Clinical Antipsychotic Trials of Intervention Effectiveness in Schizophrenia: Selective Review on Clinical Outcomes

以抗精神病藥物治療效應臨床研究評估精神分裂症的臨床治療結果：選擇性文獻回顧

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Abstract

Objectives: To summarise Clinical Antipsychotic Trials of Intervention Effectiveness with respect to clinical outcomes following the treatment of schizophrenia.
Methods: Articles were searched from PubMed with key words "Clinical Antipsychotic Trials of Intervention Effectiveness", and "CATIE" published from January 2000 to April 2008. Studies reporting original research findings concerning clinical outcomes from such trials in patients with schizophrenia were selected for review.
Results: Conventional and atypical antipsychotics had similar clinical effectiveness, neurocognitive and functional outcomes. Among atypical antipsychotics, olanzapine showed better effectiveness but worse metabolic outcomes. Medical co-morbidity was common among schizophrenic patients.
Conclusions: With reference to findings from Clinical Antipsychotic Trials of Intervention Effectiveness in schizophrenia, review of local prescribing and monitoring practice is recommended.

Key words: *Antipsychotic agents; Review; Schizophrenia*

摘要

目的：以「抗精神病藥物治療效應臨床研究」（CATIE）總結治療精神分裂症的臨床治療結果。
方法：以關鍵詞「Clinical Antipsychotic Trials of Intervention Effectiveness」和「CATIE」搜尋PubMed由2000年1月至2008年4月發表的文獻，從中挑選有關以CATIE評估精神分裂症患者臨床治療結果的研究文章作為回顧。
結果：常規和非典型抗精神病藥物的臨床效用、神經認知和功能結果均相若。非典型抗精神病藥中，以奧氮平最有效，但新陳代謝結果則較差。併發症於精神分裂症患者中是常見的。
結論：根據CATIE的研究結果，有關本地處方和監測工作的回顧研究是需要的。

關鍵詞：*抗精神病藥物、回顧、精神分裂症*

Introduction

The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) in schizophrenia study was the largest project ever conducted to evaluate treatment effectiveness in real-world schizophrenic patients. The CATIE was supported by the National Institute of Mental Health and costed about US$50 million, lasted 4 years and involved over 50 clinical sites in the United States. About 1,500 patients participated in this 3-phase study. Articles concerning this study have been published since 2003 and many findings have been reported in the ensuing years. A variety of topics have been covered, some of which caused debate about the management of schizophrenia, especially with respect to clinical outcomes. The aim of this study was to review CATIE findings in the context of clinical outcomes for schizophrenia treatment.

Methods

Reports of original research findings from the CATIE study

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about patients with chronic schizophrenia are included in this review. To identify appropriate studies, a literature search was conducted using PubMed with key words "Clinical Antipsychotic Trials of Intervention Effectiveness", and "CATIE" for articles published from January 2000 to April 2008. The search strategy yielded 124 English-language studies. The abstracts were obtained for further inspection. Eight studies were about the CATIE project for Alzheimer's disease, 9 used samples from the CATIE project for other research, 4 used CATIE assessment instruments for other research, 65 publications were editorials, reviews or correspondences about CATIE project, and 13 were unrelated. The remaining 25 studies met the inclusion criteria and were reviewed, and among them 18 dealt with clinical outcomes arising from interventions with antipsychotics.

Results

The studies selected for review deal with 4 outcome categories, namely clinical effectiveness, cognition, functionality, and metabolic status.

Clinical Effectiveness and Cost-effectiveness

According to a study by Lieberman et al,[1] 74% of the patients discontinued their study medication within 18 months. The time to discontinuation of treatment (for any reason) was significantly longer in those treated with olanzapine rather than quetiapine ($p < 0.001$) or risperidone ($p = 0.002$), but not in those receiving perphenazine or ziprasidone.[1] Any advantage was attenuated among patients with chronic schizophrenia who used illicit substances.[2] The time to discontinuation because of intolerable side-effects were similar among the groups, but the rates differed; olanzapine was associated with more discontinuations for weight gain or metabolic effects ($p < 0.001$), and perphenazine with more discontinuations for extrapyramidal effects ($p = 0.002$).[1] Among 114 patients with chronic schizophrenia who had just discontinued the older antipsychotic perphenazine (in phase 1), quetiapine (for a median of 9.9 months) and olanzapine (for a median of 7.1 months) treatment were more effective than risperidone (for a median of 3.6 months) in terms of time to discontinuation for any reason ($p < 0.05$).[3] Among 444 patients with chronic schizophrenia who had just discontinued treatment with an atypical antipsychotic in phase 1, risperidone (for a median of 7.0 months) and olanzapine (for a median of 6.3 months) were more effective than quetiapine (for a median of 4.0 months) and ziprasidone (for a median of 2.8 months) in terms of time to discontinuation for any reason ($p < 0.01$).[4] Among 99 patients with schizophrenia who experienced inadequate efficacy with an atypical antipsychotic, clozapine was more effective than switching to another newer atypical alternative ($p < 0.05$).[5] Individuals randomly assigned to olanzapine and risperidone who were continuing with their baseline medication before the CATIE study had significantly longer times until discontinuation than did those assigned to switch antipsychotics ($p < 0.01$).[6] Among schizophrenic patients without tardive dyskinesia, the average total monthly health care costs were US$300 to 600 (20-30%) lower for those on perphenazine rather than second-generation antipsychotics ($p < 0.0001$).[7] There were no significant differences in quality-adjusted life year ratings, Positive and Negative Syndrome Scale scores, and other quality-of-life measures over the 18 months between patients receiving perphenazine or any second-generation medication.[7]

Neurocognitive Outcome

Neurocognition is broadly impaired in patients with schizophrenia.[8] These deficits are modestly related to negative symptoms and are essentially independent of positive symptom severity.[8] After 2 months of antipsychotic treatment, 817 subjects completed the neurocognitive testing and all treatment groups enjoyed a small but significant improvement ($p < 0.01$).[9] A total of 303 patients were tested at 18 months and improvement in the neurocognitive composite score was greater in those taking perphenazine (0.49) than those on olanzapine (0.15; $p = 0.002$) or risperidone (0.28; $p = 0.04$).[9] Most of the cognitive improvement occurred in the first 2 months of treatment, with 0.11 improvement in the composite score ensuing from 2 to 18 months.[9]

Functional Outcome

All antipsychotic treatment groups in all phases showed modest improvements in psychosocial functioning in terms of Quality of Life Scale, and there were no significant differences among the groups in the amount of change in the scale scores after 6, 12, or 18 months.[10] Also, there were no differences between treatment groups for employment outcomes or participation in psychosocial rehabilitation.[11] Participation in either competitive or noncompetitive employment was associated with having less severe symptoms, better neurocognitive functioning, and higher scores on measures of intrapsychic functioning that encompassed motivation, empathy, and other psychological characteristics ($p < 0.05$).[12] Greater access to rehabilitation services was associated with greater participation in both competitive and noncompetitive employment ($p < 0.05$).[12]

Metabolic Outcome

The overall prevalence of hypertension was 33%, that of diabetes mellitus was about 10%, and of dyslipidaemia was about 47%.[13] The point prevalence values of treatment at the time of enrolment were 30% for diabetes, 62% for hypertension, and 88% for dyslipidaemia.[13] Nonwhite women may be especially vulnerable to undertreatment of dyslipidaemia and diabetes compared to nonwhite men ($p = 0.01$).[13] Metabolic syndrome (MS) was noted in 41% of the sample using the National Cholesterol Education Program criteria; in females it was present in 52% compared to 36% in males.[14] Comparison with a matched sample from the third National Health and Nutrition Examination Survey showed that CATIE samples were more likely to have MS ($p < 0.001$).[14] Metabolic syndrome is strongly associated with a poor self-rating of physical health and increased somatic

preoccupation among schizophrenic patients ($p < 0.05$).[15] If they had schizophrenic, the 10-year coronary heart disease risk was significantly higher than that in controls ($p = 0.0001$), both in males (9.4% vs. 7.0%) and females (6.3% vs. 4.2%).[16] Medical co-morbidity was associated with depression and neurocognitive impairment in schizophrenic patients ($p < 0.001$).[17] After 3 months of treatment, olanzapine and quetiapine had the largest mean increase in waist circumference (0.7 inches for both) followed by risperidone (0.4 inches); there was no change for ziprasidone (0.0 inches) and a decrease in waist circumference for perphenazine (-0.4 inches) [$p < 0.001$].[18] Olanzapine also demonstrated significantly different changes in fasting triglycerides at 3 months (+21.5 mg/dL) compared to ziprasidone (-32.1 mg/dL) [$p = 0.02$].[18] Olanzapine was associated with greater weight gain and abnormality of glucose and lipid metabolism.[1]

Discussion

The CATIE study provides an empirical basis for informed clinical decisions in the management of schizophrenia. Choice of antipsychotics needs to be individualised as reflected by discontinuation of study medication due to different reasons, by most of the participants. Concerning clinical effectiveness in terms of time to discontinuation, olanzapine may be more effective than risperidone and quetiapine. For patients who discontinued conventional antipsychotics, quetiapine may be more effective than risperidone. For patients who discontinued atypical antipsychotics, risperidone may be more effective than quetiapine and ziprasidone. Compared to atypical antipsychotics, the conventional agent perphenazine may confer similar clinical effectiveness, as well as neurocognitive and functional outcomes, though there might be more discontinuations due to extrapyramidal effects. These findings renew the debate on the choice between atypical and conventional antipsychotics for management of schizophrenia in terms of cost-effectiveness.

Medical co-morbidity among psychiatric patients is another influential topic raised by the CATIE schizophrenia study. These patients have a high prevalence of obesity, dyslipidaemia, MS, hypertension, and diabetes mellitus. The low treatment rate of medical co-morbidity emphasises the importance of regular physical checkups for psychiatric patients.

Like other studies, this multicentre, non–industry sponsored, long-term clinical effectiveness study had limitations. The gender ratio, mean years since first treatment, baseline antipsychotic medication, and co-morbidities are characteristics to take into account before generalisation of the findings. The allocation of patients with tardive dyskinesia to treatments other than perphenazine may affect the comparison with atypical antipsychotics. The relatively higher mean modal dose of olanzapine and lower mean modal dose of quetiapine and ziprasidone may favour the treatment effect of olanzapine. The overall 74% of discontinuation rate raises questions about the effectiveness of the mental health system.[1]

There have been many articles published about the study and its impact has been referred to in terms such as "post-CATIE era"[19] or "tsunami".[20] When applying its findings to local patients, we need to be aware of heterogeneity with respect to individual severity, disease course, and treatment response. In terms of risk-to-benefit ratio, conventional antipsychotics deserve continued consideration for patients without tardive dyskinesia. Doctor-patient relationship and integration of medications with other therapies will also be important factors in clinical management.

More atypical antipsychotics have been prescribed in East Asia[21] and the CATIE schizophrenia study serves to alert us to the extent of the physical problem. Review of local practice in prescribing and monitoring such agents is recommended.

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