

Treatment of Late-Life Schizophrenia With Neuroleptics

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Abstract

There is a dearth of literature on the effects of neuroleptics in older schizophrenia patients. In this article, we review the available literature and present findings from our own studies. Neuroleptics are effective in the treatment of late-life schizophrenia, although older patients generally need lower dosages than younger subjects. Neuroleptics, however, carry a relatively high risk of side effects such as tardive dyskinesia (TD) in middle-aged and elderly patients. By the end of 1 year of a prospective longitudinal study of neuroleptic treatment, we found a 26 percent cumulative incidence of TD among schizophrenia patients over age 45. If neuroleptics are withdrawn, there is a significant risk of a schizophrenic relapse; however, that risk is no greater in older patients than in younger ones. We offer clinical recommendations for the use of neuroleptics in the treatment of late-life schizophrenia.

Neuroleptic or antipsychotic medications are commonly prescribed for the elderly. It has been estimated that more than 90 percent of nursing home residents have a significant neuropsychiatric disability and that perhaps as many as 75 percent of these patients receive neuroleptics (Baldessarini 1985). Neuroleptics have been shown to be the most effective treatment modality for schizophrenia in general (Davis et al. 1989). Pharmacotherapy in older patients is, however, complicated by alterations in both the pharmacokinetic and pharmacodynamic

responses; either an exaggerated or a depressed response to medications can be seen. Compared with younger patients, geriatric patients show an increased variability of response and an increased sensitivity to medications (Avorn and Gurwitz 1990; Salzman 1990). Unfortunately, the published literature on neuroleptic treatment of late-life schizophrenia is extremely sparse. Below we review the published studies relevant to this area and also present findings from some of our own studies.

General Review

Therapeutic Efficacy. The antipsychotic efficacy of neuroleptics in younger adults with schizophrenia has been well documented in controlled studies conducted over the past three to four decades (Kessler and Waletzky 1981). Clinical experience and anecdotal reports indicate that this effectiveness may be extrapolated to elderly psychotic patients (Rabins et al. 1984; Makanjula 1985). Nevertheless, whereas a few studies have documented the efficacy of antipsychotic drugs with well-designed, placebo-controlled clinical trials in older schizophrenia patients, little is known about treatment of the truly old schizophrenia patients—that is, those over age 75.

A Department of Veterans' Affairs (VA) cooperative project involving 13 hospitals and 308 men

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with schizophrenia, ages 54–74 years (median age = 66 years), investigated the role of phenothiazines in the treatment of schizophrenia (Honigfeld et al. 1965). In this 24-week, double-blind, placebo-controlled study, acetophenazine and trifluoperazine were significantly more effective than placebo in treating such symptoms as motor disturbances, conceptual disorganization, manifest psychosis, and a lack of personal neatness. Acetophenazine alone was effective in reducing excitement, and it was superior to trifluoperazine in reducing irritability and increasing social competence. In a sample of 50 psychogeriatric patients, with chronic schizophrenia subjects representing the largest group, Tsuang and colleagues (1971) compared the antipsychotic efficacy of haloperidol and thioridazine in a 12-week, double-blind study of actively psychotic patients over age 60 (mean ages = 71.5 and 73.7 years for the haloperidol and thioridazine groups, respectively). The authors reported significant decreases in a number of areas of psychopathology, including anxiety, excitement, irritability, hostility, suspiciousness, hallucinatory behavior, mannerisms, tension, unusual thoughts, blunted affect, a lack of neatness, and manifest psychosis for both medication groups. Branchey and colleagues (1978) compared the efficacy of orally administered fluphenazine to thioridazine in chronic schizophrenia patients (mean age = 67 years; range = 60–81 years) following a no-drug, washout period. This was a double-blind, crossover design study. Both these phenothiazines produced modest but significant improvement in global psychopathology as measured by the

Brief Psychiatric Rating Scale (BPRS; Overall and Gorham 1962), compared to the ratings at the end of the washout period.

Some other investigators (Janzarik 1957; Kay and Roth 1961; Post 1966; Herbert and Jacobson 1967; Rabins et al. 1984; Craig and Bregman 1988; Jeste et al. 1988) have also reported on the response of older schizophrenia patients to neuroleptics. These studies, reviewed in detail by Tran-Johnson et al. (in press), are limited, however, by their non-double-blind study design (case studies, open trials, and retrospective chart reviews) and, sometimes, small sample sizes. Nevertheless, in most of the studies, neuroleptic therapy produced a positive outcome (remission or reduction of symptoms, and/or earlier discharge from the hospital). For example, Post (1966) retrospectively reviewed the course of 93 late-onset schizophrenia (LOS) patients. He divided his sample into three treatment groups. The first group was distinguished from the others in that 20 out of 24 patients received inadequate or no neuroleptic treatment. Post determined that the remaining two groups received adequate neuroleptic dosages during their course. The second group consisted of 37 inpatients, most of whom were treated with trifluoperazine 15–25 mg/day. The third group consisted of 32 outpatients treated with trifluoperazine 10–60 mg/day or thioridazine 75–600 mg/day. Post reported that none of the patients in the first group improved, whereas 62 percent of the patients receiving adequate doses of neuroleptic therapy responded. The usefulness of neuroleptic therapy in older schizophrenia patients was further supported by the results of a

study by Rabins et al. (1984). In a combined retrospective and prospective investigation, the authors reported that 30 out of 35 LOS patients treated with unspecified neuroleptic regimens improved.

Choice of Neuroleptic. With the possible exception of clozapine, which is discussed below, the available data suggest that all the commonly prescribed antipsychotic medications are equally efficacious. There is no evidence that any one class of neuroleptics is more effective in alleviating schizophrenic symptoms when given in equivalent dosages. All the "typical" neuroleptics theoretically work through the same mechanism of blocking brain dopamine (DA) receptors. Therefore, selection of an antipsychotic for use in elderly patients should be based primarily on (1) the side effect profile of the particular drug, (2) the potential adverse consequences of adding a specific antipsychotic to a preexisting medication regimen or a concomitant physical illness, and (3) a history of the patient's previous therapeutic response to a specific neuroleptic.

The side effect profiles of individual neuroleptics differ considerably, and such differences may be important in prescribing a particular medication to a patient for whom the occurrence of a particular side effect might prove dangerous. For example, in patients with preexisting parkinsonian symptoms, high-potency antipsychotics (e.g., haloperidol) may worsen tremor and rigidity. On the other hand, high-potency neuroleptics (especially haloperidol) are reported to cause lower cardiovascular toxicity than low-potency neuroleptics (e.g., thioridazine) (Ereshefsky and Richards

1992, pp. 56-57). Hence, haloperidol may be a better choice than low-potency neuroleptics among patients with preexisting cardiovascular disorders. Low-potency neuroleptics also have marked anticholinergic activity and should be avoided in patients with prostatic hypertrophy or in those who are already on other anticholinergics. Finally, an agent that previously produced a positive response in that patient or in a blood relative may be tried first, while an agent that led to an unfavorable reaction may be avoided.

Compliance. Medication non-compliance, reported to be as high as 75 percent, should be considered a potential cause of poor neuroleptic response (Ostrum et al. 1988; Lamy et al. 1992). In hospitalized patients, medication intake can be supervised; in the relatively uncontrolled outpatient setting, however, physical problems such as impaired vision may mean that instructions may be misread or that one medicine may be mistaken for another. Cognitive impairment may make it difficult for patients to remember whether they have taken their medication. In a group of patients diagnosed as having late paraphrenia, Raskind and colleagues (1979) compared the antipsychotic efficacy of a bi-monthly depot injection of fluphenazine to that of orally administered haloperidol. The investigators observed that a significantly greater proportion of patients in the fluphenazine group showed moderate to marked improvement relative to the haloperidol group. The authors did not interpret their results as suggesting superiority of fluphenazine enanthate over haloperidol as an antipsychotic. Instead, they concluded,

quite appropriately, that poor outpatient compliance with oral haloperidol was the likely reason for the observed superiority of fluphenazine enanthate in their patients. Serum levels of the neuroleptics were, however, not measured.

Clozapine. Clozapine, an atypical antipsychotic, has been reported to be effective in otherwise treatment-resistant chronic schizophrenia patients (Kane et al. 1988a). The drug has a low potential for inducing extrapyramidal symptoms (EPS), possibly because of its potent anticholinergic activity or its relatively weaker blockade of striatal D_2 receptors compared with typical neuroleptics. The side effect profile of clozapine limits its use, however. Specifically, the potential risk of agranulocytosis and the consequently mandated weekly blood monitoring protocol hinder its widespread use. Its potent anticholinergic effects, as well as its propensity to produce hypotension and sedation, further restrict its use in elderly patients. Unfortunately, data on the use of clozapine in the elderly are even more scarce than those on typical neuroleptics. We are unaware of any systematic research on the use of clozapine in elderly schizophrenia patients, although a few studies have been reported (Scholz and Dichgans 1985; Wolters et al. 1990; Wolk and Douglas 1992) on its use in treating psychosis in Parkinson's disease patients. In daily doses of 25-150 mg, clozapine was used effectively to treat psychosis in Parkinson's disease (Scholz and Dichgans 1985; Wolk and Douglas 1992). On the other hand, delirium was induced by clozapine at doses of 75-250 mg/

day in four out of six patients (Wolters et al. 1990).

In a rare case report, an 82-year-old woman with a 4-year history of paranoid schizophrenia and tardive dyskinesia (TD) was successfully managed with clozapine (Bajulaie and Addonizio 1992). After 5 weeks of clozapine therapy at 125 mg/day, her psychosis was markedly improved.

It is possible that clozapine, at doses lower than those used in younger patients, may have a role in the treatment of elderly psychotic patients who are sensitive to the EPS induced by typical neuroleptics. Only controlled, prospective studies can adequately address the risk-to-benefit ratio of clozapine in older schizophrenia patients.

Neuroleptic Dosage in Older Schizophrenia Patients: A Cross-Sectional Study

A number of studies have examined neuroleptic dosage in young adults with schizophrenia (e.g., Kane et al. 1983). In contrast, little is known about the neuroleptic dose requirements in older schizophrenia patients, except that elderly subjects need lower amounts than younger ones. Below we describe the results of an analysis of cross-sectional data on associations of neuroleptic dose with selected demographic, clinical, and neuropsychological variables in a group of 64 schizophrenia outpatients over age 45.

Methods and Materials. The subjects included 25 patients meeting *DSM-III-R* (American Psychiatric Association 1987) criteria for LOS (i.e., onset of schizophrenia after age 45) as well as our own strict research criteria (Jeste et al. 1988)

for LOS, along with 39 patients with early-onset schizophrenia (EOS) (i.e., onset of schizophrenia before age 45) who were presently over age 45. All these patients were participating in an ongoing study of late-life schizophrenia in our Geriatric Psychiatry Clinical Research Center. Patients were recruited from the San Diego VA Medical Center and Outpatient Clinic, the University of California, San Diego Medical Center and Psychiatry Outpatient Services, the San Diego County Mental Health Services, and private physicians. We excluded chronically institutionalized patients. A large majority of the schizophrenia patients came from the VA Medical Center and outpatient clinics.

The mean age (\pm standard deviation [SD]) of the patient population was 59.0 (\pm 8.4) years, and mean duration of illness was 20.8 (\pm 15.2) years. A majority (73.4%) of the patients were men, and 68.7 percent had been married at least once.

All the patients were being treated by their respective psychiatrists in an individualized, clinically optimal manner. In all cases, the treating psychiatrists were on the faculty of the University of California, San Diego. This was not, however, a controlled study of neuroleptic dosage.

Clinical and neuropsychological assessments were done by raters blind to treatment data. Briefly, the assessments included the following variables: demographics (age, gender, education, and marital status), the BPRS (Overall 1988); the Scales for the Assessment of Negative and Positive Symptoms (SANS and SAPS; Andreasen 1984a, 1984b); the Hamilton Depression Rating Scale (HAM-D; Hamilton 1967); the Ab-

normal Involuntary Movement Scale (AIMS; Guy 1976); the Mini-Mental State Examination (MMSE; Folstein et al. 1975); the Dementia Rating Scale (DRS; Mattis 1976); the Gittelman-Klein Premorbid Adjustment Scale (Gittelman-Klein and Klein 1969); and an expanded Halstead-Reitan Neuropsychological Test Battery (Heaton 1992). The neuropsychological test scores were converted to age-, gender-, and education-corrected T scores based on a large, normative sample (Heaton 1992). The lower the T score, the greater the impairment on that particular test. Different patients were on different neuroleptics, the most common one being haloperidol. Daily doses of various neuroleptics were converted to milligrams of chlorpromazine equivalent (mg CPZE) using the formula given by Jeste and Wyatt (1982, p. 3). The mean (\pm SD) neuroleptic dose in our sample was 443.0 (\pm 1,156.1) mg CPZE daily. The clinical and neuropsychological data were collected when the patients were stable medically, psychopathologically, and pharmacologically for at least several weeks.

Statistical Tests. For categorical variables (e.g., gender), we compared the daily neuroleptic doses (mg CPZE) of different groups (e.g., men vs. women) using Kruskal-Wallis analysis of variance (K-W ANOVA). Using Spearman's correlations, we correlated the neuroleptic dose with selected demographic, clinical, and neuropsychological measures, which were continuous (e.g., age) or ordinal (e.g., BPRS) variables. We used nonparametric statistics because the values for neuroleptic dose were not normally distributed

among the schizophrenia patients studied.

Results. With the K-W ANOVA, the daily neuroleptic dose was found to be significantly higher in the currently unmarried subjects than in those currently married ($p < 0.001$); it also tended to be higher in the never-married patients than in those ever married ($p = 0.06$) and higher in the EOS group than in the LOS group ($p = 0.07$). Gender and subtype of schizophrenia (paranoid vs. non-paranoid) were not associated with differences in neuroleptic dose.

The neuroleptic dose correlated significantly (Spearman's correlations; $p < 0.05$) with current age; age at onset of illness; SANS total as well as two of the SANS subscale scores (affective blunting and alogia); and performance on various neuropsychological test measures, such as Verbal and Performance IQ (Wechsler 1981), Average Impairment Rating on the Halstead-Reitan battery (Russell et al. 1970), Story and Visual Learning (Heaton et al. 1991), and Grooved Pegboard Motor Test (pegs dominant and nondominant) (Lafayette Instrument Company 1992). There were also nonsignificant trends ($p < 0.1$) for correlations between neuroleptic dose and scores on the SANS avolition/apathy subscale, Gittelman-Klein childhood and adolescence adjustment scores, and the full-scale IQ. Except for the SANS scores, which correlated positively, all the above-mentioned variables correlated negatively with the neuroleptic dose. We should stress, however, that even the significant correlations were, at best, only modest in magnitude. Thus, with the exception of T scores on the Average Impairment Rating ($r = -0.4968$,

$p < 0.001$), Grooved Pegboard: dominant hand ($r = -0.4537$, $p < 0.001$) and nondominant hand ($r = -0.4560$, $p < 0.001$), and Visual Learning ($r = -0.3582$, $p < 0.008$) measures, all the other variables correlated with neuroleptic dose at $r < 0.35$.

Discussion. This was not a controlled study of neuroleptic dose. Also, a relatively large number of correlations were performed, with a consequent possibility of a Type I error. Furthermore, most of the significant correlations were modest in magnitude. Hence, the results must be viewed with caution and treated as preliminary findings.

The inverse correlation between age and neuroleptic dose is consistent with studies reporting pharmacokinetic (higher blood levels) and pharmacodynamic (increased sensitivity to drug response) changes associated with aging (Tran-Johnson et al. 1992). Age-related pharmacokinetic alterations in drug disposition may produce higher plasma concentrations of specific neuroleptic medications in older patients compared with younger ones (Jeste et al. 1982; Yesavage et al. 1982; Movin et al. 1990). Age-related pharmacodynamic alterations at the receptor or neurotransmitter level may increase the intensity of drug response in elderly patients (Roberts and Tumer 1988). The association of later age at onset of schizophrenia with lower dosages may relate to the suggestion that LOS is better-prognosis schizophrenia than EOS (Harris and Jeste 1988; Castle and Murray 1991).

The association between unmarried status (especially current) and

higher neuroleptic dosage might suggest that a lack of spousal support was associated with a need for higher doses to control the psychotic symptoms. Alternatively, patients needing higher dosages might have been less able to get or stay married.

The trends for an inverse correlation between Gittleman-Klein childhood and adolescent adjustment scores and CPZE also suggest a need for lower dosages in patients with better premorbid adjustment (probably indicating better prognosis). Patients with specific negative symptoms (rated on the SANS) were on higher dosages of neuroleptics than patients without those symptoms. This might indicate that neuroleptics were not very effective in treating those negative symptoms, or that patients with such symptoms needed higher doses to control the overall level of psychopathology.

On a number of neuropsychological measures, CPZE correlated inversely with a patient's performance on those tests. This might indicate either that cognitively impaired patients needed higher doses of neuroleptics or that higher doses produced greater impairment on neuropsychological tests. The latter possibility is less likely (except for the Grooved Pegboard Motor Test), however, since long-term use of neuroleptics is not associated with worse performance on most cognitive tests (Heaton and Drexler 1987).

Prospective, longitudinal studies comparing different dosages of neuroleptics and assessing pharmacokinetic and pharmacodynamic measures are clearly warranted in patients with late-life schizophrenia.

Incidence of TD: A Prospective Longitudinal Study

A number of cross-sectional investigations have found a significantly greater prevalence of neuroleptic-induced TD in older patients than in younger ones (Jeste and Wyatt 1982). Saltz et al. (1991) reported a 31 percent incidence of TD after 43 weeks of cumulative treatment with neuroleptics in a group of 160 elderly (mean age = 77 years) and predominantly (72%) female subjects, with a sizable proportion being institutionalized. Sixty-seven percent of the patients had a diagnosis of organic mental syndrome and 42 percent had a psychiatric diagnosis. Subjects with both diagnoses ($n = 90$) were excluded from the following TD incidence analysis. The investigators found that patients with a nonorganic psychiatric diagnosis (mainly affective disorder) had a greater vulnerability to TD than patients diagnosed as having organic mental syndromes.

We had earlier reported a similarly high incidence of TD in middle-aged and elderly psychiatric outpatients, predominantly male (Harris et al. 1992; Jeste and Caligiuri 1993). Below we report a comparison of schizophrenia patients with patients having other diagnoses in terms of the risk of TD using a somewhat expanded group of subjects from the same ongoing study.

Methods and Materials. The patients (ambulatory care, > age 45) were enrolled early in the course of their neuroleptic treatment, many with fewer than 90 days of total lifetime treatment at the time of baseline assessment. Details of

the evaluation and treatment are described elsewhere (Harris et al. 1992; Jeste and Caligiuri 1993). Patients were treated with the lowest effective doses of neuroleptics (commonly haloperidol or thioridazine), usually less than 300 mg/day CPZE. Patients were followed at 1 month, 3 months, and every 3 months thereafter. Cumulative incidence of TD at each followup period was computed by means of the life tables analysis (Cutler and Ederer 1958).

Results. In our sample of 236 patients, 48 were diagnosed with schizophrenia, 55 with Alzheimer's disease, 33 with mood disorders, and 100 with miscellaneous diagnoses. All the diagnoses were based on *DSM-III-R* criteria and were confirmed by board-certified psychiatrists. Table 1 summarizes the demographic characteristics of the four groups.

Figure 1 shows survival curves for TD for the four diagnostic groups. The criteria for TD were similar to those used by Schooler and Kane (1982), except that our required minimum duration of total neuroleptic exposure was 1 month instead of 3 months.

The overall cumulative incidence of TD (i.e., the total number of new cases) by the end of 1 year of the study was 26 percent (95% confidence interval 23% to 30%).

This rate is somewhat lower than the 33 percent incidence rate we reported earlier (Jeste and Caligiuri 1993). That is because we had used the AIMS scores for right and left upper and lower extremities separately in the earlier analysis, while the present analysis used only one score for each set of extremities (upper and lower). Employing a somewhat more lenient criterion for the diagnosis of TD (a minimum of one score of 2 on any of the first seven items of the AIMS, instead of a minimum of one score of 3 or two scores of 2 on these items), we found the annual incidence of TD to be 45 percent (95% confidence interval 41% to 49%). There was no significant difference among the four diagnostic groups in terms of the TD incidence. Because of the relatively small sample sizes in individual diagnostic groups, we did not use the survival analysis with covariates to determine predictors of TD risk in schizophrenia patients.

Discussion. On the basis of studies of somewhat younger adults, investigators have reported a higher risk of TD among patients with mood disorders compared with schizophrenia patients (Casey and Gerlach 1986). Some researchers have found a higher prevalence of TD among patients

with evidence of organic brain damage or dysfunction (Kane et al. 1992). In contrast, Saltz et al. (1991) observed that affective disorder was a more serious risk factor for TD than was an organic mental syndrome among elderly patients. Our study suggests that among middle-aged and elderly subjects the risk of TD over a 1-year period is no different in schizophrenia outpatients than in other diagnostic groups. The notably high incidence of TD among all the patient groups over age 45 indicates a need for caution in prescribing neuroleptics in this population.

Neuroleptic Withdrawal

Literature Review. Aging of schizophrenia patients is associated with remission or a marked improvement in at least one-third of the subjects (McGlashan 1988). This fact, coupled with the high risk of TD in older patients, suggests that neuroleptic withdrawal should be an important therapeutic consideration in this patient population. Unfortunately, the literature on the subject of neuroleptic withdrawal in older (mean age > 45) schizophrenia patients is sparse. Furthermore, the published studies have had several methodologic problems, including a lack of specific

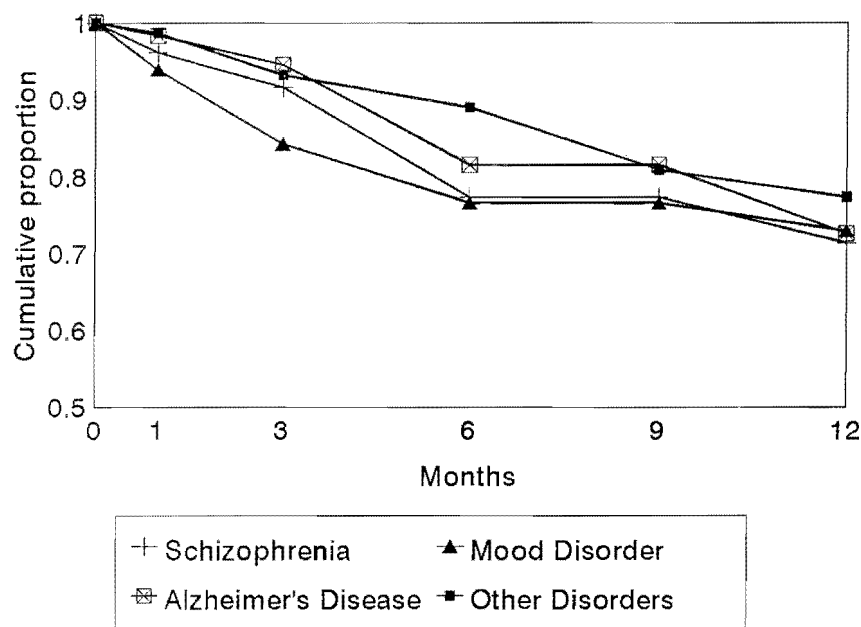
Table 1. Prospective study of tardive dyskinesia incidence: Demographics of participants

Variable	Schizophrenia (n = 48)	Alzheimer's disease (n = 55)	Mood disorders (n = 33)	Other (n = 100)
Age, yrs ¹	56.4 ± 8.0	75.6 ± 7.5	67.0 ± 10.3	65.0 ± 11.7
Gender (male), %	80.9	80	87.9	81
Education, yrs ¹	12.8 ± 3.0	11.4 ± 3.6	11.4 ± 3.0	12.9 ± 3.5

Note.—All diagnoses were based on *DSM-III-R* (American Psychiatric Association 1987).

¹Measures are mean ± standard deviation.

Figure 1. Proportion of patients surviving tardive dyskinesia (TD) (i.e., not having TD) by diagnostic group at the beginning of the specified time intervals



diagnostic criteria in some studies, variable methods and materials, relatively small sample sizes, and incomplete presentation of data.

For our review of neuroleptic withdrawal in schizophrenia patients, we included English and foreign language articles involving at least 10 subjects with a diagnosis of schizophrenia, and a comparison group of neuroleptic-maintained patients. We found only six double-blind controlled studies that included schizophrenia patients with a mean age greater than 45 years; these are described briefly in table 2.

In these six studies, the neuroleptic-withdrawn and neuroleptic-maintained groups were similar on all the listed demographic and clinical variables except for rates of relapse. For the neuroleptic-withdrawn patients, mean (\pm SD)

age was 53.4 (\pm 4.2) years, 84.2 percent patients were male, mean duration of hospitalization was 7.7 (\pm 7.1) years, mean daily neuroleptic dose at baseline was 232.4 (\pm 51.9) mg CPZE, and mean followup period was 6.3 (\pm 3.0) months. For the comparison (neuroleptic-maintained) patients, mean age was 53.3 (\pm 6.2) years, 81.4 percent patients were male, mean duration of hospitalization was 9.1 (\pm 9.6) years, mean neuroleptic dose was 311.6 (\pm 56.2) mg CPZE, and mean followup period was 6.3 (\pm 3.0) months. The mean rate of relapse for the neuroleptic-withdrawn groups in the six studies was 39.9 (\pm 12.0) percent while that for the neuroleptic-maintained groups was 11.4 (\pm 11.8) percent ($p < 0.0001$, matched-pair t test).

Some of the studies also re-

ported specific predictors of psychotic relapse following neuroleptic withdrawal. Hershon et al. (1972) reported that younger current age, longer duration of neuroleptic treatment, and higher prior neuroleptic dose were all associated with a greater risk of relapse. Andrews et al. (1976) found only higher prior neuroleptic dose as a predictor of relapse. Finally, Ruskin and Nyman (1991) reported that younger age, higher previous neuroleptic dose, higher baseline BPRS score, and recent psychiatric hospitalization were all predictors of relapse following neuroleptic withdrawal.

Adverse effects or risks of neuroleptic withdrawal other than the psychotic relapse included increased motor restlessness (Hershon et al. 1972) and social withdrawal (Andrews et al. 1976).

Our review suggests that the risk of relapse is greater in neuroleptic-withdrawn patients than in patients maintained on neuroleptics. Nonetheless, given that almost 60 percent of the patients withdrawn from neuroleptics did not relapse over a mean period of 6 months, it seems feasible to discontinue neuroleptic medication from a select population of older schizophrenia patients, if it is done carefully with adequate monitoring and followup.

Three studies (Rassidakis et al. 1970; Hershon et al. 1972; Ruskin and Nyman 1991) found younger age to be a risk factor for relapse, whereas three other studies listed in table 2 did not report any association between age and relapse rate. We did not, however, find a published study comparing the rate of relapse between patients under 45 and those over 45 years of age. Hence, we undertook the following study.

Table 2. Literature review on neuroleptic withdrawal in schizophrenia patients over age 45

Authors	n	Age: mean (yrs)	Mean hosp (yrs)	Neuroleptic	Concurrent medications	Study design	Length of followup (months)	% Relapse (time)	Predictors of relapse	Other findings
Olson and Peterson (1962)	60	51	1.5	CPZ, thioridazine	NS	Double-blind with placebo	6	29% (6 mo with placebo)	Higher ratings of "moderate depression" on the "Distress" scale	Phenothiazines may have an activating effect on chronic patients
Whittaker and Hoy (1963)	26	50	15.5	Perphenazine	Antiparkinsonian or phenadrine	Double-blind with placebo	2.5	39% (2.5 mo)	None identified	Four patients were seen to regress "to a state markedly worse" than before
Rassidakis et al. (1970)	43 (33 with SZ)	49.3	NS	Thioridazine, haloperidol, CPZ	Antiparkinsonian	Open	9	58.1% (9 mo)	Younger age at onset, younger current age, and non-paranoid subtype	No withdrawal effects were noted
Hershon et al. (1972)	32	57	NS	Trifluoperazine	Antiparkinsonian	Double-blind with placebo	4	28.1% (4 mo)	Younger current age, longer duration of neuroleptic treatment, higher previous neuroleptic dose	Motor restlessness, but not parkinsonism or dyskinesia, increased after neuroleptic withdrawal
Andrews et al. (1976)	17	About 57	6	CPZ	NS	Double-blind with placebo	10.5	35% (10.5 mo)	Higher previous neuroleptic dose	Relapsers had increased social withdrawal after neuroleptic discontinuation

Ruskin and Nyman (1991)	10	60	NS	Haloperidol	NS	Double-blind with placebo	6	50% (6 mo)	Younger age, higher previous neuroleptic dose, higher baseline BPRS, re- cent psychi- atric hospi- talization	Patients who relapsed re- constituted rapidly after neuroleptics were restarted
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Note.—CPZ = chlorpromazine; NS = not specified; SZ = schizophrenia; BPRS = Brief Psychiatric Rating Scale (Overall and Gornham 1988).

Study of Brief Neuroleptic Withdrawal. We sought to determine whether there was any significant difference in short-term clinical response of schizophrenia patients over age 45 versus those under age 45. We report here the results of a 3-week study of neuroleptic withdrawal in 20 chronic schizophrenia patients. These patients were about to enter a 2-year, double-blind, long-term safety and efficacy study of a new neuroleptic. Before entering the study, all the participants completed a 1-week taper and withdrawal from their current neuroleptics and a 2-week course of placebo before being randomized to the double-blind phase of the new treatment trial.

Subjects. The study subjects were outpatients selected from the VA Medical Center and the VA Outpatient Clinic at San Diego. The research assistant and the principal investigator attended weekly intake evaluations at the outpatient clinics to recruit patients. Additionally, patients were referred by their attending clinicians. Of the 65 patients who were screened and interviewed, 24 agreed to participate. Those who refused did so primarily because either they did not want anyone "experimenting" on them, or they were stable on their current medication regimen and did not wish to change it. The common denominator for all the patients agreeing to participate was their perception of this study as a possible opportunity to take a new medication for schizophrenia that might have fewer side effects than their current neuroleptics.

The inclusion criteria were (1) a *DSM-III-R* diagnosis of schizophrenia; (2) outpatient status for at least the past 2 months; (3) age of

18 years and older; (4) male gender; (5) a total BPRS score below 60 points; (6) a BPRS score of not more than moderately severe (5 points on a scale of 1 to 7) on any item; and (7) a Clinical Global Impressions (CGI; Guy 1976) score below 5 points (markedly ill).

The exclusion criteria were (1) a clinically significant systemic disease; (2) a history or current diagnosis of TD; (3) concurrent diagnoses of organic mental disorder, seizure disorder, mental retardation (*DSM-III-R*), substance dependence not in full remission (*DSM-III-R*), positive drug abuse screen, or idiopathic Parkinson's disease; (4) depot neuroleptics taken in the past 2 months; (5) suicidal or homicidal impulses acted on during drug-free intervals; (6) clinically significant abnormal electrocardiogram (EKG), chest x-ray, blood chemistry, or other laboratory parameters; (7) allergies to several drugs or known hypersensitivity to haloperidol; and (8) participation in another clinical trial or receipt of any experimental therapy or clozapine during the past month.

Patients were allowed to be on anticholinergic medications and short-acting benzodiazepines (such as lorazepam, temazepam, or oxazepam), if necessary, during the 3 weeks of neuroleptic taper and placebo treatment.

Methods. A complete medical and psychiatric history was obtained from the patients, from collateral sources when possible, and from clinical records. Demographic data were gathered. The principal investigator explained the protocol, and the patients signed the informed consent in the presence of a witness. A urine drug screen was required of all study participants to verify their "substance-free" status.

Each patient received a complete physical examination, performed by a member of the medical staff at the VA outpatient clinic; a chest x-ray; an EKG; and lab tests, including creatine phosphokinase, a chemistry panel, a complete blood count with differential, a thyroid panel, and urinalysis. At this juncture, all the patients were reevaluated for any significant medical findings.

We used the following rating scales: BPRS, SANS, AIMS, Quality of Life Scale (Heinrichs et al. 1984), Level of Function Scale (Hawk et al. 1975), and CGI. The ratings were performed by either the principal investigator or his research assistant. Interrater reliability was maximized by having the principal investigator and research assistant train together on all the scales administered. All the ratings were performed both at the beginning of the study and at the end of the 3-week period.

Patients' neuroleptic medication was tapered over 7 days and then discontinued. For the following 2 weeks, the patients received placebo in a single-blind fashion. Psychotic relapse was defined as a 2-point increase above baseline CGI score; or dangerousness to self or others, or uncharacteristic uncooperativeness; and need for alternative treatment (usually neuroleptic).

Results. There were no significant differences between younger (< 45) ($n = 9$) and older (≥ 45) ($n = 11$) schizophrenia patients in terms of baseline or post-withdrawal scores on the AIMS, BPRS, CGI, or other scales used (see table 3). (There was, however, a nonsignificant trend for a higher post withdrawal AIMS score in patients ≥ 45 years.) Although some patients did experience a

Table 3. Study of short-term neuroleptic withdrawal

	Age < 45 (n = 9)	Age \geq 45 (n = 11)	p Value
Age (yrs)	37.6 \pm 4.2	57.3 \pm 6.1	0.001 ¹
Education (yrs)	13.0 \pm 1.7	14.3 \pm 2.1	NS
Duration of illness (yrs)	13.6 \pm 8.1	27.6 \pm 8.3	0.002 ¹
Daily neuroleptic dose (mg CPZE)	314.7 \pm 432.3	432.5 \pm 619.0	NS
AIMS Global			
Baseline	0.25 \pm 0.45	0.50 \pm 0.52	NS
Postwithdrawal	0.22 \pm 0.44	0.64 \pm 0.51	0.07 ²
BPRS total			
Baseline	36.3 \pm 8.9	35.0 \pm 8.8	NS
Postwithdrawal	35.4 \pm 6.3	38.5 \pm 9.1	NS
BPRS depression subscale			
Baseline	7.8 \pm 3.5	7.1 \pm 3.1	NS
Postwithdrawal	6.4 \pm 3.4	7.6 \pm 3.3	NS
BPRS negative symptom subscale			
Baseline	6.3 \pm 2.6	6.3 \pm 3.8	NS
Postwithdrawal	5.6 \pm 1.7	6.4 \pm 3.2	NS
BPRS psychosis subscale			
Baseline	7.3 \pm 2.6	6.8 \pm 2.2	NS
Postwithdrawal	8.9 \pm 2.9	7.3 \pm 2.7	NS

Note.—The values represent means \pm standard deviations; mg CPZE = milligrams of chlorpromazine equivalent; AIMS = Abnormal Involuntary Movements Scale (Guy 1976); BPRS = Brief Psychiatric Rating Scale (Overall 1988); NS = not significant.

¹Two-tailed *t* test.

²Two-way analysis of variance with one repeated measure.

worsening of psychiatric symptoms, none had an exacerbation to the degree that met criteria for relapse or required reinstitution of a neuroleptic.

Discussion. The results suggest that a 2-week period of a placebo following a week of taper did not produce significant clinical changes in a small group of stable, chronic schizophrenia outpatients. There was also no differential effect on older versus younger patients. We do not know if keeping the patients off neuroleptics for longer periods would have resulted in psychotic relapse. Also, our results

may not be generalizable to patients who are less chronic and less stable than those in our study. Furthermore, we did not have a control group of patients maintained on neuroleptics. Nonetheless, our results suggest that older patients can tolerate brief neuroleptic withdrawal at least as well as younger subjects.

Given the heightened risk of TD in older patients, it seems that a trial of neuroleptic withdrawal is warranted in this population. Obviously, it should be tried only when the patients are clinically stable. Patients with a history of

relapse following neuroleptic discontinuation may not be appropriate candidates for this strategy; they may need low-dose maintenance treatment.

Clinical Recommendations

Neuroleptics are still the most effective treatment for schizophrenia in older patients just as they are in younger ones. Older patients, however, seem to require lower dosages than their younger counterparts. The annual incidence of TD in middle-aged and elderly patients is 26 percent—nearly six times the rate reported by Kane et al. (1988b) in patients with a mean age in the late-twenties. This suggests a need for considerable caution with prolonged use of neuroleptics in patients over age 45. Neuroleptic discontinuation is associated with a definite risk of psychotic relapse. Yet it is worthwhile to attempt a graduated taper of neuroleptics in chronic, stable outpatients, especially those in whom neuroleptics were never discontinued in the past. Patients with a history of relapse following neuroleptic withdrawal generally benefit from low-dose maintenance therapy.

The potential seriousness of neuroleptic-induced TD warrants obtaining competent, informed consent to treatment from patients or guardians. There are several effective, efficient methods of informing patients of the risks of neuroleptic treatment. Obtaining consent to treatment, however, should not be viewed as a one-time event but rather as a process that occurs over a period of time (Appelbaum et al. 1987). The American Psychiatric Association Task Force on TD (Kane et al. 1992) recommends informing patients of the risks asso-

ciated with neuroleptics periodically throughout treatment, and encouraging patients to monitor themselves for symptoms and to participate in discussions of the benefits and risks of the treatment. It also recommends tailoring information about TD to the individual patient's cognitive ability and particular medical situation.

Consent forms (Sovner et al. 1978) have been suggested as a possible solution to the problem of informed consent regarding neuroleptic treatment, but they present their own dilemmas. The consensus appears to be that they should not be used as a substitute for discussions between patients and psychiatrists but rather as documentation that these discussions have taken place. Also, documenting an oral informed consent in the chart can be an appropriate alternative to having a patient sign a written consent form.

There is an urgent need for controlled studies of clozapine and other atypical neuroleptics (such as remoxipride and risperidone) as well as of nonneuroleptic treatments for late-life schizophrenia. However, neuroleptics do not cure schizophrenia. Their use should be complemented by psychosocial approaches to patient management.

References

- American Psychiatric Association. *DSM-III-R: Diagnostic and Statistical Manual of Mental Disorders*. 3rd ed., revised. Washington, DC: The Association, 1987.
- Andreasen, N.C. *The Scale for the Assessment of Negative Symptoms (SANS)*. Iowa City, IA: University of Iowa, 1984a.
- Andreasen, N.C. *The Scale for the Assessment of Positive Symptoms (SAPS)*. Iowa City, IA: University of Iowa, 1984b.
- Andrews, P.; Hall, J.N.; and Snaith, R.P. A controlled trial of phenothiazine withdrawal in chronic schizophrenic patients. *British Journal of Psychiatry*, 128:451–455, 1976.
- Appelbaum, P.S.; Lidz, C.W.; and Meisel, A. *Informed Consent: Legal Theory and Clinical Practice*. New York, NY: Oxford University Press, 1987.
- Avorn, J., and Gurwitz, J. Principles of pharmacology. In: Cassel, K.; Riesenber, D.; Sorenson, L.; and Walsh, J., eds. *Geriatric Medicine*. 2nd ed. New York, NY: Springer/Verlag, 1990. pp. 66–77.
- Bajulaiye, R., and Addonizio, G. Clozapine in the treatment of psychosis in an 82-year-old woman with tardive dyskinesia. *Journal of Clinical Psychopharmacology*, 12:364–365, 1992.
- Baldessarini, R.J. *Chemotherapy in Psychiatry, Principles and Practice*. Cambridge, MA: Harvard University Press, 1985.
- Branchey, M.H.; Lee, J.H.; and Ramesh, A. High- and low-potency neuroleptics in elderly psychiatric patients. *Journal of the American Medical Association*, 239:1860–1862, 1978.
- Casey, D.E., and Gerlach, J. Tardive dyskinesia: What is the long-term outcome? In: Casey, D.E., and Gardos, G., eds. *Tardive Dyskinesia and Neuroleptics: From Dogma to Reason*. Washington, DC: American Psychiatric Press, 1986. pp. 75–97.
- Castle, D.J., and Murray, R.M. The neurodevelopmental basis of sex differences in schizophrenia. *Psychological Medicine*, 21:565–575, 1991.

- Craig, T.J., and Bregman, Z. Late onset schizophrenia-like illness. *Journal of the American Geriatrics Society*, 36:104-107, 1988.
- Cutler, S.J., and Ederer, F. Maximum utilization of the life table method in analyzing survival. *Journal of Chronic Disorders*, 8:669-712, 1958.
- Davis, J.M.; Baxter, J.T.; and Kane, J.M. Antipsychotic drugs. In: Kaplan, H.I., and Sadock, B.J., eds. *Comprehensive Textbook of Psychiatry*. Vol. 1, 5th ed. Baltimore, MD: Williams & Wilkins Company, 1989. pp. 1591-1626.
- Ereshefsky, L., and Richards, A.L. Psychoses. In: Koda-Kimble, M.A.; Young, L.Y.; Kradjan, W.A.; and Guglielmo, B.J., eds. *Applied Therapeutics: The Clinical Use of Drugs*. Vancouver, WA: Applied Therapeutics, Inc., 1992. pp. 1-42.
- Folstein, M.F.; Folstein, S.E.; and McHugh, P.R. Mini-Mental State: A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research*, 12:189-198, 1975.
- Gittelman-Klein, R., and Klein, D.F. Premorbid asocial adjustment and prognosis in schizophrenia. *Journal of Psychiatric Research*, 7:35-53, 1969.
- Guy, W., ed. *ECDEU Assessment Manual for Psychopharmacology*, revised. DHEW Pub. No. (ADM) 76-338. Rockville, MD: National Institute of Mental Health, 1976.
- Hamilton, M. Development of a rating scale for primary depressive illness. *British Journal of Social and Clinical Psychology*, 6:278-296, 1967.
- Harris, M.J., and Jeste, D.V. Late-onset schizophrenia: An overview. *Schizophrenia Bulletin*, 14:39-55, 1988.
- Harris, M.J.; Panton, D.; Caligiuri, M.P.; Krull, A.J.; Tran-Johnson, T.K.; and Jeste, D.V. High incidence of tardive dyskinesia in older outpatients on low doses of neuroleptics. *Psychopharmacology Bulletin*, 28:87-92, 1992.
- Hawk, A.; Carpenter, W.T., Jr.; and Strauss, J. Diagnostic criteria and five-year outcome in schizophrenia. *Archives of General Psychiatry*, 32:343-347, 1975.
- Heaton, R.K. *Comprehensive Norms for an Expanded Halstead-Reitan Battery: A Supplement for the Wechsler Adult Intelligence Scale—Revised*. Odessa, FL: Psychological Assessment Resources, 1992.
- Heaton, R.K., and Drexler, M. Clinical neuropsychological findings in schizophrenia and aging. In: Miller, N.E., and Cohen, G.D., eds. *Schizophrenia & Aging*. New York, NY: Guilford Press, 1987. pp. 145-161.
- Heaton, R.K.; Grant, I.; and Mathews, C.G. *Comprehensive Norms for an Expanded Halstead-Reitan Battery: Demographic Corrections, Research Findings, and Clinical Applications*. Odessa, FL: Psychological Assessment Resources, 1991.
- Heinrichs, D.W.; Hanlon, T.E.; and Carpenter, W.T., Jr. The Quality of Life Scale: An instrument for rating the schizophrenic deficit syndrome. *Schizophrenia Bulletin*, 10:388-398, 1984.
- Herbert, M.E., and Jacobson, S. Late paraphrenia. *British Journal of Psychiatry*, 113:461-469, 1967.
- Hershon, H.I.; Kennedy, P.F.; and McGuire, R.J. Persistence of extrapyramidal disorders and psychiatric relapse after withdrawal of long-term phenothiazine therapy. *British Journal of Psychiatry*, 120:41-50, 1972.
- Honigfeld, G.; Rosenbaum, M.P.; Blumenthal, I.J.; Lambert, H.L.; and Roberts, A.J. Behavioral improvement in the older schizophrenic patient: Drug and social therapies. *Journal of the American Geriatric Society*, 13:57-71, 1965.
- Janzarik, W. Zur problematik schizophrener psychosen in höheren lebensalter. *Nervenarzt*, 28:535-542, 1957.
- Jeste, D.V., and Caligiuri, M.P. Tardive dyskinesia. *Schizophrenia Bulletin*, 19:303-315, 1993.
- Jeste, D.V.; Harris, M.J.; Pearlson, G.D.; Rabins, P.; Lesser, I.; Miller, B.; Coles, C.; and Yassa, R. Late-onset schizophrenia: Studying clinical validity. *Psychiatric Clinics of North America*, 11:1-14, 1988.
- Jeste, D.V.; Linnoila, M.; Wagner, R.L.; and Wyatt, R.J. Serum neuroleptic concentrations and tardive dyskinesia. *Psychopharmacology*, 76:377-380, 1982.
- Jeste, D.V., and Wyatt, R.J. *Understanding and Treating Tardive Dyskinesia*. New York, NY: Guilford Press, 1982.
- Kane, J.M.; Honigfeld, G.; Singer, J.; Meltzer, H.Y.; and the Clozaril Collaborative Study Group. Clozapine for the treatment resistant schizophrenic: A double-blind comparison with chlorpromazine. *Archives of General Psychiatry*, 45:789-796, 1988a.
- Kane, J.M.; Jeste, D.V.; Barnes, T.R.E.; Casey, D.E.; Cole, J.O.; Davis, J.M.; Gualtieri, C.T.; Schooler, N.R.; Sprague, R.L.; and Wettstein, R.M. *Tardive Dyskinesia: A Task Force Report of the American Psychiatric Association*. Washington, DC: American Psychiatric Association, 1992.
- Kane, J.M.; Rifkin, A.; Woerner, M.; Reardon, G.; Sarantakos, S.; Schiebel, D.; and Ramos-Lorenzi, J.

- Low-dose neuroleptic treatment of outpatient schizophrenics: I. Preliminary results for relapse rates. *Archives of General Psychiatry*, 40:893-896, 1983.
- Kane, J.M.; Woerner, M.; and Lieberman, J. Tardive dyskinesia: Prevalence, incidence, and risk factors. *Journal of Clinical Psychopharmacology*, 8:52S-56S, 1988b.
- Kay, D.W.K., and Roth, M. Environmental and hereditary factors in the schizophrenias of old age ("late paraphrenia") and their bearing on the general problem of causation in schizophrenia. *Journal of Mental Science*, 107:649-686, 1961.
- Kessler, K.A., and Waletzky, J.P. Clinical use of the antipsychotics. *American Journal of Psychiatry*, 138:202-208, 1981.
- Lafayette Instrument Company. *Grooved Pegboard*. Odessa, FL: Psychological Assessment Resources, 1992.
- Lamy, P.P.; Salzman, C.; and Nevis-Olesen, J. Drug prescribing patterns, risks, and compliance guidelines. In: Salzman, C., ed. *Clinical Geriatric Psychopharmacology*. Baltimore, MD: Williams & Wilkins Company, 1992. pp. 15-37.
- Makanjulua, R.O.A. Psychiatric disorders in elderly Nigerians. *Tropical and Geographical Medicine*, 37:348-351, 1985.
- Mattis, S. Mental status examination for organic mental syndrome in the elderly patient. In: Bellak, L., and Karasu, T.B., eds. *Geriatric Psychiatry*. New York, NY: Grune & Stratton, 1976. pp. 77-122.
- McGlashan, T.H. A selective review of recent North American long-term followup studies of schizophrenia. *Schizophrenia Bulletin*, 14:515-542, 1988.
- Movin, G.; Gustafson, L.; Franzen, G.; Widerlov, E.; Soni, S.D.; Tench, D.; Nilsson, L.; and Yisak, W. Pharmacokinetics of remoxipride in elderly psychotic patients. *Acta Psychiatrica Scandinavica*, 358:176-180, 1990.
- Olson, G.W., and Peterson, D.B. Intermittent chemotherapy for chronic psychiatric inpatients. *Journal of Nervous and Mental Disease*, 134:145-149, 1962.
- Ostrum, F.E.; Hammarlund, E.R.; Christensen, D.B.; Plein, J.B.; and Kethley, J.A. Medication usage in an elderly population (1985). *Medical Care*, 23:157-170, 1988.
- Overall, J.E. The Brief Psychiatric Rating Scale (BPRS): Recent developments in ascertainment and scaling. *Psychopharmacology Bulletin*, 24:97-99, 1988.
- Overall, J.E., and Gorham, D.R. The Brief Psychiatric Rating Scale. *Psychological Reports*, 10:799-812, 1962.
- Post, F. *Persistent Persecutory States of the Elderly*. London, England: Pergamon Press, 1966.
- Rabins, P.; Pauker, S.; and Thomas, J. Can schizophrenia begin after age 44? *Comprehensive Psychiatry*, 25:290-293, 1984.
- Raskind, M.; Alvarez, C.; and Herlin, S. Fluphenazine enanthate in the outpatient treatment of late paraphrenia. *Journal of the American Geriatrics Society*, 27:459-463, 1979.
- Rassidakis, N.C.; Kondakis, X.; Panastassiou, A.; and Michalakeas, A. Withdrawal of antipsychotic drugs from chronic psychiatric patients. *Bulletin of the Menninger Clinic*, 34:216-222, 1970.
- Roberts, J., and Tumer, N. Pharmacodynamic basis for altered drug action in the elderly. *Clinics in Geriatric Medicine*, 4:127-149, 1988.
- Ruskin, P.E., and Nyman, G. Discontinuation of neuroleptic medication in older, outpatient schizophrenics: A placebo-controlled, double-blind trial. *Journal of Nervous and Mental Disease*, 179:212-214, 1991.
- Russell, E.; Neuringer, C.; and Goldstein, G. *Assessment of Brain Damage: A Neuropsychological Key Approach*. New York, NY: John Wiley & Sons, 1970.
- Saltz, B.L.; Woerner, M.G.; Kane, J.M.; Lieberman, J.A.; Alvir, J.M.J.; Bergmann, K.J.; Blank, K.; Koblenzer, J.; and Kahaner, K. Prospective study of tardive dyskinesia incidence in the elderly. *Journal of the American Medical Association*, 266:2402-2406, 1991.
- Salzman, C. Principles of psychopharmacology. In: Bienenfeld, D., ed. *Verwoerd's Clinical Geropsychiatry*. Baltimore, MD: Williams & Wilkins Company, 1990. pp. 235-249.
- Scholz, E., and Dichgans, J. Treatment of drug-induced exogenous psychosis in Parkinsonism with clozapine and fluperlapine. *European Archives of Psychiatry and Neurological Sciences*, 235:60-64, 1985.
- Schooler, N.R., and Kane, J.M. Research diagnoses for tardive dyskinesia. *Archives of General Psychiatry*, 39:486-487, 1982.
- Sovner, R.; Dimascio, A.; Berkowitz, D.; and Randolph, P. Tardive dyskinesia and informed consent. *Psychosomatics*, 19:172-177, 1978.
- Tran-Johnson, T.K.; Harris, M.J.; and Jeste, D.V. Pharmacological treatment of schizophrenia and delusional disorders of late life. In: Copeland, J.R.M.; Abou-Saleh, M.T.; and Blazer, D.G., eds. *The Psychiatry of Old Age*. New York,

NY: John Wiley & Sons, in press.

Tran-Johnson, T.K.; Krull, A.J.; and Jeste, D.V. Late life schizophrenia and its treatment: The pharmacologic issues in older schizophrenic patients. In: Alexopoulos, G.S., ed. *Clinics in Geriatric Medicine*. Philadelphia, PA: W.B. Saunders & Company, 1992. pp. 401-410.

Tsuang, M.M.; Lu, L.M.; Stotsky, B.A.; and Cole, J.O. Haloperidol versus thioridazine for hospitalized psychogeriatric patients: Double-blind study. *Journal of the American Geriatrics Society*, 19:593-600, 1971.

Wechsler, D. *Wechsler Adult Intelligence Scale—Revised*. New York, NY: The Psychological Corporation, 1981.

Whittaker, C.B., and Hoy, R.M. Withdrawal of perphenazine in chronic schizophrenia. *British Journal of Psychiatry*, 109:422-427, 1963.

Wolk, S.I., and Douglas, C.J. Clozapine treatment of psychosis in Parkinson's disease: A report of 5 consecutive cases. *Journal of*

Clinical Psychiatry, 53:373-376, 1992.

Wolters, E.C.; Hurwitz, T.A.; Mak, E.; Teal, P.; Peppard, F.R.; Remick, R.; Calne, S.; and Calne, D.B.

Clozapine in the treatment of parkinsonian patients with dopaminomimetic psychosis. *Neurology*, 40:832-840, 1990.

Yesavage, J.A.; Becker, J.; Werner, P.D.; Mills, M.J.; Holman, C.A.; and Cohn, R. Serum level monitoring of thiothixene in schizophrenia: Acute single-dose levels at fixed doses. *American Journal of Psychiatry*, 139:174-178, 1982.

Acknowledgments

This work was supported in part by USPHS grants MH-45131, MH-43693, MH-45959, and MH-49671 from the National Institute of Mental Health, and by the Department of Veterans Affairs. The brief neuroleptic-withdrawal study was supported in part by a grant from Merck, Sharp, and Dohme Research Labo-

ratories. The authors thank Lou Ann McAdams, Ph.D., and Anne Bailey, M.S., for statistical assistance.

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