Persisting Low Use of Antipsychotics in the Treatment of Major Depressive Disorder With Psychotic Features

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Objective: Practice guidelines recommend the use of a combination of an antidepressant and an antipsychotic for the pharmacologic treatment of major depressive disorder with psychotic features (MD-Psy). We assessed the extent to which the pharmacotherapy received by patients with MD-Psy under usual care conforms to these recommendations.

Method: We assessed the pharmacotherapy received under usual care conditions by 100 patients with MD-Psy prior to enrollment in STOP-PD (Study of the Pharmacotherapy of Psychotic Depression), a 12-week randomized, controlled trial comparing olanzapine plus sertraline to olanzapine plus placebo. Our assessment took place from January 2003 to May 2004. The strength of antidepressant trials was rated using the Antidepressant Treatment History Form (ATHF). The strength of antipsychotic trials or combinations of antidepressants and antipsychotics was rated using a modified version of the ATHF. We also determined whether the strength of antipsychotic or combination trials was associated with age, the duration of the current depressive episode, medical burden, cognitive status, or the severity of depressive or psychotic symptoms.

Results: Most patients with MD-Psy were treated with antidepressants (N = 82, 82%) or antipsychotics (N = 65, 65%). About half of the patients (N = 48, 48%) received therapeutic doses of an antidepressant; 10% (N = 10) received an intermediate dose of an antipsychotic, and 6% (N = 6) received a high dose. Overall, only 5% (N = 5) received a combination of an adequate dose of an antidepressant and a high dose of an antipsychotic. The strength of both antipsychotic trials (p = .021) and combination trials (p = .039) was significantly associated only with a longer duration of the current depressive episode.

Conclusions: These findings show a persisting low use of antipsychotics in the treatment of MD-Psy. Given the high morbidity rates associated with MD-Psy, it is important to continue to educate clinicians regarding its identification and treatment.

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Major depressive disorder with psychotic features (MD-Psy) is a significant public health problem. Between 15% and 25% of mixed-age patients who meet criteria for major depressive disorder present with psychotic features.[1–3] Compared with patients with nonpsychotic depression, patients with MD-Psy are more impaired and have a poorer prognosis.[4–6] Current published evidence does not support a clear strategy for the pharmacologic treatment of MD-Psy.[7,8] Studies regarding treatment of psychotic depression are few, and their results are contradictory.[7,8] A recent review calls into question the superiority of a combination of an antidepressant and an antipsychotic over monotherapy with an antidepressant.[7] However, despite these conflicting data, the American Psychiatric Association practice guidelines for the treatment of patients with major depressive disorder recommended the use of a combination of an antidepressant and an antipsychotic for the pharmacologic treatment of MD-Psy in both 1993[9] and 2000.[10] A study conducted a decade ago[11] found that very few patients with MD-Psy referred for electroconvulsive therapy (ECT) had received adequate pharmacotherapy: about one half had

received no neuroleptic (i.e., first-generation antipsychotic [FGA]) or a neuroleptic for less than 3 weeks. Almost all of those patients treated with a neuroleptic for 3 weeks or more had received low doses (i.e., doses equal to or less than 200 mg of chlorpromazine-equivalent [CPZE]). Since the conduct of this study, the use of newer antidepressants (e.g., selective serotonin reuptake inhibitors [SSRIs]) and second-generation (atypical) antipsychotics (SGAs) has become prevalent. Thus, we conducted a new analysis assessing the nature and strength of the pharmacologic treatment received by patients with MD-Psy before they enrolled in an ongoing randomized, controlled trial. Given the increased short-term tolerability of SGAs compared with FGAs,[12–14] we hypothesized that, relative to the study conducted a decade earlier, (1) the current use and the doses of antipsychotic would be higher and (2) a larger proportion of patients would be treated with combinations of an antidepressant and a high dose of an antipsychotic.

METHOD

Participants

We assessed the pharmacologic treatment received prior to enrollment by the first 100 participants in STOP-PD (Study of the Pharmacotherapy of Psychotic Depression), a National Institute of Mental Health–sponsored trial conducted at Cornell University, the University of Massachusetts, the University of Pittsburgh, and the University of Toronto. STOP-PD is a 12-week randomized, controlled trial comparing olanzapine plus sertraline to olanzapine plus placebo. Participants were enrolled at these 4 academic centers on the basis of systematic screening by trained research assistants of patients with mood and psychotic symptoms admitted to inpatient units (N = 71) or referred from outpatient clinics (N = 29).

Inclusion criteria were age 18 years and older, ability to speak English fluently, a DSM-IV diagnosis of MD-Psy based on the Structured Clinical Interview for DSM-IV (patient version; SCID),[15] a score of 21 or higher on the 17-item version of the Hamilton Rating Scale for Depression (HAM-D),[16] and the presence of 1 or more delusions as indicated by a score of 3 or greater on the delusion item of the Schedule for Affective Disorders and Schizophrenia[17] (delusion definitely present) and a score of 2 or higher on 1 or more of the conviction items of the Delusional Assessment Scale.[18] We excluded patients with any of the following: currently meets or ever met DSM-IV criteria for bipolar disorder or schizophrenia; currently meets criteria for body dysmorphic disorder, obsessive-compulsive disorder, or brief psychotic disorder; a history of substance abuse or dependence, including alcohol, within the last 3 months; a diagnosis of Alzheimer's dementia, vascular dementia, or history of ongoing significant cognitive impairment (from informant report) prior to the index episode; an unstable medical illness; medical conditions (such as hypothyroidism), metabolic abnormalities (such as folate or B_{12} deficiency), or medication (such as carbidopa) that might contribute to psychopathology, confound response to pharmacotherapy, or render participants unable to tolerate or complete the study; being pregnant or planning to get pregnant; being unable to tolerate the study medications (sertraline or olanzapine) or having failed to respond to olanzapine 15 mg/day or greater for at least 4 weeks during the current episode; or being sufficiently ill to require immediate open pharmacotherapy or ECT (e.g., due to imminent risk of suicide or refusal to eat).

Written informed consent was obtained from all participants (or substitute decision makers when applicable) using procedures approved by local institutional review boards prior to the initiation of any research assessments. Our assessment took place January 2003 to May 2004.

Clinical Assessments

Upon enrollment, in addition to the SCID and HAM-D, each participant was assessed with a battery of instruments including the 18-item Brief Psychiatric Rating Scale (BPRS),[19] the Mini-Mental State Examination (MMSE),[20] and the Cumulative Illness Rating Scale for Geriatrics (CIRS-G).[21]

Assessment of Strength of Antidepressant Treatment

The strength of each pharmacologic trial received by the participants prior to enrollment during their current episode (i.e., under usual clinical conditions) was assessed with a modified version of the Antidepressant Treatment History Form (ATHF).[22] Information regarding previous medications was obtained from all available sources including patient reports, family reports, treating physicians, medical records, and pharmacy records. We used the ATHF to rate the strength of antidepressant trials. As described in detail elsewhere,[22] the ATHF scores each antidepressant trial based on the dose and the duration of treatment as 1 (definitely inadequate), 2 (probably inadequate), 3 (probably adequate), 4 (definitely adequate), or 5 (definitely adequate antidepressant with lithium augmentation). Thus, a score of 1 corresponds to an antidepressant trial of less than 4 weeks or a trial of more than 4 weeks with a very low dose (e.g., fluoxetine or paroxetine less than 10 mg/day, sertraline less than 25 mg/day, venlafaxine less than 75 mg/day). A score of 2 corresponds to a trial of more than 4 weeks with probably inadequate doses (e.g., fluoxetine or paroxetine between 10–19 mg/day, sertraline between 25–49 mg/day, venlafaxine 75–149 mg/day). A score of 3 corresponds to a trial of more than 4 weeks of an antidepressant at an adequate (i.e., therapeutic) dose (e.g., fluoxetine 20–39 mg/day, paroxetine 20–29 mg/day, sertraline 50–149 mg/day, venlafaxine 150–299 mg/day). A score of 4 corresponds to a trial longer than 4 weeks with high doses of antidepres-

Table 1. Modified Antidepressant Treatment History Form: Rating the Strength of Antipsychotic Trials[a]

	Rating[b]		
Drug	1 (low)	2 (intermediate)	3 (high)
Chlorpromazine, mg/d	< 200	200–399	≥ 400
Fluphenazine, mg/d	< 3	3–5.9	≥ 6
Haloperidol, mg/d	< 4	4–7.9	≥ 8
Loxapine, mg/d	< 30	30–59	≥ 60
Perphenazine, mg/d	< 16	16–31	≥ 32
Aripiprazole, mg/d	< 10	10–29.9	≥ 30
Clozapine, mg/d	< 120	120–239	≥ 240
Olanzapine, mg/d	< 10	10–14.9	≥ 15
Quetiapine, mg/d	< 200	200–399	≥ 400
Risperidone, mg/d	< 3	3–5.9	≥ 6
Long-acting injectable risperidone, mg/mo	< 25	25–49	≥ 50
Sulpiride, mg/d	< 600	600–1199	≥ 1200
Ziprasidone, mg/d	< 80	80–159	≥ 160

[a]Trials lasting less than 3 weeks are rated 1 (low) regardless of the dose.
[b]See text for cutoff points for first-generation antipsychotics; for second-generation antipsychotics, equivalence between cutoff points are based on Woods[29] and Davis and Chen.[28] They propose that the following daily doses are therapeutic: Woods[29]: aripiprazole = 30 mg, clozapine = no data, olanzapine = 30 mg, quetiapine = 300 mg, risperidone = 8 mg, long-acting injectable risperidone = no data, and ziprasidone = 240 mg; Davis and Chen[28]: aripiprazole = 10 mg, clozapine = 400 mg, olanzapine = 16 mg, quetiapine = 600 mg, risperidone = 4 mg, long-acting injectable risperidone = 50 mg/mo, and ziprasidone = 80–160 mg.

sant (fluoxetine above 39 mg/day, paroxetine above 29 mg/day, sertraline above 149 mg/day, venlafaxine above 299 mg/day).

Assessment of Strength of Antipsychotic Treatment

We modified the original ATHF to score antipsychotic trials and trials of a combination of an antidepressant and an antipsychotic. We did 2 related modifications. First, instead of rating antipsychotic trials as adequate or inadequate, we rated antipsychotic trials from 1 to 3 (1: probably inadequate, 2: intermediate, 3: probably adequate). Second, we defined cutoff points to differentiate low, moderate, and high antipsychotic doses (Table 1). All trials lasting less than 3 weeks, regardless of dose, were scored 1. Trials lasting 3 weeks or more were scored 1 if the dose was low, 2 if the dose was moderate, or 3 if the dose was high. In the original ATHF, the cutoff points for antipsychotic doses are based on the studies of Spiker et al.[23] and Nelson et al.[24] In the study of Spiker et al.,[23] patients with MD-Psy had a 78% response rate when treated with a combination of amitriptyline plus perphenazine at a mean (SD) dose of 55 (17) mg/day, corresponding to 687 mg/day CPZE.[4] Nelson et al.[24] confirmed the need for high neuroleptic doses when they reported that only 25% of patients with MD-Psy responded when an antidepressant was combined with a neuroleptic at a daily dose below 400 mg/day CPZE, as compared to a 100% response rate when the neuroleptic dose exceeded 400 mg/day CPZE. On the basis of these data, the original ATHF considered an FGA dose below 400 mg/day CPZE to be inadequate. Thus, in the original ATHF, a combination of an antidepressant and an antipsychotic was considered adequate only if it involved an adequate trial of antidepressant combined for at least 3 weeks with an FGA at a dose equal to or higher than 400 mg/day CPZE.[25,26]

The dose equivalence between FGAs and SGAs is less well studied than the dose equivalence between FGAs. Furthermore, the role and optimal dose of SGAs in the treatment of MD-Psy has not yet been well established.[8] There is only 1 positive controlled study published so far.[27] In this study, a combination of fluoxetine and olanzapine was more efficacious than olanzapine monotherapy in treating MD-Psy.[27] The mean doses of olanzapine were 11.9 mg/day in the monotherapy group and 12.4 mg/day in the combination group.[27] Given this uncertainty, we defined an "intermediate" (= 2) rating: moderate doses of FGAs and SGAs from 200 to 400 mg/day CPZE (e.g., olanzapine 10–14.9 mg/day) were rated as 2 ("intermediate" rather than "inadequate" as in the original ATHF). We selected these cutoff points based on the results discussed above and equivalence between FGA and SGA doses proposed by Davis and Chen[28] and Woods[29] (Table 1).

Assessment of Strength of Combination Treatment

When an antidepressant and an antipsychotic were combined, the combination was rated from 0 to 5 based on the scores of both the antidepressant and the antipsychotic trials. A score of 0 was given when an antidepressant trial and an antipsychotic trial overlapped for less than 3 weeks or when an antidepressant was rated as 1 (regardless of the rating of the antipsychotic). Scores of 1 to 5 required the overlap of an antidepressant and an antipsychotic for 3 weeks or more. A score of 1 was given when an antidepressant was rated 2 (regardless of the rating of the antipsychotic) or when an antidepressant rated 3 or higher was combined with an antipsychotic rated 1 (due to a low dose). A score of 2 was given when an antidepressant rated 3 or above was combined with an antipsychotic rated 2. Scores of 3, 4, or 5 were given when an antidepressant rated as 3, 4, or 5, respectively, was combined with an antipsychotic rated 3. Thus, scores of 0 and 1 reflect a combination trial of low strength due to short durations or low doses of antidepressant or antipsychotic, scores of 3 and higher reflect combination trials of higher strength consisting of adequate doses of antidepressant and high doses of antipsychotic for a minimum of 3 weeks, and a score of 2 reflects intermediate combination trials consisting of therapeutic doses of antidepressant and intermediate doses of antipsychotic for a minimum of 3 weeks (Table 2). The adequacy of this intermediate category is less established in the literature; therefore, we analyzed it separately.

Table 2. Modified Antidepressant Treatment History Form: Rating the Strength of Combination Trials

Antidepressant Rating[a]	Antipsychotic Rating[a]	Combination Rating
1	1–3	0
2	1–3	1
3–5	1	1
3–5	2	2
3	3	3
4	3	4
5	3	5

[a]If the antidepressant and antipsychotic ratings had an overlap of less than 3 weeks, the combination rating is zero regardless of the antidepressant and antipsychotic ratings.

Table 3. Demographic and Clinical Characteristics of the Study Group

Characteristic	Case/N	%
Sex (female)	65/100	65
Race		
White	81/100	81
Black	13/100	13
Asian	6/100	6
Ethnicity		
Not Hispanic	91/100	91
Hispanic	9/100	9
Recurrent depression	70/100	70
Recruited on inpatient unit	71/100	71
	N	Mean (SD)
Age, y	100	56.2 (17.7)
Age at onset of first episode, y	93	42.3 (20.9)
Duration of current episode, mo	100	12.2 (30.2)
CIRS-G score	100	4.5 (4.0)
MMSE score	95	27.0 (3.1)
HAM-D-17 score[a]	100	31.2 (5.5)
HAM-D-24 score[a]	100	42.9 (8.2)
BPRS score	100	57.9 (10.9)

[a]One participant refused to answer an item; that missing item score was prorated.
Abbreviations: BPRS = Brief Psychiatric Rating Scale, CIRS-G = Cumulative Illness Rating Scale for Geriatrics, HAM-D-17 = 17-item Hamilton Rating Scale for Depression, HAM-D-24 = 24-item Hamilton Rating Scale for Depression, MMSE = Mini-Mental State Examination.

Data Analysis

On the basis of these ATHF scores, we characterized the strength of antidepressant trials, antipsychotic trials, and combination trials. In addition, since older age, shorter duration of depression, higher medical burden, more impaired cognitive status, and lower severity of depressive or psychotic symptoms could influence the recognition of psychotic features and of psychotropic doses, we used a Kruskal-Wallis χ^2 test to compare these characteristics in patients grouped according to their most highly rated antipsychotic and combination trials. We used Kruskal-Wallis χ^2 because of a high imbalance in sample sizes across the groups and potential departure from normal distribution, and we compared the following characteristics among the groups: age, the duration of the current depressive episode, medical burden (i.e., baseline CIRS-G score), cognitive status (i.e., baseline MMSE score), or the severity of depressive or psychotic symptoms (i.e., baseline HAM-D and BPRS scores). Two-sided p values are reported, and statistical significance was declared at a 2-sided α level of .05. We used SAS v8.02 (SAS Institute, Inc., Cary, N.C.) for statistical analysis.

RESULTS

Strength of Antidepressant and Antipsychotic Trials

Demographic and clinical characteristics of the 100 participants are presented in Table 3. Most patients (N = 82, 82%) received 1 or more antidepressant trials (mean [SD] number of antidepressants: 2.1 [1.3], range, 1–8). Slightly more than half (48/82) of those patients received at least 1 adequate trial (i.e., a therapeutic dose for 4 weeks or longer). Similarly, most patients (N = 65, 65%) were treated with at least 1 antipsychotic (mean [SD] number of antipsychotics: 1.5 [0.9], range, 1–6). However, only a quarter (16/65) of those patients received an antipsychotic trial rated 2 or 3 (i.e., a dose of 200 mg/day CPZE or more lasting 3 weeks or longer): 10 patients (10%) received an antipsychotic trial rated 2; 6 (6%) received an antipsychotic trial rated 3. Two of 11 participants treated with FGAs received a trial rated 2 (no patient treated with an FGA received a trial rated 3). Fifteen of 63 patients treated with SGAs received a trial rated 2 or 3 (9 rated 2; 6 rated 3). Three participants had received an ECT trial prior to enrollment in the study.

The strength of antipsychotic trials was not significantly associated with any of the patients' characteristics (age, baseline CIRS-G score, baseline MMSE score, baseline HAM-D or BPRS scores) except for duration of current depressive episode (p = .021, Table 4). Also, to assess whether low-dose antipsychotic trials were due to patients' being identified as suffering from MD-Psy shortly before enrolling in the study (and thus being unable to receive an antipsychotic for more than 3 weeks), we counted how many patients received only 1 brief trial (i.e., lasting less than 3 weeks) just prior to enrollment; there were 22 such patients. When we excluded these 22 patients from our analysis, the proportion of patients receiving intermediate or high doses of antipsychotics for 3 weeks or more increased from 16% (16/100) to 20% (16/78).

Strength of Combination Trials

Most patients (N = 57, 57%) received at least 1 combination of an antidepressant and an antipsychotic (mean [SD] number of combinations: 2.1 [1.4], range, 1–7). However, three quarters (43/57) received only combinations rated as 0 or 1 (i.e., the duration of the combination was less than 3 weeks, or the doses of at least 1 of the agents was very low). Nine patients (9%) received at least 1 combination rated as 2 (intermediate doses of antipsy-

Table 4. Characteristics of Patients Classified According to Their Most Highly Rated Antipsychotic and Combination Trials[a]

Rating	N	Age (y)	Episode Duration (mo)	CIRS-G	MMSE	HAM-D-17	BPRS
Antipsychotic trial rating							
None	35	60 (29)	3 (4)	5 (6)	28 (3)	31 (9)	57 (17)
1	49	60 (37)	6 (7)	3 (4)	28 (3)	32 (7.0)	57 (17)
2	10	54.5 (27)	6.5 (7)	2 (6)	27.5 (3)	32 (5)	59 (8)
3	6	53 (18)	15 (8)	2.5 (2)	26 (2)	24.5 (9)	54.5 (7)
Kruskal-Wallis χ^2 (df = 3)		0.893	9.772	0.747	1.769	5.264	2.581
p		.827	.021	.862	.622	.153	.461
Combination trial rating							
None	43	61 (29)	4 (4)	6 (6)	28 (3)	32 (9)	58 (16)
0–1	43	52 (36)	6 (9)	3 (5)	28.5 (3)	32 (7)	57 (19)
2	9	60 (27)	8 (7)	6 (5)	27 (3)	32 (7)	58 (4)
3–4	5	46 (18)	12 (8)	2 (1)	26 (1)	25 (7)	56 (6)
Kruskal-Wallis χ^2		2.046	8.366	3.387	5.411	2.606	0.439
p		.563	.039	.336	.144	.456	.921

[a]Values are presented as median (interquartile range).
Abbreviations: BPRS = Brief Psychiatric Rating Scale, CIRS-G = Cumulative Illness Rating Scale for Geriatrics, HAM-D-17 = 17-item Hamilton Rating Scale for Depression, MMSE = Mini-Mental State Examination.

Figure 1. Strength of Pharmacotherapy Received by 100 Patients With Major Depression With Psychotic Features Treated Under Usual Care Conditions

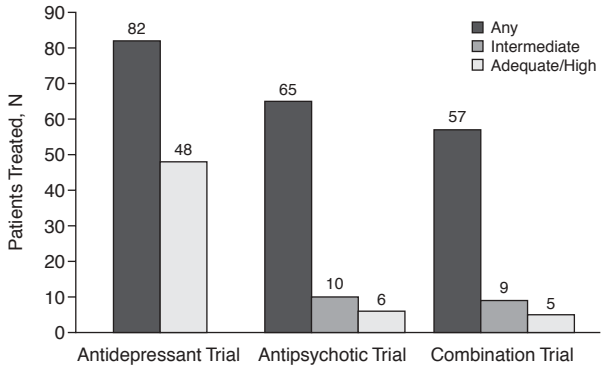
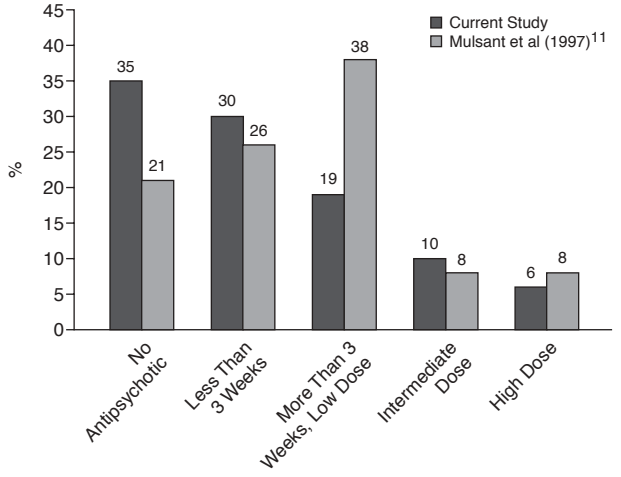


Figure 2. Antipsychotic Treatment Received by Patients With Major Depression With Psychotic Features in 2005 Versus 1997



chotic with adequate trial of antidepressant); 5 (5%) received at least 1 combination rated 3 or 4 (Figure 1). Similar to the strength of antipsychotic trials, the strength of combination trials was not significantly associated with any of the patients' characteristics (age, baseline CIRS-G score, baseline MMSE score, baseline HAM-D or BPRS scores) except for duration of current depressive episode (p = .039, Table 3). In particular, when we compared younger (< 60 years old) versus older (> 60 years old) patients, we found no difference in the proportion of patients receiving an adequate antidepressant trial (58% [N = 22] vs. 59% [N = 26]), a high-dose antipsychotic trial (9% [N = 3] vs. 9% [N = 3]), or a high-dose combination trial (10% [N = 3] vs. 7% [N = 2]).

Present Versus Previous Study

The proportion of patients treated with at least 1 antipsychotic in the present study (65%) is lower than the proportion observed a decade ago (79%),[10] but this difference is not statistically significant (p = .07) (Figure 2). In both studies, comparable proportions of patients received an antipsychotic for less than 3 weeks (14/53 vs. 30/100, p = .641) or were treated for more than 3 weeks and received doses of antipsychotics between 200 and 400 mg/day CPZE (4/53 vs. 10/100, p = .617) or above 400 mg/day CPZE (4/53 vs. 6/100, p = .712). However, in the previous study, a higher proportion had been treated for more than 3 weeks with doses of antipsychotics less than 200 mg/day CPZE (20/53 vs. 19/100, p = .011). Overall, the proportion of patients treated with a combination of an adequate antidepressant and an antipsychotic at a high dose was the same in the present study as a decade ago (2/53 vs. 5/100, p > .10).

DISCUSSION

Among 100 patients with major depressive disorder with psychotic features who were treated under usual care conditions prior to enrolling in a pharmacotherapy study, only 16% received an intermediate or high dose of an antipsychotic, and 14% received a therapeutic antidepressant trial combined with an intermediate or high dose of an antipsychotic for at least 3 weeks.

Except for duration of current episode, patient characteristics did not significantly differ among the patients who received adequate or inadequate (i.e., short duration or low medication dose) pharmacotherapy. In particular, contrary to our expectation, younger and older patients had the same likelihood of being treated with antipsychotics or combination therapy, and they received comparable doses of antipsychotic. Also, contrary to our hypotheses, the proportions of patients treated with an antipsychotic or treated with a combination of an antipsychotic and an antidepressant did not increase compared with the proportions observed a decade ago[10] (Figure 2). Thus, the potentially increased tolerability of SGAs did not lead to an increase in their use in patients with MD-Psy compared with the use of FGAs a decade ago. However, it seems that patients with MD-Psy treated currently with SGAs are less likely to be treated with the low doses that were the norm with FGAs a decade ago. In the earlier study,[11] all patients had been referred to ECT, and the authors had hypothesized that the study group was skewed toward people not responding to (or not tolerating) pharmacotherapy, possibly increasing the proportion of patients with inadequate treatment. In the present study, a similarly low proportion of patients treated with intermediate or high doses of antipsychotics was observed even though participants were recruited in a pharmacotherapy study by systematically screening all hospital admissions and by soliciting outpatient referrals. By design, these participants were all highly symptomatic. However, prior treatment history (or lack thereof) was not an inclusion or exclusion criterion. The typical participants had been sick for several months (12 on average) during which they had been treated with multiple medications (typically 1 to 3 antidepressants and 1 or 2 antipsychotics). In contrast to outpatients with nonpsychotic depression treated by academic and community psychiatrists,[30] in both the present and earlier studies, the majority of patients received antidepressant trials using therapeutic doses for adequate duration. The high proportions of patients in both studies who did not receive any antipsychotic or only received 1 briefly may be due, at least in part, to a lack of recognition of psychotic features in patients with MD-Psy. Indeed, we have found in a separate analysis that 41% of the participants in the current study did not receive a diagnosis of MD-Psy when they were seen in psychiatric emergency rooms before being admitted and enrolled.[31] Recognition of MD-Psy may be more likely as the duration of the episode lengthens. This is supported by the higher strength of pharmacotherapy in patients with episodes of longer duration. In contrast, other patient characteristics (including age or medical burden) were not associated with adequacy of treatment.

Our study has both limitations and strengths. As discussed above, patients included in this analysis were recruited upon admission to a hospital or upon outpatient referral. We do not know to what extent the treatment received by these patients is representative of the pharmacotherapy received by patients with MD-Psy in the community. Only a pharmacoepidemiologic study could address this question. Given the low prevalence of MD-Psy in the community, such a study would be difficult to conduct. In any case, if patients with treatment failure are overrepresented in our study group, it appears that treatment failure in MD-Psy is more likely to be due to inadequacy of treatment rather than lack of response to aggressive treatment. Another possible limitation is related to the paucity of data to support the chosen cutoff point for high and intermediate doses of SGAs. However, on the basis of the current available data,[28,29] these cutoff points were chosen conservatively, and they are congruent with the cutoff points used in the original ATHF for FGAs. Also, even if we lump together the patients who received intermediate and high doses of antipsychotics, our overall results do not change qualitatively.

Our results are strengthened by the multicenter design of our study. Three sites in the United States and 1 in Canada contributed to the data, increasing the generalizability of our findings and limiting the influence of idiosyncratic local practices; we found a similar pattern of low use of intermediate or high dosages of antipsychotics and low strength of antidepressant-antipsychotic combinations. At all sites, the participants underwent a systematic assessment, including a detailed characterization of their treatment history with the ATHF. The ATHF has been validated over the past 15 years,[22] and it has been shown to lead to reliable characterization of treatment history.[32]

In conclusion, this study shows a lack of change in the treatment of patients with MD-Psy over the past decade. Additional studies are needed to determine why these patients are not treated more aggressively.[31] Given the high morbidity associated with MD-Psy and the availability of validated treatment,[8] it is important to continue to educate clinicians regarding its identification and treatment.

Drug names: aripiprazole (Abilify), chlorpromazine (Thorazine, Sonazine, and others), clozapine (FazaClo, Clozaril, and others), fluoxetine (Prozac and others), fluphenazine (Prolixin and others), haloperidol (Haldol and others), loxapine (Loxitane and others), olanzapine (Zyprexa), paroxetine (Paxil, Pexeva, and others), quetiapine (Seroquel), risperidone (Risperdal, Risperdal Consta), sertraline (Zoloft and others), venlafaxine (Effexor and others), ziprasidone (Geodon).

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