



Antipsychotic Medications and the Brain

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.

The structural brain changes caused by antipsychotic drugs used to treat schizophrenia and bipolar disorder are similar in kind to structural brain changes caused by medications used to treat Parkinson's disease, epilepsy and other brain diseases, and it is a mistake to characterize them as an indication that these drugs are dangerous. Many medications widely regarded as beneficial are effective precisely because of their structural impact on the part of the body they treat.

It is also important to study the brain changes caused by antipsychotic drugs because they may shed light on how these drugs work and/or predict the risk of side effects. The merits of antipsychotic use additionally need to be considered within context of the considerable impacts of not using them, which include early mortality and heightened risk for arrest, incarceration, homelessness, victimization and violence, including suicide.

BACKGROUND

Findings that antipsychotic drugs produce structural brain changes should not surprise us. Schizophrenia and bipolar disorder are known to produce structural brain changes as part of the disease process; it is reasonable to expect drugs that treat the diseases effectively to do the same.

Some opponents of antipsychotic medication misunderstand such research, arguing that brain changes prove antipsychotic drugs are dangerous and should not be used. On the contrary, structural brain changes result from medications for many brain disorders and are associated with their effectiveness. Levodopa, a mainstay of treatment for Parkinson's disease for controlling tremor, has been shown to produce some changes in the cellular mitochondria and neuronal degeneration. Phenobarbital, widely used for many years to reduce seizures in 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 reduce seizures in 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 also may cause structural changes to those parts. Some drugs used to treat heart disease, for example, change the structure of the heart.

Ogawa, N., Edamatsu, R., Mizukawa, K., Asanuma, M., Kohno, M., Mori, A. (1993). Degeneration of dopaminergic neurons and free radicals. *Advances in Neurology*, 60, 242–250.

Fishman, R.H.B., Ornoy, A., Yanai, J. (1989). Correlated ultrastructural damage between cerebellum cells after early anticonvulsant treatment in mice. *International Journal of Developmental Neuroscience*, 7, 15–26.



Volk, B., Kirchgässner, N. (1985). Damage of Purkinje cell axons following chronic phenytoin administration: an animal model of distal axonopathy. *Acta Neuropathologica*, 67, 67–74.

Bahn, S., Ganter, U., Bauer, J., Otten, U., Volk, B. (1993). Influence of phenytoin on cytoskeletal organization and cell viability of immortalized mouse hippocampal neurons. *Brain Research*, 615, 160–169.

STRUCTURAL BRAIN CHANGES

There is considerable ongoing research on the effects of antipsychotic drugs on brain structure, primarily first-generation medications such as haloperidol. 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 antipsychotic drugs, making it difficult to differentiate their impacts. Additionally, studies of antipsychotic drug effect have been inconsistent, with the majority of studies showing an effect and a minority showing none. The most thorough study to date, conducted by Ho and colleagues, performed repeated magnetic resonance imaging (MRI) brain scans in 211 individuals with schizophrenia for an average of seven years. Those individuals who took more antipsychotics had greater decreases in their brain gray matter volume.

Ho, B.C., Andreasen, N.C., Ziebell, S., Pierson, R., Magnotta, V. (2011). Long-term antipsychotic treatment and brain volumes: a longitudinal study of first-episode schizophrenia. *Archives of General Psychiatry*, 68, 128–137.

Moncrieff, J., Leo, J. (2010). A systematic review of the effects of antipsychotic drugs on brain volume. *Psychological Medicine*, 40, 1409–1422.

Navari, S., Dazzan, P. (2009). Do antipsychotic drugs affect brain structure? A systematic and critical review of MRI findings. *Psychological Medicine*, 39, 1763–1777.

Boonstra, G., van Haren, N.E.M., Schnack, H.G., Cahn, W., Burger, H., Boersma, M., de Kroon, B., Grobbee, D., Hulshoff Pol, H.E., Kahn, R.S. (2011). Brain volume changes after withdrawal of atypical antipsychotics in patients with first-episode schizophrenia. *Journal of Clinical Psychopharmacology*, 31, 146–153.

- **Increase in size of the striatum.**

An increase in the size of the striatum (composed of the caudate and putamen and part of the basal ganglia) has been found in human MRI studies of individuals taking selected antipsychotic drugs exclusive of 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.

Chakos, M.H., Lieberman, J.A., Bilder, R.M., Borenstein, M., Lerner, G. (1994). Increase in caudate nuclei volumes of first-episode schizophrenic patients taking antipsychotic drugs. *American Journal of Psychiatry*, 151, 1430–1436.



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Li, M., Chen, Z., Deng, W., He, Z., Wang, Q., Jiang, L., Ma, X., Wang, Y., Chua, S.E., Cheung, C., McAlonan, G.M., Sham, P.C., Collier, D.A., Gong, Q., Li, T. (2012). Volume increases in putamen associated with positive symptom reduction in previously drug-naïve schizophrenia after 6 weeks antipsychotic treatment. *Psychological Medicine*, 42, 1475–1483.

- **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.”

Selemon, L.D., Lidow, M.S., Goldman-Rakic, P.S. (1999). Increased volume and glial density in primate prefrontal cortex associated with chronic antipsychotic drug exposure. *Biological Psychiatry*, 46, 161–172.

- **Increased number of synapses (connections between neurons) and changes in the proportions and properties of the synapses.**

The increased number includes changes in the distribution and the subtypes of synapses. The changes have been found primarily in the caudate nucleus of the striatum; 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, but it is not yet clear what they indicate. Whether they are related to the efficacy of the drug or a marker for side effects remains to be determined. If the latter, developing a tool to identify such changes in living individuals could provide an early marker for tardive dyskinesia and thus indicate which individuals should not take these drugs. Most such studies have been carried out in rats; 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.

Konopaske, G.T., Dorph-Petersen, K.A., Pierri, J.N., Wu, Q., Sampson, A.R., Lewis, D.A. (2007). Effect of chronic exposure to antipsychotic medication on cell numbers in the parietal cortex of macaque monkeys. *Neuropsychopharmacology*, 32, 1216–1223.

Konopaske, G.T., Dorph-Petersen, K.A., Sweet, R.A., Pierri, J.N., Zhang, W., Sampson, A.R., Lewis, D.A. (2008). Effect of chronic antipsychotic exposure on astrocyte and oligodendrocyte numbers in macaque monkeys. *Biological Psychiatry*, 63, 759–765.

- **Many of these studies assessed the effects of haloperidol (Haldol), a first-generation antipsychotic.**

Fewer studies have been done in second-generation antipsychotics than in first-generation medications. Those that have been conducted 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.



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Kopelman, A., Andreasen, N.C., Nopoulos, P. (2005). Morphology of the anterior cingulate gyrus in patients with schizophrenia: relationship to typical neuroleptic exposure. *American Journal Psychiatry*, 162, 1872–1878.

Massana, G., Salgado-Pineda, P., Junqué, C., Perez, M., Baeza, I., Pons, A., Massana, J., Navarro, V., Blanch, J., Morer, A., Mercader, J.M., Bernardo, M. (2005). Volume changes in gray matter in first-episode neuroleptic-naïve schizophrenic patients treated with risperidone. *Journal of Clinical Psychopharmacology*, 25, 111–117.

Lieberman, J.A., Tollefson, G.D., Charles, C., Zipursky, R., Sharma, T., Kahn, R.S., Keefe, R.S.E., Green, A.I., Gur, R.E., McEvoy, J., Perkins, D., Hamer, R.M., Gu, H., Tohen, M. (2005). Antipsychotic drug effects on brain morphology in first-episode psychosis. *Archives of General Psychiatry*, 62, 361–370.

Panenka, W.J., Khorram, B., Barr, A.M., Smith, G.N., Lang, D.J., Kopala, L.C., Vandorpe, R.A., Honer, W.G. (2007). A longitudinal study on the effects of typical versus atypical antipsychotic drugs on hippocampal volume in schizophrenia. *Schizophrenia Research*, 94, 288–292.

Vita, A., De Peri, L. (2007). The effects of antipsychotic treatment on cerebral structure and function in schizophrenia. *International Review of Psychiatry*, 19, 431–438.

Koolschijn, P.C., van Haren, N.E.M., Cahn, W., Schnack, H.G., Janssen, J., Klumpers, F., Hulshoff Pol, H.E., Kahn, R.S. (2010). Hippocampal volume change in schizophrenia. *Journal of Clinical Psychiatry*, 71, 737–744.

van Haren, N.E., Schnack, H.G., Cahn, W., van den Heuvel, M.P., Lepage, C., Collins, L., Evans, A.C., Hulshoff, H.E., Kahn, R.S. (2011). Changes in cortical thickness during the course of illness in schizophrenia. *Archives of General Psychiatry*, 68, 871–880.

- **Changes in white matter.**

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

Szeszko, P.R., Robinson, D.G., Ikuta, T., Peters, B.D., Gallego, J.A., Kane, J., Malhotra, A.K. (2014). White matter changes associated with antipsychotic treatment in first-episode psychosis. *Neuropsychopharmacology*, 39, 1324–1331.

CONCLUSION

The meaning of medication-related brain changes is not yet known. Individuals with schizophrenia who have more severe symptoms usually take higher doses of antipsychotic medication and also have more brain structural changes. Whether the brain changes are due to the severity of the symptoms or the higher dose of antipsychotics and whether – if the latter – the brain changes are ultimately helpful or harmful remains to be established.

David Lewis, MD, a leading schizophrenia researcher, summarized the situation in commenting on the study by Ho and colleagues:

Do the reductions in brain volume associated with antipsychotic medications impair function or are they related to the therapeutic benefits of these medications . . . ? (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



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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, D.A. (2011). Antipsychotic medications and brain volume: do we have cause for concern? *Archives of General Psychiatry*, 68, 126—127.