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# Evidence based treatment of schizophrenia: do we know enough

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## Evidence Based Medicine

# Evidence based treatment of schizophrenia: Do we know enough?

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### Background

Schizophrenia is a disorder which lasts for a person's lifetime. Treating it is a formidable challenge for clinician's considering the chronic nature of its course, rate of relapse, side effects of medicines and limited choice of medications. Since 1950s, with the advent of Chlorpromazine efforts have been made to alleviate the symptoms of schizophrenia and make them useful in terms of social and occupational functioning. Expected success of Antipsychotic (AP) medications depends on the results of the efficacy and effectiveness trials.[1]

Numerous studies have been done to evaluate the efficacy of conventional and atypical antipsychotic.[2-5] There are many issues with these studies: some had limited sample size, mostly comparing antipsychotics with placebo and others were sponsored by pharmaceutical industry. In a study analyzing the role of pharmaceutical industry in influencing results, Heres et al concluded that in around 92% of studies results were skewed towards funding industry.[6] This could be due to the fact that the Industry spends huge sum of money in developing a compound through tedious process of research and only clinically viable compounds see the light of Phase II and III research. Another issue is the usefulness of the efficacy trial in real world clinical situation where situation is much different; patients often have co-morbid condition, chronic nature of the condition and explicit preferences for therapy dictates decision making.

### Catie - Study Design and Results:

Clinical Antipsychotics Trial of Intervention Effectiveness (CATIE) is the double-blind randomized-

control trial, conducted in naturalistic settings across fifty seven geographical and variable clinical setting sites of United States of America (USA).[7] The study was conducted on 1493 patients, from October 2001 to December 2004. The idea behind such a trial was to have high internal and external validity. The trial was funded by National Institute of Mental Health. The aim was to asses and compare effectiveness of first generation and second generation (atypical) antipsychotics. The study also looked into side effects of medications. It also intends to measure the efficacy of Clozapine over other atypical APs. Study was conducted in three phases. Primary out-come measure was "time to discontinue", for any cause; lack of tolerability; lack of efficacy; clinical decision and patient decision. Secondary outcome measure was assessed by scores on Positive and Negative syndrome scale (PANS) and scores on Clinical global impression scale (CGI). Higher scores point towards more severe psychopathology and severity of illness respectively. Safety was also measured at intervals to see any neurological, metabolic and laboratory derangement. For estimation of primary out-come measure, authors used Kaplan-Meier curve. Cox proportional-hazards regression model was used to compare treatment groups.

**PHASE 01:** A total of 1493 patients were assigned to double blind treatment with olanzapine (7.5 mg to 30 mg per day), perphenazine (8 to 32 mg per day), quetiapine (200 to 800 mg per day), ziprasidone (40 to 160 mg per day) or risperidone (1.5 to 6 mg per day) for up to 18 months. People with Tardive dyskinesia were excluded to receive perphenazine. These patients were not with the first episode of psychosis. Data from one center (n=33) was excluded due to data integrity issues. Out of 1460 individuals who were randomized initially, 371 completed the phase 1 trial (1089 discontinued).

**PHASE 02:** In the stage 543 patients entered in to two pathways; "efficacy" pathway with clozapine (n=99) or "tolerability" (n=444) pathway with ziprasidone. A total of 509 patients left the study before the start of this phase.

**PHASE 03:** This was an open-label phase of the study. Patients were free to select one among 09 AP regimens; 270 patients entered in this phase of the trial.

Results of this study were published in different journals as they came up.[7-9] The most prominent finding was all-cause discontinuation rate of 74% at 18 months. In terms of discontinuation of medication due to any cause before the completion of the study, Olanzapine fared better then Quetiapine (hazard ratio, 0.63; P<0.001) Risperidone (hazard ratio, 0.75: P=0.0002) and also with other medications. The discontinuation due to intolerable side effects was similar among all the groups, with more individuals discontinuing Olanzapine due to weight gain (07 percent or more of the baseline body weight) and increase in glycosylated haemoglobin, cholesterol and triglyceride leading to metabolic syndrome. In case of perphenazine Extrapyramidal symptoms were the most common reason for discontinuation (08 percent vs. 02 percent to 04 percent, P=0.002).

Research team was unable to find any superior efficacy of Atypical over conventional AP, i.e. Perphenazine. Perphenazine was however most cost-effective when compared with newer atypical APs. Clozapine was the most effective compound compared with all the other antipsychotics used in this study. Irrespective of the class of antipsychotics, there was improvement in neuro-cognitive functioning. However this effect remained significant only for two months. Among all, Ziprasiodne was most weight neutral and did not come up with any metabolic side-effects. In the last phase which was open label, very few patients selected conventional antipsychotics (Fluphenazine decanoate, n=09 or Perphenazine, n=04)

## Critique:

One of the main critiques of this study is that researchers have used drug doses which are on the higher side compared to actual clinical practice. This could have caused a difference in the results. Another objection was that although the total period of study was 18 months, much more than previous studies, it was still short considering the long course of schizophrenia, delays in response and side-effects of medications. . Open label component of the trial could have also caused a possible bias.[10]

CATIE results are important in view of the prevailing health care situation in Pakistan; health is an out of pocket expenditure for most Pakistanis. Government's contribution is dismally low, i.e. US $ 04 out of US $ 18 per capita. Considering the Global economic recession, affordable health care is becoming a challenge for most patients and their family members. Given the lack of difference between the efficacy of conventional and atypical APs, an affordable care becomes a reality to the vast majority of patients with schizophrenia in a developing country like Pakistan. Given the extra pyramidal side effects (EPSE) with conventional APs and Metabolic syndrome with atypical APs clinicians are advised caution in terms of drug prescription. Every patient who is on AP should be reviewed periodically for dose-adjustment in order to achieve symptoms remission, review drug side effects and enhance compliance.

In conclusion the best practice evidence on treatment of schizophrenia remain open to interpretation given the trade-offs between efficacy, side effects, affordability and implicit personal preferences. The perennial question, that do

we know enough, still remains unanswered.

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