

Antipsychotic Medications and Brain Volume

Do We Have Cause for Concern?

SINCE THE INITIATION OF ANTIPSYCHOTIC DRUG therapy for schizophrenia, clinical observations and empirical studies have demonstrated that these medications bring benefit and harm. Consequently, efforts to develop new antipsychotic medications during the past 50 years have been motivated, at least partly, by the desire to enhance the benefit to harm ratio relative to existing medications. In this issue of the *Archives*, Ho and colleagues¹ examine one arm of this ratio by asking whether antipsychotic medications contribute to progressive brain volume reductions in schizophrenia. Individuals early in the course of schizophrenia (n=211) were treated with antipsychotic medications according to standard clinical practice and followed up longitudinally with clinical assessments and serial magnetic resonance imaging (MRI) scans (between 2 and 5 scans per individual) for a mean of 7 years. The authors found that the amount of exposure to antipsychotic medication predicted decrements in cerebral gray and white matter volumes and increased the volume of the putamen. Illness duration and severity were also associated with smaller brain volume measures, but the relationship between antipsychotic medication use and brain volume remained significant after accounting for the effects of illness severity and duration and substance abuse history. Interestingly, changes in brain volume with time were similar for all classes of antipsychotic medications (ie, typical antipsychotics, atypical [ie, excluding clozapine] antipsychotics, and clozapine).

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The study by Ho and colleagues represents a remarkable and unique effort in terms of cohort sample size and number of measures obtained over time. However, the authors carefully note that the role of antipsychotic medications in the apparently progressive changes in brain volume needs to be considered cautiously because “identifying an association does not necessarily indicate a causal relationship.” Indeed, demonstrating causality or even imputing the direction of an association in human studies is always challenging. In this case, it is particularly difficult to infer causality because ethical issues preclude a more definitive study design involving placebo-treated individuals with schizophrenia and antipsychotic-exposed healthy comparison individuals.² An alternative means to address this issue may be available due to the increasing trend toward prescription of antipsychotic medications in the treatment of mood disorders, in which disease-

related decrements in brain volume are less prominent and widespread than in schizophrenia. Thus, a longitudinal comparison of brain volume changes in depressed individuals with and without exposure to antipsychotic medications, similar to that in the study by Ho and colleagues, may be feasible and informative. Although a negative result from such a study would not be conclusive because the possibility of a medication-by-diagnosis interactive effect on brain volume that is distinctive to schizophrenia could not be excluded, a positive finding would suggest a conserved medication effect that is independent of diagnosis or underlying disease process.

Although accompanied by a different set of interpretive limitations, studies of the effects of antipsychotic medications in experimental animals offer at least 2 important strengths for testing the hypothesis that antipsychotic medications cause a reduction in brain volume: the control of potential confounding factors and the demonstration of a biological mechanism. A previous study reported that administration of twice-daily oral haloperidol or olanzapine for approximately 2 years to young adult monkeys at doses producing trough serum drug levels in the range known to be therapeutic in humans was associated with total brain volumes approximately 10% smaller than those of matched placebo-treated animals.³ Histologic evaluation revealed that the haloperidol- and olanzapine-exposed animals had smaller cortical gray matter volume, greater cortical neuron density without a difference in total neuron number, and lower glial cell number,^{4,5} findings that parallel the results of postmortem studies in schizophrenia.⁶ (It is important to note that many other molecular and histologic findings from postmortem studies of schizophrenia were not found in these animals,⁷ which suggests it is possible to distinguish disease from drug effects.) Although these findings are consistent with the conclusion of Ho and colleagues that at least some of the structural brain alterations in schizophrenia are the consequence of antipsychotic medications, all the brain measures in the monkey study were made in postmortem tissue, precluding a within-individual design, and thus were not capable of excluding the possibility that the observed differences between antipsychotic- and placebo-exposed monkeys were present prior to drug administration. A recent study (S. Kapur, MD, written communication, October 5, 2010) addressed this issue by using serial MRIs in vivo and postmortem MRI and stereological tissue measures to assess brain volume in rats given 8 weeks of antipsychotic medications at doses that produced levels of dopamine D₂ receptor associated with therapeutic efficacy in humans. They found that haloperidol- and olanzapine-exposed rats

showed smaller brain volumes over time relative to matched control animals.

Although proof that antipsychotic medications cause reductions in brain volume in individuals with schizophrenia remains elusive, the findings of Ho and colleagues, in concert with those of the aforementioned animal studies and prior reports in humans,⁸ raise the important question of the clinical significance of the observed brain volume changes. Do the reductions in brain volume associated with antipsychotic medications impair function or are they related to the therapeutic benefits of these medications? Many individuals with schizophrenia discontinue taking typical and antipsychotic medications because of limited efficacy and poorly tolerated adverse effects.⁹ The observation by Ho and colleagues that the amount of antipsychotic treatment predicted the degree of brain volume reduction leaves open the possibility that the patients who benefitted the most continued to receive antipsychotic treatment and subsequently had the greatest brain volume changes. The idea that strategic reductions in brain volume can be functionally beneficial is supported by the improvements in cognitive capacity that accompany cortical gray matter volume reductions during adolescence.¹⁰ Alternatively, as suggested by Ho and colleagues, perhaps antipsychotic medications improve symptoms and contribute to progressive brain tissue reductions through different actions on separate brain circuits.

A classic maxim in clinical medicine is to treat the patient, not the laboratory test—or in this case, the MRI. Thus, the findings of Ho and colleagues should not be construed as an indication for discontinuing the use of antipsychotic medications as a treatment for schizophrenia. But they do highlight the need to closely monitor the benefits and adverse effects of these medications in individual patients, to prescribe the minimal amount needed to achieve the therapeutic goal, to consider the addition of nonpharmacological approaches that may improve outcomes,¹¹ and to continue the pursuit of new antipsychotic medications with different mechanisms of action and more favorable benefit to harm ratios.

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