CORRESPONDENCE

Clozapine Alone versus Clozapine and Risperidone for Refractory Schizophrenia

TO THE EDITOR: Honer et al. (Feb. 2 issue)[1] showed that clozapine augmented with risperidone is unlikely to yield a moderate-to-large effect in patients with refractory schizophrenia. They conclude that there is no support for antipsychotic polypharmacy, a view also apparent in the accompanying editorial by Davis.[2] However, their confidence interval for the difference in the change in scores on the Positive and Negative Syndrome Scale still includes small-to-moderate effect sizes (0.3 to 0.5). Given the individual suffering and economic burden due to schizophrenia,[3] we think that even a moderate effect of combined treatment is worth considering. Moreover, although the primary analysis was rightly performed according to the intention-to-treat principle, the authors did not address the effect of patient compliance (e.g., by per-protocol analysis). Thus, their conclusion seems to be premature. Rather, augmenting clozapine in cases of treatment-resistant schizophrenia with second-generation antipsychotic agents possessing a favorable neuropharmacologic profile requires evaluation in randomized, controlled trials with larger sample sizes. Furthermore, the study presented does not provide evidence against the combination of different psychopharmacologic approaches.[4]

Guido Grass, M.D.
Martin Hellmich, D.Med.Sc.
F. Markus Leweke, M.D.
University of Cologne
50924 Cologne, Germany
m.leweke@uni.de

1. Honer WG, Thornton AE, Chen EYH, et al. Clozapine alone versus clozapine and risperidone with refractory schizophrenia. N Engl J Med 2006;354:472-82.
2. Davis JM. The choice of drugs for schizophrenia. N Engl J Med 2006;354:518-20.
3. Wu EQ, Birnbaum HG, Shi L, et al. The economic burden of schizophrenia in the United States in 2002. J Clin Psychiatry 2005;66:1122-9.
4. Kontaxakis VP, Ferentinos PP, Havaki-Kontaxaki BJ, Roukas DK. Randomized controlled augmentation trials in clozapine-resistant schizophrenic patients: a critical review. Eur Psychiatry 2005;20:409-15.

THIS WEEK'S LETTERS

TO THE EDITOR: The editorial by Davis concerning the lack of benefit from the augmentation of clozapine with risperidone in patients with schizophrenia who had a partial response incorrectly describes our study[1] as showing results that are opposite to those of Honer et al. In fact, we found and reported that placebo was superior to risperidone.[1] Honer et al. explicitly stated that their results were consistent with ours. Furthermore, Davis implies that our study was biased because it was funded by industry. We reported that our study received funding from two foundations and industry (the manufacturer of risperidone). Davis also contrasted the results of his meta-analyses of industry-funded clinical trials, which found advantages of atypical over typical antipsychotic drugs, with the results of the Clinical Antipsychotic Tri-

als of Intervention Effectiveness, funded by the National Institute of Mental Health, which did not find such advantages. This further implied that industry-funded studies may be unreliable. Careful evaluation of studies is necessary before making such judgments.

Herbert Y. Meltzer, M.D.
Vanderbilt University School of Medicine
Nashville, TN 37212
herbert.meltzer@vanderbilt.edu

A. Elif Anıl Yağcıoğlu, M.D.
Hacettepe University
06532 Ankara, Turkey

Berna Binnur Kıvırcık Akdede, M.D.
Dokuz Eylül University School of Medicine
35340 Izmir, Turkey

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1. Anıl Yağcıoğlu AE, Kıvırcık Akdede BB, Turgut TI, et al. A double-blind controlled study of adjunctive treatment with risperidone in schizophrenic patients partially responsive to clozapine: efficacy and safety. J Clin Psychiatry 2005;66:63-72.

TO THE EDITOR: In the editorial, Davis notes that the risk of agranulocytosis from clozapine is about 1 percent and that mortality can be reduced by weekly monitoring of platelet counts. Clozapine causes a loss of neutrophils through an idiopathic marrow-suppressive effect on myeloid maturation (pure white-cell aplasia) that occurs in approximately 0.22 to 0.44 percent of exposed patients, as reported at an advisory meeting of the Food and Drug Administration in June 2003.[1] The current estimate of the rate of agranulocytosis is lower than originally reported and is based on more recent monitoring data. The monitoring of the white-cell count as indicated in the package insert provides a safe system for the detection of severe neutropenia and agranulocytosis occurring with clozapine. Although thrombocytopenia associated with clozapine has been observed, its incidence is quite low and rarely requires intervention. Physicians prescribing clozapine should maintain monitoring of the white-cell count, not the platelet count.

Stanton L. Gerson, M.D.
Case Western Reserve University
Cleveland, OH 44106
slg5@case.edu

1. Overview of issues for Psychopharmacological Drugs Advisory Committee: WBC monitoring for clozapine. June 2003. (Accessed April 6, 2006, at www.fda.gov/ohrms/dockets/ac/03/slides/3959S1_01_FDA-Rocoosin.ppt.)

THE AUTHORS REPLY: In all fairness, Grass and colleagues should also note that, on the basis of the confidence interval from our study, a small-to-moderate effect size of similar magnitude favoring placebo augmentation is equally likely. Indeed, an advantage of augmentation of clozapine with placebo as compared with augmentation with risperidone for positive symptoms was reported elsewhere.[1] We observed a moderate disadvantage with risperidone augmentation in terms of working memory (effect size, −0.68) and evidence of glucose dysregulation, tempering any enthusiasm for this particular strategy. The study completion rate was 96 percent, and the results were no different when the three patients who discontinued treatment were excluded. Risperidone has a high affinity for dopamine D2 receptors and was chosen to complement the low affinity of clozapine — a more specific suggestion of a "favorable neuropharmacologic profile" would be welcomed. Other classes of drugs, such as anticonvulsants or antidepressants, might augment the effects of clozapine, but more comparisons with placebo augmentation are needed. We hope that the evidence for or against the value of antipsychotic polypharmacy will soon catch up with the widespread implementation of this practice.

William G. Honer, M.D.
University of British Columbia
Vancouver, BC V5Z 1L8, Canada
honer@interchange.ubc.ca

Allen E. Thornton, Ph.D.
Simon Fraser University
Burnaby, BC V5J 1S6, Canada

G. William MacEwan, M.D.
University of British Columbia
Vancouver, BC V5Z 1L8, Canada

1. Anıl Yağcıoğlu AE, Kıvırcık Akdede BB, Turgut TI, et al. A double-blind controlled study of adjunctive treatment with risperidone in schizophrenic patients partially responsive to clozapine: efficacy and safety. J Clin Psychiatry 2005;66:63-72.

THE EDITORIALIST REPLIES: I made an error in reading the numbers in the results table of the study by Yağcıoğlu et al. This randomized trial did not demonstrate a benefit of augmentation of clozapine with risperidone as compared with augmentation with placebo. Thus, the studies by Honer et al. and Yağcıoğlu et al. provide consistent evidence that risperidone augmentation does not produce an additional benefit over clozapine. Since a higher dose of risperidone was used in

the study by Yağcıoğlu et al., this study does not suggest that the negative findings of the Honer study resulted from an inadequate dose of risperidone. I apologize for my mistake. I found no evidence of bias in terms of pharmaceutical-industry sponsorship on the efficacy data from the randomized, controlled trials comparing second-generation with first-generation antipsychotic agents. All these drugs are effective, but randomized, controlled trials establish clozapine as the most efficacious.[1,2] However, the initial European experience found clozapine associated with agranulocytosis in about 1 to 2 percent of the patients (one third of cases were fatal). I agree with Dr. Gerson's conclusions. Mandatory monitoring of white-cell counts does indeed greatly minimize the risk of this complication.

John M. Davis, M.D.
University of Illinois at Chicago
Chicago, IL 60614

1. Wahlbeck K, Cheine M, Essali A, Adams C. Evidence of clozapine's effectiveness in schizophrenia: a systematic review and meta-analysis of randomized trials. Am J Psychiatry 1999;156:990-9.
2. Meltzer HY, Alphs L, Green AI, et al. Clozapine treatment for suicidality in schizophrenia: International Suicide Prevention Trial (InterSePT). Arch Gen Psychiatry 2003;60:82-91. [Erratum, Arch Gen Psychiatry 2003;60:735.]

Hypertonic Saline for Cystic Fibrosis

TO THE EDITOR: We question the selection by Elkins et al.[1] and Donaldson et al.[2] (Jan. 19 issue) of 7 percent hypertonic saline, which can result in bronchoconstriction, in these studies of therapy for cystic fibrosis. Elkins et al. report a fall of 94 ml in the forced expiratory volume in one second (FEV_1) after the first dose of medication, which is greater than the reported final improvement in FEV_1 of 68 ml. Conversely, Donaldson et al. do not specify any change in FEV_1 with the use of 7 percent hypertonic saline. Robinson et al.[3] have compared mucociliary clearance with the use of different concentrations of hypertonic saline and did not find any difference in efficacy between solutions of 3 percent and 7 percent hypertonic saline solutions. We have shown that the use of 3 percent hypertonic saline is effective and has the additional advantage of not causing a substantial change in FEV_1, oxygen saturation, or symptom score.[4] Hence, the choice of the strength of the hypertonic saline solution administered should be based on the potential effects of hypertonic saline on pulmonary function, oxygen saturation, palatability, and the patient's preference.

Imran Aziz, M.B., B.S.
Royal Albert Edward Infirmary
Wigan WN1 2NN, United Kingdom

Jack A. Kastelik, M.D.
Castle Hill Hospital
Cottingham HU16 5JQ, United Kingdom
j.a.kastelik@hull.ac.uk

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2. Donaldson SH, Bennett WD, Zeman KL, Knowles MR, Tarran R, Boucher RC. Mucus clearance and lung function in cystic fibrosis with hypertonic saline. N Engl J Med 2006;354:241-50.
3. Robinson M, Hemming AL, Regnis JA, et al. Effect of increasing doses of hypertonic saline on mucociliary clearance in patients with cystic fibrosis. Thorax 1997;52:900-3.
4. Kastelik JA, Aziz I, Morice AH. Sputum induction in young cystic fibrosis patients. Eur Respir J 2001;17:832.

TO THE EDITOR: Donaldson and colleagues report that hypertonic saline after pretreatment with amiloride did not result in a sustained increase in mucus clearance or improvement in lung function or respiratory symptoms because of inhibition of apical membrane water permeability. Animal airways have a moderate osmotic water permeability and express aquaporin water channels, one of which is aquaporin-3.[1-3] In Table 1 of their article, the authors report that 50 percent of the patients in each of the two study groups received inhaled steroids concomitantly. Corticosteroids have been found to induce the expression of aquaporin-3 in A549 cells, a human airway epithelial-cell line derived from lung adenocarcinoma, in vitro.[3] In addition, hypertonicity induces the expression of aquaporin-3 in Madin–Darby canine-kidney cells, a renal epithelial-cell line, in vitro.[4] Perhaps patients receiving concomitant treatment with inhaled steroids should have been studied separately, in order to identify the possible contribution of aquaporin-3 overexpression to hypertonic saline treatment.

Sotirios Zarogiannis, B.Sc.
Chrissi Hatzoglou, M.D., Ph.D.
Konstantinos Gourgoulianis, M.D., Ph.D.
University of Thessaly
41222 Larissa, Greece
szarog@med.uth.gr

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