Antipsychotics and brain shrinkage: an update

joannamoncrieff / December 13, 2013

Evidence that antipsychotics cause brain shrinkage has been accumulating over the last few yearsbut the psychiatric research establishment is finding its own results difficult to swallow. A new paper by a group of American researchers once again tries to 'blame the disease,' a time honoured tactic for diverting attention from the nasty and dangerous effects of some psychiatric treatments. In 2011, these researchers, led by the former editor of the American Journal of Psychiatry, Nancy Andreasen, reported follow up data for their study of 211 patients diagnosed for the first time with an episode of 'schizophrenia'. They found a strong correlation between the level of antipsychotic treatment someone had taken over the course of the follow up period, and the amount of shrinkage of brain matter as measured by repeated MRI scans. The group concluded that "antipsychotics have a subtle but measurable influence on brain tissue loss" (1).

This study confirmed other evidence that antipsychotics shrink the brain. When MRI scans became available in the 1990s, they were able to detect subtle levels of brain shrinakge in people diagnosed with schizophrenia or psychosis. This lead to the idea that psychosis is a toxic brain state, and was used to justify the claim that early treatment with antipsychotics was necessary to prevent brain damage. People even started to refer to these drugs as having "neuroprotective" properties, and schizophrenia was increasingly described in neo-Kraeplinian terms as a neurodegenerative condition (2).

The trouble with this interpretation was that all the people in these studies were taking antipsychotic drugs. Peter Breggin suggested that the smaller brains and larger brain

cavities observed in people diagnosed with schizophrenia in th
using the less sensitive CT scans), were a consequence of an
no one took him seriously. It was assumed that these findings
abnormalities that were thought to constitute schizophrenia, an
paid much attention to the effects of drug treatment. Where the
antipsychotics were explored, however, there were some indica
might have a negative impact on brain volume (4).

In 2005, another American group, led by Joseph Lieberman wh
study, published the largest scanning study up to that point of
episode of psychosis or schizophrenia (5). The study was func
consisted of a randomised comparison of Lilly's drug olanzapin
drug haloperidol. Patients were scanned at the start of the stud
year later and patients' scans were compared with those of a c
volunteers. At 12 weeks haloperidol treated subjects showed a statistically significant reduction of the brain's grey matter (the nerve cell bodies) compared with controls, and at one year both olanzapine and haloperidol treated subjects had lost more grey matter than controls. The comparative degree of shrinkage in the olanzapine group was smaller than that in the haloperidol group, and the authors declared the olanzapine-related change not to be statistically significant because, although the result reached the conventional level of statistical significance (p=0.03) they said they had done so many tests that the result might have occurred by chance. In both haloperidol and olanzapine treated patients,however, there was a consistent effect that was diffuse and visible in most parts of the brain hemispheres.

The idea that schizophrenia or psychosis represent degenerative brain diseases was so influential at this point, that the authors first explanation for these results was that olanzapine, but not haloperidol, can halt the underlying process of brain shrinkage caused by the mental condition. They did concede, however, that an alternative explanation might be that haloperidol causes brain shrinkage- they never admitted that olanzapine might do this.

It seems as if Eli Lilly and its collaborators were so confident about their preferred explanation, that they set up a study to compare the effects of olanzapine and haloperidol in macaque monkeys. This study proved beyond reasonable doubt that both antipsychotics cause brain shrinkage. After 18 months of treatment monkeys treated with olanzapine or haloperidol, at doses equivalent to those used in humans, had approximately 10% lighter brains that those treated with a placebo preparation (6).

Still psychiatrists went on behaving as if antipsychotics were essentially benign and arguing that they were necessary to prevent an underlying toxic brain disease (7). Andreasen's 2011 paper was widely publicised however, and it started to be increasingly acknowledged that antipsychotics can cause brain shrinkage. Almost as soon as the cat was out of the bag, however, attention was diverted back to the idea that the real problem is the mental condition.

Later in 2011 Andreasen's group published a paper that reasserted the idea that schizophrenia is responsible for brain shrinkage. In this paper there was barely a mention of the effects of antipsychotics that were revealed in the group's earlier paper (8). What the authors did in the second paper was to assume that any shrinkage that could not be accounted for by the analysis of antipsychotic effects must be attributable to the underlying disease. The way they had analysed drug treatment in the first paper, however, only looked for a *linear* association between antipsychotic exposure and changes in brain volume. A linear analysis only detects an association that is smooth and consistent- in other words an association in which brain volume shrinks by a consistent amount with each increment in antipsychotic exposure. It seems from other evidence however, that antipsychotics have non-linear as well as linear effects. There appears to be a threshold effect, for example, whereby initial exposure to antipsychotics has the largest impact, followed by a levelling out of the impact as duration of exposure reaches a certain level (9). In any case, without a comparison group which has not been medicated, a virtual impossibility in this day and age, it is simply not possible to conclude that any part of the observed effect is not drug-induced.

The latest paper by this research group replicates the findings on antipsychotic-induced brain shrinkage, but also claims that brain volume reduction is related to having a 'relapse' (10). Relapse was defined retrospectively by the research team for the purposes of this particular analysis, however, and not at the time the study data were collected. Moreover, the definition of relapse only refered to a deterioration in symptoms, and not to any changes in functioning. But the group's previous analysis of severity of symptoms, using data collected at the time, found that severity had only a weak association with brain volume changes, and moreover that symptom severity was correlated with antipsychotic exposure (1). The most recent analysis ignores the probable association between antipsychotic treatment intensity and relapse, but it seems likely that people undergoing periods of 'relapse,' or more accurately deterioration of symptoms, would be treated with higher doses of antipsychotics. If this is so, and the two variables 'relapse' and 'treatment intensity' are correlated with each other, then the analysis is questionable since the statistical methods used assume that the variables are independent of each other.

So Andreasen's group have found strong evidence of an antipsychotic induced effect, which they have replicated in two analyses now. The predictive value of the severity of symptoms, on the other hand (which is essentially how relapse was defined) was weak and none of their analyses are able to confirm that any factor has effects that are independent of those caused by drug treatment.

These researchers seem determined to prove that 'schizophrenia' causes brain shrinkage, although their data simply cannot establish this, as none of their subjects seem to have gone without drug treatment for any significant length of time. Their recent analysis once again confirms the damaging effects of antipsychotics, but the authors largely discount the effects of drug treatment and conclude that patients must

not stop their antipsychotics. The only concession made to the antipsychotic-induced changes the study reveals is the suggestion that low doses of antipsychotics should be used where possible.

Yet other prominent psychiatric researchers have now abandoned the idea that schizophrenia is a progressive, neurodegenerative condition, and do not consider that Andreasen's study provides evidence of this (11). Bizarrely, Nancy Andreasen is a co-author of a recently published meta-analysis which combines results of 30 studies of brain volume over time, which clearly confirms the association between antipsychotic treatment and brain shrinkage (specifically the grey matter) and finds no relationship with severity of symptoms or duration of the underlying condition (12).

What should antipsychotic users and their families and carers make of this research. Obviously it sounds frightening and worrying, but the first thing to stress is that the reductions in brain volume that are detected in these MRI studies are small, and it is not certain that changes of this sort have any functional implications. We do not yet know whether these changes are reversible or not. Of course the value of antipsychotics has been much debated, and their utility depends on the particular circumstances of each individual user, so it is impossible to issue any blanket advice. If people are worried, they need to discuss the pros and cons of continuing to take antipsychotic treatment with their prescriber, bearing in mind the difficulties that can be associated with coming off these drugs (13). People should not stop drug treatment suddenly, especially if they have been taking it for a long time.

People need to know about this research because it indicates that antipsychotics are not the innocuous substances that they have frequently been portrayed as. We still have no conclusive evidence that the disorders labelled as schizophrenia or psychosis are associated with any underlying abnormalities of the brain, but we do have strong evidence that the drugs we use to treat these conditions cause brain changes. This does not mean that taking antipsychotics is not sometimes useful and worthwhile, despite these effects, but it does mean we have to be very cautious indeed about using them.

This blog is a slightly revised version of one that appeared on Mad in America in June 2013.

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