Concomitant Medications May Not Improve Outcome of Antipsychotic Monotherapy for Stabilized Patients With Nonacute Schizophrenia

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Background: There are virtually no controlled data suggesting that concomitant psychotropic medications (CPMs) improve outcome in schizophrenia after the acute phase. Despite that, polypharmacy (with all of its disadvantages) is far more common than monotherapy. To our knowledge, there have been no published reports of prospective systematic investigations of the efficacy of unrestricted CPM use in nonacute schizophrenia.

Method: This was a naturalistic, systematic study using a sample of 53 stabilized patients with DSM-IV-TR schizophrenia from 1 clinical practice setting including both private patients and patients from controlled research studies of the effectiveness of antipsychotics. Since there are meager controlled or systematic data on the effectiveness of CPM use with antipsychotics in nonacute schizophrenia, we tested the clinical strategy of CPM use by gradually tapering all CPMs (except antianxiety agents). The aim was to determine if the CPM improved outcome, had no effect, or worsened outcome using the Clinical Global Impressions-Improvement scale before and after taper, over at least 3 months and in some cases up to 18 months after discontinuation. Data were gathered from July 2002 to June 2005.

Results: For 21 patients undergoing 22 antidepressant tapers, no change was noted in 18 of 22 tapers, while in 3 improvement was noted and in 1 worsening was noted. For the 12 patients on treatment with mood stabilizers, no change was noted in 10 of 13 discontinuations, while in 3 mild worsening was noted. One patient was on treatment with both modafinil and trazodone and reported no change after tapering each in separate discontinuation trials, while another 3 patients were taking sleeping medications and also noted no change after discontinuation.

Conclusion: For most stabilized, chronic patients with schizophrenia, tapering adjunctive medications did not change outcome. This naturalistic study further defines the limits of efficacy of some concomitant classes of medications in patients with chronic schizophrenia who are already receiving adequate antipsychotic therapy.

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The use of atypical antipsychotics in combination with other psychotropic medications to treat schizophrenia and schizoaffective disorder is now accepted clinical practice.[1–3] In addition to use of an atypical antipsychotic as the primary medication, treatment may be augmented with a short-acting benzodiazepine (for agitation), an antidepressant (for varying degrees of depressive symptomatology, negative symptoms, or even demoralization),[4] or a mood stabilizer (for impulsivity, irrationality, or mood swings).[5–7] Often, 2 antipsychotics are used concurrently in the hope that lower dosages of each agent may reduce the occurrence of adverse effects and/or that the combination may maintain or even enhance efficacy.[8–10]

In contrast to clinical practice, most controlled clinical research studies limit the use of concomitant psychotropic medications (CPMs). Although there are a number of reports in the literature that have characterized antipsychotic and concomitant medication use patterns, drug-drug interactions, and antipsychotic polypharmacy prescribing patterns in schizophrenic patients, most of these studies are retrospective and/or rely on prescription data.

There are virtually no controlled data suggesting that CPMs improve outcome in schizophrenia after the acute phase.[11] Despite that, CPMs are almost universally utilized by clinicians (for a variety of reasons), and polypharmacy (with all its disadvantages) is far more common than monotherapy.[12] Since it is relatively unlikely that a controlled study of these issues will be funded, we decided to test one of these clinical strategies, that is, combining an antipsychotic with a CPM. We used a natural-experiment design in the context of both private practice and controlled studies of the relative efficacy of antipsychotics. To our knowledge, there have been no published reports of prospective investigations of systematic discontinuation of concomitant medication in this patient population (i.e., nonacute, stabilized patients with schizophrenia).

METHOD

The patients came either from a consecutive series of private patients in the Stanford Schizophrenia Clinic (a tertiary academic center in Stanford, Calif.) or from 3 research studies of antipsychotics for patients with schizophrenia. One study examined the effectiveness of switching from a prestudy antipsychotic to either a first-generation antipsychotic in decanoate form or a second-generation antipsychotic.[13] The other 2 compared oral first-generation and second-generation antipsychotics.[14] The studies involved both first- and second-generation antipsychotics including perphenazine, haloperidol decanoate, fluphenazine decanoate, clozapine, olanzapine, quetiapine, risperidone, ziprasidone, and aripiprazole. In all cases, patients were stabilized and randomized, then followed for at least 3 and in some cases 18 months. In one study, they were re-randomized to new treatment in the event of treatment failure. All of the studies aimed at determining the long-term effectiveness and safety/tolerability of the newer atypical antipsychotics, relative to each other and also to conventional antipsychotics. Data were gathered from July 2002 to June 2005.

As part of the baseline assessment, patients were asked to report all medications they were currently prescribed. We measured use of at least 1 of the following 7 classes of psychotropic medications: first-generation antipsychotics, second-generation antipsychotics, antidepressants, antianxiety agents, sedative-hypnotics, and mood stabilizers including lithium.

All patients met DSM-IV-TR criteria for schizophrenia, while none fulfilled criteria for schizoaffective disorder or major depressive disorder or were in an acute manic or depressive episode. A broad range of "real world" patients participated, including some with comorbid conditions (e.g., minor medical problems or substance use disorders, although none were consistent users of major substances such as cocaine or methamphetamines) that would exclude them from most clinical trials. Treatment-resistant patients were excluded. We identified 53 patients on treatment with CPMs. Of these, 37 were stabilized on their antipsychotic sufficiently (and consented) to allow tapering of their 40 CPMs (Tables 1–3). Of those, 21 were taking antidepressants (1 patient taking 2 antidepressants), 12 were taking mood stabilizers (1 patient taking 2 mood stabilizers), and 4 were taking 5 other agents (modafinil or sedatives). Three patients were tapered off 2 medications in the same class, while in 1 case, 3 medications from 3 different classes were tapered. We did not attempt to taper antianxiety agents, as in most cases recurring episodic agitation or severe anxiety requiring benzodiazepines was a consistent problem. Obviously, there were patients who were excluded because they were screen failures, were early treatment dropouts, or were not on treatment with any CPMs. In the study with the largest number of patients, of 39 patients on treatment with CPMs, we were able to stabilize 26.

The key design feature was to taper after stabilization on an antipsychotic, usually in the first 6 months from first contact. It was done slowly, over 3 to 6 months, in conjunction with ongoing, frequent contact with the patient and (almost always) a significant other. If the patient reported worsening on a consistent basis over a 2-week period, treatment with the same medication and dosage was restarted. In some cases (13 patients), benzodiazepines were started after the patient entered treatment or the study—but in no case was a benzodiazepine added after treatment with a concomitant medication was stopped to control emerging symptoms. Each patient was evaluated before and after taper by the principal investigator and by an independent rater using the Clinical Global Impressions-Improvement scale.[15] The minimum time patients were followed was 3 months, and most patients were followed for more than 1 year, with monthly administration of the CGI-I in most cases, until the study ended or the patient switched care for reasons of geographic treatment accessibility.

RESULTS

For 21 patients undergoing 22 antidepressant tapers, no change was noted in 18 of 22 tapers, while in 3 improvement was noted and in 1 worsening was noted (Table 1). For the 12 patients on treatment with mood stabilizers, no change was noted in 10 of 13 discontinuations, while in 3 mild worsening was noted, including complaints of increased lability, insomnia, jitters, and/or mood swings (Table 2). These 3 patients were restarted on treatment with their same medications and reported returning to their prediscontinuation state over 2 to 4 days. One patient was on treatment with both modafinil and trazodone and reported no change after tapering both in separate discontinuation trials (Table 3). Four patients (in-

Table 1. Antidepressant Concomitant Medication, Dose, and Global Outcome

						CGI Outcome		
Patient No.	Age (y)	Race	Gender	Medication	Dose, mg/d	Better	Unchanged	Worse
1	37	W[a]	M	Paroxetine	10		✓	
2	30	W	M	Paroxetine	30		✓	
3	50	A	M	Paroxetine	20		✓	
4	41	W	M	Buspirone	30		✓	
5	26	W	M	Sertraline	100		✓	
6	54	A	F	Fluvoxamine	200		✓	
7	34	A	M	Fluoxetine	20	✓		
8	22	W[a]	M	Mirtazapine	15		✓	
9	23	W	M	Citalopram	30		✓	
10	20	W	M	Citalopram	20		✓	
11	21	A	M	Sertraline	200		✓	
12	25	W	M	Bupropion	450	✓		
13	42	W	M	Clomipramine	250		✓	
				Fluoxetine	20		✓	
14	37	W	M	Bupropion	200		✓	
15	36	W[a]	M	Fluoxetine	20	✓		
16	21	W	M	Escitalopram	20		✓	
17	47	W	F	Fluoxetine	60		✓	
18	40	W	M	Imipramine	100		✓	
19	41	W	M	Clomipramine	75		✓	
20	18	W	M	Bupropion	300			✓
21	33	W	M	Venlafaxine	150		✓	

[a]Hispanic.
Abbreviations: A = Asian, CGI = Clinical Global Impressions scale, F = female, M = male, W = white.

Table 2. Mood Stabilizer Concomitant Medication, Dose, and Global Outcome

						CGI Outcome		
Patient No.	Age (y)	Race	Gender	Medication	Dose, mg/d	Better	Unchanged	Worse
1	18	W[a]	F	Divalproex	1000		✓	
2	19	W	M	Lithium	600			✓
3	22	W	M	Carbamazepine	1200			✓
4	33	W	F	Divalproex	750		✓	
5	42	W	M	Divalproex	250		✓	
6	50	W	M	Gabapentin	900		✓	
7	23	W	M	Lithium	600		✓	
8	20	W	M	Divalproex	1500		✓	
9	37	W	M	Lamotrigine	800		✓	
10	41	W	M	Divalproex	1500		✓	
11	18	W	M	Gabapentin	1200			✓
12	33	W	M	Gabapentin	400		✓	
				Topiramate	150		✓	

[a]Hispanic.
Abbreviations: CGI = Clinical Global Impressions scale, F = female, M = male, W = white.

cluding the previously mentioned patient) were taking sleeping medications and noted no or minor changes in sleep after discontinuation.

DISCUSSION

This is the first study in a consecutive sample, culled from 1 practice site (i.e., larger than the usual anecdotal case reports), to systematically measure outcome of discontinuing concomitant antidepressant or mood-stabilizing medication in a sample of chronic patients with schizophrenia who had been stabilized on treatment with an antipsychotic. With rare exceptions, antidepressants or mood stabilizers did not add much to outcome. It is possible that many of the CPMs had been appropriate and helpful when they were started, but the need for their long-term (indefinite) use had not been established. If a patient gets better after a second drug is added, it might be due to more time on treatment with the first drug and not the addition of the second drug. Likewise, since many clinicians subscribe to the notion that "what gets you well keeps you well," we are not advocating stopping or (drastically and rapidly) reducing dosing of an effective medication once patients achieve a steady state of improvement.

There are definitive data in general medicine showing that combinations are much more effective than monotherapy, supported by many randomized blinded studies with a good understanding of mechanism—in chronic

Table 3. Miscellaneous Concomitant Medication, Dose, and Global Outcome

						CGI Outcome		
Patient No.	Age (y)	Race	Gender	Medication	Dose, mg/d	Better	Unchanged	Worse
1	20	W	M	Modafinil	100		✓	
				Trazodone	50		✓	
2	43	W	M	Temazepam	15	✓		
3	40	W	M	Trazodone	25		✓	
4	32	A	M	Phenobarbital	30		✓	

Abbreviations: A = Asian, CGI = Clinical Global Impressions scale, M = male, W = white.

pain, for example.[16] The real question is, which combinations for what indications? Too often in psychiatry, a "last ditch" medication is added and either does not help or just appears to help. This is because, with the passage of time, the patient improves not because of, but in spite of, the additional medications. In either case, patients end up on treatment with many medications. For example, there is some controlled evidence that antidepressants are useful in depression when the disorder fulfills criteria for DSM-IV major depressive disorder superimposed on schizophrenia.[1] However, antidepressants in general are not helpful in chronic schizophrenia because what is called "depression" is usually demoralization, which is more responsive to psychotherapeutic intervention than medication.[17] One of the patients put it as follows: "I get 'depressed' because I realize I am schizophrenic and I can't do anything about it." We found that withdrawal of antidepressants does not lead to rapid recurrence, but, this said, hopefully future research will identify indications in which withdrawing these medications is of proven value. No evidence suggests that clinical judgment is a much better guide than data. Lastly, we caution that the lack of evidence for general benefit of CPM use may reflect that the question has not been adequately studied rather than that CPMs are beneficial, as some suggest.

There are a number of limitations in accepting these data. First and most importantly, this was neither a randomized nor a double-blind trial. Therefore, one cannot assume that the observed lack of effect was due to the drug discontinuation. The result may be due, for example, to these patients' responsivity to the attention they were receiving from the research team. The sample may have been treatment resistant to these particular CPMs. Second, results might have been different if CPMs were given in higher doses, but this is unlikely as most CPM dose regimens were within accepted clinical guidelines (Tables 1–3). Third, there may have been rater bias—although clinical ratings were consistent with those of independent raters, as well as patient and family reports. Fourth, at this juncture, since antipsychotic medication in some cases was blinded, we do not know which antipsychotic(s) a patient might have been taking—which may bear on outcome. We should also note that since we did not attempt taper of CPMs from patients who did not stabilize, we are unable to answer the question of whether this group of patients is helped or harmed by addition of CPMs to their antipsychotic.

In summary, since polypharmacy for schizophrenia is the most usual strategy in practice, this study was designed to systematically test the notion that many CPMs (here, antidepressants and mood stabilizers) are not only not beneficial or effective, but may worsen quality of life, induce side effects, and create drug interactions that decrease medication efficacy.[1 8] In addition, and importantly for many settings and patients, costs increase dramatically. Also, of course, the more complex the medication regimen, the lower the adherence.[12] A major challenge is motivating demoralized and/or depressed patients to continue treatment without adding nonhelpful medications; individual and family psychotherapy may be useful in this respect. Of course, if patients worsen when their CPMs are withdrawn, the treatment can be promptly restarted (as we did here with no untoward effects). The issue is to continually rechallenge a longstanding polypharmacologic regimen over the clinical course.

CONCLUSION

The clinical question is, "When is it clinically appropriate and safe to taper CPMs?" In this study, for most stabilized, chronic patients with schizophrenia, tapering adjunctive medications did not change outcome. The data should encourage clinicians who have chronic, relatively stabilized patients on treatment with multiple medications to carefully attempt to withdraw the adjunctive medications while monitoring clinical status. This naturalistic study further defines the limits of efficacy of some concomitant classes of medications in patients with chronic schizophrenia who are already receiving adequate antipsychotic therapy.

Drug names: aripiprazole (Abilify), bupropion (Wellbutrin and others), buspirone (BuSpar and others), carbamazepine (Equetro, Carbatrol, and others), citalopram (Celexa and others), clomipramine (Anafranil and others), clozapine (Clozaril, FazaClo, and others), divalproex (Depakote), escitalopram (Lexapro and others), fluoxetine (Prozac and others), fluphenazine (Prolixin and others), gabapentin (Neurontin and others), lamotrigine (Lamictal and others), lithium (Eskalith, Lithobid, and others), mirtazapine (Remeron and others),

modafinil (Provigil), olanzapine (Zyprexa), paroxetine (Paxil, Pexeva, and others), quetiapine (Seroquel), risperidone (Risperdal), sertraline (Zoloft), temazepam (Restoril and others), topiramate (Topamax), trazodone (Desyrel and others), venlafaxine (Effexor), ziprasidone (Geodon).

Disclosure of off-label usage: The authors have determined that, to the best of their knowledge, bupropion, buspirone, carbamazepine, citalopram, clomipramine, divalproex, escitalopram, fluoxetine, fluvoxamine, gabapentin, lamotrigine, lithium, mirtazapine, modafinil, paroxetine, phenobarbital, sertraline, temazepam, topiramate, trazodone, and venlafaxine are not approved by the U.S. Food and Drug Administration for the treatment of schizophrenia.

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