The Effect of Antipsychotic Treatment on Cortical Gray Matter Changes in Schizophrenia: Does the Class Matter? A Meta-Analysis and Meta-Regression of Longitudinal Magnetic Resonance Imaging Studies

Supplemental Information

Data Extraction, Collection and Management

Change in severity of psychotic symptoms during the follow-up was computed as the mean percent per item change from baseline to the end point of rating scales of illness severity, namely Positive and Negative Syndrome Scale (PANSS), Scales for Assessment of Positive and Negative Symptoms (SAPS and SANS) or Brief Psychiatric Rating Scale (BPRS). Most of the included studies (1) reported PANSS containing 30 items with range 0-6. Two studies used BPRS with 18 items and range 1-7 and four studies used SAPS+SANS with 50 items together and range 0-5. When a study reported more than one psychometric measure, we decided to include PANSS first and BPRS or SAPS+SANS second. We transformed the total scores to a mean per-item score and calculated a "percentage of baseline per-item score" to follow the improvement during the antipsychotic therapy.

The chlorpromazine equivalent (CPZ-Eq) was calculated in each study using the following proportion: Dose (mg) of a given antipsychotic administered to patients: X (CPZ-Eq to be derived) = equivalent dose of the individual antipsychotic (in mg) to 100 mg of CPZ: 100. When the cumulative intake of antipsychotics was reported in the original paper or reported by the authors on request, the mean daily dose (MDD) (CPZ-Eq) was derived by dividing the cumulative intake by the duration of the follow-up in days. Conversely, when not directly reported or provided by the authors, cumulative exposure to antipsychotics during the interscan interval was computed by multiplying the duration of the follow-up in days by the maintenance MDD expressed as CPZ-Eq. When the MDD of antipsychotics was reported separately at

baseline and at follow-up scans, the MDD (CPZ-Eq) was computed as the arithmetic mean between these two values.

For the whole sample of studies included in the present meta-analysis the mean values of the moderators investigated were the following: 1) cumulative exposure to antipsychotic medication during the interscan interval (mean: 259.592 ± 224.617 CPZ-Eq); 2) MDD of antipsychotics during the interscan interval (mean: 326.53 ± 111.61 CPZ-Eq); 3) age of patients (mean: 26.19 ± 6.51 years); 4) duration of follow-up (mean: 24.73 ± 17.79 months); 5) change in severity of psychotic symptoms during the follow-up (mean percent per item change from baseline to the end point: 48.80 ± 22.14); 6) percentage of substance abusers in the study sample (mean: 18.73 ± 22.86).

Subgroup Meta-Analysis on Studies Comparing Directly the Effect of First-Generation and Second-Generation Antipsychotics on Cortical Gray Matter Volume

Lieberman *et al.* (2) directly addressed the effects of a second-generation antipsychotic (SGA) (olanzapine) and a first-generation antipsychotic (FGA) (haloperidol) on cerebral gray (GM) and white matter volumes in first-episode schizophrenia, reporting substantial progressive (global) GM loss over a 1-year period in patients on haloperidol, but not in those treated with olanzapine. Garver *et al.* (3) reported a significant increase in cortical GM volume over the first 28 days of treatment in patients with schizophrenia who were administered risperidone or ziprasidone compared with those treated with haloperidol, who showed a decrease in GM volume over the same period. Crespo-Facorro *et al.* (4) found that haloperidol, risperidone and olanzapine had similar effects on cortical GM volumes, overall and lobes, after 1 year of treatment. In fact, a subgroup meta-analysis conducted on these 3 randomized controlled longitudinal studies confirmed the hypothesis of a different impact on brain morphology of FGAs and SGAs. This analysis demonstrated a significant decrease of GM volumes in patients treated with FGAs (56 patients; ES g = -0.34, CI -0.60 to -0.08, *P* = 0.009), while the decrease found in

subjects treated with SGAs was not significant (90 patients; ES g = -0.19, CI -0.39 to 0.05; *P* > 0.05). Moreover, the meta-regressions conducted to assess the impact of the amount of antipsychotic intake on brain volume changes over time demonstrated a significant correlation between GM volume loss and the variable "MDD of antipsychotics" in patients treated with haloperidol (*Z* = -2.10, *P* = 0.035), with higher MDD associated with a greater decrease of GM volume, while such a correlation was not significant, and even inverse, for patients treated with SGAs (*Z* = 1.15, *P* = 0.249).

Table S1. Subgroup meta-analysis of cortical gray matter changes in studies analyzing patients treated with FGAs or mixed antipsychotic treatment (FGAs and SGAs).

Brain Region	No. of Studies	No. of Patients	Effect Size * (95% CI)	Effect Size *P* Value
Whole-brain GM	14	888	−0.27 (−0.34 to −0.21)	<0.001
Frontal lobe GM	9	774	−0.26 (−0.40 to −0.12)	<0.001
Temporal lobe GM	8	701	−0.15 (−0.22 to −0.07)	<0.001
Parietal lobe GM	8	701	−0.24 (−0.31 to −0.17)	<0.001

*A negative coefficient indicates loss over time of cortical gray matter volume.

Table S2. Subgroup meta-analysis of cortical gray matter changes in studies analyzing patients treated only with SGAs.

Brain Region	No. of Studies	No. of Patients	Effect Size (95% CI)	Effect Size *P* Value
Whole-brain GM	12	214	−0.10 (−0.31 to 0.10)	0.315
Frontal lobe GM	6	117	0.01 (−0.40 to 0.44)	0.929
Temporal lobe GM	6	117	0.16 (−0.11 to 0.44)	0.254
Parietal lobe GM	6	117	−0.14 (−0.51 to 0.23)	0.463

Supplemental References

1. Fusar-Poli P, Smieskova R, Kempton MJ, Ho BC, Andreasen NC, Borgwardt S (2013): Progressive brain changes in schizophrenia related to antipsychotic treatment? A meta-analysis of longitudinal MRI studies. *Neurosci Biobehav Rev* 37: 1680–1691.

2. Lieberman JA, Tollefson GD, Charles C, Zipursky R, Sharma T, Kahn RS, *et al.* (2005): HGDH Study Group. Antipsychotic drug effects on brain morphology in first-episode psychosis. *Arch Gen Psychiatry* 62: 361–370.

3. Garver DL, Holcomb JA, Christensen JD (2005): Cerebral cortical gray expansion associated with two second-generation antipsychotics. *Biol Psychiatry* 58: 62–66.

4. Crespo-Facorro B, Roiz-Santiáñez R, Pérez-Iglesias R, Pelayo-Terán JM, Rodríguez-Sánchez JM, Tordesillas-Gutiérrez D, *et al.* (2008): Effect of antipsychotic drugs on brain morphometry. A randomized controlled one-year follow-up study of haloperidol, risperidone and olanzapine. *Prog Neuropsychopharmacol Biol Psychiatry* 32: 1936–1943.