COMBINATIONS OF MOOD-STABILIZERS WITH ANTIPSYCHOTICS AS TREATMENT STRATEGIES IN HOSPITALIZED PSYCHIATRIC PATIENTS

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Summary

Object: Since psychotropic polytherapy is widely used despite limited evidence of efficacy and safety, we evaluated combinations of mood-stabilizers with antipsychotics. We also compared current findings with prior samples, to evaluate changes in psychotropic prescription practices involving antipsychotic-mood stabilizer treated inpatients.

Method: Medical records of McLean Hospital inpatients treated with antipsychotics for ≥ 3 consecutive days during March-May 2002 were reviewed. In 344 inpatients prescribed an antipsychotic in 2002, we contrasted those also given a mood-stabilizer or not regarding clinical features, type and doses of all psychotropics, and clinical changes during hospitalization.

Results: Mood-stabilizers were given to 63.7% (n=219) of antipsychotic-treated subjects. Usage ranked: divalproex > gabapentin > lithium > lamotrigine = topiramate > carbamazepine > oxcarbazepine > levitiracetam; 22% (n=76) of all 344 subjects received ≥ 2 mood-stabilizers. Diagnoses associated with combination-treatment ranked: major affective (54%) > primary psychotic (26%) > other (19%).

Conclusions: Mood-stabilizer co-treatment remains prevalent, particularly combinations of anticonvulsants with modern antipsychotics.

Key Words: Anticonvulsant – Antipsychotic Combination therapy - Mood stabilizer - Lithium

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Introduction

Mood-stabilizing drugs are widely employed in contemporary psychiatry (Citrome et al. 2002, Ghaemi 2002). Indicated primarily for bipolar disorder, these agents are also employed empirically for other affective, schizoaffective, and even primarily psychotic disorders, often to reduce agitation, lability, aggression, and impulsivity (Citrome et al. 2002, Baldessarini and Tarazi 2006). Combination treatments may provide additional benefit over monotherapy for the management of various phases of bipolar disorder, controlling effectively acute phases and reducing relapse (Lin et al. 2006). Despite broad empirical applications of psychotropic combinations, experimental testing of relative effectiveness and safety of specific combinations remains rare (Citrome et al. 2002, Ghaemi 2002, Baldessarini and Tarazi 2006, Besag and Berry 2006). Few, largely inconclusive, studies suggest potential benefits of combining anticonvulsants or lithium with antipsychotics in primary psychotic disorders, but the tolerability and safety of such relatively expensive combinations remain uncertain (Citrome et al. 2002, Leucht et al. 2002, Basan et al. 2004, Leucht et al. 2004, Besag and Berry 2006). Although pharmacokinetic interactions between mood-stabilizing and antipsychotic drugs may affect the efficacy and toxicity, those drugs are often prescribed together (Besag and Berry 2006). Very few double-blind, placebo-controlled studies have been conducted on the uses of combination treatments with mood-stabilizing and antipsychotic drugs (Besag and Berry 2006). Nonetheless, a plethora of retrospective case reviews, open trials, and case reports have served

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to launch the use of combination treatments with mood stabilizers and antipsichotics for a variety of conditions, such as controlling mood symptoms, agitation and aggressive behavior. (Citrome and Volavka 1997, Lin et al. 2006).

Given current interest in combination treatments for severe psychiatric illnesses, and limited information about the prevalence, effectiveness, and tolerability of specific combinations, we surveyed antipsychotic-mood-stabilizer co-treatment among McLean Hospital psychiatric inpatients and compared findings to earlier surveys (Baldessarini et al. 1995, Centorrino et al. 2002).

Method

Following the McLean Hospital IRB approval, we reviewed medical records of McLean Hospital inpatients treated with antipsychotics during March-May 2002. Among 344 inpatients prescribed an antipsychotic in March-May 2002, we analyzed those also given a mood-stabilizer versus those treated with an antipsychotic alone.

For both antipsychotics and mood-stabilizers, a primary agent was that prescribed for the majority of hospital days, at doses within manufacturers' recommended therapeutic ranges (standard doses ≥ 3 days). Mood-stabilizing agents used for <3 consecutive days or at doses below the recommended range were considered adjunctive; we also recorded as-needed use of mood-stabilizers. For the purpose of this study, we only analyzed primary agents. To facilitate dosing comparisons, we employed chlorpromazine (mg/day) dose-equivalents (Centorrino et al. 2002, Woods 2003, Centorrino et al. 2005, Baldessarini and Tarazi 2006) and lithium carbonate dose-equivalents of putative mood-stabilizers, based on the potency ratio (PR) of each agent determined from its approximate median manufacturer's recommended daily dose, as follows: lithium carbonate (PR 1.00, 1050mg/day), carbamazepine (PR 1.17, 900mg), divalproex (PR 0.70, 1500mg), gabapentin (PR 0.78, 1350mg), lamotrigine (PR 3.82, 275mg), levitiracetam (PR 0.53, 2000mg), oxcarbazepine (PR 1.00, 1050mg), topiramate (PR 3.82, 275mg), and zonisamide (PR 3.50, 300mg).

We collected information on demographics, DSM-IV discharge diagnoses, presenting illnesses, antipsychotic and mood-stabilizer dosing, and use of other psychotropics during hospitalization. Subjects were categorized by consensus, using DSM-IV diagnoses and other available information, as having: a major affective disorder (bipolar disorder, major depression, mood disorder-NOS), primary psychotic disorder (schizophrenia, schizoaffective disorder, psychosis-NOS), or other conditions (dementia, substance abuse, miscellaneous). We rated admission/discharge clinical status with the Clinical Global Impression (CGI) and Global Assessment of Functioning (GAF) scales, based on consensus by experienced investigators, who were blind to polytherapy vs. monotherapy (Centorrino et al. 2004, Centorrino et al. 2002). Considering the same 3-months observation period of earlier surveys, we also compared current findings with prior samples, to evaluate changes in psychotropic prescription practices involving combinations of antipsychotic and mood stabilizer treatments (Baldessarini et al. 1995, Centorrino et al. 2002).

Statistical analyses with Statview-5 (SAS Corp.; Cary, NC) yielded means and standard deviations (SD) for continuous data, compared by ANOVA methods and t-tests (paired for within-subject comparisons). Statistical significance required two-tailed $p<0.05$, at stated degrees-of-freedom (df). Multivariate analysis examined odds ratios. We compared new findings with those reported earlier (Baldessarini et al. 1995, Centorrino et al. 2002) for 1993 (N=299), and 1998 (N=377 cases).

Results

Among antipsychotic-treated inpatients, 219/344 (63.7%) also received a mood-stabilizer: in 193/344 (56.1%) subjects the mood-stabilizer was considered a *primary* agent, in 26 (7.6%) *adjunctive*, and in 50 (14.5%) only *as-needed*.

Among the 193 subjects given mood-stabilizer as primary co-treatment, we found that the co-treatment was more common among subjects with major affective disorder (Table 1). Days-in -hospital significantly differed little with antipsychotics and mood-stabilizer use as primary agents versus antipsychotic alone (Table 1).

Among 193 patients given mood-stabilizers as a primary co-treatment, 42 [21.8%] received ≥ 2 such agents. Their prevalence ranked: *divalproex* (35.3%), *gabapentin* (21.7%), *lithium carbonate* (17.9%), *lamotrigine* (8.1%), *topiramate* (8.1%), *carbamazepine* (4.7%), *oxcarbazepine* (3.4%), and *levetiracetam* (0.8%). Primary mood-stabilizers/patient increased from 0.8 ± 0.8 at admission to 1.3 ± 0.6 at discharge, with a 12% increase in lithium-equivalent dose between admission and discharge (1145 ± 790 vs. 1299 ± 836 mg/day; paired-t [df=126] = 4.2, $p<0.0001$). Women received a primary mood-stabilizer more often than men (61.4% vs. 48.6%; c^2[df=1]=5.5, p=0.02), with no sex-difference in mean daily lithium-equivalent doses of mood-stabilizers at any time. Patients given ≥ 2 vs. only one mood-stabilizer received twice-greater lithium-equivalent daily doses at discharge (2170 ± 974 vs. 1049 ± 593 mg/day; F [df=1; 182] = 82.9, $p<0.0001$).

Not surprisingly, patients treated with a mood-stabilizer received more psychotropics at discharge (Table 1). At discharge, rates of antidepressant and sedative prescriptions, as well as the number of antipsychotics/patient (1.1 ± 0.4 vs. 1.1 ± 0.6), were similar with vs. without use of a primary mood-stabilizer. However, total daily chlorpromazine-equivalent doses of antipsychotics at discharge averaged 41% greater when a primary mood-stabilizer was included (Table 1). Second-generation agents represented 90.2% of primary antipsychotic prescriptions among combination-therapy cases given a primary mood-stabilizer.

Factors strongly associated with combination treatment (more psychotropics/patient, higher discharge antipsychotic doses, and slightly longer hospitalization) suggest more severe or treatment-resistant illness. Nevertheless, CGI and GAF admission, discharge, and improvement ratings did not differ with/without mood-stabilizer co-treatment (Table 1).

Multivariate analysis of factors identified in bivariate comparisons indicated more psychotropics/

Table 1. *Characteristics of psychiatric inpatients treated with an antipsychotic plus a mood-stabilizer vs. an antipsychotic alone*

	Mood-Stabilizer[a] + Antipsychotic (N=193)	**Antipsychotic Only** (N=151)	Statistic[b] (F or χ^2)	p
Demographics				
Age (years)	44.2 ± 16.2	45.5 ± 18.9	0.42	0.52
Women (%)	64.2	51.7	5.5	0.02
Diagnostic groups (%)		7.8	0.02	
Major affective disorder	53.9	39.7	—	—
Primary psychotic disorder	24.2	34.5	—	—
Other disorders	21.9	25.8	—	—
During hospitalization				
Hospitalization (days)	15.7 ± 12.5	13.4 ± 11.1	3.3	0.07
Psychotropics/patient (%)	3.6 ± 1.3	2.4 ± 1.3	98.1	<0.0001
Psychotropics at discharge				
Antipsychotic dose (mg/day)[c]	359 ± 330	255 ± 263	9.4	0.0024
≥3 agents/patient (%)	28.7	14.1	9.65	0.0002
Antidepressants (%)	59.1	60.3	0.05	0.82
Benzodiazepines (%)	31.1	35.2	0.64	0.42
Clinical assessments				
Baseline CGI	5.6 ± 0.7	5.6 ± 0.7	0.02	0.89
Improvement in CGI (%)[d]	39.4 ± 22.0	39.6 ± 22.0	0.01	0.91
Baseline GAF	26.8 ± 8.4	26.3 ± 8.4	0.24	0.62
Improvement in GAF (%)[d]	44.0 ± 17.0	42.0 ± 22.0	1.1	0.30

a. Primary mood-stabilizer only: standard dose ≥3 days.
b. F-statistic (df = 1; 342) for continuous measures, χ^2 (df = 1) for categorical comparisons.
c. Chlorpromazine-equivalent total daily dose at discharge.
d. Improvement between hospital admission and discharge.

Table 2. *Multivariate analysis of factors associated with combinations of mood-stabilizers[a] with antipsychotics in hospitalized psychiatric patients*

Independent variables	Odds Ratio (OR)	95% CI	χ^2	p
Higher antipsychotic dose[b]	3.38	[1.81–3.38]	14.5	<0.0001
Affective > psychotic or others[c]	1.97	[1.05–3.46]	4.5	0.033
Women > men	1.68	[1.09-2.59]	5.5	0.019
More drugs/patient[d]	1.49	[1.20–1.84]	13.4	0.0002
Longer hospitalization	1.05	[1.03–1.08]	19.1	0.0001

Multivariate analysis is by logistic regression, following preliminary findings of bivariate comparisons, involving 344 subjects (193 given combination treatment vs. N=151 given antipsychotics without mood-stabilizers). Factors are ranked by strength of association with combination treatment (OR). Overall model-fit is highly significant (χ^2[df=4]=67.9; p<0.0001).
Factors not significantly related to use of combination therapy included sex, age, type of antipsychotic (first vs. second-generation), and %-change in CGI or GAF scores between admission and discharge.

a. Used as "primary" mood-stabilizers (standard doses ≥3 days).
b. Chlorpromazpine-equivalent at discharge (median-split).
c. Major affective vs. primary psychotic or other disorders.
d. Psychotropics prescribed at discharge.

case at discharge, higher antipsychotic doses at discharge, more women given combination treatment and longer hospitalization when a mood-stabilizer was used (Table 2). As expected, mood-stabilizer co-treatment was most common among patients with a major affective diagnosis.

Concomitant use of mood-stabilizers with antipsychotics has changed considerably over the past decade. The present finding that 63.7% of antipsychotic-treated inpatients also received a mood-stabilizer compares to 54.6% of similar inpatients in 1998, however this practice was much more prevalent in 1993 when 84.3% of antipsychotic-treated patients received an anticonvulsant and 70.2% received lithium (Baldessarini et al. 1995). Meanwhile, use of lithium as a primary co-treatment declined by over 50% from 1993 to 2002. Of note, men were twice as likely to receive mood-stabilizers with antipsychotics in 1993, although in 2002 women were significantly more likely to receive such treatment.

Discussion

Use of mood-stabilizers with antipsychotics remains a common practice found among nearly two-thirds (64%) of antipsychotic-treated inpatients in 2002. Nevertheless, research evidence that such combination therapy is safe and effective, other than in acute mania, is remarkably limited (Citrome et al. 2002, Ghaemi 2002), and requires additional formal evaluation for a range of doses and specific combinations of agents.

As expected, 88.2% (82/93) of antipsychotic-treated patients diagnosed with bipolar disorder in our sample also received mood-stabilizers. However, nearly one-quarter (53/219, 24%) of such combination therapy were associated with DSM-IV diagnoses of schizophrenia or other primary psychotic disorders, and another 22% involved conditions as diverse as dementia and substance-use disorders. Citrome et al. (2002) similarly reported a 20.9% increase in mood-stabilizer co-treatment between 1994 and 2001 among inpatients diagnosed with schizophrenia. We suspect that broadening applications of psychotropic combinations may reflect unsatisfactory responses to monotherapies, particularly for illnesses severe enough to warrant hospitalization. However, no significant differences on the admission, discharge, and improvement of clinical status comparing patients with/without mood-stabilizer co-treatment were found in our survey. The use of such co-treatment may be also driven by the need to reduce specific symptoms such as agitation, lability, aggression, and impulsivity (Citrome et al. 2002, Baldessarini and Tarazi 2006) other than to control effectively acute phases and reduce relapse among subjects with bipolar disorder (Lin et al. 2006). In order to evaluate specific symptoms related to the use of such co-treatment further studies needs to be done. Polytherapy might be also driven by administrative efforts to reduce costs by limiting length of hospitalization. Among patients treated with antipsychotics and mood-stabilizer versus antipsychotic alone, we found little differences of days in hospital.

Concomitant use of mood-stabilizers with antipsychotics has changed considerably over the past decade. Nearly two-thirds (64%) of antipsychotic-treated inpatients also received a mood-stabilizer compares to 54.6% of similar inpatients in 1998 (Baldessarini et al. 1995, Centorrino et al. 2002). The use of lithium as a primary co-treatment declined by over 50% from 1993 to 2002 (Baldessarini et al. 1995, Centorrino et al. 2002). Several retrospective case reviews, open trials, and case reports have served to launch the use of combination treatments with mood stabilizers and antipsichotics for a variety of conditions such as controlling mood symptoms, agitation and aggressive behavior (Citrome and Volavka 1997, Lin et al. 2006).

These results should be also interpreted in light of study limitations. For example, it is possible that the results might have been overly influenced by the idiosyncratic prescribing practices of individual psychiatry residents or attendings who were on rotation during the 3-month period. Also, the 3-month snapshot of prescribing practices at a single academic institution might not actually be representative of practices in other inpatient settings. However, in order to decrease bias related to that, it was considered the same three months period (March-May) of earlier studies when comparisons where done (Baldessarini et al. 1995, Centorrino et al. 2002).

In conclusion, our findings support the impression that co-therapy involving combinations of antipsychotics with putative mood-stabilizing agents is very prevalent, particularly with anticonvulsants whose efficacy in most psychiatric applications remains largely unproved (Baldessarini and Tarazi 2006). Additional studies of the differential efficacy, tolerability, interactions, and safety of specific combinations of antipsychotics and mood-stabilizers for particular clinical conditions are required.

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