high doses of antipsychotic drugs are well tolerated and the profound lack of treatment options for the neuroleptic non-responsive patient" (Wirshing et al., 1994).

The data obtained from subjects in the medication-free at baseline arm confirm the modest efficacy of a typical neuroleptic, haloperidol, in the treatment of the chronic patient.

Collapsing across treatment groups, only seven of the 21 patients showed significant improvement in positive symptoms. Six of the seven responders came from the 50 and 100% blockade groups, suggesting a greater efficacy at lower doses. It is interesting to note that in the 50% blockade group, three patients improved while two became significantly worse. Although the numbers are small, these data would suggest that 50% blockade is obtained by a dose near the therapeutic threshold. The therapeutic threshold has also been determined based on the premise that both antipsychotic benefits and EPS occurred at or near the same dose (Haase, 1961; Deniker, 1989). Thus, therapy could be individualized by titrating patients to the dose at which EPS appear. However, until recently, there were only two small prospective clinical trials (Simpson and Angus, 1970; McEvoy et al., 1986) which showed therapeutic equivalency between the threshold and standard dosage, even though the threshold dose was significantly smaller. Recently, McEvoy et al. (1991) determined that the threshold dose for haloperidol in 106 RDC schizophrenics or schizoaffectives was 3.7 ± 2.3 mg/day, a dose which is remarkably similar to that obtained in the 50% blockade group. Ninety-five of the patients in the McEvoy et al. (1991) study were then randomly assigned to either continue receiving the threshold dose or to receive a dose 2–10 times higher (mean $= 11.6 \pm 4.7$ mg/day). There was no significant difference in therapeutic benefit between the two groups. Similarly, we observed no greater rate of response for patients in the 100% blockade and 10 ng/ml group.

Using a 10 mg/day cutoff, numerous fixed dose studies have shown low dose haloperidol treatment to be as effective as high dose treatment. For example, Levinson et al. (1990) studied 53 acutely psychotic patients randomly assigned to double-blind treatment with either 10, 20 or 30 mg/day of oral fluphenazine. After 4 weeks of treatment, improvement was not dose related. The best clinical response was seen in patients at 0.3 mg/kg/day (or 20 mg/day for a 70 kg individual). At this dose, side effects were frequent and the authors suggested doses closer to 0.2 mg/kg would be more patient-friendly. These authors also noted that the presence of akathisia predicted poor response. Van Putten et al. (1990) examined the response of 80 schizophrenic patients randomly assigned to receive either 5, 10 or 20 mg of haloperidol for 4 weeks. The 20 mg dose was slightly superior to the lower doses during the first 2 weeks but not thereafter. After 2 weeks, patients assigned to the 20-mg dose showed deterioration as measured by changes in the withdrawal-retardation subscale of the Brief Psychiatric Rating Scale (BPRS) and by increased akinesia and akathisia. The authors suggested that the 20-mg dose may have substantial 'psychotoxic' effects. Rifkin et al. (1991) randomly assigned 87 newly admitted inpatients with schizophrenia to receive 10, 30 or 80 mg/day of haloperidol for a maximum of 6 weeks. No difference in antipsychotic effect was found among the groups which led the authors to conclude that doses higher than 10 mg/day have no additional benefit for most patients. Stone et al. (1995) randomly assigned 24 acutely psychotic patients to receive 4, 10 or 40 mg/day haloperidol. After 2 weeks both the 4- and 10-mg/day groups showed a significant reduction in symptoms while the 40-mg/day group

did somewhat more poorly (as assessed by change in the total BPRS score). The 4-mg/day haloperidol dose was associated with a mean plasma level of 1.9 ng/ml. By inference from the data presented in the Introduction, this plasma level should be associated with a D_2 receptor occupancy level of between 50 and 75% and probably closer to 50%. Similar to the results of Stone et al. (1995), Janicak et al. (1994) have reported on antipsychotic response in patients targeted to 1.9, 13.4 and 39.6 ng/ml of haloperidol; the preliminary report noted no difference in the response rate after 2 weeks of treatment.

Overall, the data from the current study and from the studies noted above illustrate that antipsychotic response (when present) in the acutely psychotic chronic patient is probably associated with a relatively modest level of D_2 receptor occupancy.

In addition to the studies cited above, three recent studies have demonstrated the efficacy of significant dose reduction from relatively higher levels of neuroleptic at baseline. Liberman et al. (1994) reduced daily dosages of haloperidol by an average of 63% (from 63.1 to 23.1 mg/day) in 13 treatment-refractory patients. Significant improvements in positive symptoms, depression, anxiety and side effects resulted. Similarly, significant improvements in positive symptoms and overall BPRS scores were reported by Smith (1994) in their dose reduction study of 16 chronically hospitalized ($x = 11.5$ years) schizophrenic women. Here, doses were reduced an average of 62% (from roughly 45 to 16 mg/day in haloperidol equivalent doses). Finally, Inderbitzin et al. (1994) reduced standard doses of fluphenazine decanoate by 50% in a group of chronic schizophrenics ($n = 20$) and compared them to a control group ($n = 17$) whose doses were unchanged. The experimental group experienced significantly fewer side effects, and there was no difference in the number of relapses between groups. In comparison, the present dose reduction study showed a trend toward improvements in positive symptomatology, underscoring that *some* chronic patients benefit from very low doses. Among those who do not derive benefit, only a portion of them deteriorate clinically, while others exhibit no loss of the therapeutic benefit derived from higher doses.

Significant changes in negative (and general) symptoms were observed in relatively few subjects. In this regard, both Meltzer (1985) and Goldberg (1985) have suggested that typical neuroleptic drugs are efficacious for the treatment of negative symptoms, although the magnitude of the effect is small compared to their efficacy for positive symptoms. Finally, it should be noted that we found no differences in side-effects among the three treatment groups (Table 2). These data are similar to those obtained by Rifkin et al. (1991) but differ from the results of Van Putten et al. (1990).

The data from the dose-reduction arm clearly illustrate that the standard dose of neuroleptic often can be significantly reduced in chronic patients with no loss of therapeutic benefit. The patients in the 100% blockade group had on average a daily dose reduction from 20 to 11 mg/day and a 65% reduction in the plasma haloperidol level. Compared to the patients maintained at 10 ng/ml, there were no differences in change scores for positive, general and negative symptoms. The latter results are somewhat different from those obtained by Leblanc et al. (1994). These authors examined the effect of 50% dose-reduction in 32 schizophrenic patients receiving >18 mg/day of haloperidol; after reduction the authors noted a *significant reduction* in psychopathology both in terms of negative symptoms and the total BPRS score. The difference between their results and ours may be that the dose of haloperidol was not reduced sufficiently in the 100% blockade group to observe a change in the negative symptoms.

It is of interest to note that four of six subjects assigned to the placebo group showed a significant deterioration. These data suggest a much greater effectiveness of antipsychotic drugs than was evident from the data obtained with the medication-free at baseline subjects. The reason(s) for this difference are not entirely clear. However, it is of interest to note the 70% difference in the daily dose of haloperidol required to block the GH response, clearly indicating marked biological differences between the subjects in the two study arms. The higher daily dose in the dose-reduction

arm may reflect receptor up-regulation and/or other 'tolerance'-like mechanisms associated with chronic neuroleptic administration. From a practical point of view, subjects in the dose-reduction arm appeared more neuroleptic 'dependent'. This dependency must be relatively short-lived since many of the subjects in the medication-free arm had a long history of neuroleptic exposure. However, this dependency will confound comparisons between studies. The threshold dose for a dose-reduction study will be significantly higher than the threshold dose for a medication-free patient. Perhaps, if the rate of dose-reduction was slower than that used in this study (50%/week), equivalent threshold doses would be obtained.

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