www.cfpc.ca

Letters ❖ Correspondance

Introducing nurse practitioners

One of the most important issues that primary care physicians will be dealing with in the immediate future is the introduction of nurse practitioners. A paper[1] published by the Ontario College of Family Physicians (OCFP), "Implementation Strategies: Collaboration in Primary Care—Family Doctors & Nurse Practitioners Delivering Shared Care," does much to increase my apprehension over the role of nurse practitioners in the future. The OCFP lists many functions that nurses will perform. What it does not clearly spell out is that family doctors should be coordinating patient care, not nurse practitioners.

Many of us do not believe that nurse practitioners should be diagnosing and treating "minor illnesses," and the right of nurse practitioners to refer directly to medical specialists puts them in direct conflict with our practices.

I hope that, as an organization representing family practice, the OCFP's willingness to undermine a profession should be contested. Who are they really representing? Family practice or nurse practitioners?

—T. Nicholas, MD
Aurora, Ont
by mail

Reference

1. Way D, Jones L, Busing N. *Implementation strategies: collaboration in primary care—family doctors & nurse practitioners delivering shared care.* Toronto, Ont: Ontario College of Family Physicians; 2000.

Response

Doctors working with nurses—what a revolutionary concept. Why would the Ontario College of Family Physicians (OCFP) participate in research into successful collaboration between family physicians and nurse practitioners? The answer is simple: we believe we can find a better model of collaboration than the one being proposed by our nursing colleagues. Like Dr Nicholas, OCFP's major point of departure is the firm belief that family doctors remain the coordinators of care.

Change theorists believe that 25% of people eagerly embrace the opportunity to participate in developing policy that shapes change. The OCFP and our colleagues at the Ontario Medical Association are leaders in Ontario and are working hard to ensure that primary care renewal results in positive changes for family physicians and their patients.

Dr Nicholas might be among the 75% of people who resist change because they see problems that they believe might outweigh benefits. Wise planners recognize that there is much to learn from listening to the concerns of people like Dr Nicholas. Through listening and especially through channeling the energy of resisters into positive action, barriers to change can be identified and removed. We invite Dr Nicholas to join with us in molding primary care renewal recommendations in a manner that further strengthens family medicine in this country.

—David Mathies, MD
President,
Ontario College of Family Physicians

Make your views known!

Contact us by e-mail at
letters.editor@cfpc.ca
on the College's website at
www.cfpc.ca
by fax to the Scientific Editor at
(905) 629-0893 or by mail to
Canadian Family Physician
College of Family Physicians
of Canada
2630 Skymark Ave
Mississauga, ON L4W 5A4

...

Faites-vous entendre!

Communiquez avec nous par
courier électronique:
letters.editor@cfpc.ca
au site web du Collège:
www.cfpc.ca
par télécopieur au
Rédacteur scientifique
(905) 629-0893
ou par la poste
Le Médecin de famille canadien
Collège des médecins de famille
du Canada
2630 avenue Skymark
Mississauga, ON L4W 5A4

Drug review "surprises" reader

In the review of the drug olanzapine originally published in *Prescrire International*[1] and reprinted in *Canadian Family Physician*,[2] I was surprised by the authors' conclusion that olanzapine offers "nothing new. There is no evidence that olanzapine is any more effective than other neuroleptics for schizophrenia. Its safety, especially for the liver and heart, remains to be established." This review provides a disservice to any Canadian family doctor wishing to keep abreast of new developments in psychiatric treatments and deserves rebuttal.

The authors state that the global efficacy of olanzapine was not significantly different from that of haloperidol. Despite response rates of 52% to 34% ($P > .001$) in favour of olanzapine over haloperidol,[3] the authors argue that the heterogeneity of the patient sample made the results difficult to interpret. Rather, this trial was one of the largest psychopharmacology trials ever conducted under a single protocol, with almost 2000 subjects in 17 countries, involving a research population

that indeed can be generalized to real clinical populations.

The authors criticize olanzapine for not being significantly different from haloperidol in efficacy for "positive" symptoms (hallucinations, delusions, and agitation). However, enhanced benefits with new antipsychotics are not necessarily greater efficacy for positive symptoms but rather include improved efficacy for negative symptoms, tolerability, safety, and compliance.

In regard to efficacy for "negative" symptoms (poverty of thought, apathy, and social withdrawal), olanzapine was better than haloperidol in two of the three trials referred to in the summary table.

The authors argue that olanzapine's safety profile is suspect, stating that subclinical cases of elevated transaminase levels, increased blood pressure, and QT prolongation were observed in clinical trials. Attention is paid to data showing 9.4% of olanzapine patients had elevated transaminase levels suggesting "an increased risk for hepatitis." This is despite not one reported case of hepatitis. Antipsychotics are known to release hepatic transaminases. Although transient elevation in alanine aminotransferase (ALT) values (to 200 IU/L or more) was noted in 1.9% of more than 2000 patients receiving olanzapine, these values typically declined with continued treatment.[4] The authors argue that the most worrisome adverse effects are cardiovascular, raised blood pressure, and prolonged QT interval. The evidence presented was from one trial where the mean rise in systolic blood pressure was a trivial 3.6 mm Hg. Electrocardiogram recordings in 8% of patients revealed QT prolongation by a mean of 2.82 milliseconds, suggesting a "potential for torsade de pointes." This was emphasized despite again not having one reported case. The authors fail to even mention olanzapine's minimal effects on serum prolactin levels. Rates of serum prolactin elevation due to olanzapine have been approximately half to one third of those observed with haloperidol and were significantly more transient.[5]

The authors argue against acknowledging olanzapine as an "atypical" antipsychotic. This is in contrast to accepted consensus in the field. Atypicality is defined as "antipsychotic action in most patients at doses that do not cause significant acute or subacute extrapyramidal side effects (EPSE)."[6] The "Canadian Clinical Practice Guidelines for the Treatment of Schizophrenia" state that treatment with clozapine, olanzapine, quetiapine, and risperidone (at lower doses) markedly reduces acute EPSE.[7]

Middle-aged and elderly outpatients treated with relatively low doses of first-generation antipsychotics have been shown to have a 29% cumulative annual incidence of tardive dyskinesia (TD).[8] The incidence of TD with atypical antipsychotics is likely to be lower given that EPSE has been found to be a risk factor for TD.[8] The low risk of TD for patients taking clozapine has already been well established,[9] and data for olanzapine thus far have revealed an equally low risk.[1] Lower rates of EPSE and TD are important for improved drug tolerability and compliance in younger populations and are essential for safety of antipsychotic use in the elderly. Olanzapine has shown promise as a safe antipsychotic for elderly patients with various psychotic conditions, including psychosis secondary to dementia.[10,11]

The authors fail to comment on olanzapine's excellent drug interaction profile. Olanzapine metabolism has little potential to be inhibited and does not inhibit other drug metabolism by cytochrome P-450 enzymes. Many first-generation antipsychotics (haloperidol, perphenazine, thioridazine, and zuclopenthixol) are extensively metabolized by cytochrome P-450 2D6. This enzyme is present in a limited and finite quantity in hepatocytes; is functionally deficient in 5% to 10% of whites; shows overall reduced rates of activity in Asians; and might be inhibited by a host of other medications frequently prescribed to schizophrenics, including paroxetine and fluoxetine.[12]

Compared with any first-generation antipsychotic, the advantage of treating schizophrenia with olanzapine is likely related to overall response rate, negative symptom response rate, EPSE profile, effect on prolactin levels, risk of TD, safety of use in the elderly, and lack of pharmacokinetic drug interactions.

Prescrire's own rating of "a real advance" would have been more appropriate.

—Richard W. Shulman, MD CM, FRCPC
Mississauga, Ont
by mail

Note: Dr Shulman is a paid consultant and speaker for continuing medical education for Eli Lilly Canada Inc, the manufacturer and distributor of olanzapine.

References

1. Olanzapine. *Rev Prescr* 1999;19(196):411-5.
2. Prescrire. Evidence-based drug reviews. Olanzapine. Keep an eye on this neuroleptic [Prescrire]. *Can Fam Physician* 2000;46:321-6 (Eng), 330-6 (Fr).
3. Tollefson GD, Beasley CM Jr, Tran PV, Street JS, Krueger JA, Tamura RN, et al. Olanzapine versus haloperidol in the treatment of schizophrenia and schizoaffective and schizophreniform disorders: results of an international collaborative trial. *Am J Psychiatry* 1997;154:457-65.

4. Zyprexa product monograph. *Compendium of pharmaceuticals and specialties*. 35th ed. Ottawa, Ont: Canadian Pharmacists Association; 2000.
5. Crawford AM, Beasley CM Jr, Tollefson GD. The acute and long-term effect of olanzapine compared with placebo and haloperidol on serum prolactin concentrations. *Schizophr Res* 1997;26(1):41-54.
6. Meltzer HY. Atypical antipsychotic drugs. In: Bloom FE, Kupfer DJ. *Psychopharmacology: the fourth generation of progress*. New York, NY: Raven Press, Ltd; 1995. p. 1277-86.
7. Working Group for the Canadian Psychiatric Association and the Canadian Alliance for Research on Schizophrenia. Canadian clinical practice guidelines for the treatment of schizophrenia. *Can J Psychiatry* 1998;43(Suppl 2):29s-33s.
8. Jeste DV, Rockwell E, Harris MJ, Lohr JB, Lacro J. Conventional vs newer antipsychotics in elderly patients. *Am J Geriatr Psychiatry* 1999;7(1):70-6.
9. Owens MJ, Risch SC. Atypical antipsychotics. In: Schatzberg AF, Nemeroff CB. *The American Psychiatric Press textbook of psychopharmacology*. Washington, DC: American Psychiatric Press, Inc; 1995. p. 263-80.
10. Solomons K, Geiger O. Olanzapine use in the elderly: a retrospective analysis. *Can J Psychiatry* 2000;45:151-5.
11. Street JS, Clark WS, Ganner KS, Cummings JL, Bymaster FP, Tamura RN, et al. Olanzapine treatment of psychotic and behavioral symptoms in patients with Alzheimer disease in nursing care facilities. *Arch Gen Psychiatry* 2000; 57:968-76.
12. Shulman RW, Özdemir V. Psychotropic medications and cytochrome P450 2D6: pharmacokinetic considerations in the elderly. *Can J Psychiatry* 1997;42(Suppl 1):4S-9S.

Response

We read with interest your comments. Concerning the global efficacy of olanzapine versus haloperidol, the three comparative trials, whose results conflict, must be considered together. The two trials involving patients with homogeneous diagnoses (acute-phase schizophrenia) failed to demonstrate the superiority of olanzapine over haloperidol. The third trial, which favoured olanzapine, suffers from heterogeneous recruitment that hinders the interpretations of the results.

Furthermore, while the two negative trials used the global Brief Psychiatric Rating Scale (BPRS) score, the trial favouring olanzapine used only part of the scale to constitute a "positive and negative syndrome scale," an approach that is methodologically incorrect. Leaving statistical differences to one side, what is the clinical relevance of a difference of 3 points between groups in the change in the BPRS score in the trial favouring olanzapine? Overall, no global difference in efficacy between olanzapine and haloperidol is demonstrated by these trials.

Regarding positive symptoms, the three available trials yielded the same results, ie, no difference between olanzapine and haloperidol. You appear to accept this. For our part, we consider that the efficacy of conventional neuroleptics on positive symptoms is far from optimal and would like to have more effective treatments.

As for negative symptoms, two of the three trials favour olanzapine, but the results call for close scrutiny. In the HGAD trial,[1] only patients treated with a high dose of olanzapine (16.3 mg) improved more than patients receiving haloperidol. This was not the case for the treatment group receiving a mean olanzapine dose of 11.6 mg. The mean olanzapine dose recommended in France is 10 mg/d. In the United States, the *Physicians' Desk Reference* (*PDR*)[2] lists no evidence that an olanzapine dose of more than 10 mg is more effective than 10 mg. The HGAJ trial,[3,4] which also favours olanzapine, is biased by the use of a high dose of haloperidol (11.8 mg) that can provoke depressive disorders mimicking negative symptoms. The report[5] by the European Medicines Evaluation Agency supports our point of view: "as the haloperidol doses were possibly too high (mean modal maintenance dose 11.8 mg) and could potentially induce depression mimicking negative symptoms, it is difficult to conclude that olanzapine is undoubtedly more efficacious on negative scores than haloperidol."

Our description of adverse effects is objective and reflects clinical trial data. The absence of clinical cases of hepatitis or torsades de pointes in clinical trials does not prove the safety of olanzapine: these events might be too rare to have been observed in only 2500 treated patients. Other neuroleptics with these types of toxicity were only incriminated in spontaneous postmarketing notifications. For example, it took many years to show the risk of torsades de pointes with thioridazine and cisapride, which caused some fatalities. It is therefore important that health professionals be vigilant about drugs.

Furthermore, weight gain while using olanzapine is a real problem, as noted in the *PDR*.[2] Contrary to your comment, our article mentions this risk, of which patients must be informed. We also note that your comment does not reproach us for not mentioning the diabetogenic risk of olanzapine, even though cases of aggravated or de novo diabetes have been published.

Regarding the rise in prolactin, if it is smaller on olanzapine than on haloperidol, this appears to have no major clinical consequences, as stated in the *PDR*.[2]

The *PDR* indicates that "the risks of using olanzapine in combination with other drugs have not been extensively evaluated in systematic studies."[2] This means that such events might be seen postmarketing. For example, a case of convulsions on the clomipramine-olanzapine combination has been published.[6]

We disagree with the widespread use by pharmaceutical companies (at least in France) of the term "atypical neuroleptic" to promote prescription of these drugs. Neuroleptics such as olanzapine, risperidone, and clozapine have the severe adverse effects of other neuroleptics, such as late-onset dyskinesias and malignant syndromes. The frequency might be lower, but the risk exists; when needed, these drugs should be used with care.

The main questions raised by the olanzapine assessment file remain to be answered: is olanzapine effective for psychoses resistant to other neuroleptics, and is olanzapine more effective than other recent neuroleptics that have few neurologic adverse effects, such as amisulpride (not available in Canada) or risperidone?

—Dr Bruno Toussaint
Editor-in-chief, La revue Prescrire

References

1. Beasley CM Jr, Tollefson G, Tran P, Satterlee W, Sanger T, Hamilton S. Olanzapine versus placebo and haloperidol: acute phase results of the North American double-blind olanzapine trial. *Neuropsychopharmacology* 1996;14(2):111-23.
2. Zyprexa. In: *Physicians' desk reference*. Montvale, NJ: Medical Economics Company, Inc; 2000. p. 1649-53.
3. Tollefson GD, Beasley CM Jr, Tran PV, Street JS, Krueger JA, Tamura RN, et al. Olanzapine versus haloperidol in the treatment of schizophrenia and schizoaffective and schizophreniform disorders: results of an international collaborative trial. *Am J Psychiatry* 1997;154:457-65.
4. Tollefson GD, Sanger TM, Lu Y, Thieme ME. Depressive signs and symptoms in schizophrenia: a prospective blinded trial of olanzapine and haloperidol. *Arch Gen Psychiatry* 1998;55:250-8.
5. European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products. *European public assessment report—Zyprexa*. London, Engl: European Agency for the Evaluation of Medicinal Products; 12 April 1999. p. 16.
6. Deshauer D, Albuquerque J, Alda M, Grof P. Seizures caused by possible interaction between olanzapine and clomipramine. *J Clin Psychopharmacol* 2000;20(2):283-4.