A Double-Blind Randomized Comparison of Nortriptyline Plus Perphenazine Versus Nortriptyline Plus Placebo in the Treatment of Psychotic Depression in Late Life

Benoit H. Mulsant, M.D.; Robert A. Sweet, M.D.; Jules Rosen, M.D.; Bruce G. Pollock, M.D., Ph.D.; George S. Zubenko, M.D., Ph.D.; Tracy Flynn, M.S. Ed.; Amy E. Begley, M.A.; Sati Mazumdar, Ph.D.; and Charles F. Reynolds III, M.D.

Objective: To conduct the first randomized study comparing the efficacy of an antidepressant alone versus an antidepressant plus a neuroleptic in the treatment of late-life psychotic depression.

Method: The efficacy of nortriptyline plus placebo versus nortriptyline plus perphenazine was compared in 36 patients aged 50 years or older presenting with a major depressive episode with psychotic features (DSM-III-R criteria). Patients were started openly on nortriptyline treatment titrated to therapeutic levels. They were then randomly assigned under double-blind conditions to addition of perphenazine or placebo. Outcomes were compared in the 2 treatment groups using measures including the Hamilton Rating Scale for Depression (HAM-D) and the Brief Psychiatric Rating Scale (BPRS); side effects were assessed with the Geriatric Movement Disorder Assessment.

Results: Both treatments were well tolerated. Of the 36 randomly assigned patients, 2 (1 in each group) dropped out due to treatment-related adverse effects. Four additional patients dropped out for administrative reasons. Thirty patients received nortriptyline for at least 4 weeks combined with either perphenazine (N = 14) or placebo (N = 16) for at least 2 weeks (median = 9 weeks). There was no significant difference between the completers in the 2 treatment groups when comparing their scores on the HAM-D, the BPRS, its psychoticism subscale, or any side effects measure. Rates of response (defined as resolution of both depression and psychosis) did not differ significantly in the 2 groups (nortriptyline-plus-perphenazine group, 50% vs. nortriptyline-plus-placebo group, 44%).

Conclusion: When treating older patients with psychotic depression, the addition of a moderate dose of a traditional neuroleptic to a tricyclic antidepressant was well tolerated but did not improve efficacy. This finding supports existing data suggesting that the pathophysiology (and thus the required treatment) of psychotic depression may be different early and late in life.

(J Clin Psychiatry 2001;62:597–604)

Received April 26, 2000; accepted Nov. 2, 2000. *From the Intervention Research Center for the Study of Late-Life Mood Disorders, Department of Psychiatry, University of Pittsburgh School of Medicine (all authors); the Western Psychiatric Institute and Clinic, University of Pittsburgh Medical Center (Drs. Mulsant, Sweet, Rosen, Pollock, Zubenko, and Reynolds and Mss. Flynn and Begley); and the Geriatric Research, Education, and Clinical Center, VA Pittsburgh Health Care System (Dr. Mulsant), Pittsburgh, Pa.*

Supported in part by United States Public Health Service grants MH-49786, MH-30915, MH-52247, MH-01613, MH-01153, and MH-01509 from the National Institute of Mental Health, Rockville, Md.

Financial disclosure: Dr. Mulsant has received grant/research support from the National Institute of Mental Health, Pfizer/Eisai, Janssen, AstraZeneca, and SmithKline Beecham; is a consultant for Janssen and Pfizer; is on the speakers bureau for Pfizer/Eisai, Janssen, AstraZeneca, and SmithKline Beecham; is a major stock shareholder in Biogen; and has received honoraria from Pfizer/Eisai, Janssen, AstraZeneca, and SmithKline Beecham. Dr. Sweet has received grant/research support from Janssen and Lilly and is on the speakers bureau for Janssen. Dr. Pollock has received grant/research support from the National Institute of Mental Health, Solvay, Forest Laboratories, SmithKline Beecham, Pharmacia & Upjohn, and Pfizer; is a consultant for SmithKline Beecham, Forest Laboratories, Janssen, Pharmacia & Upjohn, and Organon Inc.; is on the speakers bureau for GlaxoWellcome, SmithKline Beecham, Parke-Davis, Pfizer, Janssen, Lundbeck, and Forest; and is on the scientific advisory board for Janus Pharmaceuticals. Dr. Reynolds has received grant/research support from Forest Laboratories and SmithKline Beecham.

Presented in part at the 12th annual conference of the American Association for Geriatric Psychiatry, March 14–17, 1999, New Orleans, La., and at the 39th annual meeting of the New Clinical Drug Evaluation Unit, June 1–4, 1999, Boca Raton, Fla.

The authors acknowledge the contributions of John P. Foglia, Dr. P.H.; Margaret A. Kirshner, B.A.; and Denise A. Sorisio, B.S., to the analysis of blood levels of drug.

Reprint requests to: Benoit H. Mulsant, M.D., Western Psychiatric Institute and Clinic, 3811 O'Hara St., Pittsburgh, PA 15213 (e-mail: mulsantbh@msx.upmc.edu).

Two meta-analyses of 23 mostly naturalistic studies have shown that only about one third of mixed-age patients with psychotic major depression ("delusional depression") respond when they are treated with a tricyclic antidepressant (TCA) alone, whereas more than three quarters respond when they are treated with a combination of a TCA and a neuroleptic.[1,2] This high rate of response is comparable to the rate of response expected with electroconvulsive therapy (ECT), often considered the treatment of choice for major depressive disorder with psychotic features.[3–7] Two randomized controlled trials conducted under double-blind conditions have confirmed a very high

response rate in mid-life patients with psychotic depression who received a combination of amitriptyline plus high-dose perphenazine.[8–10] Based on these results, the practice guidelines of the American Psychiatric Association strongly recommend the use of a combination of an antidepressant and a neuroleptic for the pharmacotherapy of major depressive disorder with psychotic features.[3,4] One quarter to one half of elderly depressed patients admitted to a psychiatric hospital present with psychotic features[11–15] and thus may require treatment with such a combination. However, we are not aware of any published prospective randomized study comparing the efficacy of an antidepressant alone versus an antidepressant plus a neuroleptic in the treatment of psychotic major depression in late life.[14,16,17] Furthermore, most older patients could not tolerate the very high doses of neuroleptics that were used in the 2 randomized trials in mid-life subjects (i.e., modal doses of perphenazine of 32 mg/day[8] and 32–64 mg/day[10]). Thus, we conducted a randomized double-blind trial comparing the tolerability and the efficacy of nortriptyline plus perphenazine versus nortriptyline plus placebo in a group of older patients who presented with a major depressive episode with psychotic features. We hypothesized that the tolerability of nortriptyline plus placebo would be higher but the efficacy of nortriptyline plus perphenazine would be better.

METHOD

Recruitment

Western Psychiatric Institute and Clinic is a teaching hospital that both provides psychiatric care to a large urban catchment area and serves as a referral center for psychiatric patients from suburban and rural southwestern Pennsylvania.[18–20] All inpatients admitted between October 1991 and October 1997 were screened for eligibility in the trial. Subjects who met the following criteria were invited to participate: were aged 50 years and older; met DSM-III-R criteria[21] for a major depressive episode with psychotic features (mood congruent or incongruent delusions and/or hallucinations); had no known history of schizophrenia, schizoaffective disorder, delusional disorder, or manic episode; had a Hamilton Rating Scale for Depression (HAM-D)[22] baseline score of 18 or above; and had no specific medical condition contraindicating treatment with either nortriptyline (e.g., QRS interval longer than 120 ms or bifascicular bundle-branch block) or perphenazine (e.g., diagnosis of Parkinson's disease). Of note, since psychotic depression can cause significant cognitive impairment in older persons,[23,24] it is often not possible to reliably distinguish patients with psychotic depression and reversible cognitive impairment from patients with a primary dementia and comorbid depression and psychosis until the psychotic depression is successfully treated.[21,25–27] Thus, patients with cognitive impairment were included as long as they did not carry a diagnosis of dementia antedating the onset of their mood and psychotic symptoms. In addition to the inpatients recruited by systematic screening at Western Psychiatric Institute and Clinic, 1 inpatient at a local state hospital and 4 outpatients referred by their outpatient treatment team who met the same eligibility criteria were enrolled in the trial. Procedures for inpatients and outpatients were similar. In accordance with the rules of the University of Pittsburgh Institutional Review Board, all subjects (or their legal representatives) provided written informed consent after the research procedures had been fully explained.

Assessment

All subjects received a comprehensive evaluation performed by a multidisciplinary geropsychiatric team.[18–20] This evaluation included a psychiatric history and mental status examination, a social history, a medical history and physical examination, and a battery of laboratory tests, including brain imaging as indicated. In addition, trained research clinicians assessed the patients with a semi-structured interview[19] that yields ratings on the 17-item HAM-D and the Brief Psychiatric Rating Scale (BPRS); the Global Assessment Scale[28]; the Cumulative Illness Rating Scale, adapted for geriatrics[29]; a standardized version of Folstein's Mini-Mental State Examination (MMSE)[30]; the Asberg Rating Scale for Side Effects[31]; and the Geriatric Movement Disorder Assessment,[32] a structured examination that yields ratings on the Simpson Extrapyramidal Symptom scale (SEPSS), the Barnes Akathisia Scale, and the Abnormal Involuntary Movement Scale. During the study period, interrater reliability of the research clinicians was monitored annually, and intraclass correlation coefficients measuring interrater reliability for the research instruments remained good to excellent. Based on all information available, Axis I diagnoses were established according to the criteria of the DSM-III-R[21] during a consensus conference attended by at least 3 faculty psychiatrists (including B.H.M. or R.A.S.) and the research staff. Age at onset of primary psychiatric disorder and length of the major depressive episode were also determined during this conference.

Treatment

After a washout of other psychotropic medications, except for lorazepam, which was used throughout the study as needed to treat severe agitation, anxiety, or insomnia, subjects were started openly on nortriptyline that was titrated to yield a therapeutic plasma level (target = 100 ng/mL or 380 nmol/L; range, 50–150 ng/mL). Once plasma nortriptyline level was within the therapeutic range, subjects were randomly assigned to addition of perphenazine or placebo under double-blind conditions. Doses of perphenazine (or placebo) were adjusted based on operationalized guidelines. Typically, subjects were

given an initial dose of 4 mg that was increased by 4 mg every 3 to 7 days until patients showed a therapeutic response, extrapyramidal symptoms (EPS) were detected on clinical examination, or a maximum dose of 24 mg/day was reached. Doses of perphenazine/placebo could be decreased if a patient experienced significant EPS. All study medications were taken once a day in the evening. Plasma nortriptyline levels were monitored regularly as previously described,[33] and nortriptyline doses were adjusted to maintain a therapeutic plasma level. Since perphenazine can inhibit the metabolism of nortriptyline,[33] these dose adjustments were made by nonblinded psychiatrists (J.R. or R.A.S.) who were not involved in the care of the subjects. In addition, plasma levels of perphenazine and its major metabolites were measured for research purposes as previously described.[33,34]

Throughout the study, inpatients were clinically reassessed weekly and rated with the instruments listed above. The study was terminated for patients who had shown no or minimal improvement after treatment with nortriptyline for a minimum of 4 weeks combined with double-blind treatment with perphenazine/placebo for a minimum of 2 weeks. The decision to terminate the study was made by the subjects' treatment team in collaboration with the study investigators. Subjects who were improving continued to be followed weekly while they were inpatients. At discharge, subjects were offered to be followed by one of the investigators (B.H.M.) on an as-needed schedule until they had received treatment with nortriptyline combined with perphenazine/placebo for up to 16 weeks. After completing the study, the blind was broken and all subjects were treated as deemed necessary by their psychiatrist.

Data Analysis

For this analysis, patients who were randomly assigned but received their assigned medication (perphenazine or placebo) for less than 2 weeks were considered dropouts. Those who received nortriptyline for 4 weeks or more combined with either perphenazine or placebo for 2 weeks or more were considered completers and were included in the efficacy analysis. Demographic and clinical characteristics of the patients assigned randomly to perphenazine or placebo were compared using Fisher exact test or Wilcoxon rank sum test, as appropriate. Clinical outcomes were similarly compared. For this analysis, categorical response was defined as follows: a patient was judged to be a full responder if he or she experienced full resolution of both depressive symptoms (as reflected by a final total HAM-D score of 10 or below) and psychotic symptoms (as reflected by final scores of 1 ["none"] or 2 ["doubtful or trivial"] for BPRS items 11 [suspiciousness], 12 [hallucinatory behaviors and statements], and 15 [unusual thought content]). Nonresponse was defined as persistence of both significant depressive symptoms (HAM-D score of 15 or above) and psychotic symptoms (scores on BPRS items 11, 12, or 15 of 3 ["Mild"] or higher). Patients who were neither full responders nor nonresponders (i.e., they had residual depressive or psychotic symptoms) were classified as partial responders.

RESULTS

During the study period, 2242 inpatients were screened and 5 other patients were referred to the study, 101 patients were invited to participate, and 54 signed informed consent statements. Of these 54 subjects, 2 were found to have a contraindication to nortriptyline, and 52 were started on nortriptyline treatment openly. Of these 52 subjects, 16 were not randomly assigned for the following reasons: 3 subjects showed a rapid improvement of both their depressive and psychotic symptoms on treatment with nortriptyline alone and were not deemed appropriate for the double-blind phase of the study, 4 were terminated prematurely due to side effects attributed to nortriptyline (2, confusion; 1, electrocardiogram [ECG] changes; 1, hypotension and gait instability), and 9 were discontinued from the protocol for administrative reasons (e.g., they withdrew consent or were found to be ineligible).

Thus, 36 subjects openly titrated on nortriptyline treatment were randomly assigned to perphenazine (N = 17) or placebo (N = 19) under double-blind conditions. Of the 17 randomly assigned to perphenazine, 3 (18%) dropped out before receiving nortriptyline and perphenazine for at least 2 weeks (1 experienced EPS, 1 refused to take the blinded study capsules, and 1 withdrew consent). Of the 19 randomly assigned to placebo, 3 (16%) dropped out before receiving nortriptyline and placebo for at least 2 weeks (1 had ECG changes, 1 experienced worsening of clinical status, and 1 withdrew consent). Thus, 30 patients received nortriptyline for at least 4 weeks combined with either perphenazine (N = 14) or placebo (N = 16) for at least 2 weeks.

At baseline, the 2 treatment groups did not differ significantly on any demographic or clinical variables analyzed (Table 1). Completers were openly titrated on treatment with nortriptyline during a mean ± SD of 14.6 ± 3.1 days (median = 14 days; range, 8–21 days) followed by nortriptyline combined with either perphenazine or placebo under double-blind conditions for a mean of 8.4 ± 5.3 weeks (median = 9 weeks; range, 2–16 weeks). At the time of random assignment and at completion of the trial, mean doses and plasma levels of nortriptyline were not significantly different (see Table 1). Perphenazine and placebo were titrated in a similar fashion, and the mean doses did not differ significantly (Table 2).

There were no significant differences between the 2 treatment groups at baseline (i.e., initiation of nortriptyline), time of random assignment, or completion of the trial on any of the following: rate of response or mean scores on HAM-D, BPRS, or BPRS psychoticism subscale

Table 1. Demographic, Clinical, and Treatment Characteristics of Completers of at Least 4 Weeks of Nortriptyline Treatment Plus at Least 2 Weeks of Placebo or Perphenazine Treatment[a]

Characteristic	Nortriptyline Plus Perphenazine (N = 14) %			Nortriptyline Plus Placebo (N = 16) %			Statistic S	Statistic Z	p Value
Gender, female	71			75			…	…	.99
Race, white	100			94			…	…	.99
Marital status									
Married	29			31			…	…	.15
Widowed	71			44					
Single/separated/divorced	0			25					
	Mean	SD	Median	Mean	SD	Median			
Age, y	74	8	72	71	10	71	232.0	0.60	.55
Age at onset of illness, y	57	22	59	54	22	62	201.0	0.24	.81
Duration of episode, mo	16	27	5	10	24	3	201.5	1.62	.11
Length of inpatient stay, d[b]	41	19	36	48	28	39	209.0	–0.31	.76
CIRS-G score	8	4	8	9	3	9	164.5	0.81	.42
MMSE score	26	4	28	25	4	27	215.5	0.22	.83
GAS score	36	7	35	33	10	30	241.0	0.99	.32
Nortriptyline at random assignment									
Dose, mg/d	64.3	25.4	50	67.2	33.8	50	216.5	0	.99
Plasma level, ng/mL	87.4	31.5	83.5	83.7	44.2	73.5	119.0	0.23	.82
Nortriptyline at completion									
Dose, mg/d	63.2	45.2	50	76.3	34.6	75	182.0	–1.47	.14
Plasma level, ng/mL	120.1	31	114.5	101.4	30.9	98	241.5	1.35	.18
Perphenazine/placebo (highest tolerated)									
Dose, mg/d	18.9	5.1	18	19.3	5.1	20	211.0	–0.22	.82
Plasma level, ng/mL	4.2	4.5	2.3	0	0	0	NA	NA	NA

[a]Abbreviations: CIRS-G = Cumulative Illness Rating Scale, adapted for geriatrics; GAS = Global Assessment Scale; MMSE = Mini-Mental State Examination; NA = not applicable. Symbol: … = not applicable; Fisher exact test used.
[b]These 30 subjects were all inpatients.

(see Table 2).[8,9] Rates of response to nortriptyline plus perphenazine and nortriptyline plus placebo were 50% (N = 7) and 44% (N = 7), respectively (p = .99, Fisher exact test) (Table 3). Both treatments were tolerated similarly with no differences in final scores on the Asberg Rating Scale for Side Effects or the EPS subscale of the SEPSS or rates of akathisia or tardive dyskinesia (see Table 2). However, 1 subject randomly assigned to perphenazine who had no known history of exposure to neuroleptics in the past and no evidence of movement disorder at baseline developed some abnormal tongue movements consistent with tardive dyskinesia.

DISCUSSION

To our knowledge, this randomized double-blind comparison of an antidepressant combined with a neuroleptic versus an antidepressant alone for the treatment of psychotic major depression is only the third such trial to be published and the first one to be conducted in older subjects (Table 4). Its major findings are that, contrary to our hypotheses, older patients with psychotic major depression tolerated nortriptyline and nortriptyline combined with perphenazine similarly, and they responded similarly but modestly to both treatments.

The major limitation of this study is the small number of subjects who completed the study. However, this number is comparable to the number of younger subjects who have completed published randomized controlled studies of the pharmacotherapy of psychotic depression (see Table 4). Our findings both confirm and contradict the results of these and other published studies. As reported in younger patients, less than half (44%) of our older subjects presenting with psychotic depression responded fully to therapeutic plasma levels of a TCA (nortriptyline) given alone for 4 weeks or longer (mean = 10 weeks, median = 11 weeks). This response rate is much lower than the response rate of 78% we recently reported in a comparable group of elderly patients with nonpsychotic major depression who were treated similarly under randomized double-blind conditions with nortriptyline for 4 to 6 weeks.[39] However, the response rate we observed is comparable to the response rates to a TCA alone reported in patients with psychotic depression: 41% in 17 mid-life patients (aged below 65 years) treated for 5 weeks with amitriptyline alone,[9] 40% in 10 mid-life patients treated for 6 weeks with amitriptyline alone[35] (see Table 4), and 40% in 10 older patients (mean age = 65 ± 9 years) who were able to tolerate high plasma levels (> 300 ng/mL) of desipramine in an open trial.[40]

We found that combining perphenazine (8–24 mg/day) with nortriptyline did not significantly improve the response rate in our older subjects, which confirms noncontrolled data obtained in 2 groups of older patients with

Table 2. Clinical Outcome Among Completers[a]

Measure	Nortriptyline Plus Perphenazine (N = 14) Mean	SD	Median	Nortriptyline Plus Placebo (N = 16) Mean	SD	Median	Statistic S	Z	p Value
HAM-D score									
Baseline	26.3	3.5	27	26.7	5.5	27	179.5	–0.39	.69
Random assignment	20.3	3.5	21	19.6	6.2	19.5	229.5	0.50	.62
Completion	11.4	7.3	9.5	10.4	7.3	8.5	227.5	0.42	.68
% Change[b]	–55.5	33.4	–76	–59.9	26.8	–62	193	0.18	.85
BPRS score									
Baseline	51.0	7.5	48	53.5	10.5	49	174	–0.65	.52
Random assignment	44.0	9.5	42.5	45.3	12.5	45	213	–0.15	.88
Completion	30.9	10.7	28.5	31.7	13.9	26.5	222.5	0.21	.84
% Change[b]	–40.1	19.3	–47.7	–40.4	23.2	–53.3	188	0.00	.99
BPRS psychoticism subscore[c]									
Baseline	29.2	4.3	29	30.8	6.4	30	172.5	–0.72	.47
Random assignment	24.6	6.4	24	25.3	8.1	23	215.5	–0.04	.97
Completion	16.1	7.2	15	16.8	8.6	13.5	217.5	0.00	.99
Side effect score									
Baseline	19.7	6.2	19	16.7	5.5	17	209.5	0.95	.34
Random assignment	13.8	3.7	13.5	15.8	8.2	12	212.5	–0.17	.87
Completion	10.1	5.9	9	9.6	5.2	9	220	0.10	.92
EPS subscore[d]									
Baseline	0.77	0.98	0.5	0.48	0.49	0.4	123.5	0.50	.62
Random assignment	0.36	0.33	0.3	0.46	0.53	0.3	212.5	–0.17	.87
Completion	0.81	0.81	0.7	0.40	0.46	0.2	254.5	1.57	.12
Akathisia[e]	N (%)			N (%)					
Baseline	9 (75)			7 (64)			…		.67
Random assignment	9 (64)			8 (50)			…		.48
Completion	4 (29)			4 (25)			…		.99
Tardive dyskinesia[f]									
Baseline	6 (50)			3 (27)			…		.40
Random assignment	5 (36)			4 (25)			…		.69
Completion	7 (50)			3 (19)			…		.12

[a]Abbreviations: BPRS = Brief Psychiatric Rating Scale, EPS = extrapyramidal symptoms, HAM-D = Hamilton Rating Scale for Depression. Symbol: ... = not applicable. Fisher exact test used.
[b]Change between baseline and completion.
[c]BPRS items 1, 2, 3, 4, 5, 11, 12, and 15.
[d]Simpson Extrapyramidal Symptom scale items 3, 4, 5, 6, and 9; available for only 12 (perphenazine group) and 11 (placebo group) subjects at baseline.
[e]Based on Barnes Akathisia Scale objective rating; available for only 12 (perphenazine group) and 11 (placebo group) subjects at baseline.
[f]Based on Abnormal Involuntary Movement Scale global rating; available for only 12 (perphenazine group) and 11 (placebo group) subjects at baseline.

Table 3. Clinical Outcome Among Completers: Categorical Response

Outcome	Nortriptyline Plus Perphenazine (N = 14) N (%)	Nortriptyline Plus Placebo (N = 16) N (%)	p Value[a]
Resolution of depression[b]	7 (50)	9 (56)	.99
Resolution of psychosis[c]	9 (64)	9 (56)	.72
Overall response[d]			
Full responders	7 (50)	7 (44)	
Partial responders	4 (29)	5 (31)	.99
Nonresponders	3 (21)	4 (25)	

[a]Fisher exact test used.
[b]Total score of 10 or less on Hamilton Rating Scale for Depression.
[c]Scores of 1 or 2 for Brief Psychiatric Rating Scale items 11, 12, and 15.
[d]Full response = resolution of both depression and psychosis; see Method for partial response and nonresponse definitions.

psychotic depression treated openly with nortriptyline plus perphenazine.[17,41] Only 50% of subjects in our study responded fully to this combination, much less than the approximately four fifths of mid-life patients with psychotic depression who were reported to respond to a TCA plus a neuroleptic in several open trials[2] and to amitriptyline plus perphenazine in 2 double-blind randomized trials (see Table 4).[8–10] In these 2 trials, doses of perphenazine (i.e., 32–64 mg/day) were 2- to 3-fold higher than the doses used in our older patients (i.e., 12–24 mg/day). In a retrospective study of 35 mixed-age patients (age range, 23–78 years old) with psychotic depression treated with a combination of desipramine plus perphenazine, 100% (6 of 6) of those receiving 40 mg/day or more of perphenazine responded, while only 40% (10 of 25) receiving 32 mg/day or less responded (p = .03). Our response rate is comparable to the response rate of the patients treated openly with lower doses of perphenazine. Thus, it is possible that we would have observed a significantly higher response rate if we had treated our patients with higher perphenazine doses. However, in one retrospective study,[17] older patients who had received combination pharmacotherapy with neuroleptic doses comparable to those found effective in younger adults responded as poorly as those treated with lower neuroleptic doses. Furthermore, our patients' plasma perphenazine levels were in the range reported to be associated with resolution of psychosis in younger patients.[10,42,43] Also, only 5 of our subjects randomly assigned to perphenazine tolerated the maximum dose of 24 mg/day, and while EPS scores were not significantly different between our 2 treatment groups, there appears to be a trend for patients who received perphenazine to have more EPS (see Table 2). Therefore, it is unlikely that our subjects could have tolerated significantly higher doses of perphenazine without experiencing the significant EPS that have been associated with functional impairment, falls, and increased mortality.[44] Indeed, in a recent report on 27 older patients with psychotic depression who had responded to ECT, patients randomly assigned under double-blind conditions to be continued on treatment with nortriptyline plus relatively

Table 4. Randomized Controlled Trials of the Pharmacologic Treatment of Psychotic Major Depression[a]

Study	No. of Completers (inpatients)	Age (y) Mean	Age (y) SD	Duration (wk)	Treatments Compared (doses in mg/d)	N	Response Rate (%)
Spiker et al, 1985,[9] 1986[10]	51	44	13	5	Amitriptyline (TL)	17	41
					Perphenazine (32–64)	16	19
					Amitriptyline (TL)/perphenazine (24–64)	18	78
Anton and Burch, 1990[8]	38	45	12	2–4	Amitriptyline (200)/perphenazine (32)	21	86
					Amoxapine (400)	17	82
Bellini et al, 1994[35]	48	48	12	6	Fluvoxamine (300)	13	69
					Fluvoxamine (300)/haloperidol (0.1 mg/kg)	11	45
					Desipramine (150)	10	40
					Desipramine (150)/haloperidol (0.1 mg/kg)	14	64
Zanardi et al, 1996[36]	37	54	13	6	Sertraline (150)[b]	24	75
					Paroxetine (50)[c]	13	46
Zanardi et al, 1998[37]	71	47	10	6	Fluvoxamine (300)	36	80
					Fluvoxamine (300)/pindolol (7.5)	35	81
Zanardi et al, 2000[38]	26	51	11	6	Fluvoxamine (300)	14	79
					Venlafaxine (300)	12	58
This study	30	72	8	4–18	Nortriptyline (TL)	16	44
					Nortriptyline (TL)/perphenazine (8–24)	14	50

[a]Abbreviation: TL = therapeutic plasma levels.
[b]Six patients with diagnosis of bipolar disorder were also receiving long-term lithium treatment.
[c]Four patients with diagnosis of bipolar disorder were also receiving long-term lithium treatment.

low-dose perphenazine (8–16 mg/day) suffered significantly more severe EPS and a greater number of falls than patients randomly assigned to nortriptyline plus placebo (and they had the same relapse rate).[45]

It is also possible that the relatively low response rate to nortriptyline plus perphenazine we observed in our patients was due to heterogeneity in our study group. In many older patients, depression and/or psychosis may be presenting symptoms of a dementing or other organic disorder,[46] and these patients may be less likely to respond to pharmacotherapy. Limiting the analysis to the 26 completers who received a consensus research diagnosis of major depression (i.e., excluding 3 subjects with consensus diagnoses of primary degenerative dementia and 1 subject with a consensus diagnosis of psychotic disorder not otherwise specified [NOS] and depressive disorder NOS) did not substantially change the results: 54% of subjects treated with nortriptyline plus perphenazine were responders, 23% were partial responders, and 23% were nonresponders versus 46%, 31%, and 23% of those treated with nortriptyline plus placebo ($p = .99$, Fisher exact test). Still, it is probable that some of these older patients with "pure" major depression had subtle undetected neurodegenerative changes. When the treatment groups were collapsed, patients with an MMSE score of 27 or above seemed to have a better response than the patients with an MMSE score below 27 (i.e., resolution of depression, 61% versus 36%; resolution of psychosis, 72% versus 36%). However, due to the small Ns, these differences were not statistically significant ($p = .26$ and $p = 0.12$ respectively, Fisher exact test).

When examined in the context of other studies (e.g., references 47–50), our results suggest that the pathophysiology of psychotic major depression and its response to pharmacotherapy may be different early and late in life. Although most of our subjects showed no gross cognitive impairment, several studies comparing older patients who had psychotic and nonpsychotic depression have consistently shown increased cognitive impairment in those with psychotic depression.[23,51–53] Psychotic depression in late life has also been associated with higher rates of cerebrovascular risk factors and brain changes on magnetic resonance imaging[49,52,53] and with an increase in frequency of the APOE-ε4 allele frequency.[54] These findings raise the question of whether, in a significant subgroup of elderly patients, psychotic depression is the clinical expression of an underlying incipient organic brain disorder (e.g., Alzheimer's disease or cerebrovascular disease) rather than a variant of major depression. Answering this question awaits longitudinal studies with postmortem examination. In the meantime, ECT should probably remain the treatment of choice for older inpatients with psychotic depression.[4,6,55,56] The mediocre response we observed with a combination of a TCA and a traditional neuroleptic (and the potential toxicity of both) and other indirect evidence suggest that when ECT is not available or when older patients refuse ECT, newer antidepressants affecting serotonergic neurotransmission and atypical antipsychotic agents, alone or in combination, may be preferable. So far, this evidence has been inferred from data collected in older patients with dementia and psychosis[14,57–61] and in younger patients with psychotic depression.[5,35–38,62–69] A large clinical trial is now needed to confirm these small randomized studies and naturalistic case series. Such a trial should include both younger and older patients with psychotic depression so that it could also directly address whether this disorder responds differently to pharmacotherapy early and later in life.

Drug names: amitriptyline (Elavil and others), desipramine (Norpramin and others), fluvoxamine (Luvox), haloperidol (Haldol and others), lorazepam (Ativan and others), nortriptyline (Pamelor and others), paroxetine (Paxil), perphenazine (Trilafon and others), sertraline (Zoloft), venlafaxine (Effexor).

REFERENCES

1. Chan CH, Janicak PG, Davis JM, et al. Response of psychotic and nonpsychotic depressed patients to tricyclic antidepressants. J Clin Psychiatry 1987;48:197–200
2. Kroessler D. Relative efficacy rates for therapies of delusional depression. Convuls Ther 1985;1:173–182
3. American Psychiatric Association. Practice Guideline for Major Depressive Disorder in Adults. Am J Psychiatry 1993;150(suppl 4):1–26
4. American Psychiatric Association. Practice Guideline for the Treatment of Patients With Major Depressive Disorder [Revision]. Am J Psychiatry 2000;157(suppl 4):1–45
5. Coryell W. Treatment of psychotic depression. J Clin Psychiatry 1998; 59(suppl 1):22–27
6. Mulsant BH, Rosen J, Thornton JE, et al. A prospective naturalistic study of electroconvulsive therapy in late-life depression. J Geriatr Psychiatry Neurol 1991;4:3–13
7. Schatzberg AF, Rothschild AJ. Psychotic (delusional) major depression: should it be included as a distinct syndrome in DSM-IV? Am J Psychiatry 1992;149:733–745
8. Anton RF, Burch EA. Amoxapine versus amitriptyline combined with perphenazine in the treatment of psychotic depression. Am J Psychiatry 1990; 147:1203–1208
9. Spiker DG, Weiss JC, Dealy RS, et al. The pharmacological treatment of delusional depression. Am J Psychiatry 1985;142:430–436
10. Spiker DG, Perel JM, Hanin I, et al. The pharmacological treatment of delusional depression, pt 2. J Clin Psychopharmacol 1986;6:339–342. Correction 1987;7:A23
11. Baldwin RC, Jolley DJ. The prognosis of depression in old age. Br J Psychiatry 1986;149:574–583
12. Burvill PW, Hall WD, Stampfer HG, et al. The prognosis of depression in old age. Br J Psychiatry 1991;158:64–71
13. Meyers BS, Greenberg R. Late-life delusional depression. J Affect Disord 1986;11:133–137
14. Mulsant BH, Gershon S. Neuroleptics in the treatment of psychosis in late-life: a rational approach. Int J Geriatr Psychiatry 1993;8:979–992
15. Nelson JC, Conwell Y, Kim K, et al. Age at onset in late-life delusional depression. Am J Psychiatry 1989;146:785–786
16. Martinez RA, Mulsant BH, Meyers BS, et al. Delusional depression in late-life: a research agenda. Am J Geriatr Psychiatry 1996;4:77–84
17. Meyers BS. Late-life delusional depression: acute and long-term treatment. Int Psychogeriatr 1995;7:113–124
18. Mulsant BH, Stergiou A, Keshavan MS, et al. Schizophrenia in late-life: elderly patients admitted to an acute care psychiatric hospital. Schizophr Bull 1993;19:709–721
19. Mulsant BH, Sweet RA, Rifai AH, et al. The use of the Hamilton rating scale for depression in elderly patients with cognitive impairment and physical illness. Am J Geriatr Psychiatry 1994;2:220–229
20. Zubenko GS, Mulsant BH, Rifai AH, et al. Impact of acute psychiatric inpatient treatment on major depression in late life and prediction of response. Am J Psychiatry 1994;151:987–994
21. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised. Washington, DC: American Psychiatric Association; 1987
22. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960;23:56–62
23. Kunik ME, Champagne L, Harper RG, et al. Cognitive functioning in elderly depressed patients with and without psychosis. Int J Geriatr Psychiatry 1994;9:871–874
24. Rabins PV, Merchant A, Nestadt G. Criteria for diagnosing reversible dementia caused by depression: validation by 2-year follow-up. Br J Psychiatry 1984;144:488–492
25. Alexopoulos GS, Meyers BS, Young RC, et al. The course of geriatric depression with "reversible dementia": a controlled study. Am J Psychiatry 1993;150:1693–1699
26. Emery VO, Oxman TE. Update on the dementia spectrum of depression. Am J Psychiatry 1992;149:305–317
27. Mulsant BH, Pollock BG, Nebes RD, et al. Depression in Alzheimer's dementia. In: Heston LL, ed. Progress in Alzheimer's Disease and Similar Conditions. Washington, DC: American Psychiatric Press; 1997:161–175
28. Endicott J, Spitzer RA, Fleiss JL. The Global Assessment Scale: a procedure for measuring overall severity of psychiatric disturbance. Arch Gen Psychiatry 1976;33:766–771
29. Miller MD, Paradis CF, Houck PR, et al. Rating chronic medical illness burden in geropsychiatric practice and research: application of the Cumulative Illness Rating Scale (CIRS). Psychiatry Res 1992;41:237–248
30. Molloy DW, Alemayehu E, Roberts R. Reliability of a standardized Mini-Mental State Examination compared with the traditional Mini-Mental State Examination. Am J Psychiatry 1991;148:102–105
31. Asberg M, Cronholm B, Sjoqvist F, et al. Correlation of subjective side effects with plasma concentrations of nortriptyline. Br Med J 1970;4: 18–21
32. Sweet RA, DeSensi EG, Zubenko GS. Reliability and applicability of movement disorder rating scales in the elderly. J Neuropsychiatry Clin Neurosci 1993;5:56–60
33. Mulsant BH, Foglia JP, Sweet RA, et al. The effect of perphenazine on the concentration of nortriptyline and its hydroxymetabolites in older patients. J Clin Psychopharmacol 1997;17:318–320
34. Foglia JP, Sorisio D, Kirshner MA, et al. Quantitative determination of perphenazine and its metabolites in plasma by high-performance liquid chromatography and coulometric detection. J Chromatogr B Biomed Appl 1995;668:291–297
35. Bellini L, Gasperini M, Gatti L, et al. A double blind study with fluvoxamine vs desipramine combined with placebo or haloperidol in delusional depression. In: Langer S, Brunello NR, Racagni G, eds. Critical Issues in the Treatment of Affective Disorders. Basel, Switzerland: Karger; 1994: 32–36
36. Zanardi R, Franchini L, Gasperini M, et al. Double-blind controlled trial of sertraline versus paroxetine in the treatment of delusional depression. Am J Psychiatry 1996;153:1631–1633
37. Zanardi R, Franchini L, Gasperini M, et al. Faster onset of action of fluvoxamine in combination with pindolol in the treatment of delusional depression: a controlled study. J Clin Psychopharmacol 1998;18:441–446
38. Zanardi R, Franchini L, Serretti A, et al. Venlafaxine versus fluvoxamine in the treatment of delusional depression: a pilot double-blind controlled study. J Clin Psychiatry 2000;61:26–29
39. Mulsant BH, Pollock BG, Nebes RD, et al. A double-blind randomized comparison of nortriptyline and paroxetine in the treatment of late-life depression: six-week outcome. J Clin Psychiatry 1999;60(suppl 20): 16–20
40. Brown RP, Kocsis JH, Glick ID, et al. Efficacy and feasibility of high dose tricyclic antidepressant treatment in elderly delusional depressives. J Clin Psychopharmacol 1984;4:311–315
41. Mulsant BH, Perel JM, Sweet RA, et al. Pharmacotherapy of psychotic depression in late-life [abstract]. Psychopharmacol Bull 1995;30:634
42. Bolvig-Hansen L, Larsen N. Therapeutic advantages of monitoring plasma concentrations of perphenazine in clinical practice. Psychopharmacology 1985;87:16–19
43. Mazure CM, Nelson JC, Jatlow PI, et al. The relationship between blood perphenazine levels, early resolution of psychotic symptoms, and side effects. J Clin Psychiatry 1990;51:330–334
44. Pollock BG, Mulsant BH. Antipsychotics in older patients: a safety perspective. Drugs Aging 1995;6:312–323
45. Meyers BS, Alexopoulos GS, Kakuma T, et al. Continuation treatment of geriatric psychotic depression. In: New Research Program and Abstracts of the 152nd Annual Meeting of the American Psychiatric Association; May 19, 1999; Washington, DC. Abstract NR534:217
46. Chen P, Ganguli M, Mulsant BH, et al. The temporal relationship between depressive symptoms and dementia. Arch Gen Psychiatry 1999;56: 261–266
47. Aberg-Wistedt A, Wistedt B, Bertilsson L. Higher CSF levels of HVA and 5-HIAA in delusional compared to nondelusional depression. Arch Gen Psychiatry 1985;42:925–926
48. Contreras F, Navarro MA, Menchon JM, et al. Growth hormone response to growth hormone releasing hormone in non-delusional and delusional depression and healthy controls. Psychol Med 1996;26:301–307
49. Obrien JT, Ames D, Schweitzer I, et al. Clinical, magnetic resonance imaging and endocrinological differences between delusional and non-delusional depression in the elderly. Int J Geriatr Psychiatry 1997;12:

211–218
50. Schatzberg AF, Posener JA, Rothschild AJ. The role of dopamine in psychotic depression. Clin Neuropharmacol 1995;18:S66–S73
51. Bowers MB Jr, Swigar ME, Jatlow PI, et al. Plasma catecholamine metabolites and early response to haloperidol. J Clin Psychiatry 1984;45: 248–251
52. Lesser IM, Miller BL, Boone KB, et al. Brain injury and cognitive function in late-onset psychotic depression. J Neuropsychiatry Clin Neurosci 1991;3:33–40
53. Simpson S, Baldwin RC, Jackson A, et al. The differentiation of DSM-III-R psychotic depression in later life from nonpsychotic depression: comparisons of brain changes measured by multispectral analysis of magnetic resonance brain images, neuropsychological findings, and clinical features. Biol Psychiatry 1999;45:193–204
54. Zubenko GS, Henderson R, Stiffler JS, et al. Association of the APOE epsilon 4 allele with clinical subtypes of late life depression. Biol Psychiatry 1996;40:1008–1016
55. Tew JD, Mulsant BH, Haskett RF, et al. Acute efficacy of ECT in the treatment of major depression in the old-old. Am J Psychiatry 1999;156: 1865–1870
56. Tew JD, Mulsant BH, Towers A. ECT in older patients with physical illness. In: Melding P, Draper B, eds. Handbook of Consultation and Liaison Psychiatry for Older People. London, England: Oxford University Press. In press
57. Katz IR, Jeste DV, Mintzer JE, et al, for the Risperidone Study Group. Comparison of risperidone and placebo for psychosis and behavioral disturbances associated with dementia: a randomized, double-blind trial. J Clin Psychiatry 1999;60:107–115
58. Mulsant BH, Pollock BG, Rosen J. Newer antidepressants and antipsychotics in geriatric psychiatry. Ann Long-Term Care 1997;5:240–248
59. Pollock BG, Mulsant BH, Sweet RA, et al. An open pilot study of citalopram for behavioral disturbances of dementia: plasma levels and real-time observations. Am J Geriatr Psychiatry 1997;5:70–78
60. Pollock BG, Rosen J, Mulsant BH. Antipsychotics and selective serotonin reuptake inhibitors for the treatment of behavioral disturbances in dementia of the Alzheimer type: a review of clinical data. Consultant Pharmacist 1999;4:1227–1234
61. Sweet RA, Pollock BG. Treating psychosis in older adults. In: Katz IR, Oslin DW, eds. Annual Review of Gerontology and Geriatrics: Psychopharmacologic Interventions in Later Life. Berlin, Germany: Springer; 1999:225–248
62. Gatti F, Bellini L. Fluvoxamine alone in the treatment of delusional depression. Am J Psychiatry 1996;153:414–416
63. Muller-Siecheneder F, Muller MJ, Hillert A, et al. Risperidone versus haloperidol and amitriptyline in the treatment of patients with a combined psychotic and depressive syndrome. J Clin Psychopharmacol 1998;18: 111–120
64. Rothschild AJ, Samson JA, Bessette MP, et al. Efficacy of the combination of fluoxetine and perphenazine in the treatment of psychotic depression. J Clin Psychiatry 1993;54:338–342
65. Rothschild AJ, Bates KS, Boehringer KL, et al. Olanzapine response in psychotic depression. J Clin Psychiatry 1999;60:116–118
66. Sacchetti E, Conte G, Guarneri L, et al. Effectiveness of fluvoxamine and paroxetine in major depression with psychotic features. Hum Psychopharmacol 1997;12:277–278
67. Wolfersdorf M, Barg T, König F, et al. Paroxetine as antidepressant in combined antidepressant-neuroleptic therapy in delusional depression: observation of clinical use. Pharmacopsychiatry 1995;28:56–60
68. Zanardi R, Franchini L, Gasperini M, et al. Long-term treatment of psychotic (delusional) depression with fluvoxamine: an open pilot study. Int Clin Psychopharmacol 1997;12:195–197
69. Zarate CA, Rothschild A, Fletcher KE, et al. Clinical predictors of acute response with quetiapine in psychotic mood disorders. J Clin Psychiatry 2000;61:185–189