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Use of combinations of antipsychotics: McLean Hospital inpatients, 2002

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Background The empirical use of combinations of antipsychotic agents appears to be increasing with little research support for the relative efficacy, safety or cost-effectiveness of this practice. Such treatment was evaluated in hospitalized psychiatric patients.
Methods Samples of consecutive inpatients treated with ≥ 2 ('polytherapy') vs 1 antipsychotic ('monotherapy') were matched on age, sex, diagnosis and admission clinical ratings, and these groups were compared on total daily chlorpromazine-equivalent doses, days in hospital, and changes in clinical ratings between admission and discharge.
Results The study sample included 69 polytherapy and 115 well-matched monotherapy subjects. Despite matching for initial CGI and GAF ratings, polytherapy was associated with high PANSS subscale scores of positive symptoms among affective psychosis, and relatively greater PANSS subscale ratings of excitement-agitation among patients diagnosed with schizophrenia. Estimated clinical improvement during hospitalization was similar among poly- and monotherapy patients, but total daily CPZ-eq doses at discharge averaged twice-greater with polytherapy, and hospitalization lasted 1.5 times longer.
Conclusions Antipsychotic polytherapy as well as the types of agents combined may reflect clinician responses to particular symptom patterns. The value of specific combinations of antipsychotic agents and their comparison with monotherapies requires specific, prospective, randomized and well-controlled trials that consider matching on clinical characteristics and truly comparable doses across regimens. Copyright © 2005 John Wiley & Sons, Ltd.

KEY WORDS — antipsychotics; combination; polytherapy; polypharmacy; schizophrenia; bipolar disorder

Antipsychotic polytherapy — specifically, concurrent treatment with two or more antipsychotic agents — has been encountered recently among 11%–41% of psychiatric patients receiving at least one antipsychotic (Stahl, 1999a, b; Tapp *et al*., 2003; Anon, 1999; Centorrino *et al*., 2002, 2004; Freudenreich and Goff, 2002; Meltzer and Kostokaglu, 2002; Oepen, 2002; McCue *et al*., 2003; Schumacher *et al*., 2003; Ganguly *et al*., 2004; Lerner *et al*., 2004; Millen, 2004; Baldessarini and Tarazi, 2005). Despite the apparently substantial prevalence of this empirical practice, evidence of its potentially superior efficacy compared with treatment with single antipsychotic drugs remains unproved and largely untested (Oepen, 2002; McCue *et al*., 2003; Schumacher *et al*., 2003; Centorrino *et al*., 2004; Ganguly *et al*., 2004; Lerner *et al*., 2004; Millen, 2004; Baldessarini and Tarazi, 2005). There are certain specific circumstances in which the use of two or more antipsychotic drugs simultaneously may be clinically appropriate, particularly during gradual conversion from one agent to another in the case of intolerable adverse effects or

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inadequate efficacy (Stahl, 1999a, b; McCue *et al*., 2003). It might also be possible to produce different clinical effects by combining agents of dissimilar neuropharmacology (Meltzer and Kostokaglu, 2002; Oepen, 2002; Baldessarini and Tarazi, 2005; Kapur and Remington, 2001). However, the view that clinical efficacy can be enhanced by deliberate combinations of antipsychotics is supported by very limited evidence, mainly from uncontrolled case reports concerning a limited range of specific combinations, and evidence of the safety and cost-effectiveness of such combinations is even more meager (Baldessarini and Tarazi, 2005; Goss, 1995; McCarthy and Terkelsen, 1995; Bacher and Kaup, 1996; Henderson and Goff, 1996).

Given the striking disparity between an evidently widespread clinical practice and very limited information to support its use, current practices at a major psychiatric teaching hospital were reviewed regarding the use of antipsychotic agents in combinations compared with antipsychotic monotherapy in a matched sample of inpatients. The prevalence of antipsychotic polytherapy was examined, both overall and in specific types of combinations, and demographic and clinical factors were compared among patients treated with antipsychotic mono- vs polytherapy to test for possible differences at either admission or discharge among patients receiving such treatments.

METHODS

Subjects

Computer-based pharmacy records were used to identify all McLean Hospital inpatients prescribed an antipsychotic within a 3-month period (March 1–May 31) in 2002, following review and approval by the hospital IRB for the present study protocol, requiring anonymous analysis and reporting of aggregate data. Data collected from medical and computerized pharmacy records included: sex and age; clinical presentation at admission, and DSM-IV discharge diagnosis; clinical status at admission and discharge; initial, maximum and discharge doses of all antipsychotics, and prescriptions for all other psychotropics. Antipsychotic doses were compared as chlorpromazine-equivalent (CPZ-eq) mg/day (Centorrino *et al*., 2002; Baldessarini and Tarazi, 2005; Woods, 2003). In each case the antipsychotic agent given at the highest daily dose for the greatest number of days was considered the 'primary' agent.

Using data obtained from pharmacy records, *polytherapy* 'cases' given two or more antipsychotic drugs simultaneously for a least 3 consecutive days during hospitalization were identified. Then each case was matched to at least one *monotherapy* 'comparator' subject hospitalized within the same 3-month period and given only one antipsychotic agent at a time. Subjects were matched by sex, age (within 7 years), diagnosis-type (defined below), and by admission clinical global impression ([CGI], within 1 point) and global assessment of functioning ([GAF], within 10 points) scores.

Clinical assessments

DSM-IV diagnoses were categorized as: [1] *psychotic disorder* (schizophrenia or schizophreniform disorder, schizoaffective disorder, or psychosis not otherwise specified), [2] *major affective disorder* (bipolar disorder, major depression and mood disorder not otherwise specified), or [3] *other disorders* (including dementia, substance abuse and other miscellaneous conditions).

Based on medical records, two investigators (PS, GS) independently scored subjects at admission and discharge on the CGI, GAF and Positive and Negative Syndrome Scale (PANSS). Preliminary inter-rater reliability assessments with these methods yielded high levels of agreement (kappa statistics ≥ 0.80 for CGI, GAF and PANSS total score). The percentage changes in these three assessments between admission and discharge were determined for each patient. Additionally, six subscales derived from the PANSS were used to compare specific symptoms between cases and comparators: [1] *negative* (PANSS items: N4, N2, N3, G16, N6, N1, G13); [2] *positive* (modified: items P1, G9, P3, P6, P5, G12); [3] *disorganized* (G10, G11, N5, P2, N7); [4] *excited* (P7, G14, P4, G8); [5] *depression* (G6, G3); and [6] *anxiety* (G1, G2, G4) (Emsley *et al.*, 2003).

Treatment assessments

Polytherapy cases were classified as to the apparent clinical 'appropriateness' of the simultaneous use of ≥ 2 antipsychotic agents, based on consensus by two or more authors, at least one of whom was a senior clinical investigator. Antipsychotic polytherapy considered possibly *appropriate* included cases involving the following: [1] transitions from one drug to another; [2] maintaining another agent with ongoing clozapine treatment; [3] adding a second agent for sleep or agitation when a first antipsychotic was at a maximum tolerated dose; [4] adding a

second-generation agent to ongoing treatment with a long-acting injected neuroleptic (haloperidol or fluphenazine decanoate) that proved to be insufficient alone; [5] use of combinations of two antipsychotics specifically involving at least one modern agent, with both agents given at maximum tolerated doses following earlier trials of antipsychotic monotherapy.

Cases of antipsychotic polytherapy considered potentially *questionable* included: [1] addition of a second antipsychotic agent without an adequate trial of monotherapy at maximally tolerated doses; [2] combining two or more orally administered conventional neuroleptics; [3] use of more than one antipsychotic with none given at a maximum tolerated dose; and [4] simultaneous initiation of more than one antipsychotic agent at one time.

Data analyses

Factors and clinical outcomes associated with antipsychotic poly- vs monotherapy other than those used to match the cases and comparators were examined, with particular attention to contrasting antipsychotic doses (initial, maximum and final), hospital length-of-stay (LOS), and changes in clinical ratings during hospitalization. Antipsychotic polytherapy cases and matched monotherapy comparison subjects were contrasted using negative binomial regression for prior hospitalization counts, and generalized least-squares regression methods (Gaussian family) for changes in clinical rating scale scores from baseline, adjusting for CPZ-eq daily doses and hospital LOS in certain analyses. Regression analyses also included adjustment for clustering on matched pairs. For selected contrasts, several covariates were considered in additional modeling, including sex, current age, diagnostic category, number of previous hospitalizations, and baseline CGI and GAF scores.

Post-modeling tests (χ^2) were carried out for selected contrasts. For some bivariate comparisons involving continuous measures with non-Gaussian distributions, nonparametric, Spearman rank-correlation (r_s) methods were used. CPZ-eq dose and LOS data were positively skewed (few patients had unusually high doses or long hospitalizations) and so were log-normalized before analysis. Modeling fits were checked using partial-residual plotting methods. Robust estimates of standard errors were obtained when feasible.

Averaged continuous data are reported as means with standard deviations ($\pm$SD), except for the skewed dose and LOS data, for which medians $\pm$ SD are reported. Statistical significance required 2-tailed $p < 0.05$, at stated degrees of freedom (df). Analyses employed Stata® (Stata Corp, College Station, TX) or Statview-5® (SAS Corp, Cary, NC) microcomputer programs. Selected results were compared with similar data from 1998 (Centorrino *et al*., 2002).

RESULTS

A total of 184 patients were studied: 69 antipsychotic polytherapy cases and 115 monotherapy comparison subjects (1.7 comparators/case). The matching algorithm yielded close matching in the poly- vs monotherapy treatment groups, by sex (60% women), age (overall average: 44.1 ± 15.4 years), proportion of diagnostic types and GAF score at hospital admission (Table 1). Specifically, psychotic and major affective disorder diagnoses were well balanced between antipsychotic poly- vs monotherapy subjects (43.4% vs 36.5% psychotic; 40.6% vs 42.6% major affective), and mean illness severity (CGI) and functional status ratings (GAF) were very similar at intake (Table 1). Though not included as a matching variable, PANSS

Table 1. Patient characteristics

	Polytherapy ($n = 69$)		Monotherapy ($n = 115$)	
	n	%	*n*	%
Sex[a]				
Female	41	59	69	60
Male	28	41	46	40
Diagnosis type[a]				
Psychotic disorder	30	43.4	42	36.5
Major affective disorder	28	40.6	49	42.6
Other	11	16.0	24	20.9
	Mean	SD	Mean	SD
Age (years)[a]	43.2	14.8	44.7	15.8
Length-of-stay (days)	19.8[b]	14.8	12.9	8.9
Admission illness ratings				
CGI[a]	5.9	0.7	5.7	0.6
GAF[a]	23.6	7.7	25.1	8.0
PANSS (total)[c]	83.8	18.4	80.9	16.2
Discharge illness ratings[c]				
CGI	3.3	1.0	3.3	1.1
GAF	46.4	10.6	48.5	11.1
PANSS (total)	49.2	14.2	47.0	14.4

[a]Factor used as a matching variable.
[b]Significantly greater than the mean length of stay for monotherapy comparators (F [df = 1; 68] = 15.7, $p < 0.0001$).
[c]No significant differences were found between the treatment groups on PANSS total scores at admission (F [df = 1; 68] = 1.3, $p = 0.26$) and discharge (F [df = 1; 68] = 1.0, $p = 0.31$), discharge CGI ratings (F [df = 1; 68] = 0.13, $p = 0.72$), and discharge GAF ratings (F [df = 1; 68] = 1.7, $p = 0.20$).

Table 2. Antipsychotic dosing and other psychotropics

	Polytherapy ($n=69$)		Monotherapy ($n=115$)		Analysis			
	Mean	SD	Mean	SD	Ratio	(95% CI)	Statistic (F or z)	p
Total antipsychotic dose (CPZ-eq mg/day)								
Initial	418	284	202	191	2.07	(149–283)	37.9	<0.0001
Peak	660	449	303	222	2.18	(251–463)	51.7	<0.0001
Final	508	434	250	215	2.03	(157–360)	25.6	<0.0001
Psychotropics/patient								
Admission (total)	2.09	1.80	2.08	1.81	1.00	(−0.24, 0.24)	0.03	0.973
Antipsychotics	0.88	0.83	0.48	0.50	1.83	(0.33–0.90)	4.19	<0.0001
Mood-stabilizers	0.54	0.76	0.55	0.78	0.98	(−0.42–0.37)	0.11	0.915
Antidepressants	0.42	0.67	0.72	0.79	0.58	(−0.94, 0.14)	2.65	0.008
Sedatives	0.25	0.53	0.33	0.57	0.76	(−0.88, 0.29)	0.99	0.324
Discharge (total)	3.32	1.41	2.89	1.53	1.15	(0–0.28)	1.95	0.051
Antipsychotics	1.80	0.58	0.93	0.26	1.94	(0.54–0.73)	13.4	<0.0001
Mood-stabilizers	0.83	0.71	0.74	0.77	1.12	(−0.15, 0.38)	0.82	0.410
Antidepressants	0.70	0.85	0.84	0.84	0.82	(−0.51, 0.12)	1.21	0.227
Sedatives	0.33	0.53	0.38	0.56	0.87	(−0.61, 0.33)	0.57	0.569

total scores also were similar in both treatment groups (Table 1).

Among *non*-matched variables (Table 1), hospital LOS averaged 15.5 ± 11.9 days overall and was 1.5 times longer among antipsychotic polytherapy cases (19.8 ± 14.8 vs 12.9 ± 8.9 days), suggesting greater illness severity or greater treatment-resistance. In addition, the number of psychotropic agents prescribed per patient did not differ significantly at admission between treatment groups, but polytherapy cases, as expected, were given more psychotropics at discharge (3.3 ± 1.4 vs 2.9 ± 1.5; χ^2 [df = 1] = 3.8, $p = 0.051$), accounted for as additional antipsychotics, although not more mood stabilizers, antidepressants or sedatives (Table 2).

Specific combinations used

At discharge a total of 228 antipsychotic agents were prescribed among the overall sample of 184 subjects (1.2 antipsychotics/case; range 0–3 agents/case, overall, and 1.8 agents/person among polytherapy cases). Frequency of use of specific agents among all subjects ranked: olanzapine (37.0%), risperidone (34.8%), quetiapine (33.2%), haloperidol (14.7%), perphenazine (10.3%), clozapine (9.2%), other typical neuroleptics (8.2%) and ziprasidone (6.5%). In 85.2% of monotherapy subjects and 75.3% of polytherapy cases, the primary antipsychotic agent prescribed was a second-generation drug (81.5% overall).

Second-generation antipsychotics far outnumbered conventional neuroleptics as primary agents, and were prescribed as primary agents for other diagnoses (97.1%) significantly more than for psychotic (72.2%) or major affective (83.1%) conditions (χ^2 [df = 2] = 8.8, $p = 0.0124$). The most frequently prescribed combinations were a second-generation antipsychotic plus a conventional neuroleptic (26/69) or two second-generation agents (26/69), together accounting for 75.4% (52/69) of polytherapy cases. At admission, those receiving a combination of second-generation plus conventional agents had higher overall PANSS scores (93.3 ± 18.1 vs 74.5 ± 17.4; F [df = 1; 50] = 14.5; $p = 0.0004$) than those receiving concomitant treatment with two second-generation agents. Patients treated with a second-generation plus a conventional antipsychotic agent specifically scored higher on *positive* (22.1 ± 7.0 vs 15.0 ± 7.3; F [df = 1; 50] = 12.8; $p = 0.0008$), *negative* (21.4 ± 10.9 vs 16.0 ± 6.2; F [df = 1; 50] = 4.9; $p = 0.0319$) and *disorganized* (12.5 ± 5.9 vs 9.7 ± 3.9; F [df = 1; 50] = 4.07; $p = 0.049$) PANSS symptom subscales at admission compared with those receiving two second-generation agents. Hospital LOS averaged 31% longer among those given a combination of a conventional and a modern agent than among those receiving two modern agents.

Antipsychotic dosing

The daily total individual CPZ-eq dose of antipsychotic drugs at discharge averaged 347 ± 339 mg among all 184 subjects. Daily discharge dosing among patients with psychotic disorders was 1.6 times higher

than for patients with major affective disorders (467 ± 399 vs 301 ± 297 mg/day; F [df = 2; 68] = 10.92, $p = 0.005$) and 2.3 times greater than for patients with other conditions (467 ± 399 vs 202 ± 178 mg/day; F [df = 2; 68] = 10.92, $p = 0.000$). Dose did not differ significantly between men and women (426 ± 316 vs 321 ± 354 mg/day; F [df = 1; 171] = 3.8, $p = 0.052$), though significantly lower discharge doses were prescribed with increasing age (F [df = 1; 68] = 5.81, $p = 0.019$). Likewise, among polytherapy cases alone, those with psychotic diagnoses received 1.8 times higher average total daily CPZ-eq antipsychotic doses at discharge than those with nonpsychotic illnesses (677 ± 490 vs 379 ± 338 mg; F [df = 1; 33] = 17.7, $p = 0.0039$). Of note, total daily dosing of polytherapy vs monotherapy subjects at discharge was 2.1 times greater (677 ± 490 vs 316 ± 224 mg; F [df = 1; 33] = 17.8, $p = 0.0002$) among those with psychotic disorder diagnoses, and 1.8 times greater (425 ± 364 vs 230 ± 226 mg; F [df = 1; 29] = 6.61, $p = 0.0155$) among subjects with major affective diagnoses.

Patients treated with antipsychotic polytherapy additionally received significantly greater CPZ-eq total daily doses at admission relative to monotherapy comparators (238.0 ± 280.4 vs 131.5 ± 204.6; F [df = 1; 68] = 7.91, $p = 0.006$). Moreover, total daily CPZ-eq antipsychotic dose increased significantly more from admission to discharge among patients treated with antipsychotic polytherapy vs monotherapy when adjusting for dose at admission (271 ± 428 vs 119 ± 229 mg increase; F [df = 1; 68] = 8.29, $p = 0.005$; %-change: 95.6 ± 166 vs 37.5 ± 150; F [df = 2; 57] = 8.73, $p = 0.015$). Of note, the number of antipsychotic agents prescribed increased 2.0-fold for both treatment groups from admission to discharge.

Clinical changes

From admission to discharge, polytherapy and monotherapy subjects showed similar improvement in CGI scores (% change: 42.9 ± 18.5 vs 42.4 ± 20.0; F [df = 1; 68] = 0.03, $p = 0.864$) and in GAF ratings (% change: 113.0 ± 75.8 vs 110.3 ± 81.7; F [df = 1; 68] = 0.07, $p = 0.793$). Similarly, PANSS total scores at discharge did not differ significantly between patients treated with polytherapy vs monotherapy, (49.2 ± 14.2 vs 47.0 ± 14.0; F [df = 1; 68] = 1.04, $p = 0.311$), nor did improvement in this rating differ between the two treatment groups (39.9 ± 15.0% vs 41.2 ± 15.0%; F [df = 1; 68] = 0.32, $p = 0.572$). Interestingly, however, significant differences were found between polytherapy cases and monotherapy comparators at admission on certain PANSS symptom subscales, whereby patients treated with polytherapy scored significantly higher on positive symptoms (19.6 ± 7.8 vs 15.4 ± 6.9; F [df = 1; 68] = 20.49, $p < 0.0001$) and correspondingly lower on depressive symptoms (3.4 ± 2.0 vs 6.5 ± 3.3; F [df = 1; 68] = 6.15, $p = 0.016$). At discharge, polytherapy patients continued to score higher on positive symptoms (11.2 ± 4.4 vs 9.3 ± 3.8; F [df = 1; 68] = 0.002), with higher scores on the excited subscale as well (6.8 ± 3.3 vs 6.0 ± 2.4; F [df = 1; 68] = 3.41, $p = 0.069$).

Specifically, polytherapy patients with a schizoaffective diagnosis scored significantly higher on positive symptoms at both admission and discharge (respectively, 24.3 ± 5.8 vs 17.5 ± 6.4; F [df = 1; 17] = 12.5, $p = 0.003$; 13.7 ± 4.4 vs 9.6 ± 3.0; F [df = 1; 17] = 8.40, $p = 0.01$) and considerably lower on PANSS ratings of negative symptoms at admission (16.9 ± 7.8 vs 21.8 ± 9.5; F [df = 1;17] = 3.8, $p = 0.068$) relative to patients of the same diagnosis who received treatment with monotherapy. At admission, patients diagnosed with bipolar disorder who received treatment with antipsychotic polytherapy similarly scored significantly higher on the positive symptom subscale (17.9 ± 8.3 vs 12.4 ± 5.5; F [df = 1; 16] = 6.99, $p = 0.018$) and additionally lower on the depression subscale (4.9 ± 2.5 vs 7.1 ± 3.2; F [df = 1; 16] = 6.19, $p = 0.024$) than comparable patients treated with monotherapy. Subjects with schizophrenia who received polytherapy did not differ significantly from those receiving monotherapy in initial ratings of positive symptoms, but were rated as more excited (14.7 ± 6.2 vs 8.5 ± 3.6; F [df = 1; 9] = 10.4, $p = 0.010$), with correspondingly greater change in this rating during hospitalization (-8.7 ± 5.5 vs -3.0 ± 3.2; F [df = 1; 9] = 7.3, $p = 0.024$).

Appropriateness for polytherapy

In 44/69 (63.8%) cases given antipsychotic polytherapy, such treatment was rated as possibly clinically *appropriate*. In the remaining 25 cases, polytherapy was rated as potentially *questionable* for the following reasons: 13 of the 25 questionable treatment cases received two antipsychotic agents at relatively low doses, and the remaining 12 cases received treatment with a second antipsychotic without an adequate trial of monotherapy. Age, sex, diagnostic class and LOS were not related to the suggested appropriateness of antipsychotic polytherapy.

Subjects with questionable indications for antipsychotic polytherapy were prescribed more

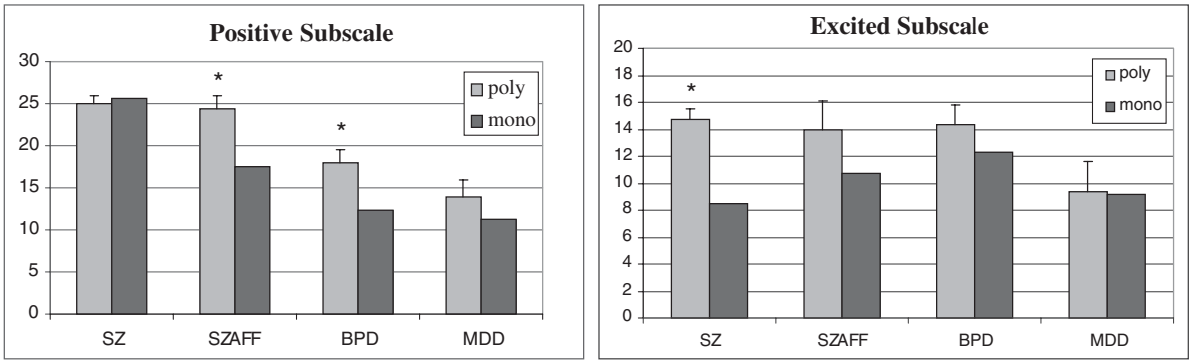

Figure 1. PANSS *positive* and *excited* subscales at admission by diagnosis for patients treated with mono- vs polytherapy. Diagnoses: SZ, schizophrenia; SZAFF, schizoaffective disorder; BPD, bipolar disorder; MDD, major depression. Data are mean ± SEM.
*$p < 0.05$. Regression analysis adjusted for clustering on matched pairs

antipsychotics per person at discharge than those involving usage considered *appropriate* (2.0 ± 0.4 vs 1.6 ± 0.6 agents/person; $F[\mathrm{df} = 1;\ 67] = 7.8$, $p = 0.0068$). However, at discharge, the average total daily CPZ-eq antipsychotic dose, as well as the co-prescription of other psychotropic agents (mood-stabilizers, antidepressants or sedatives) did not differ between these two sub-groups. While CGI, GAF and PANSS total as well as subscale scores at admission did not differ with the apparent appropriateness of polytherapy, cases with *questionable* indications for antipsychotic polytherapy had greater GAF scores at discharge (50.0 ± 8.6 vs 44.3 ± 11.1; $F[\mathrm{df} = 1;\ 67] = 4.91$, $p = 0.03$) with correspondingly greater improvement in this rating from admission to discharge (26.3 ± 8.3 vs 20.9 ± 10.1; $F[\mathrm{df} = 1;\ 67] = 5.14$, $p = 0.0267$) than those whose indications for polytherapy were considered *appropriate*.

Comparisons with previous findings

In 2002, as in 1998, mean final antipsychotic doses were substantially and similarly higher among polytherapy patients regardless of diagnosis. Olanzapine was the most frequently prescribed antipsychotic in both the 1998 and 2002 samples, though its prescription rate decreased by 20.3% from 1998. Prescriptions for risperidone alternatively increased 80.3% from 1998 to 2002. In both years, the most commonly used antipsychotic combinations were either a conventional plus a second-generation agent or two second-generation agents.

Overall, in 1998 and 2002, total PANSS scores at admission revealed no significant differences between polytherapy cases and monotherapy comparators on these ratings. In this analysis with PANSS subscale assessments, distinct symptom differences at admission were uncovered between patients who receive treatment with antipsychotic polytherapy and monotherapy comparators of the same diagnosis. Methodologically, comparisons of the 1998 and 2002 samples suggest that more specific assessments may be required to capture the clinical differences between patients who receive inpatient treatment with polytherapy and those treated with one antipsychotic agent alone.

DISCUSSION

A particularly interesting finding is that PANSS subscale scores at admission (not included among matching factors) were different among psychiatric patients who received antipsychotic polytherapy vs monotherapy during hospitalization. Specifically, polytherapy cases diagnosed with either bipolar or a schizoaffective disorder, but not schizophrenia or other nonaffective psychotic disorders, had higher initial scores on the PANSS *positive-symptoms* subscale. Tapp and colleagues (2003) also found an association between simultaneous use of more than one antipsychotic drug and prominent positive psychotic symptoms, but mainly in patients diagnosed with schizophrenia. Among the present subjects diagnosed with schizophrenia, it was found that antipsychotic polytherapy was associated with higher initial PANSS scores on the *excited-symptoms* subscale of the PANSS. Greater ratings of 'excitation' in schizophrenia patients as well as greater ratings of 'positive symptoms' among bipolar and schizoaffective patients given more than one antipsychotic agent may reflect greater concern

among clinicians and nursing staff about potentially uncontrolled or dangerous behaviors in such patients. The overall 1.5-times longer length of hospitalization among polytherapy cases vs monotherapy comparators also could imply a more severe course of illness among patients receiving two or more agents. It is suggested that such clinical characteristics of patients might well encourage relatively aggressive pharmacological treatments, including the use of more than one antipsychotic agent, and even under questionable *appropriateness*.

The most common antipsychotic combinations involved a second-generation plus a conventional antipsychotic, or combinations of two modern agents. Of note, subjects who received a combination of a second-generation plus a conventional agent had significantly higher admission CGI, lower GAF and higher PANSS-total and subscale (positive, negative and disorganized) scores than those who received only second-generation agents. It has been suggested that the different mechanisms of action of modern antipsychotic and conventional neuroleptics may provide a pharmacological rationale for combination therapy with pharmacodynamically dissimilar agents (Ganguly *et al*., 2004; Kapur and Remington, 2001), and such considerations probably tend to favor combinations of older and newer agents, even though this concept remains clinically untested. Alternatively, the use of new and old antipsychotics together may reflect greater confidence of some clinicians in older neuroleptics to control positive symptoms rapidly.

Interestingly, patients given second-generation plus conventional agents did not differ significantly from those given two modern antipsychotics on any clinical measures at discharge, including CGI, GAF and total PANSS or its subscales. Nevertheless, the present uncontrolled experience is inadequate to suggest that specific types of drug combinations can be selected rationally, though they point the way to prospective and controlled trials comparing specific types of combinations and dose-matched monotherapies in patients with particular clinical characteristics. It is proposed that matching poly- and monotherapy patients with the same CPZ-eq total daily doses is an essential component to designing such studies, particularly in view of the evidence presented here that antipsychotic polytherapy was associated with about 96% higher total CPZ-eq daily doses than were found with antipsychotic monotherapy.

In conclusion, the present clinical observations suggest that antipsychotic polytherapy may reflect clinician responses to particular symptom patterns or other clinical characteristics of patients, and that the types of agents combined may also bear some relationship to patient characteristics. If these impressions are valid, they suggest that matching on such variables as severity of positive symptoms and levels of excitement or agitation may be appropriate in the design of prospective trials of specific drug-combinations and their comparison to dose-equivalent antipsychotic monotherapies.

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