# Letters to the Editor

## Combination Therapy: Is Clinical Practice Leading the Way?

**Sir:** In "Antipsychotic Polypharmacy: Squandering Precious Resources?"[1] Dr. Stahl's primary recommendation that we should give adequate and extended trials of atypical antipsychotics as alternatives to combination therapy is good advice and no doubt largely accepted in clinical practice. However, the recommendation to try some agents at higher doses, particularly olanzapine and quetiapine, suffers the same difficulties the author noted for combination therapy. Namely, this option is not supported by good controlled data, atypicality may be compromised, and the cost increases dramatically.

Another espoused alternative, clozapine, while the most effective option for refractory psychosis, can prove challenging to administer. Side effects such as sedation, gastrointestinal dysfunction, orthostasis, agranulocytosis, weight gain, and other metabolic disturbances give many pause. Clozapine is also the most expensive antipsychotic. Our facility recently conducted a review of 193 patients administered 2 or more antipsychotics for 21 days or longer (R.W., M.S., unpublished data, January 2001). Interestingly, we found that the mean cost for clozapine in monotherapy was substantially greater than the mean cost for risperidone, olanzapine, and quetiapine used concomitantly with another antipsychotic (except clozapine). In fact, of all of the orders for combination therapy, only 19% were more expensive than the mean price of monotherapy with clozapine, and these were all orders for olanzapine with risperidone.

There are many practical reasons why atypical antipsychotics are being coadministered. We know that many patients will be partial responders to any given antipsychotic. To improve response, the available pharmacologic options are limited to switching medication or augmenting the existing medication. Switching medications can be time consuming, there is a risk of relapse, and the odds are that the result will be similar to but not significantly better than with previous medications. Aside from attempts to improve efficacy, combination therapy has also been successful in decreasing the side effects associated with atypical antipsychotics. The amelioration of sedation, sexual dysfunction, weight gain, and other metabolic disturbances are pragmatic applications.[2–5]

There is much we do not know regarding the etiology of schizophrenia and the mechanisms of action of the antipsychotic medications. It is quite likely that dopamine, and possibly serotonin, blockade are but 2 factors that produce an antipsychotic effect in a disorder that is increasingly being recognized as heterogeneous. Additionally, it is evident that clinical trials, in part by virtue of their strict inclusion/exclusion criteria, leave out many of the patients who are seen every day in clinics and hospitals.[6–8] Therefore, the gold standard of randomized, double-blind, placebo-controlled trials should be viewed with healthy caution. This is also why anecdotal case studies and naturalistic studies are prevalent and useful in psychiatry, where clinical practice is often the vanguard of innovation.[9]

Lastly, monotherapy with conventional drugs, although the least expensive recommendation, risks greater side effects, including tardive movement disorders. It would seem prudent to combine 2 atypical antipsychotics that have benign side effects, especially when considering the practical issues and possibility of enhanced efficacy noted above.

Much of the initial use of combination therapy was likely the result of "stalled switches"; however, as experience with the use of the atypical antipsychotics grows, the rational concomitant use of these agents to reduce side effects and/or enhance efficacy appears to be growing.

*The authors report no financial affiliation or other relationship relevant to the topic of this letter.*

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**Ron Welch, B.Sc.Pharm.**
**Mark Snaterse, B.Sc.Pharm.**
Alberta Hospital Edmonton
Edmonton, Canada


## Dr. Stahl Replies

**Sir:** Welch and Snaterse propose that clinical practice is leading the way to rational use of antipsychotic polypharmacy that enhances efficacy and/or reduces side effects of these agents. They prefer polypharmacy to the various alternatives I proposed in a recent Brainstorms[1]: high doses of olanzapine or quetiapine, the use of clozapine, or the inconvenience of switch-

ing from one antipsychotic to another. These authors also propose that, contrary to "squandering precious resources," polypharmacy is actually less expensive than clozapine (in Canada) and that randomized controlled trials should be viewed with healthy caution.

While I enthusiastically agree that randomized controlled trials do not provide all of the evidence necessary for clinical practice[2,3] and that they must be balanced with sophisticated clinical expertise largely derived from experience and the detailed study of individual patients[4] such as these authors obviously undertake in their own practices, there are also pitfalls to this approach[5,6] that can mesmerize many of us into following the Pied Piper into expensive and irrational therapeutic selections. Too much faith in clinical experience can amount to nothing more than "eminence-based medicine"[5] that leads to "making the same mistakes with increasing confidence over an impressive number of years."[6] The case of antipsychotic polypharmacy is especially problematic in terms of the evidence versus the experience and also its costs.

Antipsychotic monotherapies are well accepted for the treatment of psychosis due to compelling evidence from numerous large randomized controlled trials and meta-analyses.[2,7] This evidence is good as far as it goes, but it often fails to address certain patients of great concern to clinicians, namely those who do not respond to antipsychotic monotherapies and those for whom a greater-than-median improvement of psychosis (usually defined as > 30% reduction of symptoms in randomized controlled trials) is sought. For these patients, there is a growing body of experience, but not randomized controlled trials, that indicates that antipsychotic polypharmacy may be useful. The question is when to elect this option on the basis of all of the evidence and experience available today.

First, the easy parts of this debate are the initial recommendations I made for alternatives to antipsychotic polypharmacy,[1] namely, that, despite some inconvenience in switching, prescribers must try every available monotherapy and also optimize the trials of each monotherapy prior to attempting polypharmacy. On this point, the evidence is indisputable (see, for example, references 2 and 7). However, too often, monotherapies are tried for only 4 to 8 weeks, whereas the evidence suggests that it can take 16 weeks or longer for symptoms in the majority of patients to improve by 30%[8] and up to a year for some patients to improve by 60%.[9] Also, as the authors point out, prescribers sometimes fall into a polypharmacy trap[10] due to the common fallacy that improvement after adding drug B to drug A can be due only to synergy between them. It is also possible that the improvement is due to drug B alone, and that drug A should be discontinued. It is even possible that the improvement is due to more time on treatment with drug A alone, and that drug B should be discontinued.

Second, there is now evidence from randomized controlled trials that supports the therapeutic value of both divalproex augmentation[11] and high-dose olanzapine administration,[12] 2 of my other recommendations for alternatives to polypharmacy. Finally, the cost of clozapine versus polypharmacy may be different in various settings and in various countries. In Canada, where these authors work, the costs of new antipsychotics are as little as one fourth their cost in the United States, and using low doses of 2 atypicals may not be as expensive as other alternatives there. But in the United States, the cost of this practice is of great concern. For example, a recent study of polypharmacy within the California Medicaid program showed that 11% of patients received 2 antipsychotics for more that 60 consecutive days[13] and about half of these, or approximately 5000 patients, received 2 of the first-line agents risperidone, olanzapine, and quetiapine, which are, respectively, the first, second, and eighth most expensive among the 1750 drugs covered by the program. Drug costs for polypharmacy patients were 3 times greater than for patients who received just 1 drug.

And what is the evidence to support this practice of atypical polypharmacy with expensive first-line agents? There are no randomized controlled trials and only 9 case reports of risperidone-olanzapine, 2 case reports of risperidone-quetiapine, and 1 case report of olanzapine-quetiapine polypharmacy in the published literature,[14] several of which show lack of efficacy or even toxicity rather than benefit with the combinations. Payors such as California Medicaid are currently looking into reducing the very high overall costs of these drugs by curtailing some high cost–low evidence practices such as atypical antipsychotic polypharmacy rather than complete removal of the availability of some members of this class.[14]

For now, it seems reasonable to suggest that antipsychotic polypharmacy, especially of risperidone, olanzapine, quetiapine, and ziprasidone, should be done only after truly adequate trials of multiple monotherapies. The evidence suggests that, following such trials and prior to consideration of polypharmacy, divalproex augmentation, high doses of olanzapine, and/or monotherapy with clozapine or a conventional antipsychotic should be considered. If a trial of 2 antipsychotics is elected, it should be done with close monitoring in a time-limited trial and continued only when clear therapeutic benefits result. In the meantime, we eagerly await the results of adequate trials to help us determine the costs versus the benefits of antipsychotic polypharmacy.

*The author reports no financial affiliation or other relationship relevant to the topic of this letter.*

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**Stephen M. Stahl, M.D., Ph.D.**
Neuroscience Education Institute
Carlsbad, California

## Analgesic Effect of Antidepressants

**Sir:** Detke et al.[1] recently demonstrated that a new dual action antidepressant, duloxetine, can improve depression and associated painful physical symptoms. To date, 6 meta-analyses[2–7] have been consistent in demonstrating that antidepressants have an analgesic effect in all forms of chronic pain separate from their antidepressant effect. There is also significant evidence[8,9] that the dual action antidepressants have a more consistent analgesic effect versus that of selective serotonin reuptake inhibitors. Thus, the analgesic effect of duloxetine[1] is expected. As such, duloxetine may hold promise as an antidepressant that may help chronic pain patients who are usually depressed.[10]

In an associated commentary, Fava[11] raised 2 interesting questions that had been previously addressed in the pain literature: (1) is the correlation between somatic symptoms and depression strong or weak? and (2) what is the potential effect of somatic symptoms on depression? In a recent evidence-based structured review[10] (not a meta-analysis), my colleagues and I attempted to determine whether, in depressed chronic pain patients, depression preceded or followed the development of chronic pain. The results of this review were the following: (1) depression is more common in chronic pain patients than in controls; (2) the preponderance of the evidence indicated that depression followed the development of chronic pain; (3) however, depression predisposition increased the likelihood of the development of depression following the development of chronic pain; (4) and most important, there was a relationship between the perceived severity and frequency of pain and the development of depression. If chronic pain is to be considered a somatic symptom, then this report[10] partially addresses the 2 questions raised by Dr. Fava. I would agree with his recommendation that psychiatry needs to develop tools to specifically evaluate somatic symptoms. Somatic symptoms may precede the development of depression and thus be etiologically related to depression onset.

*Dr. Fishbain reports no financial affiliation or other relationship relevant to the subject matter of this letter.*

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**David A. Fishbain, M.D., F.A.P.A.**
University of Miami School of Medicine
University of Miami Comprehensive Pain
and Rehabilitation Center
Miami, Florida

## Dr. Detke Replies

**Sir:** My colleagues and I appreciate the comments by Dr. Fishbain, who has contributed much to our understanding of the importance of pain and its overlap with depression. He elegantly summarized the evidence regarding dual serotonin and norepinephrine reuptake inhibitors in chronic pain conditions. Our preclinical studies of duloxetine in animal pain models[1] are consistent with this evidence. However, the first clinical evidence we had that duloxetine was effective in the treatment of painful physical symptoms came in the study Dr. Fishbain is referring to, which was published in the *Journal* in April 2002.[2]

We also agree with Dr. Fishbain's interpretation of the literature on chronic pain patients. As he notes, for these patients, the preponderance of the evidence suggests that depression develops after the painful condition and that there is a relationship between the severity and frequency of the pain and the development of depression. However, the issue of which comes first, the mood disturbance or the pain, may be patient sample– and instrument-dependent.[3,4]

We would add that the patients we studied did not have chronic pain conditions in general. They had major depressive disorder (DSM-IV), and they were excluded if they had other significant medical diagnoses. Nevertheless, these patients had moderate levels of pain (a mean of approximately 25 on a 100-point visual analog scale), and duloxetine was effective in significantly reducing their pain. In primary care, 69% of patients with depression present with only physical symptoms.[5] Additionally, in patients who present with physical complaints, up to 60% have painful physical complaints, including headache, back pain, stomachaches, and poorly localized musculoskeletal pains.[6,7] Because of these facts, we believe that painful physical symptoms, which are common in major depressive disorder, may be distinct in some ways from chronic pain conditions, although both seem to be effectively treated by dual serotonin and norepinephrine reuptake inhibitors.

Finally, we believe that studies of duloxetine and other medications will help enhance our understanding of the impor-

tance of painful physical symptoms with and without depression and assist in the elucidation of mechanisms for treating various persistent/chronic pain symptoms and conditions.

*Dr. Detke is an employee and major stock shareholder of Eli Lilly and Company.*

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**Michael J. Detke, M.D., Ph.D.**
Lilly Research Laboratories
Indianapolis, Indiana
Indiana University School of Medicine
Indianapolis, Indiana
McLean Hospital and Harvard Medical School
Belmont, Massachusetts


## Prolonged Erections Associated With Ziprasidone Treatment: A Case Report

**Sir:** The ischemic form of priapism (previously known as *low-flow priapism*) is a rare but well-recognized complication of antipsychotic agents resulting from their $\alpha_1$-adrenergic blocking action.[1] Several cases have been documented with conventional antipsychotics, especially the phenothiazines.[2] Of the first 4 novel antipsychotics approved by the U.S. Food and Drug Administration for the treatment of psychosis, clozapine, risperidone, and olanzapine have been associated with priapism in various case reports, whereas quetiapine thus far has not.[3]

Ziprasidone is a recently marketed (2001) novel antipsychotic agent with a chemical structure unrelated to any other antipsychotic currently available. Clinical trials have demonstrated the drug to be effective for the treatment of psychosis, with a total incidence and severity of adverse events similar to those of placebo.[4] We report a case of a patient with prolonged erections during treatment with ziprasidone.

***Case report.*** Mr. A, a 32-year-old African American man with a history of schizophrenia (DSM-IV) beginning in his early twenties, was treated for several years with haloperidol, then with risperidone, 3 mg b.i.d., for about 3 years. The risperidone largely alleviated his hallucinations and delusions but eventually caused extrapyramidal symptoms that the patient found bothersome. Olanzapine, 15 mg q.h.s., was prescribed for about a year and was also effective, but resulted in weight gain. Quetiapine was then tried but did not adequately control his psychotic symptoms. When ziprasidone became available, Mr. A was changed to ziprasidone, 20 mg b.i.d. After 2 weeks, the dosage was increased to 40 mg b.i.d., and this dosage was sufficient to suppress his psychotic symptoms. At this point, Mr. A was taking no other medications.

At a clinic visit 3 months after the dosage increase, Mr. A expressed concern when he said, "Something is happening to my nature." He related that during the preceding month, he had had several unwanted penile erections that lasted up to an hour. These sometimes occurred without sexual stimulation or desire, were not pleasurable, and often did not resolve with ejaculation. He estimated about 3 such episodes per week, mostly at night. However, an episode had occurred during the daytime, causing him to have to leave work. The erections were described as uncomfortable or mildly painful, and he said he would rate the pain as a 3 on a scale from 1 to 10. Spontaneous detumescence occurred within a few hours with each episode.

Mr. A's wife confirmed that the erections had occurred as he had described. At times, Mr. A attempted to relieve the erections by having intercourse, although it was not pleasurable for him. According to his wife, intercourse during the episodes could last over 20 minutes, and his erections did not resolve with ejaculation.

His medical and surgical histories were unremarkable. He denied any alcohol or drug use, and there was no history of urologic trauma. Results of a physical examination and complete laboratory workup including complete blood cell count, chemistry profile, and urinalysis revealed no abnormality. Hemoglobin electrophoresis was negative for hemoglobin S or sickle cell trait. Ziprasidone was discontinued and treatment with risperidone, 4 mg q.h.s., was instituted. During the following few days, Mr. A experienced 2 similar prolonged erections, which lasted about 30 minutes each. The problem then fully resolved and has not recurred. The lower dose of risperidone has been adequate for the treatment of the schizophrenia without causing significant extrapyramidal symptoms.

It is likely that Mr. A's prolonged erections were associated with ziprasidone. Prior to treatment with the drug, he had had no history of this problem. There was a close temporal relationship between the occurrence of the prolonged erections and the institution of ziprasidone, and the abnormal erections ceased with discontinuation of the drug. He was taking no other medications, and a complete urologic evaluation revealed no other likely etiology.

Like conventional antipsychotics, novel antipsychotics may rarely cause priapism. The literature documents at least 8 cases that have been associated with clozapine, 3 with risperidone, and 5 with olanzapine.[3,5,6] Case reports of priapism related to quetiapine and ziprasidone have not previously been published (1 case of priapism, unpublished, occurred during ziprasidone premarketing clinical trials, but the relationship of the event to ziprasidone use apparently was not clearly established[7]). However, the lack of reports of cases associated with ziprasidone may reflect its relatively short time on the market.

Prolonged unwanted erections are recognized as a precursor to priapism,[8,9] and cases in which such erections preceded priapism in patients treated with psychotropics have been reported.[10] A case of prolonged erections lasting 15 to 30 minutes associated with risperidone and requiring no treatment other than discontinuation of the drug has also been reported.[11] The occurrence of prolonged erections with ziprasidone suggests that the drug may cause priapism, particularly in view of the fact that it has the highest affinity for $\alpha_1$-adrenergic receptor

blockade among the novel antipsychotics. $\alpha_1$-Adrenergic blockade affinities of novel antipsychotics defined as $10^{-7} \times 1/K_d$ (where $K_d$ = equilibrium dissociation constant in molarity) are ziprasidone, 38; risperidone, 37; clozapine, 15; quetiapine, 12; and olanzapine, 2.3.[12]

Cases of this type might suggest that the occurrence of atypical or prolonged erections in a patient taking ziprasidone or other antipsychotic agents should be considered a potential early presentation of priapism and may represent a *forme fruste* of the disorder. Physicians who prescribe these medications must be aware of such complications and employ caution when necessary. Because quetiapine is the only novel antipsychotic not yet associated with priapism or prolonged erections and has relatively low $\alpha_1$-adrenergic blockade affinity, it may ultimately prove to be the drug of choice for patients with psychosis who have previously experienced such symptoms.

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**Roy R. Reeves, D.O., Ph.D.**
**Ray Kimble, M.D.**
G.V. (Sonny) Montgomery VA Medical Center
University of Mississippi School of Medicine
Jackson, Mississippi