Do Antipsychotic Drugs Change Brain Structure?
(updated November 2014)

SUMMARY:
Changes in brain structure are caused both by the disease process of schizophrenia and bipolar disorder and by the antipsychotic drugs used to treat these diseases. Different antipsychotic drugs may have different effects. It is important to study the brain changes caused by antipsychotic drugs, since this may tell us how these drugs work and/or predict which individuals are more likely to experience side effects. The changes caused by antipsychotic drugs used to treat schizophrenia and bipolar disorder are similar in kind to structural brain changes caused by drugs used to treat Parkinson’s disease, epilepsy, and other brain diseases. It is incorrect to characterize these brain changes as an indication that these drugs are dangerous or should not be used.

Background: The findings that antipsychotic drugs produce structural brain changes should not be a surprise. Schizophrenia and bipolar disorder are known to produce structural brain changes as part of the disease process, so it is reasonable to expect drugs that are effective in treating these diseases to do likewise. Some opponents of the use of antipsychotic medication misunderstand such research, arguing that brain changes prove that antipsychotic drugs are dangerous and should not be used. On the contrary, this research is very important and may eventually led to better and more effective medications.

Furthermore, many drugs known to be effective in other brain disorders also produce structural brain changes. For example, levodopa, a mainstay of treatment for Parkinson’s disease, has been shown to produce some changes in the cellular mitochondria and neuronal degeneration. Phenobarbital, widely used for many years to treat some forms of epilepsy, has been shown to produce “lasting effects on fine structure of cells” in the cerebellum. And diphenylhydantoin, also commonly used to treat epilepsy, has been shown to produce “marked dystrophic changes in the Purkinje cell axons” and to interfere with the formation of neuronal processes. Drugs used to treat diseases of other parts of the body (e.g., heart, joints) also may cause structural changes to those parts.


There is considerable ongoing research on the effects of antipsychotic drugs on brain structure. The majority of the work to date has been carried out in rats and needs to be replicated in...
humans, since there are substantial species variation in brain structure and function. The following structural brain changes appear to be caused by antipsychotic drugs.

- **Decreased brain volume with associated increased volume of the ventricles.** These changes appear to be caused both by the disease process and by the effects of antipsychotics, so it is difficult to determine how much is caused by one and how much by the other. In addition, the studies of antipsychotic drug effect have been inconsistent, with the majority of studies showing an effect, but a minority not showing one. The most impressive study done to date was a study by Ho et al. in which 211 individuals with schizophrenia were followed for an average of 7 years during which time they had repeat MRI scans. Those individuals who took more antipsychotics had greater decreases in their brain gray matter volume.


- **Increase in size of the striatum.** An increase in the size of the striatum (the striatum is composed of the caudate and putamen and is part of the basal ganglia) has been found in human MRI studies of individuals taking some antipsychotic drugs but not clozapine. The increased size is thought to be due both to increased blood flow and to structural changes of the neurons. It is not known whether this increased blood flow has any relationship to either the efficacy of the drug or its side effects.


- **Increased density of glial cells in the prefrontal cortex.** Glial proliferation and hypertrophy of the prefrontal cortex is reported to be “a common response to antipsychotic drugs” and may “play a regulatory role in adjusting neurotransmitter levels or metabolic processes.”

• **Increased number of synapses (connections between neurons) and changes in the proportions and properties of the synapses.** This includes changes in the distribution and subtypes of synapses. The changes have been found primarily in the caudate nucleus of the striatum, and there is some evidence that they may also occur in layer six of the prefrontal cortex but not elsewhere. The changes may be secondary to the effects of the antipsychotic drug on dopamine or glutamate neurotransmitters. It is not yet clear what these changes mean; they may be related to the efficacy of the drug or possibly be a marker for side effects. If the latter, being able to identify such changes in living individuals could potentially provide an early marker for tardive dyskinesia and thus indicate which individuals should not take these drugs. Most of these studies have been carried out in rats, so it is not yet known how applicable the findings are to humans.

• **Decrease in the gray matter in the parietal lobe associated with a decrease in glial cells but no decrease in neurons.** This research has been carried out on monkeys by giving them antipsychotic drugs and then assessing the effect on the brain.


• **Abnormal connectivity.** A Swiss study examined white matter connectivity in the brains of 17 never-treated individuals at high risk for psychosis (ARMS); 21 individuals with first-episode psychosis of whom 7 had never been treated; and 20 normal controls. Abnormal white matter connectivity was most marked among those who had never been treated; those on antipsychotics had a more normal pattern of connectivity.


• **Many of these studies assessed the effects of haloperidol (Haldol), a first-generation antipsychotic.** Fewer studies have been done with second-generation antipsychotics. Those that have been done suggest that the effects on brain structure may be somewhat different. For example, a study from the Netherlands (van Haren et al.) reported that first and second generation antipsychotics produced very different effects on brain structure.


Changes in white matter. Several studies have reported subtle changes in white matter in association with the use of antipsychotic drugs.


**So what does it all mean?** It is not yet clear what these medication-related brain changes mean. Individuals with schizophrenia who have more severe symptoms usually take higher doses of antipsychotic medication and also have more brain structural changes. The question is: are the brain changes due to the more severe symptoms or to the higher dose of antipsychotics? And, if the latter, are these brain changes ultimately helpful or harmful? Dr. David Lewis, a leading schizophrenia researcher, summarized the situation in commenting on the study by Ho et al:

> Do the reductions in brain volume associated with antipsychotic medications impair function or are they related to the therapeutic benefits of these medications?...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, and to continue the pursuit of new antipsychotic medications with different mechanisms of action and more favorable benefit to harm ratios.

Lewis DA. Antipsychotic medications and brain volume: do we have cause for concern? *Archives of General Psychiatry* 2011;68:126-7