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Review

Are structural brain changes in schizophrenia related to antipsychotic medication? A narrative review of the evidence from a clinical perspective

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Abstract: Some observational studies and literature reviews suggest that antipsychotic drug use is associated with loss of grey or white matter in patients with schizophrenia, whereas others have contradicted this finding. Here, I summarize and critique the available evidence and put it in the context of clinical practice. This narrative review pools evidence from observational and experimental studies in humans and animals on the relationship between antipsychotic medication use and brain structure and function in patients with schizophrenia. To summarize, the observational evidence in patients with schizophrenia and the experimental evidence in animals suggest that antipsychotic drugs can cause reductions in brain volume, but differ as to where those effects are manifest. The experimental evidence in patients is inconclusive. There is stronger and more consistent evidence that other factors, such as alcohol and cannabis use, are likely causes of progressive brain changes in schizophrenia. Overall, I argue the case against antipsychotics is not proven and the jury is out on any significance of putative antipsychotic-induced brain changes. Taken in the context of strong evidence from clinical trials that antipsychotic drugs have beneficial effects on symptoms, function, relapse and cognition, and observational evidence that treatment normalizes other imaging indices and reduces mortality, the balance of probabilities is that antipsychotic drugs do not cause adverse structural brain changes in schizophrenia.

Keywords: antipsychotic drugs, magnetic resonance imaging, outcome, schizophrenia

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Introduction

Schizophrenia has a variable presentation, course and outcome. Up to one half of patients can be held to have a good outcome [1] but a meta-analysis of 50 naturalistic follow-up studies concluded that only 13.5% of patients with schizophrenia recover in the long term.[2] This figure is very similar to the repeated findings from prospective longitudinal studies that about one fifth of people diagnosed with schizophrenia will be symptom free without antipsychotic medication on long-term follow up. For example, the AESOP-10 study showed that approximately 20% of people with schizophrenia had no psychotic symptoms and were not taking antipsychotics at 8 years or more of follow up.[3]

Antipsychotic benefits

Antipsychotic medication can have dramatic benefits in acute schizophrenia. In a systematic review and meta-analysis, Leucht and colleagues[4] included 167 double-blind, randomized controlled trials (RCTs) with 28,102 participants, mainly with chronic disease. At least a 'minimal' response occurred in 51% of the antipsychotic-treated group *versus* 30% in the placebo group, and 23% *versus* 14% had a 'good' response. Quality of life and functioning also improved, even in the short term. Antipsychotics are also very effective at relapse prevention,[5] and the effect size is strong and greater even than seen for most drugs in general medicine.[6] A meta-analysis of 65 studies reported that 27% of patients with

schizophrenia receiving antipsychotic medication had relapses at 7–12 months compared with 64% of patients who had medication withdrawn and switched to placebo.[5] Patients with stable disease for 3–6 years still relapsed after antipsychotic withdrawal. Sensitivity analysis to address supersensitivity/rebound psychosis showed that even when only patients who had not relapsed for 3, 6 or 9 months after study start were included, antipsychotics were still more efficacious than placebo.

Based on available evidence on relapse prevention, patients with first-episode psychosis should receive antipsychotics for 1 year, and those with multiple episodes should receive medication for 3–6 years (because there are no longer-term trial data).[5,7] The duration of treatment needs to be individualized and based on the severity of psychotic episodes and side effects. Overall, however, there is a good deal of evidence that antipsychotic drugs improve long-term outcome in schizophrenia,[8] and very little evidence that they lead to a poor outcome. It has therefore become commonplace for patients with schizophrenia to remain on the same or similar doses of antipsychotic medication for years and even decades. A natural conservatism amongst clinicians, keen to avoid relapse and further hospitalization, is compounded by pressures on services that can make regular review difficult. Moreover, after referral of patients back to primary care, GPs are afraid to change the antipsychotic dose, let alone stop it.

Antipsychotic harms

Antipsychotic drugs also have a propensity to cause troublesome adverse effects. About 5% will have one or more adverse effects, such as movement disorder, sedation or weight gain, which can be attributed to the drug.[5] Patients do not like taking antipsychotic medication long term and some recent evidence suggests that doing so can impair the prospects of recovery[9] and potentially reduce brain volume (see below).

The open, randomized controlled MESIFOS trial[9] found that patients with remitted first-episode psychosis who continued on maintenance antipsychotic therapy were initially functioning better at 18 months than those who underwent dose reduction or discontinuation. In addition, relapse rates were 20% higher in patients who discontinued antipsychotics compared with patients who continued to take them. However, by 7 years, after 5 years of unspecified treatment, those in the dose-reduction/discontinuation arm were functioning better than those in the maintenance arm. They had a higher rate of recovery (symptomatic and functional remission: 40.4%) than those who had originally received maintenance therapy (17.6%). Notably, however, only 20% of patients could discontinue antipsychotics successfully and the doses of antipsychotic drugs were similarly low in the two arms of the study, making the findings difficult to interpret.

Antipsychotic-associated structural brain changes

It has been clear for 20 years or so that schizophrenia is associated with widespread reduction in brain volume compared with groups of healthy controls, particularly in prefrontal and medial or superior temporal lobes. Some of these studies also suggested an association between first-generation antipsychotic drug use and increases in the volume of parts of the basal ganglia, especially the globus pallidus, which might be reversed upon switching to second-generation drugs and clozapine.[10–12]

Initially, these differences were interpreted as developmental but it is now clear that there are progressive reductions in both grey and white matter in patients with schizophrenia. Olabi and colleagues[13] systematically reviewed the literature and found that the differences between patients and controls in annualized percentage volume change were −0.07% for whole brain volume, −0.59% for whole brain grey matter, −0.32% for frontal white matter, −0.32% for parietal white matter, −0.39% for temporal white matter, and +0.36% for bilateral lateral ventricles.

Gradually, evidence began to accrue that antipsychotic drugs were associated with progressive reduction in grey matter volume, but relationships with the type or dose of drug, illness duration and site of apparent changes were very variable across studies. Very few studies had the power to detect the size of the effect.[14,15]

One particularly notable study substantially added to the evidence that antipsychotic drugs might actually cause structural brain changes in schizophrenia. Ho and colleagues[16] examined no fewer than 211 patients who each had an average of three structural magnetic resonance imaging

(MRI) scans over an average of 7 years. These sequential MRI scanning investigations showed that patients with schizophrenia had an increase in lateral ventricular volume and a reduction in grey matter volume over time that was associated with increasing antipsychotic dose and the researchers could not find a similar relationship with illness features. There was also an apparent dose–response effect for lateral ventricular volumes, but the correlation between time on treatment and grey matter volume was stronger in those on an 'intermediate dose' (mean 392 mg chlorpromazine equivalents) than those on higher or lower doses.[16]

There are several other problems with this and similar studies. Such naturalistic studies may be subject to bias because patients with the best outcome may selectively stop antipsychotic treatment. In other words, antipsychotic dose and duration is increased in the most ill patients, who are also those most likely to show the greatest brain changes over time. Indeed, there is a well replicated association between progressive loss of grey matter and poor outcome, but none of those studies have examined any potentially mediating effect of antipsychotic drugs (see below).

Experimental evidence

Clearly, the only means by which to know for sure whether antipsychotic drugs cause structural brain changes in schizophrenia, over and above those associated with the illness and associated factors, is to conduct a RCT in patients and include serial structural MRI. This is however far easier said than done. To my knowledge, there are two such published accounts and both attest to the difficulties of such studies rather than delivering clear results. Leiberman and colleagues[17] randomized 263 patients with first-episode psychosis to haloperidol or olanzapine and attempted to follow them up over two years. Haloperidol was associated with reduced whole brain and prefrontal grey matter volumes whereas olanzapine was not, and healthy controls showed some increases over time, but attrition from the trial was so high as to make the results impossible to interpret.

Roiz-Santianez and colleagues[18] investigated the effects of risperidone ($n = 16$), olanzapine ($n = 18$) and low doses of haloperidol ($n = 18$) on cortical thickness changes during a 1-year follow-up period in a relatively small sample of patients with schizophrenia spectrum and found no significant differences between groups. *Post hoc* comparisons indicated that a control group had a thicker cortical thickness than the risperidone treatment group.

For ethical reasons, neither of these studies was able to include an untreated patient control group. These days, given the overwhelming evidence for the benefits of antipsychotic drugs in schizophrenia, it is only animal (or perhaps cellular) models that can incorporate such an untreated control arm. In a series of studies, researchers in Pittsburgh gave adolescent or young adult macaque monkeys differing antipsychotic medications for up to 2 years using drug administration paradigms at doses that produce trough serum drug levels in the range known to be therapeutic in humans.[19] Chronic administration of either haloperidol or olanzapine was associated with smaller grey matter volume, lower glial cell number, and higher neuron density without a difference in total neuron number in the cerebral cortex, findings that parallel the results of postmortem schizophrenia studies.[20,21] These similarities support the interpretation that some of the alterations in brain morphology reported in schizophrenia are attributable to the effects of antipsychotic medication, but the changes (of about 8–10%) were greater than those typically reported even in chronic schizophrenia, the differences many other studies note between first- and second-generation antipsychotics were not evident, and one cannot rule out species effects.

Studies of rats have reached similar but different conclusions. Chronic (8 weeks) exposure to both haloperidol and olanzapine resulted in significant decreases in whole-brain volume (6–8%) compared with vehicle-treated control subjects, driven mainly by a decrease in frontal cerebral cortex volume (8–12%). Hippocampal, corpus striatum, lateral ventricles, and corpus callosum volumes were not significantly different from control subjects, suggesting a differential effect on the cortex. These results were corroborated by *ex vivo* MRI scans and decreased cortical volume was confirmed postmortem by stereology. However, further examination showed that in the anterior cingulate cortex (ACC) treatment had no effect on the total number of neurons or S100β+ astrocytes in the ACC; rather, an increase in the density of these cells was observed. Thus, whilst the available animal literature generally suggests an adverse effect of antipsychotic drugs on grey

matter, the available studies do not agree on the cell populations implicated.[22,23]

Known influences on brain structure in schizophrenia

One further group of studies is relevant; those that show the effects of other factors associated with schizophrenia on the structure of the brain. These factors include pre-illness developmental influences and risk factors for schizophrenia, as well as post-illness factors. There are in fact many of these and some of them have considerably stronger evidence for their effects on the brain in health and illnesses such as schizophrenia.

In our own work, as part of the Edinburgh High Risk Study of Schizophrenia (EHRS), we have shown the effects of family history, childhood maltreatment, alcohol and cannabis use on differences in several brain volumes between young people at elevated familial risk and healthy controls.[24–26] We have also shown, in a total of 434 structural MRI scans collected over 10 years, that reductions in prefrontal and temporal lobe volumes of about 1% per year are evident in those who go on to develop International Classification of Diseases (ICD)-10 schizophrenia from an average of 2.5 years before the onset of diagnosable disorder and that such changes correlate strongly with increasing symptom severity.[27] All of these changes occurred in untreated at risk individuals and so antipsychotic medication cannot be invoked as an explanation.

Longitudinal twin studies from Utrecht have also shown that whole brain volume reductions in patients are at least partly due to the heritability of the condition.[28] In addition, patients with first-episode psychosis who use cannabis show a greater grey matter volume reduction at 5-year follow up than patients who are nonusers and healthy controls.[29]

It is also now clear that alcohol causes cortical shrinkage in healthy individuals even at low dosage.[30] Two notable studies have shown that effects are if anything greater in people with schizophrenia who drink to excess, especially in the prefrontal cortex.[31,32] Two recent systematic reviews strongly suggest that chronic cannabis use reduces grey matter in both healthy and clinical populations, especially in the CB1 receptor rich prefrontal cortex.[33,34] In addition, substance misuse (alcohol or drugs) in patients with schizophrenia has been shown to wipe out the relapse prevention benefits of adherence to antipsychotic medication.[35]

The deleterious impact of relapses and the other benefits of antipsychotics

It is important that clinicians and patients realize the ongoing benefits of antipsychotic medication in schizophrenia and the dangers of stopping treatment.

It would be a great shame if, at most, suggestive evidence of grey matter reductions led to systematic undertreatment and an increase in attendant risks.

Psychiatrists tend to overestimate patients' adherence to antipsychotic medication and numerous data suggest that 50% or more of patients with schizophrenia are poorly adherent or nonadherent.[36] Patients with partial or full nonadherence to antipsychotics are at significant risk of relapse. Discontinuation of antipsychotic medication after remission of first-episode psychosis or in established illness significantly increases the risk of relapse compared with maintenance therapy. Indeed, stopping antipsychotic medication is the most powerful predictor of relapse.[37]

Gradual discontinuation may be associated with a lower rate of relapse compared with abrupt discontinuation[38] but even low doses of antipsychotics are associated with greater relapse rates than higher doses[39,40] and relapse rates are higher with intermittent treatment than continuous treatment.[41]

Relapse has a major negative impact on patients with schizophrenia and is associated with worse prognosis, worse cognitive function, risk of injury to self and others, risk of hospitalization, decreased quality of life and self-esteem, and reduced ability to regain previous levels of health, functioning and support.[42,43] For example, the diagnosis of schizophrenia at a young age makes it difficult to enter work, and frequent absences jeopardize job prospects. Having a job improves general and mental health and wellbeing, and people with schizophrenia who are employed are much more likely to achieve functional remission than those who are not.[44,45] Repeated relapses may also lead to reduced responsiveness or refractoriness to antipsychotic medication.[46,47] Relapse can therefore have devastating clinical consequences,

which are likely to be of much greater consequence than some possible antipsychotic drug-mediated reduction in grey matter. Indeed, relapse and rehospitalization are themselves also associated with greater brain tissue loss.[48,49]

One other major benefit of antipsychotic medications in schizophrenia deserves special mention: they save lives! On average, people with schizophrenia die 14.5 years earlier than the general population, with 60% of excess deaths due to suicide and accidents, and 40% to natural causes.[50] Reasons for the excess natural deaths include lifestyle issues (e.g. high rates of smoking, possible self neglect, lack of exercise), and reduced access to healthcare services.[51] The available RCT evidence suggests antipsychotic treatment reduces mortality overall,[5,52] but death is thankfully such a rare event in trials that observational studies have to be relied upon to answer this question. Several longitudinal studies in several countries and healthcare settings have found a lower risk of mortality in antipsychotic-treated patients with schizophrenia compared with untreated patients.[53,54]

Concluding remarks

RCTs have established beyond any reasonable doubt that antipsychotic medication is highly effective in treating the acute symptoms of schizophrenia and reducing relapse. They also seem highly likely to generally improve function and quality of life, and prolong life, despite notable adverse effects. Overall, antipsychotic drugs do far more good than harm in patients with schizophrenia. They also have an increasingly clear role in the management of bipolar disorder.

However, antipsychotics are often inappropriate and may be damaging if used in some other psychotic disorders (e.g. brief psychotic disorder, psychotic disorder due to a general medical condition, substance-induced psychotic disorders), and approximately 20% of patients with schizophrenia do not need antipsychotic treatment beyond at most a short period. Predicting which patients fall into this category is at present not possible. The judicious management of patients with schizophrenia remains, therefore, aiming to maintain patients on the lowest possible effective dose. RCT evidence supports treating most patients for 1–2 years after they have responded to treatment for an acute episode. Clinical practice suggests that once they are stable the dose can be reduced cautiously, perhaps in increments every 3 months or so, to allow time for the dose to be increased again if needed. Patients with schizophrenia should be made aware that stopping antipsychotic medication is the most powerful predictor of relapse.

Systematic reviews and meta-analyses have established that there is progressive loss of grey and white matter in patients with schizophrenia, and suggest that antipsychotic medication may contribute to this. However, the available patient studies are inconsistent as to whether grey or white matter is particularly affected and whether first- or second-generation antipsychotic drugs are implicated. Such observational studies are prone to many biases and, unlike RCTs, cannot show a causal relationship. Experimental studies in animals suggest an effect, but the cell populations affected are inconsistent. Overall, the evidence is inconclusive. There is much more consistent and convincing evidence that other factors, including stress, alcohol and cannabis, contribute to progressive loss of brain substance in humans and animals.

The broader literature on the cognitive and imaging effects of antipsychotics in schizophrenia also argues against a generally noxious influence. Systematic reviews have shown that initiating antipsychotic treatment in patients with first-episode psychosis produces sustained cognitive improvement for up to 2 years.[55,56] Similarly, the bulk of the functional imaging literature suggests that antipsychotics normalize activation and connectivity patterns in patients with schizophrenia.[57,58]

The same benefits seems to accrue in spectroscopy studies.[59,60] It is difficult to see how antipsychotic medication can normalize functional measures and yet have an apparently adversely impact on brain structure, but some studies suggest exactly that.[61] One possible interpretation is that brain structure actually increases during an acute psychotic episode, possibly through inflammatory processes, and that a reduction is in fact a normalization. Another is that there may be a subgroup who show reductions, possibly those who do not benefit clinically from antipsychotic drugs because they have a different (nonhyperdopaminergic) pathophysiology or because they have dopamine supersensitivity.

Or perhaps it is those on the highest doses who are rendered so immobile or sedated as to be able to do little in the way of everyday activities and therefore show a ‘disuse atrophy’ of grey and

white matter through reduced dendritic arborization or myelin sheath thickness.

Another critical piece of the puzzle, is that (as far as I am aware) there have been no studies which have shown antipsychotic drugs to adversely impact on brain structure and to have adverse functional effects. It is clear that patients with schizophrenia who have the greatest loss of grey matter over time tend to have the worst outcome,[62,63] but there is no clear evidence that antipsychotic medication rather than some other factors are responsible.

To sum up, there is currently insufficient evidence to conclude that antipsychotics cause brain tissue loss in schizophrenia. There are other more likely causes. There is no clear relationship between antipsychotic-induced brain changes and cognitive impairment or functional decline. The matter can likely only be finally settled by suitably large and placebo-controlled trials of patients on or off antipsychotic medication with serial imaging investigations.

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