

A decade after the CATIE study, the focus has shifted from effectiveness to neuroprotection

This past September, exactly 10 years after publication of the primary findings of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study¹—namely, that effectiveness (defined as all-cause discontinuation) was not different across first-generation antipsychotics (FGAs) and second generation antipsychotics (SGAs)—a new meta-analysis by Vita et al² of differences in cortical gray-matter change between those 2 classes of antipsychotics offers a reminder: The clinical focus of the CATIE study overlooked important neurobiological and neuroprotective differences between FGAs and SGAs.

How drastically 1 decade can change the scientific perspective! Vita et al's meta-analysis and meta-regression encompassed all 18 MRI studies of cortical gray matter in patients with schizophrenia.² Earlier studies (published between 1983 and 2014) had lumped together patients who were receiving an FGA and those receiving an SGA, and authors reported overall reduction in cortical gray matter with prolonged antipsychotic treatment.

Remarkable findings emerge

When Vita et al² analyzed FGA- and SGA-treated patients separately, however, they found a significant reduction in cortical gray matter in the FGA group but not in the SGA group. In fact, while higher daily dosages of FGAs were associated with greater reduction in cortical gray matter, higher dosages of SGAs were associated with lower cortical gray matter reduction and, in some samples, with an *increase* in volume of cortical gray matter.

The researchers hypothesized that the differential effects of FGAs and SGAs might be attributable to the neurotoxicity of typical FGAs and the neuroprotective effect of atypical SGAs.

Hindsight

The key neurobiological difference between FGAs and SGAs reported by Vita et al² was not addressed in the CATIE study, leading, at that time, to a rush to judgment that all antipsychotics are the same. This conclusion emboldened managed-care organizations to mandate use of older (and cheaper) generic FGAs instead of newer (and more expensive) SGAs—most of which have become available as generic equivalents since the CATIE study was completed.



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First-generation and second-generation antipsychotics might have similar clinical effectiveness but they have very different neurobiological effects

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Investigators in the CATIE study—of which I was one—cannot be blamed for not focusing on neurotoxicity and neuroprotection; those data were not on the psychiatry's radar when the CATIE study was designed in 1998. The major focus was on whether SGAs (new on the scene in the late 1990s) were more efficacious, safe, and tolerable (that is, more effective) than FGAs.

In fact, the first study reporting that SGAs stimulated neurogenesis (in animals) was published in 2002,³ when the CATIE study was more than half complete. Research into the neuroprotective properties of SGAs then grew rapidly. In fact, the principal investigator of the CATIE study conducted a head-to-head comparison of FGA haloperidol and SGA olanzapine in a sample of first-episode schizophrenia patients⁴; over 1 year of follow-up, it was determined that patients in the haloperidol-treated group exhibited significant brain volume loss on MRI but those in the olanzapine-treated group did not. This study was published in 2005—the same year the CATIE study was published!

SGAs offer neuroprotection

Over the past decade, the neuroprotective effects of SGAs⁵ and the neurotoxic effects of FGAs⁶ have been studied intensively, revealing that SGAs have multiple neuroprotective effects. These effects include:

- stimulation of the production of new brain cells (neurons and glia), known as neurogenesis^{5,7,8}
- an increase in neurotrophic factors, such as nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF),⁹ which are found at a significantly low level in patients with psychosis¹⁰
- reversal of phencyclidine (PCP)-induced changes in gene expression¹¹

- neuroprotection against ischemic stroke¹²⁻¹⁴

- reversal of PCP-induced loss of dendritic spines in the frontal cortex¹⁵

- prevention of oligodendrocyte damage caused by interferon gamma-stimulated microglia^{16,17}

- reversal of loss of dendritic spines in the prefrontal cortex induced by dopamine depletion¹⁸

- an anti-inflammatory effect^{19,20}

- protection against β -amyloid and hydrogen peroxide-induced cell death²¹

- protection against prefrontal cortical neuronal damage caused by dizocilpine (MK-801)²²

- reversal of a PCP-induced decrease in the glutathione level and alteration of antioxidant defenses²³

- protection of cortical neurons from glutamate neurotoxicity.²⁴

One reason why SGAs are neuroprotective, but FGAs are not, can be attributed to their receptor profiles. FGAs block dopamine D2 receptors far more than serotonin 2A receptors, whereas SGAs do the opposite: They block 5-HT2A receptors 500% to 1,000% more than they block D2 receptors. This difference is associated in turn with a different neurobiological and neuroprotective profiles, such as a decrease or an increase in BDNF.^{25,26}

Neither similar nor interchangeable

Since publication of the findings of the CATIE study, the primary investigator has proposed that neuroprotection can be a therapeutic strategy to prevent neurodegeneration and neurodeterioration associated with schizophrenia.²⁷ Given the preponderance of data showing that SGAs have numerous neuroprotective properties but FGAs have many neurotoxic effects,⁶ the message to psychiatric practitioners, a decade after the CATIE study, is that the 2 generations of antipsychotic agents are not

really similar or interchangeable. They might have similar clinical effectiveness but they exert very different neurobiological effects.

The proof of the pudding is in the eating: Despite the findings of the CATIE study, the vast majority of psychiatrists would prefer to treat their own family members with an SGA, not an FGA, if the need for antipsychotic medication arises.



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