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Letter to the Editor

The need for drug-naive research in first-episode psychosis: a response to Moncrieff & Leo (2010)

Moncrieff & Leo (2010) provide a thorough overview of the literature on the association between use of antipsychotic medication and global brain volume changes. One of the central arguments of the piece is that some of the brain abnormalities observed in schizophrenia patients are not a consequence of the illness itself but in fact result from antipsychotic medication. The mechanisms by which the structure of the brain is influenced by antipsychotic medication is currently not well understood. The authors argue that there is an urgent need for studies that randomize first-episode psychosis patients to either treatment with antipsychotic medication or to withhold antipsychotic treatment for a few weeks while studying the effect of antipsychotics on brain structure. Such studies would inform the issue of the relative role of antipsychotic medication and the progression of psychosis in brain changes associated with psychotic disorders.

Our group at the Early Psychosis Prevention and Intervention Centre (EPPIC) in Melbourne, Australia, is currently conducting a trial with such a design (Francey *et al.* 2010). The study involves randomizing

first-episode psychosis patients to two different treatments – intensive psychosocial intervention plus antipsychotic medication *versus* intensive psychosocial intervention plus placebo – with the primary outcome being social functioning at 6 months. The study was prompted by first-episode psychosis services' increased ability to identify people as early as possible after the onset of psychosis, reducing the duration of untreated psychosis. This has meant, as in other areas of health care, that different treatment approaches may be indicated. It is possible, in line with clinical staging and stepped care principles, that the immediate introduction of antipsychotic medication may not be necessary for all first-episode psychosis patients, but that comprehensive psychosocial intervention may constitute effective treatment at least for a subgroup of patients at this very early stage of disorder (McGorry *et al.* 2006, 2010). Structural magnetic resonance imaging scans are being performed at baseline prior to randomization and after 12 weeks. If both intervention groups display similar structural brain changes over the course of intervention then we can infer that these changes are more likely to be associated with the progression of psychosis rather than due to antipsychotic medication, especially if the experimental groups are similar in other respects. However, if certain structural brain changes only occur in the group treated with medication then these changes are more likely to be related to antipsychotics. Of course, it is entirely possible that antipsychotic medications could be neuroprotective and retard or prevent brain changes which derive from underlying neuroprogressive changes (Lieberman *et al.* 2005; DeLisi, 2008).

The study described above is currently in the recruitment phase. We agree with Moncrieff and Leo that studies of this sort, that effectively provide an experimental manipulation of the duration of psychosis untreated with antipsychotic medication, are necessary to disentangle the effects of antipsychotic medications and the putative neurobiological processes associated with brain changes in psychotic disorders. Clearly, studies of this nature need to be conducted with strict ethical guidelines, including close monitoring of patients and a low threshold for withdrawal or discontinuation.

Declaration of Interest

None.

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