Knowledge Notes

Effectiveness of First Generation Antipsychotic Drugs Versus Second Generation Antipsychotic Drugs

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Objectives

To compare efficacy of first generation antipsychotics with that of second generation antipsychotics.

Background

Antipsychotic drugs for the treatment of schizophrenia have been available for over 50 years. Some 15 years ago clozapine became available and was hailed as a revolutionary drug. This was followed by the development of several other atypical or second-generation antipsychotics (olanzapine, risperidone, quetiapine, ziprasidone, are the last not yet been widely available in Canada). Advantages claimed for these newer drugs included better efficacy for both negative and positive symptoms, mood, reduced neurological side effects and cognitive enhancement. The result of an increase in efficacy in treating these symptoms is supposed to be improved tolerability and adherence to drug treatment. However, second generation antipsychotics are also associated with considerably increased medication costs. Drug trials of second generation antipsychotics conducted by manufacturers have also been heavily criticized for being short-term and using participants not representative of patients seen in actual practice. A study in the UK, known as CUtLASS and study in the U.S. known as CATIE were undertaken to address questions of efficacy and cost between first generation and second generation antipsychotics.

Method

CATIE

CATIE was a double-blind trial involving just less than 1500 patients with chronic schizophrenia who randomly received one of the four second-generation antipsychotic medications, mentioned above, or perphenazine, a medium potency first-generation antipsychotic. The primary outcome for the trial was discontinuation of the drug and switching to another antipsychotic for any reason. This was a multisite study. The subjects were stable outpatients with a 14 year mean duration of illness. Medication was prescribed under double-blind conditions but dosages could be adjusted depending on clinical condition and were found to match general clinical practice.

CUtLASS

The UK CUtLASS study was a smaller study in two parts. The first part, involving 227 people with schizophrenia who were being considered for changes in treatment because of poor response or side effects, was an open randomized trial comparing first-generation versus second-generation drugs other than clozapine (amisulpride, olanzapine, quetiapine, or risperidone). The second part of CUtLASS compared clozapine with other second-generation drugs in 136 patients who have not responded to at least two previous medications. The results of this trial clearly show an advantage to clozapine in symptom improvement and patient preference.

Results

CATIE

All drugs showed limitations, 74% of patients were discontinued from their randomized treatment over 18 months with a median time to discontinuation of between four and five months. Olanzapine had the lowest discontinuation rate of 64% (this is still a high rate). The other second-generation drugs showed little difference between each other or from perphenazine. Each of the second-generation drugs showed a different side effect profile; olanzapine was most associated with metabolic side effects, risperidone with hyperprolactinemia, quetiapine with anticholinergic side effects and perphenazine had the highest discontinuation rate for extrapyramidal side effects. Second-generation drugs were not found to be back to for negative symptoms or cognitive deficits. A second stage included those who discontinued the first phase because of lack of efficacy and who were then included in an open label clozapine versus other second-generation antipsychotic, again with time to discontinuation as the primary outcome. Clozapine was found to be twice as effective as the other second-generation medications with the time to discontinuation twice that of the next best.

CUtLASS

Primary outcome was quality of life at 1 year, and symptoms were the main secondary outcome. Assessments were made to blind the treatment condition. After one year (81% follow-up) for both quality of life and symptoms, not only was no advantage shown for second-generation drugs, but those on the first-generation medications did better including on extrapyramidal side effects.

The investigators in both these trials had the initial assumption that second-generation antipsychotics would prove superior, which was not generally supported by the findings. In both trials clozapine proved superior in the management of treatment resistant patients.

Conclusions

Two large trials of antipsychotic medications in clinically representative patients in the US and UK supported by non-commercial funding unexpectedly showed that the newer antipsychotics (atypical or second-generation) with the exception of clozapine were no better than older drugs when used in patients with a long duration of schizophrenia, were

more expensive and had different side effect profiles. Clinicians should carefully consider (particularly when making medication changes in chronic patients) whether they can justify using more expensive second-generation drugs rather than using first-generation antipsychotics. These trials did not consider the role of long-acting antipsychotic medications.

It should also be noted that medications actually contribute a relatively small proportion to the overall cost of treating schizophrenia. In the CUtLASS study medication costs in the first generation arm were just 2.1%, and 3.8% in the second-generation arm with clozapine patients accounting for 4% of the overall treatment costs. In the CATIE study perphenazine was significantly less costly than the second-generation drugs.

References

Lewis S., Lieberman J. CATIE and CUtLASS: can we handle the truth? British Journal of Psychiatry (2008) 192, 161-163