Study shows newer schizophrenia treatments no more effective than old

Findings provide clues as to what targets future drugs should avoid.

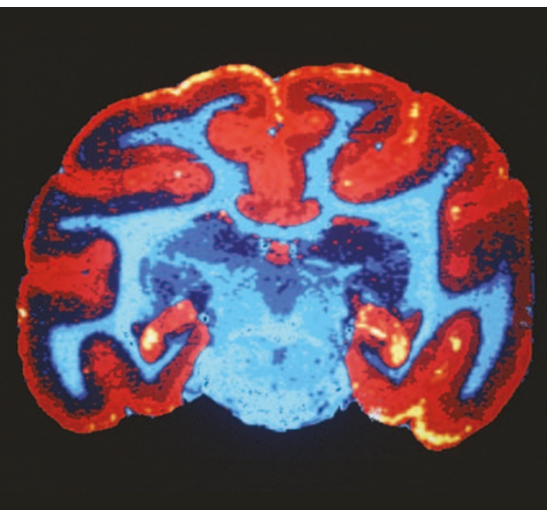
Simon Frantz

A recent study provides evidence that 'second-generation' schizophrenia treatments are little better than their older counterparts (Lieberman, J. A. *et al. N. Engl. J. Med.* 353, 1214–1223; 2005). But researchers say there's potentially a silver lining in these cloudy findings — understanding why these drugs aren't much of an improvement could help make future treatments safer and more effective.

The CATIE trial, which was funded by the National Institutes of Health, pitted perphenazine, a generic drug available since the 1950s, head-to-head against olanzapine (Zyprexa; Lilly), quetiapine (Seroquel; AstraZeneca), risperidone (Risperdal; Janssen Pharmaceutica) and ziprasidone (Geodon; Pfizer). Olanzapine performed moderately, yet significantly, better than perphenazine, but as a whole the researchers saw no substantial advantage in the newer medications.

There is a potential downside in immediately switching to older, cheaper generic treatments though, as there were large differences in patient's responses to the newer drugs. "What works for one person may not work for another," said Jeffrey Lieberman, Principal Investigator of the CATIE trial and Chair of the Department of Psychiatry, Columbia University and Director of the New York State Psychiatric Institute.

But even taking this into account, the study shows clearly that the newer generation of antipsychotics isn't the success it was hoped to be.



The first of the newer treatments, known as 'atypical' antipsychotics, was clozapine, which was discovered almost 50 years ago. But clozapine, considered the gold-standard treatment for schizophrenia in view of its efficacy, causes a host of adverse effects, including the blood disorder agranulocytosis, which has limited its prescription to around 10% of schizophrenia patients.

Identifying the secret to clozapine's effectiveness has been difficult, as the drug binds to tens of receptors. So researchers made educated guesses as to what could be the key receptors responsible for clozapine's efficacy — mainly based on the fact that it has weaker dopamine D_2 receptor antagonism and stronger antagonism at serotonin 5-HT_{2A} receptors than the older treatments — and designed what they hoped were better drugs with greater selectivity for these receptors.

Of the newer drugs, the most successful in the trial, olanzapine, behaves more like clozapine than its more targeted contemporaries quetiapine, risperidone and ziprasidone. "We can infer that hitting a multiplicity of molecular targets is probably better than just targeting two, which is what all the other drugs were mainly designed to do," says Bryan Roth, Director of the National Institute of Mental Health Psychoactive Drug Screening Program. "The question is what will make these compounds better — olanzapine's pharmacology is so complex."

It's not just the hunting for how these drugs work that is proving to be a headache. Side effects were a problem in the study: three-quarters of the patients switched medications, and olanzapine was linked to weight gain and unwelcome metabolic changes.

It has been proposed that the metabolic effects could be due to blocking H_1 histamine and 5-HT_{2C} serotonin receptors, which evidence suggests can affect appetite. And there are genetic effects too. Lilly has presented unpublished data from a whole-genome-wide scan of 1 million single-nucleotide polymorphisms (SNPs), which shows that a huge number of SNPs have a small effect in weight gain, making the detection of causative genes difficult.

Although the metabolic effects are proving difficult to anticipate, it would be regrettable if the study results had a negative effect on industry's efforts in schizophrenia research, says Michael Spedding, Deputy Director of Research at Servier. "The trial shows that the wave of newer treatments hasn't brought about as great a revolution as the first one, but work needed to develop the second-generation compounds has generated a lot of mechanistic research that has been important in understanding schizophrenia," says Spedding .

Spedding says that looking for a third generation of treatments will also require better models. "Screening compounds with these new models will help us find compounds that are quite different from the current batch."

The NIH is ploughing more funds into this area, and together with industry, will test compounds that are approved for use in human research in proof-of-principle studies for cognitive improvements. The NIH is also beginning an initiative to find predictors of metabolic problems in individual patients that could be used by pharma to refine drug development.

There's no lack of focus on the problem, says Roth. "We now know what targets to avoid — now we're taking a bet on what targets to add."

"Understanding why these drugs aren't much of an improvement could help make future treatments safer and more effective."