Psychiatria Danubina, 2010; Vol. 22, No. 2, pp 323–328 *Conference paper*

WHAT DO LARGE SCALE STUDIES OF MEDICATION IN SCHIZOPHRENIA ADD TO OUR MANAGEMENT STRATEGIES?

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SUMMARY

Introduction: *A number of large naturalistic trials have reported in recent years comparing second generation antipsychotic drugs with their predecessors. The conclusions they draw have rightly sparked much debate, but are these studies truly comparable? If not, which of them are most methodologically robust and are these the studies most suitable as a foundation for* clinical *care guidelines with a strong evidence base. We aimed to conduct a review of the current literature to establish the appropriateness of several recent major clinical studies being used as the basis for clinical guidelines.*

Method: *A literature search using the PUBMED database was carried out. Five major studies comparing antipsychotic efficacy were selected as possible candidates and subjected to further analysis.*

The studies were:

- *CUTLASS (Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia study);*
- *CATIE (Clinical Antipsychotic Trials of Intervention Effectiveness study);*
- *SOHO (Schizophrenia outpatients Health Outcomes study);*
- *CAFE (Comparison of Atypicals in First Episode study);*
- *EUFEST (European First Episode Schizophrenia Trial).*

Discussion: *The trials:*

- *CAFE - the trial, although well randomised and blinded, uses discontinuation as a primary endpoint - this is hard to draw conclusions from: patients may discontinue due to side effects, due to lack of efficacy or with against medical advice for a multitude of reasons. As a secondary endpoint, the study does make use of a PANSS scoring system to measure efficacy, adding some weight to the conclusion that olanzapine, quetiaine and risperidone in early psychosis patients have equivalent efficacies.*
- *CATIE - This trial was a comparative study, and so lacked a control arm and used discontinuation of medication an inverse measure of efficacy - an easily quantifiable event, but making for difficult interpretation. However most criticism has been directed at the unusually low (quitiapine, ziprasidone) and high (olanzapine and perphenazine) doses of drug used, which were reflected in their differing rates of efficacy.*
- *CUtLASS This trial allows for less generalisation of its findings to the general population as it makes use a specific sub-population (those switching from one medication to another after a period of treatment). Also some patients were prescribed oral medications and some depot injections - making comparisons difficult due to possible differences in compliance.*
- *EUFEST This trial makes use of discontinuation as an endpoint with the weaknesses we have described. Treatment of first episodes of psychosis is shown to be feasible, but it could not suggest if haloperidol or second generation drugs may be more efficacious.*
- *SOHO – This trial hindered by the observational design of the study and small numbers reaching the primary end point (4%) caution should be exercised in the conclusion that olanzapine is superior to risperidone, quetiapine or typical antipsychotics.*

Conclusion: *There is much information useful for clinical practice to be gathered from the results of these major studies, however, interpretation is hampered by both variations and weakness in study design. On balance it does appear that different antipsychotics possess differing efficacy, but also of relevance to the development of sound clinical guidelines is their differing side effects profile.*

Key words: *anti-psychotics – effectiveness – efficacy – recovery – schizophrenia - first episode psychosis*

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INTRODUCTION

A number of large naturalistic trials have reported in recent years comparing second generation antipsychotic drugs with their predecessors. The conclusions they draw have rightly sparked much debate, but are these studies truly comparable? If not, which of them are most methodologically robust and are these the studies most suitable as a foundation for *clinical* care guidelines with a strong evidence base.

These studies have attempted to demonstrate the efficacy in practice of second generation drugs as compared to first generation drugs. The results of these studies have been hotly debated and various conclusions have been drawn. However, it is necessary to question what methodological issues have arisen in these studies, and hence how safe are the conclusions. It is now also necessary to examine what findings appear to have been demonstrated by these trials, and whether certain findings are corroborated by several trials, while other

trial results contradict each other. Conclusions need to be drawn as to whether the trials are useful for developing guidelines for the use of antipsychotics in the management of psychotic illness, what findings are corroborated by several trials, and indeed, whether methodological flaws might undermine some conclusions from some of the studies.

We aimed to conduct a review of the current literature to establish the appropriateness of several recent major clinical studies being used as the basis for clinical guidelines.

METHOD

A literature search was carried out in Pubmed. Five major studies comparing antipsychotic efficacy were selected as possible candidates and subjected to further analysis

The studies were:

- CUTLASS (Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia study);
- CATIE (Clinical Antipsychotic Trials of Intervention Effectiveness study);
- SOHO (Schizophrenia outpatients Health Outcomes study);
- CAFÉ (Comparison of Atypicals in First Episode study);
- EUFEST (European First Episode Schizophrenia Trial).

RESULTS

We here summarise the reported outcomes of these five trials as reported in the relevant publications as reported in pubmed and to which we make due reference, from which we have abstracted the data, before discussing them in the discussion section of this article.

Table 1. A tabular comparison of some major antipsychotic trials

Trial	Year	Design	Primary End Point	Secondary End Point
Cafe	2007	Randomised, double blind, flexible dose, multicentre trial	Discontinuation of medication for any reason	Reduction in positive and negative symptom score
Catie	2005	Multicentre randomised, uncontrolled interventional	Discontinuation of medication due to inefficacy	Discontinuation of medication for any reason
Cutlass	2006	Randomised, single blind	Quality of life scores, cost	Side effect reporting
Eufest	2008	Open Randomised Control Trial	Discontinuation of medication for any reason	Changes in psychopathology warranting reassessment
Soho	2008	Prospective, Observational	Functional and Symptomatic recovery for a minimum of 24 months	Functional remission or an acceptable quality of life

Two studies dealt with Chronic Patients

The Schizophrenia Outpatients Health Outcomes (SOHO) study was a prospective, observational study of antipsychotic treatment in an outpatient setting, which took place over three years. In SOHO, (Gasquet et al. 2008, Suarez et al. 2008, Novick et al. 2009, Haro et al. 2009) Recovery was seen as an endpoint of the study. SOHO defined Recovery as a long-lasting symptomatic and functional remission accompanied by an adequate quality of life for a minimum of 24 months and until the 36-month visit. Novick et al determined the frequency and predictors of recovery in patients with schizophrenia during 3 years of antipsychotic treatment in the prospective, observational SOHO study (Novick et al. 2009). Of the 6642 patients analysed, 33% were observed to achieve long-lasting symptomatic remission, 13% achieved long-lasting functional remission, 27% achieved long-lasting adequate quality of life, and 4% were assessed to have achieved recovery during the 3 year follow-up period. A logistic regression study showed that social functioning at study entry , including having good occupational/vocational status, living independently and being socially active, as well as adherence with taking medication were factors which were significantly associated with achieving recovery(Novick et al. 2009). On the other hand, Higher negative symptom severity, higher BMI and lack of effectiveness quoted as the reason for the change of medication at baseline were factors at baseline which were associated with a lower likelihood of achieving recovery (Novick et al. 2009). Treatment with olanzapine was also observed to be associated with a higher frequency of recovery,when compared with risperidone, quetiapine, typical antipsychotics (oral, depot) and patients who were taking two or more different antipsychotic medications (Novick et al. 2009). There were no differences among the patients taking olanzapine, clozapine and amisulpride(Novick et al. 2009). It was advised by the authors that the results should be interpreted conservatively due to the observational, nonrandomised study design, however these results do indicate that only a small proportion of patients with schizophrenia achieve recovery and they suggest that social functioning, medication adherence and type of antipsychotic are important predictors of recovery (Gasquet et al. 2008, Suarez et al. 2008, Haro et al. 2009). In SOHO, treatment effectiveness and tolerability varied among antipsychotic medications in previously untreated patients with schizophrenia (Haro

et al. 2009). SOHO has also contributed to knowledge regarding first episode psychosis, since data from this 3-year, prospective, observational study have been used to compare the effectiveness (in terms of treatment discontinuation) and the tolerability of olanzapine, risperidone, other atypicals and typical antipsychotics in 1009 previously untreated outpatients with schizophrenia who started anti-psychotic monotherapy at baseline (Haro et al. 2009).A Kaplan-Meier survival analysis was used by Haro et al to estimate the time to treatment discontinuation by the treatment group(Haro et al. 2009), while Haro used Cox proportional hazards regression models to identify the variables associated with treatment discontinuation while making adjustments for baseline differences between treatment groups (Haro et al. 2009). Haro also used logistic regression models in order to compare the tolerability profiles of the different treatment groups (Haro et al. 2009). Of the 931 patients analyzed, 31.9% discontinued the medication initiated at baseline during the 3-year follow-up (Haro et al. 2009). Olanzapine had the lowest rate of discontinuation rate (28.9%), followed by other atypicals (34.0%), risperidone (36.2%) and typical antipsychotics (44.5%) (Haro et al. 2009). Compared to olanzapine, the risk of treatment discontinuation was higher with typical antipsychotics (hazard ratio HR 1.75; 95% confidence intervalCI 1.11, 2.78 respectively) (Haro et al. 2009) or risperidone (HR 1.36; 95% CI 1.02, 1.82 respectively) (Haro et al. 2009). A higher baseline Clinical Global Impression (CGI) positive score was associated with a higher risk of treatment discontinuation (HR 1.18; 95% CI 1.06, 1.30) (Haro et al. 2009). It was found that Olanzapine was associated with a lower frequency of extrapyramidal symptoms than other antipsychotics,as well as with fewer prolactin-related adverse events than risperidone and other atypical antipsychotics, but with greater weight gain than typicals and risperidone (Haro et al. 2009). Comparisons with the other atypical group in all analyses was limited due to its small sample size (n=50). Haro et al accepted that given the observational study design, the results must be interpreted conservatively (Haro et al. 2009).

CATIE, (Clinical Antipsychotic Trials of Intervention Effectiveness), carried out by Lieberman et al. in 2005, is another study of the use of anti-psychotics in chronic Schizophrenia (Lieberman et al. 2005). In CATIE, a total of 1493 patients with schizophrenia were recruited at 57 sites in the United States and randomly assigned to receive olanzapine (7.5 to 30 mg per day), perphenazine (8 to 32 mg per day), quetiapine (200 to 800 mg per day), or risperidone (1.5 to 6.0 mg per day) for up to 18 months. Ziprasidone (40 to 160 mg per day) was included after it had been approved by the Food and Drug Administration(Lieberman et al. 2005). The main aim (primary outcome measure)of the study was to identify differences in the overall effectiveness of these treatments (Lieberman et al. 2005). Overall, 74 percent of all the patients discontinued the study medication before 18 months had elapsed.These included 1061 of the 1432 patients who received at least one dose (Lieberman et al. 2005).They included 64 percent of those assigned to olanzapine, 75 percent of those assigned to perphenazine, 82 percent of those assigned to quetiapine, 74 percent of those assigned to risperidone, and 79 percent of those assigned to ziprasidone (Lieberman et al. 2005). The time to the discontinuation of treatment for any cause was significantly longer in the olanzapine group than in the quetiapine ($P<0.001$) or risperidone ($P=0.002$) group, but not in the perphenazine ($P=0.021$) or ziprasidone ($P=0.028$) group (Lieberman et al. 2005). The times to discontinuation because of intolerable side effects were similar among the groups, but the rates differed ($P=0.04$). Olanzapine was associated with more discontinuation for weight gain or metabolic effects, while perphenazine was associated with more discontinuation for extrapyramidal effects (Lieberman et al. 2005). The majority of patients in each group discontinued the treatment to which they had been assigned owing to inefficacy or intolerable side effects, while some gave other reasons(Lieberman et al. 2005). Olanzapine was the most effective in terms of the rates of discontinuation, while the efficacy of the conventional antipsychotic agent perphenazine appeared similar to that of quetiapine, risperidone, and ziprasidone (Lieberman et al. 2005). Olanzapine was associated with greater weight gain and increases in measures of glucose and lipid metabolism (Lieberman et al. 2005).

Two studies dealt with First Episode of Psychosis Patients.

Café, standing for Comparison of Atypicals in First Episode, (McEvoy et al. 2007, Perkins et al. 2008) was a 52- week randomized, double-blind, flexible-dose, multicenter study which evaluated the overall effectiveness (as measured by treatment discontinuation rates) of olanzapine, quetiapine, and risperidone in patients early in the course of psychotic illness (McEvoy et al. 2007). Patients were randomly assigned to treatment with olanzapine (2.5-20 mg/day), quetiapine (100-800 mg/day), or risperidone (0.5-4 mg/day) administered in twice-daily doses. Statistical analyses tested for non-inferiority in all-cause treatment discontinuation rates up to 52 weeks as the primary outcome measure, and was based on a prespecified noninferiority margin of 20%. In other words, it was expected that 20% of patients would discontinue treatment (McEvoy et al. 2007). A total of 400 patients were randomly assigned to treatment with olanzapine (N=133), quetiapine (N=134), or risperidone (N=133). The mean modal prescribed daily doses of medication were 11.7 mg for olanzapine, 506 mg for quetiapine, and 2.4 mg for risperidone (McEvoy et al. 2007). At week 52, treatment discontinuation rates for all causes were 68.4%, 70.9%, and 71.4% for olanzapine, quetiapine, and risperidone, respectively (McEvoy et al. 2007). The reductions in total score on the Positive and Negative Syndrome Scale (PANSS) were similar for the three treatment groups, however reductions in PANSS

positive subscale scores were greater in the olanzapine group (at 12 weeks and at 52 weeks or withdrawal from study) and in the risperidone group (at 12 weeks) (McEvoy et al. 2007). The most commonly reported adverse events for olanzapine were drowsiness (53%), weight gain (51%), and insomnia (38%); for quetiapine, drowsiness (58%), increased sleep hours (42%), and weight gain (40%); and for risperidone, drowsiness (50%), menstrual irregularities in women (47%), and weight gain (41%) (McEvoy 2007). It therefore appeared that Olanzapine, quetiapine, and risperidone had comparable effectiveness in patients suffering from early-psychosis, as was indicated by similar rates of all-cause treatment discontinuation (McEvoy et al. 2007). Of the 400 patients who were randomly assigned to treatment, 115 patients who discontinued treatment against medical advice and 119 persons who completed the study were compared (Perkins et al. 2008). Poor treatment response ($p<0.001$) and low medication adherence ($p=0.02$) were shown to be independent predictors of discontinuation against medical advice (Perkins et al. 2008). Ongoing substance abuse, ongoing depression, and failure of treatment response significantly predicted poor medication adherence ($p<0.01$) (Perkins et al. 2008). Higher cognitive performance at baseline and ethnicity (being black american) were also associated with lower medication adherence ($p<0.05$) (Perkins et al. 2008). An association between poor medication adherence and insight into their illness at study entry was found at the level of a trend ($p=0.059$) (Perkins et al. 2008). Therefore, this study demonstrated the importance of treatment response in predicting discontinuation against medical advice and poor adherence to medication in first-episode patients (Perkins et al. 2008). These results also supported interventions to improve behaviours linked with adherence, particularly by targeting substance use disorders and depressive symptoms (Perkins et al. 2008).

EUFEST, The European First Episode Schizophrenia Trial (Kahn et al. 2008), aimed to compare the effectiveness of second-generation antipsychotic drugs with that of a low dose of haloperidol, in first-episode schizophrenia(Kahn et al. 2008). It was an open randomised controlled trial of haloperidol versus second-generation antipsychotic drugs which took place in 50 sites, in 14 countries(Kahn et al. 2008). Patients who were eligible were aged 18-40 years, and met appropriate diagnostic criteria for schizophrenia, schizophreniform disorder, or schizoaffective disorder. Four hundred and ninety-eight patients (n=498) were randomly assigned by a web-based online system to haloperidol (1-4 mg per day; n=103), amisulpride (200- 800 mg per day; n=104), olanzapine (5-20 mg per day; n=105), quetiapine (200-750 mg per day); n=104), or ziprasidone (40-160 mg per day; n=82) (Kahn et al. 2008).Follow-up took place at one year. The primary outcome measure was treatment discontinuation for any cause. Neither the Patients nor their treating physicians were blinded to the assigned treatment. Analysis was by intention to treat(Kahn et al. 2008). The number of patients who discontinued treatment for any cause within 12 months was 63 (Kaplan-Meier estimate 72%) for haloperidol, 32 (40%) for amisulpride, 30 (33%) for olanzapine, 51 (53%) for quetiapine, and 31 (45%) for ziprasidone (Kahn et al. 2008). Comparisons with haloperidol showed lower risks for any-cause discontinuation with amisulpride (hazard ratio HR) 0.37, 95% CI 0.24-0.57), olanzapine (HR 0.28 0.18-0.43), quetiapine (HR 0.52 0.35-0.76), and ziprasidone (HR 0.51 0.32-0.81). However,Khan et al reported that symptom reductions were virtually the same in all the groups, at around 60% (Kahn et al. 2008). Therefore, this trial shows that clinically meaningful antipsychotic treatment of first-episode of schizophrenia is achievable, for at least one year (Kahn et al. 2008). However, the trial reporters did not conclude that second-generation drugs were more efficacious than haloperidol, since the reporters felt that discontinuation rates were not necessarily consistent with symptomatic improvement (Kahn et al. 2008).

A cost-utility study

The Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS 1) (Jones et al. 2006) was a study which aimed to compare the cost utility of first generation antipsychotics to that of second generation antipsychotics in chronic patients. Thus its aim was different from the other four trials. The aim was to test the hypothesis that in people with schizophrenia requiring a change in treatment, Second Generation Antipsychotics (SGAs) other than clozapine are associated with improved quality of life over one year compared with First Generation Antipsychotics (FGAs) (Jones et al. 2006). Two hundred and twenty-seven people aged 18 to 65 years,who suffered from schizophrenia as defined by DSM-IV and related disorders, who received a medication review because of inadequate response to treatment or because of adverse effects from medication were offered randomized prescription of either FGAs or SGAs (other than clozapine), with the choice of individual drug being made (from an agreed list of medications for each group) by the managing psychiatrist (Jones et al. 2006). The main outcome measures were Quality of Life Scale scores, symptoms, adverse effects, participant satisfaction, and costs of care(Jones et al. 2006). The result of the study was that the primary hypothesis ,that there would be significant improvement in Quality of Life Scale scores during the first year after commencement of SGAs vs FGAs was excluded(Jones et al. 2006). Participants in the FGA arm demonstrated a trend toward greater improvements in Quality of Life Scale and symptom scores over the first year (Jones et al. 2006). The participants reported no clear preference for either drug group, and costs were similar.(Jones et al. 2006) On this basis it was concluded that in people with schizophrenia whose medication is changed for clinical reasons, there was no disadvantage across one year in terms of quality of life, symptoms, or associated costs of care if FGAs were used rather than nonclozapine SGAs (Jones et al. 2006). In the reporters' view, neither inadequate power nor patterns of drug discontinuation accounted for the result.

DISCUSSION

The design of the CUtLASS study has drawn criticism, and here we append our own (Agius et al. 2008). CUtLASS allows for less generalisation of its findings to the general population as it makes use a specific sub-population (those switching from one medication to another after a period of treatment). Also some patients were prescribed oral medications and some depot injections - making comparisons difficult due to possible differences in compliance. Close scrutiny of the study shows that, even though there is no doubt that the results of the study and its statistical analysis appear to be robust enough, the design of the study itself does not allow for any generalisation of the findings to a general statement regarding the cost utility of second and first generation anti-psychotic therapy outside of the study sample itself (Agius et al. 2008). Particular issues which arise include; The choice, as a starting point of the study, of patients requiring a change of medication, either by reason of efficacy or of side effects. This excludes, from any estimate of cost efficacy all patients whose first antipsychotic treatment – often a second generation drug, -has proved appropriate and effective (Agius et al. 2008). The fact that, since over 40% of patients in the First Generation anti- psychotic group were put on Sulpride, these patients represent a most unusual group, since Sulpride is a drug among the first generation group which has some unusual properties compared to the rest of the group, making it similar to amisulpride, which is considered to be within the second generation group (Agius et al. 2008). The question arises as to whether the terms First Generation and Second Generation groups of anti-psychotics are at all meaningful, given the heterogeneity in terms of pharmaceutical properties of the antipsychotics within each group; Indeed , does Typicality and Atypicality have the same meaning as First or Second Generation (Agius et al. 2008)? There is also the issue of anti-psychotic combination treatment, which suggests the presence in this study of particularly difficult to treat patients (Agius et al. 2008). Furthermore, within the first generation group, some patients were put on depot injectable preparations while others were put on oral medications. In the second generation group, all patients were put on oral medication, so there were differences in compliance issues and how they could be expressed by patients in the two groups (Agius et al. 2008). There is the difficulty, given that the only total readings on the Quality of Life scale are presented and compared in the findings, of being clear what precise improvement of 'Quality of Life' occurred in the First and Second generation groups (Agius et al. 2008). The lack of reporting, during the study, of any other interventions, such as Cognitive Therapy or Assertive Case Management which could have impacted on the quality of life of some study patients more than on others is also an issue (Agius et al. 2008), and, indeed, this issue arises with all of the studies reported, since the only variable measured in all the studies is the choice of medication, while schizophrenia is an illness which is treated by other interventions as well as medication alone. All of these factors taken together suggest that the conclusion that there is no difference in cost efficacy between first and second generation medications must remain a matter for further exploration despite the findings of this study. In particular it seems unwise to use the CUtLASS data as a reason for not using atypical antipsychotics in patients with first and early episodes of psychotic illness (Agius et al. 2008).

Attempts have been made to equate the CATIE and CUtLASS findings, but given the disparate aims and methodologies of these two trials, it is difficult to see how such attempts can be cogently done.

All of the trials have differences in study design such that direct comparisons are made difficult . Furthermore, each study has had different aims, and therefore it may be unfair to extrapolate to studies outcomes which they were never designed to prove.

The SOHO study compares recovery with olanzapine, clozapine, amisulpride, risperidone, quetiapine, and typical antipsychotics (oral, depot). These were the antipsychotics available when the study was designed. It is an observational study, and as such, it has been able to provide three year data. However, the observational nature of the study gives rise to the need for caution in the interpretation of the data. SOHO is hindered by the observational design of the study and the small numbers reaching the primary end point (4%). Hence, caution should be exercised in the conclusion, based on SOHO alone, that olanzapine is superior to risperidone, quetiapine or typical antipsychotics.

CATIE was a randomised study lasting only 18 months. It included olanzapine, perphenazine, quetiapine, risperidone, with Ziprasidone being added on later. It is notable for its very high discontinuation rate -74% before 18 months. Effectiveness appears to have been measured in terms of discontinuation of Medication, an arguable measure of outcome. It is of note that 30 mg was the upper permitted dose of medication with olanzapine in CATIE, which is above the licenced dose, while all other doses were within the licenced dosage range. CATIE was a comparative study, and so lacked a control arm and used discontinuation of medication which is an inverse measure of efficacy - an easily quantifiable event, but making for difficult interpretation. However most criticism has been directed at the unusually low (quitiapine, ziprasidone) and high (olanzapine and perphenazine) doses of drug used, which were reflected in their differing rates of efficacy.

CAFE was a 52-week randomized, double-blind study which evaluated the overall effectiveness , again as measured by treatment discontinuation rates, of olanzapine, quetiapine, and risperidone in patients early in the course of psychotic illness. While the maximal dose of olanzapine and quetiapine was the maximal licensed dose, that of risperidone was 4mg, below the maximal recommended dose of 6 mg.

CAFE, although well randomised and blinded, uses discontinuation as a primary endpoint - this is hard to draw conclusions from: patients may discontinue due to side effects, due to lack of efficacy or with against

medical advice for a multitude of reasons. As a secondary endpoint, the study does make use of a PANSS scoring system to measure efficacy, adding some weight to the conclusion that olanzapine, quetiaine and risperidone in early psychosis patients have equivalent efficacies.

EUFEST also aimed to compare the effectiveness of second-generation antipsychotic drugs with that of a low dose of haloperidol, in first-episode schizophrenia. Effectiveness was also measured by all cause discontinuation. It should be noted that in this study, the maximal dose of quetiapine was 50mg,clearly below the highest licenced dose, and risperidone was omitted from the study, which is inexplicable given its wide usage in first episodes of schizophrenia. Treatment of first episodes of psychosis is shown to be feasible, but the study could not suggest if haloperidol or second generation drugs may be more efficacious.

Hence, EUFEST can only be interpreted as a comparison between the medications considered and a low dose of Haloperidol.

None of the studies discussed take into account Aripiprazole, a medication of novel action which was not available when the studies were first designed.

However, a few conclusions may be drawn from the collective view of these studies. In the first place, differences between the outcomes of using the different antipsychotics studied have been described, so that it must be concluded that the oft quoted statement by regulatory organisations such as NICE that all antipsychotics are of similar efficacy must be seen as at least inexact. Secondly, within the limitations noted, particularly the limitation that effectiveness is measured on the basis of rate of discontinuation, a dubious measure at best, CATIE, EUFEST, and SOHO do seem to suggest that olanzapine is more effective than other medications. Clearly, it is concern about metabolic effects which has prevented this observation being acted upon in terms of choice of medication, and much work is yet to be done to discover a safe, optimally effective antipsychotic, with a minimal side effect profile.

It is worth noting that whereas CAFÉ showed that Poor treatment response and low medication adherence were independent predictors of discontinuation against medical advice (Perkins et al. 2008), EUFEST demonstrated that discontinuation rates were not necessarily consistent with symptomatic improvement (Kahn et al. 2008), this emphasizes the difficulty in using overall discontinuation rates as an outcome measure, or a measure of the effectiveness of treatment with medication.

CONCLUSION

There is much information useful for clinical practice to be gathered from the results of these major studies, however, interpretation is hampered by both variations and weakness in study design. On balance it does appear that different antipsychotics possess differing efficacy, but also of relevance to the development of sound clinical guidelines is their differing side effects profile.

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