Low Use of Neuroleptic Drugs in the Treatment of Psychotic Major Depression

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Objective: *The adequacy of pharmacologic treatment received by patients with psychotic major depression was evaluated.* *Method:* *The authors systematically assessed the pharmacotherapy received by 187 depressed patients before initiation of ECT and compared the medication trials of those with psychotic (N=53) and nonpsychotic (N=134) depression.* *Results:* *Despite a median of four medication trials and median index episode duration of 20 weeks, only two (4%) of the patients with psychotic depression received at least one adequate pharmacotherapy trial. In contrast, 70 (52%) of the patients with nonpsychotic depression received at least one adequate trial. Twenty-five (47%) of the patients with psychotic depression received either no neuroleptic treatment (N=11) or treatment for less than 3 weeks (N=14). Only eight (15%) received a daily neuroleptic dose higher than 200 mg of chlorpromazine equivalents.* *Conclusions:* *These findings suggest that many patients with psychotic major depression referred for ECT receive inadequate pharmacotherapy because of either the absence or the inadequate use of neuroleptic medication.*

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Two meta-analyses of a literature comprising 23 studies found that approximately one-third of patients with major depression with psychotic features respond when treated with a tricyclic antidepressant alone. In contrast, more than three-quarters respond to treatment with either ECT or a combination of a tricyclic antidepressant and a neuroleptic (1, 2). This finding has been confirmed by two randomized, double-blind trials (3, 4) and has been extended in two open studies in which a serotonin reuptake inhibitor and a neuroleptic were combined (5, 6). As a result, the APA practice guideline strongly recommends an antidepressant and neuroleptic combination in the pharmacotherapy of major depression with psychotic features (7).

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To determine the frequency with which such antidepressant and neuroleptic combinations are used in clinical practice, we evaluated the pharmacotherapy received by patients with psychotic and nonpsychotic major depression who were being referred for ECT.

METHOD

Subjects participated between June 1992 and February 1996 in a multicenter study that prospectively examined the relationship of medication resistance to ECT response and subsequent relapse. Detailed study methods have been described previously (8). In brief, patients referred for ECT at three teaching hospitals had to meet Research Diagnostic Criteria for primary, unipolar, major depressive episode; diagnoses were based on interviews that used the Schedule for Affective Disorders and Schizophrenia (9). If psychotic features were present at any time during the index episode, the episode was classified as psychotic. Duration, dose, and blood levels (if available) of each medication received during the index episode before referral for ECT were assessed on the basis of information derived from interviews with the patients, family members, and treating physicians as well as from pharmacy, hospital, and outpatient records. The strength of each trial was rated according to previously validated (8, 10) operational criteria: a rating of 0 indicated the absence of treatment; a trial that was clearly or probably inadequate was given a rating of 1 or 2; a rating of 3, 4, or 5 indicated an adequate trial. For instance, any antidepressant trial for treatment of nonpsychotic depression that had been administered for less than 4 weeks was given a rating of 1, while a desipramine trial of at least 4 weeks with plasma levels higher than 125 ng/ml was given a rating of 4. For psychotic depression, a treatment trial with an antidepressant alone was given a rating no higher than 2; ratings of 3 or higher required

TABLE 1. Demographic and Clinical Characteristics of Patients With Psychotic and Nonpsychotic Depression[a]

Characteristic	Patients With Psychotic Depression (N=53)		Patients With Nonpsychotic Depression (N=134)			
	N	*%*	*N*	*%*	χ^2 *(df=1)*	*p*
Female	34	64	91	68	0.24	0.24
Recurrent episodes	40	75	105	78	0.50	0.48
Received at least one adequate medication trial	2	4	70	52	56.94	0.0001
	Mean	*SD*	*Mean*	*SD*	*t (df=185)*	*p*
Age (years)	64.6	15.4	60.8	18.3	1.32	0.19
Rating of the strongest medication trial[b]	1.6	0.7	2.9	1.3	6.58	0.0001

[a]Median length of depressed episode before ECT was 20 weeks (range=2–260) for the patients with psychotic depression and 32 weeks (range=2–416) for the patients with nonpsychotic depression (Mann-Whitney Z=2.65, p=0.008).
[b]0=no medication trial; 1 or 2=clearly or probably inadequate trial; 3–5=adequate trial.

combination of an antidepressant (for at least 4 weeks) with a neuroleptic at a daily dose of 400 mg of chlorpromazine equivalents for at least 3 weeks (11). Written informed consent was obtained after complete study description.

Demographic and clinical variables were compared between patients with psychotic and nonpsychotic depression by using two-tailed chi-square, t, or Mann-Whitney U tests, as appropriate.

RESULTS

The study group consisted of 125 women and 62 men, 180 (96%) of whom were Caucasian. The mean age of the subjects was 62 years (SD=18). The median length of the episode of depression before ECT was 25 weeks (range=2–416 weeks), and the median number of medication trials was four (range=0–30). Psychotic features were present during the index episode of depression in 53 patients (28%). Despite receiving a comparable number of medication trials before ECT, patients with psychotic depression were significantly less likely than those with nonpsychotic depression to have received at least one adequate pharmacotherapy trial (rated 3 or higher) (table 1). Of the patients with psychotic depression, 25 (47%) had been given either no neuroleptic (N=11) or a neuroleptic for less than 3 weeks (N=14). Twenty-eight patients (53%) had received a neuroleptic for at least 3 weeks; the daily doses in chlorpromazine equivalents that these patients received were less than 200 mg (38%, N=20), between 200 and 400 mg (8%, N=4), and 400 mg or higher (8%, N=4). Only two patients (4%) received an adequate antidepressant and neuroleptic combination.

DISCUSSION

In this study, more than 95% of patients with psychotic major depression who were being referred for ECT had received inadequate pharmacotherapy. Several explanations for this result should be considered. First, since the subjects were being referred for ECT, the study group was skewed toward patients with lower treatment adequacy (e.g., patients who had responded to an adequate antidepressant and neuroleptic combination were not included). Nevertheless, the frequency of adequate pharmacotherapy was more than 20-fold lower in patients with psychotic depression than in those with nonpsychotic depression. Some psychotic patients may not have received adequate pharmacotherapy because a decision had been made to treat them with ECT instead. However, both groups had received a median of four medication trials.

Alternatively, since our subjects were classified as being psychotic on the basis of research interviews, psychotic features in some cases may not have been recognized by treating physicians. Still, the inadequate use of neuroleptics in most of the patients with psychotic major depression requires another explanation. Their psychotic features were almost certainly identified, since these features constitute the main indication for neuroleptic use in the treatment of depression (7). Side effects may have limited the neuroleptic dose in some patients, but it is unlikely that side effects were a common limiting factor, since even older patients with psychotic major depression can usually tolerate moderate-potency neuroleptics at doses of at least 200 mg/day of chlorpromazine equivalents (12). Furthermore, there was no difference in neuroleptic frequency of use (χ^2=0.90, df=1, p<0.98) or dose (χ^2=0.97, df=2, p<0.60) between the 19 younger (under 60) and the 34 older patients with psychotic depression. Thus, neuroleptic underdosing appears to be the primary problem. How valid was our threshold for an adequate neuroleptic trial in major depression with psychotic features? Spiker et al. (4), who titrated perphenazine blindly on the basis of clinical response, reported a mean daily dose of 688 mg of chlorpromazine equivalents (SD=213). Nelson et al. (13) confirmed the need for fairly high neuroleptic doses (i.e., 400 mg or more of chlorpromazine equivalents). They reported that only 25% of patients with psychotic major depression responded when antidepressant treatment was combined with a neuroleptic at a daily dose below 400 mg of chlorpromazine equivalents, as compared to a 100% response rate when the neuroleptic dose exceeded 400 mg of chlorpromazine equivalents. Thus, in all but four of our patients, neuroleptic doses were probably subtherapeutic, and only two of these patients received adequate concomitant antidepressant treatment.

Previous research has documented a high rate of inadequate pharmacotherapy in patients with major depression (10). This study suggests that this problem

may be particularly common for patients with major depression with psychotic features. Despite the results of controlled studies (3, 4) and published APA practice guidelines (7), some patients with psychotic major depression do not receive any neuroleptic treatment, possibly because of a lack of recognition of their psychotic features, while many others receive neuroleptics at lower than the minimum effective dose. If confirmed, these findings emphasize the need for further education about the recognition and treatment of psychotic depression (14, 15).

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