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Comparative Effectiveness of Atypical Antipsychotics in Schizophrenia

What have Real-World Trials Taught Us?

Azizah Attard[1,2] and *David M. Taylor*[1,2]

1 Pharmacy Department, South London and Maudsley NHS Foundation Trust, Denmark Hill, London, UK
2 Institute of Pharmaceutical Science, King's College, London, UK

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Abstract

Real-world, effectiveness studies add an important new dimension to the evaluation of the benefits of individual antipsychotics. Efficacy studies have already shown the unique effectiveness of clozapine, and suggested improved outcomes for olanzapine compared with some atypical antipsychotics and a reduced tendency to produce acute and chronic movement disorders for

atypical compared with typical drugs. Recent effectiveness studies largely confirm these prior observations. The CATIE (Clinical Antipsychotic Trials of Intervention Effectiveness), CUtLASS (Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study) and SOHO (Schizophrenia Outpatient Health Outcomes) programmes confirmed the superiority of clozapine over other antipsychotics; CATIE and SOHO also confirmed olanzapine as probably the second most effective antipsychotic. Effectiveness studies have confirmed the high incidence of adverse metabolic effects with clozapine, olanzapine and (with less certainty) quetiapine but the ZODIAC (Ziprasidone Observational Study of Cardiac Outcomes) study found no excess cardiovascular events or deaths for olanzapine compared with ziprasidone. Prior observations on reduced frequency of movement disorders for second-generation versus first-generation antipsychotics were also largely (but not uniformly) supported.

Overall, recent real-world studies have done much to confirm prior observations from efficacy-based randomized, controlled trials.

1. Introduction

The development and introduction of second-generation antipsychotics (SGAs) has led to an expectation for better pharmacological treatment of schizophrenia. In addition to this, the range of outcomes for identifying success with antipsychotic therapy has expanded and has begun to include consideration of negative and cognitive symptoms. Initial studies involving SGAs concentrated on the essentials (safety and efficacy). Trials were short term (up to 8 weeks), randomized and placebo controlled to fulfil regulatory requirements. These short-term trials have now given way to longer, larger clinical effectiveness trials. The aim of these larger trials essentially is to examine to what extent therapeutic efficacy is translated into clinical effectiveness and to answer the question: what is the most effective antipsychotic to treat schizophrenia?

The four clinical effectiveness studies on SGAs included in this article are CATIE (Clinical Antipsychotic Trials of Intervention Effectiveness), CUtLASS (Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study), SOHO (Schizophrenia Outpatient Health Outcomes) and ZODIAC (Ziprasidone Observational Study of Cardiac Outcomes). The main objectives, description and outcomes of each trial are summarized below.

2. CATIE

The main objective of CATIE was to determine the comparative effectiveness of a representative conventional antipsychotic (perphenazine) and different atypical antipsychotics in chronic schizophrenic patients as measured by time to treatment discontinuation.[1] Table I summarizes the main description of CATIE and the main outcomes.

In addition to the main body of CATIE trials listed above, several other studies and analyses were carried out within the population.

2.1 Extrapyramidal Side Effects Trial

The CATIE EPSE (Extrapyramidal Side Effects) trial[7] used a variety of measures of dystonia, parkinsonism, akathisia and tardive dyskinesia (TD) and analysed incidence rates and continuous rating scales. They found no substantial and significant differences between the SGA and perphenazine or between any pair of the SGAs in the incidence of treatment-emergent extrapyramidal symptoms (EPS) and change in EPS ratings.[7] There was a trend towards a higher proportion of patients in the risperidone and perphenazine group to have medications added to treat akathisia compared with patients in the olanzapine, quetiapine and ziprasidone groups.[7] The dose range of perphenazine used in the CATIE trials was

Table I. Description and main outcomes of the CATIE trial (US) [not industry sponsored]

Trial	No. of participants	Drugs involved	Description	Outcome measures	Main outcomes
CATIE[2] Phase 1 and 1a	1460	Olanzapine Risperidone Quetiapine Perphenazine Ziprasidone	Patients with chronic schizophrenia who were considering a switch of AP or not currently taking an AP were randomly assigned to double-blind treatment. Of the 1460 patients, 1432 were included in the analysis as 28 patients did not take their assigned medication. Phase 1a included 231 people who had signs of TD and were excluded from being randomly assigned to perphenazine	Primary outcome: time to discontinuation	Of the 1432 patients, 74% (1061) discontinued their treatment for any cause before 18 mo: olanzapine 64%, perphenazine 75%, quetiapine 82%, risperidone 74% and ziprasidone 79%. No statistical analysis was done to compare the rates of discontinuation. Median time to discontinuation was 4.6 mo overall; and for olanzapine 9.2 mo. Time to treatment discontinuation for any cause was significantly longer for olanzapine than for quetiapine (HR 0.63; $p < 0.001$) or risperidone (HR 0.75; $p = 0.002$). Although the time to treatment discontinuation was longer for olanzapine compared with perphenazine and ziprasidone, the difference was not statistically significant after adjustment for multiple comparisons
Phase 1b[3]	114	Olanzapine Risperidone Quetiapine	Patients who were randomly assigned to perphenazine in phase 1a but then discontinued were randomly assigned to double-blind treatment with olanzapine, risperidone or quetiapine		The time to discontinuation was significantly longer for patients treated with quetiapine (median 9.9 mo) and olanzapine (7.1 mo) than with risperidone (3.6 mo)
CATIE[4] Phase 2E[3]	99	Clozapine Olanzapine Quetiapine Risperidone	Patients who had discontinued treatment in phase 1 because of poor effect were randomly assigned to open-label clozapine or double-blind treatment with olanzapine, quetiapine or risperidone	Primary outcome: time to discontinuation	Of the 99 patients, 69% ($n = 68$) discontinued treatment for any cause before completion of the study; clozapine 56%, olanzapine 71%, quetiapine 93% and risperidone 86%. Time to all-cause discontinuation was significantly longer for clozapine (median 10.5 mo) than for quetiapine (median 3.3 mo) or risperidone (median 2.8 mo) but not for olanzapine (median 2.7 mo). Clozapine was significantly superior to all 3 other APs in time to discontinuation due to lack of efficacy

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Table I. Contd

Trial	No. of participants	Drugs involved	Description	Outcome measures	Main outcomes
Phase 2T[5]	444	Olanzapine Risperidone Quetiapine Ziprasidone	Patients who discontinued treatments for any reason in phase 1 were then randomly assigned to double-blind treatment with an SGA that they had not previously received	Primary outcome: time to discontinuation	Of the 444 patients, treatment discontinuation for any cause occurred in 64% to 84% of patients; olanzapine 67%, quetiapine 84%, risperidone 64%, ziprasidone 77%. The time to treatment discontinuation was significantly longer for patients treated with risperidone (median 7.0 mo) and olanzapine (median 6.3 mo) than with quetiapine (median 4.0 mo) and ziprasidone (median 2.8 mo)
Phase 3[6] Open label	270	Aripiprazole Clozapine Fluphenazine IM Olanzapine Risperidone Quetiapine Perphenazine Ziprasidone Combination therapy	Patients who had discontinued medication in phase 1 and 2 were then eligible for phase 3	Primary outcome: time to discontinuation	106 (39%) patients discontinued treatment before completion of the study. The mean treatment duration was 7.7 mo. There were no substantial differences between treatments in the proportion of patients who discontinued the commonly selected regimens (range 33–46%). The rates of discontinuation for lack of efficacy were lower for clozapine, risperidone, quetiapine and ziprasidone (0–5%) compared with aripiprazole, olanzapine and combination AP treatment (13–18%) [p = 0.013]

AP = antipsychotic; **HR** = hazard ratio; **IM** = intramuscularly; **SGA** = second-generation antipsychotic; **TD** = tardive dyskinesia.

chosen to minimize the potential for EPS. Despite this, the original report from CATIE showed significantly more patients (8% vs 2–4%, p = 0.002) discontinued perphenazine because of EPS.[4]

The reason for this discrepancy could be because the former trial looked at the incidence of EPS separately, excluding from the analysis those who had a specific EPS at baseline. This method may be useful for determining incidence of emergent side effects but does not allow for pooled incidence of all types of EPS. The rating scales used in the CATIE EPSE trial were more sensitive compared with the original trial because they were not simply looking at reasons for discontinuation.

2.2 Change in Metabolic Syndrome Parameters Trial

The Change in Metabolic Syndrome Parameters Trial[8] trial used the National Cholesterol Education Programme (NCEP) derived diagnostic criteria for the metabolic syndrome (summarized in table II).

Among the 933 subjects who had baseline and 3-month data, metabolic syndrome could be classified in 660 patients. In this all-classifiable group, within 3 months, the proportion of patients meeting criteria for metabolic syndrome was highest for olanzapine (+9.1%) and this difference was significant compared with ziprasidone (–7.8%) [p = 0.001]. This study also indicated that quetiapine when used at higher dosages had a significant effect on increasing central adiposity and high-density lipoprotein (HDL) [in White subjects] despite not having an effect on glucose homeostasis.

2.3 Staying versus Switching Trial

Phase 1 of the CATIE trial allowed for analysis of patients who continued with their original

antipsychotic medication before entry into CATIE compared with those who were randomized to switch their antipsychotic medication. The first analysis compared patients who were randomly assigned to olanzapine or risperidone and had been taking the same drug prior to CATIE ('stayers', n = 139), and patients who were assigned to olanzapine and risperidone as a new medication ('switchers', n = 496).[9] This analysis found that switchers discontinued the study drug more rapidly than those who were assigned to stay on the medication they had been taking previously.[9] An additional analysis compared outcome measures that included symptoms, neurocognition, quality of life, neurological side effects, weight and heath costs.[10] These analyses concluded that there was no advantage in switching to a new medication in any of the outcome measures and found that patients who stayed on olanzapine gained more weight.[10]

2.4 Cost-Effectiveness Trial

An analysis of cost effectiveness[11] was performed through the CATIE trial and involved 1424 patients. This analysis demonstrated significantly lower total health costs for the perphenazine group. The difference was attributed to the lower drug costs associated with perphenazine in the context of no significant differences in healthcare costs.

Table II. National Cholesterol Education Programme derived diagnostic criteria for the metabolic syndrome (≥3 criteria must be present to establish diagnosis)

Criteria	Measurement
Waist circumference	
Men	>101.6 cm
Women	>88.9 cm
Fasting triglycerides	≥150 mg/dL
High density lipoprotein	
Men	<40 mg/dL
Women	<50 mg/dL
Blood pressure	≥130/85 mmHg or on antihypertensive medication
Fasting glucose	≥100 mg/dL or on insulin or hypoglycaemic medication

3. CUtLASS

The main objective of CUtLASS 1 was to test the hypothesis that SGAs other than clozapine are associated with improved quality of life across 1 year compared with first-generation antipsychotics (FGAs) in people with schizophrenia who required a change in treatment.[12] Additionally, a cost-effectiveness analysis was carried out.[13] CUtLASS 2 was designed to test the hypothesis that the use of clozapine (compared with other SGAs) would be associated with improvement in quality of life over 1 year and that this improvement would be associated with fewer symptoms, improved patient satisfaction and possibly lower total health costs.[14,15]

Table III summarizes the main description of CUtLASS and the main outcomes.

4. SOHO

The main objective of SOHO was to compare outcomes of patients initiating olanzapine with those patients initiating other antipsychotic medication. Table IV summarizes the main description of SOHO and the main outcomes.

In addition to the main body of the SOHO trials listed above, several other studies and analyses were carried out within the population.

4.1 Tardive Dyskinesia: 6-Month Evaluation and Early Extrapyramidal Side Effects Analysis Trials (Pan European)

The Tardive Dyskinesia – 6-Month Evaluation compared the incidence and persistence of TD between patients with schizophrenia who were treated with SGA and FGA at baseline, 3 months and 6 months. Of 10 972 patients who were enrolled, 9912 were considered in the analysis for TD at baseline and 912 (9%) were diagnosed with existing TD. By 6 months, only 8632 were analysed due to missing data and eligibility. The rate of emerging TD was higher in the FGA group than in the SGA group (3.8% vs 0.9% [odds ratio {OR} = 0.29; 95% CI 0.18, 0.46]). In order to remove any possibility of industry-sponsored bias, olanzapine was excluded for a second comparison

Table III. Description and main outcomes of the CUtLASS trial[12,13] (UK) [not industry sponsored]

Trial	No. of participants	Drugs involved	Description	Outcome measures	Main outcomes
CUtLASS 1 12, 26 and 52 wk analysis	227	All FGAs and SGAs in the UK available at the time (other than clozapine)	Participants were identified by their psychiatrist as having inadequate response to or to be intolerant of their medication and needing a change in therapy. Patients were then randomized to receive either an FGA or an SGA and the patients consultant psychiatrist chose the individual drug in each class before randomization. Before randomization, of the 227 patients, 207 patients were prescribed FGAs and 44 patients SGAs. 84 (37%) patients were taking depot FGAs; 47 of these patients were randomized to receive FGAs and 37 patients SGAs. 28 (12%) patients were receiving more than one antipsychotic; 13 of these patients were randomized to receive an FGA and 15 an SGA. There were slightly more patients receiving depot FGAs who were randomized to the FGA arm than the SGA arm (44% and 37%, respectively). The economic component of this trial was the Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study	Primary outcome: QLS.[16] Cost analysis outcome included QALYs using the EQ-5D[17]	There was no significant difference in QLS between FGA and SGA arms. Patients in the FGA arm were doing numerically better in terms of QLS at 52 wk (FGA mean QLS = 53.3 [SD = 21.2]; SGA mean QLS = 51.3 [SD = 19.6]). There was a trend toward lower mean direct costs in patients allocated to the FGA arm. Drug costs accounted for only a small proportion of costs (2.1% in the FGA arm and 3.8% in the SGA arm) and the major costs in both groups are from psychiatric hospital admissions. This study concluded that there is no evidence to suggest SGAs are more cost effective than FGAs
CUtLASS 2[15,18] 12, 26 and 52 wk analysis	136	All FGAs and SGAs in the UK available at the time	Participants were identified by their psychiatrist as having inadequate response or intolerance to 2 or more previous antipsychotic drugs. Patients were then randomized to receive either clozapine or another SGA and the patients consultant psychiatrist chose the individual drug in each class before randomization. There were 136 patients enrolled with 67 randomized to clozapine and 69 to a non-clozapine SGA (all patients changed medication). Prior to randomization to the SGA arm, 44 patients (64%) were being treated with an FGA; 30 of these via a depot. The remaining patients were receiving a non-clozapine SGA. The economic component of this trial was the Cost Utility of the Second Generation Antipsychotics in People with Psychosis and Eligible for Clozapine	Primary outcome: QLS.[16] Cost analysis outcome included QALYs using the EQ-5D[17]	At 1 y, 54% of patients remained on the assigned medication in the clozapine arm and 57% remained on SGA (4 patients had required a further change in antipsychotic). The difference in QLS between the two arms at 52 wk was not statistically significant (clozapine mean QLS change = 12.7 [SD = 16.8] and SGA mean QLS change = 10.2 [SD = 18.3]). Clozapine was associated with higher costs and higher QALYs than other SGAs for the 12-mo period following a change in therapy. If clozapine were to be initiated in the community setting rather than as an inpatient then the use of clozapine could be associated with lower costs and higher QALYs compared with other SGAs

EQ-5D = EuroQol-5 Dimension; **FGA** = first-generation antipsychotic; **QALY** = quality-adjusted life-year; **QLS** = quality of life scores; **SGA** = second-generation antipsychotic.

Table IV. Description and main outcomes of the SOHO trial[a]

Trial	No. of participants	Drugs involved	Description	Outcome measures	Main outcomes
Baseline[19]	10 205	Focused on olanzapine but also included all FGAs and SGAs in Europe from Sep 2000 to early 2005	Of the 10 972 patients, 767 (7%) were excluded at baseline due to failure to meet the entry criteria or failure of treatment cohort allocation	Primary outcome measures: time to treatment discontinuation, clinical severity (CGI),[20] HR-QOL (EQ-5D)[17]	At baseline, 5376 patients started olanzapine, 1918 started risperidone, 790 started quetiapine (at enrolment quetiapine was not available in Portugal or France), 328 started amisulpride (at enrolment amisulpride was not available in Denmark, Greece, Netherlands or Spain), 327 started clozapine, 688 started oral typical antipsychotics, 485 started depot typical antipsychotics and 268 started more than one antipsychotic tended to be younger and have more severe illness. Patients receiving depot medications had a history of non-compliance. Patients receiving their first antipsychotic for schizophrenia were most likely to receive an atypical agent
6-mo,[21] European countries	9 028	Focused on olanzapine but also included all FGAs and SGAs in Europe from Sep 2000 to early 2005	Of the 10 205 at baseline, 9028 (88.5%) patients were evaluated at 6 mo	Response was defined as a decrease of 2 points in the CGI from a baseline of 4–6 points or a decrease of 1 point from a baseline of 1–3 points	In total, 53.2% of patients responded to treatment; response ranged from 41.4% for depot antipsychotics to 59.1% for clozapine. Patients receiving risperidone, quetiapine, amisulpride, oral and depot typical antipsychotics were significantly less likely to respond than those receiving olanzapine, ORs range from 1.32 (95% CI 1.16, 1.49) to 1.84 (95% CI 1.46, 2.3)
6-mo previously untreated patients, European countries	919	Focused on olanzapine but also included all FGAs and SGAs in Europe from Sep 2000 to early 2005	Of the 10 972 patients enrolled, 1033 had never been treated with antipsychotics. Only 919 were included in the analysis as the remaining 114 were in treatment cohorts with <40 patients, which would provide inadequate precision for the estimates on the longitudinal analysis. Of the 919 patients, 650 received olanzapine, 224 risperidone and 45 an FGA as their first treatment for schizophrenia	Response was defined as a decrease of 2 points in the CGI from a baseline of 4–6 points or a decrease of 1 point from a baseline of 1–3 points	At 6 mo, a similar proportion of patients remained on olanzapine and risperidone monotherapy (67.4% and 83.3%, respectively), whereas the proportion in the typical cohort was lower (69.1%). The response rate in clinical symptoms was 70.4% for olanzapine, 61.7% for risperidone and 73.8% for typical antipsychotics. This response rate was significantly lower for risperidone compared with olanzapine (OR 0.63; 95% CI 0.44, 0.90; p = 0.012), whereas there was no significant difference in response rate between typical antipsychotics and olanzapine

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Table IV. Contd

Trial	No. of participants	Drugs involved	Description	Outcome measures	Main outcomes
12-mo[22] IC-SOHO, 27 countries, intercontinental	5 833	Olanzapine Quetiapine Risperidone Haloperidol	This study was an intercontinental study and included patients from 27 countries	CGI was validated using CGI-SCH.[23] Responders were identified as those with CGI-SCH ≥4 that decreased by 2 or more points and those with CGI-SCH ≥3 that decreased by 1 point or more. For the subset of responders, relapse was defined as a reversal of the improvement in overall CGI-SCH score back to severity or worse at baseline and an increase in the overall CGI-SCH score by 2 or more points from the best (lowest) overall score recorded at previous visits	The olanzapine group had the highest proportion of patients who had responded at some time during the 12-mo treatment period (81%) followed by risperidone (73.7%), quetiapine (64.0%) and haloperidol (59.3%). Olanzapine- and risperidone-treated patients had higher odds of response compared with quetiapine (OR = 0.29; 95% CI 0.17, 0.48) and haloperidol (OR = 0.24; 0.15, 0.38). The risk of relapse was lower with olanzapine, risperidone and quetiapine compared with haloperidol (OR compared with olanzapine = 6.52; 3.10, 13.93)
24-mo treatment discontinuation,[24] European countries	6 915	Focused on olanzapine but also included all FGAs and SGAs in Europe from Sep 2000 to early 2005	9885 patients who were only prescribed one antipsychotic after the baseline visit. Analysis only included 6915 patients as these patients were evaluated at all timepoints until the 24 mo visit	Primary outcome measure: discontinuation of treatment	Overall, 30% of all patients discontinued medication before 2 y. Olanzapine (23%) and clozapine (24%) had lowest discontinuation rates, while quetiapine (49%), amisulpride (46%), oral typical (44%) and depot typical antipsychotics (35%) had higher discontinuation percentages. No statistical analysis was done to compare the rates of discontinuation
24-mo remission in previously untreated,[25] European countries	701	Focused on olanzapine but also included all FGAs and SGAs in Europe from Sep 2000 to early 2005	Of 1009 patients who had not previously been treated and prescribed only one antipsychotic, 701 patients were included in the follow-up analysis. Of the 701 patients included, 464 patients were taking olanzapine, 155 risperidone, 21 quetiapine, 13 amisulpride and 48 were taking FGAs	Primary outcome measure: remission was defined as a period of at least 6 mo in which the patient was rated at most mildly ill CGI ≤3 and the patient must have not been hospitalized due to schizophrenia during the 6-mo period	Predictors of symptomatic remission included a lower BMI, lower symptom severity in terms of overall CGI, CGI negative and CGI cognitive scores and having hostile behaviour

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Table IV. Contd

Trial	No. of participants	Drugs involved	Description	Outcome measures	Main outcomes
36-mo treatment discontinuation,[26] European countries	7 728		From baseline 7728 patients taking antipsychotic monotherapy were included in the analysis	Primary outcome measure: discontinuation of treatment	The proportion of patients who discontinued medication for any cause was 33.8% for clozapine, 36.4% for olanzapine, 42.7% for risperidone, 50.2% for depot typical antipsychotics, 50.4% for amisulpride, 53.1% for oral typical antipsychotics and 66.1% for quetiapine. The HR of treatment discontinuation for any cause was higher for quetiapine (2.22; 95% CI 2.00, 2.51), oral typical antipsychotics (1.7; 1.46, 1.97), amisulpride (1.63; 1.33, 2.0), depot typical antipsychotics (1.43; 1.19, 1.7) and risperidone (1.28 1.16, 1.42) compared with olanzapine.
36-mo treatment discontinuation in previously untreated, European countries	931		Of the 1009 patients from baseline who were previously untreated with an antipsychotic and started antipsychotic monotherapy, 936 patients had at least one follow-up visit and were included in the analysis. A further 5 patients who had started clozapine were excluded	Primary outcome measure: discontinuation of treatment	By 36 mo, 31.9% of all patients had discontinued the antipsychotic medication initiated at baseline. The percentage of patients who discontinued medication at 36 mo were 28.9% for olanzapine, 34.7% for other atypical antipsychotics (amisulpride and quetiapine), 36.2% for risperidone and the highest was 44.5% for typical antipsychotics. The HR for discontinuation of treatment by 36 mo was highest for typical antipsychotics (HR 1.76; 95% CI 1.11, 2.78)
36-mo recovery, European countries	6 642		Of the original sample of patients, those patients who had no more than one missing visit within the 36-mo period were included	Primary outcome measure: recovery was defined as simultaneously achieving long-lasting symptomatic and functional remission and an adequate quality of life for a minimum of 24 mo and maintained until the 36-mo visit	Of 6642 patients, 33% achieved long-lasting symptomatic remission, 13% long-lasting functional remission, 27% long-lasting adequate quality of life and 4% recovery during the 3-y follow-up. Olanzapine was associated with a higher frequency of recovery compared with risperidone (OR = 0.562; 95% CI 0.371, 0.850), quetiapine (OR = 0.201; 0.073, 0.566), oral typical antipsychotics (OR = 0.440; 0.205, 0.944), depot typical antipsychotics (OR = 0.297; 0.104, 0.845) and those taking two or more antipsychotics (OR = 0.564; 0.363, 0.876). There was no difference among the patients taking clozapine, amisulpride and olanzapine

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Table IV. Contd

Trial	No. of participants	Drugs involved	Description	Outcome measures	Main outcomes
36-mo remission and relapse,[27] European countries	6 516		Of the original sample of patients, those patients who had no more than one missing visit within the 36-mo period were included	Primary outcome measure: remission and relapse. Remission was defined as a period of at least 6 mo in which the patient was rated at most mildly ill with a score ≤3 in the CGI overall, CGI positive, CGI negative and CGI cognitive score and maintained for a period of 6 mo or more. Additionally the patient must have not been hospitalized due to schizophrenia during the 6-mo period. Relapse was defined as an increase of at least 2 points on the CGI overall severity score from the minimum score achieved by the patient during the follow-up assessments resulting in a CGI score ≥4 or having hospitalization	The proportion of patients achieving remission in the SOHO study during the first year was 38.2% and at some point during the 3-y follow-up was 64.6%. The regression analysis demonstrated that social functioning at entry into the study (having a spouse or partner, paid employment and social contracts) was one of the most important predictors of achieving symptomatic remission. Patients never before treated for schizophrenia were also significantly more likely to achieve remission. A longer duration of illness and being male were associated with a worse prognosis, as was higher clinical severity (positive, negative and cognitive scores). Risperidone (OR = 0.74; 95% CI 0.66, 0.83), quetiapine (OR = 0.66; 0.56, 0.77), oral typical antipsychotics (OR = 0.64; 0.55, 0.74) and depot typical antipsychotics (OR = 0.59; 0.51, 0.69) were associated with less favourable outcomes than olanzapine. There were no differences in outcome between olanzapine and clozapine
36-mo HRQOL,[28] European countries	9 340		Of the original sample of patients, this analyses was restricted to those treatment groups with at least 100 patients initiating antipsychotics at baseline	HR-QOL was assessed using the EQ-5D[17], a patient-rated, generic instrument that consists of 2 parts (a series of descriptive questions on general health and a visual analogue scale)	Improvements were higher during the first 6 mo of antipsychotic treatment; however, the improvements were not homogenous for all patients. Patients with the best HR-QOL scores did not experience improvements throughout continuous treatment, those with second best HR-QOL scores only experienced improvements after 30 continuous months of treatment. Shorter duration of illness, earlier age of first contact, being in paid employment and being more socially active at entry were associated with better outcomes. There were no significant differences in HR-QOL changes among medication cohorts

a Ten European countries: recruitment highest in Germany (n = 3449), Italy (n = 3016) and Spain (n = 2053). Industry sponsored.

BMI = body mass index; **CGI** = Clinical Global Impression; **CGI-SCH** = Clinical Global Impression – Schizophrenia; **EQ-5D** = EuroQol-5 Dimension; **FGA** = first-generation antipsychotic; **HR** = hazard ratio; **HR-QOL** = health-related quality of life; **IC-SOHO** = Intercontinental Schizophrenia Outpatient Health Outcomes; **OR** = odds ratio; **SGA** = second-generation antipsychotic.

and the rate of emerging TD was 3.8% for FGA versus 1.4% for SGA (OR = 0.43; 95% CI 0.25, 0.72). Persistence of TD for FGA was 60.8% versus 46.7% for SGA (OR = 0.60; 95% CI 0.33, 1.11).[29]

Another analysis examined whether EPS predicted onset of TD at 1 year. 8036 patients were analysed as these patients had data on all four occasions: baseline, 3, 6 and 12 months after the study began. In order to take into account the waxing and waning course of TD, a sensitivity analysis approach was used with two risk sets: a broad risk set included all individuals with no TD at baseline; a narrow risk set included all individuals with no TD at baseline and 3 months. The total incidence of TD was 3% (95% CI 2.6, 3.4) in the broad risk set and 1.6% (95% CI 1.4, 1.9) in the narrow risk set. The sensitivity of baseline EPS as a test for TD (the percentage of patients who developed TD who had EPS at baseline) was 50% (broad risk = 53%; narrow risk = 46%). The authors concluded that the clinical implications of this study were that strategies aimed at reducing risk factors for EPS in the whole population are more likely to reduce TD morbidity, and that the sensitivity and specificity of EPS as a baseline test for TD were too low to justify a high-risk prevention strategy.[30]

4.2 36-Month Tolerability Trial (Pan European)

The incidence of EPS and TD, anticholinergic use, loss of libido or impotence, amenorrhoea, galactorrhoea or gynaecomastia and weight change was assessed in 4939 patients who started antipsychotic monotherapy.[31] Assessments occurred at baseline, 3, 6, 12, 18, 24, 30 and 36 months. Of the 4939 patients included in the analysis, 2922 (59.2%) were classed as completers.

EPS were present at baseline in 31.6–44.4% of patients across treatment cohorts and were related to the medications the patients were taking before the baseline visit. Decreases in the percentage of patients with EPS after 36 months occurred in all patient cohorts; the largest improvement occurred in the clozapine and olanzapine cohort. TD was present at baseline in 9% of patients ranging from 7.9% to 12.3%. After 36 months, the incidence of TD varied from 3.4% in the olanzapine group to 8.6% in the depot group. Among the patients who did not have TD at baseline, 2.3% had TD at 36 months. The results for each drug cohort at 36 months are olanzapine (1.7%), risperidone (2.7%), quetiapine (1.3%), amisulpride (2.4%), clozapine (3.3%), oral typical (5.0%) and depot typical (3.8%).

Loss of libido/impotence was a frequent adverse event among patients in all treatment cohorts at baseline; range 46.2–56.5%. Decreases in the percentage of patients suffering loss of libido and impotence occurred in all treatment cohorts. Patients receiving olanzapine were less likely to suffer loss of libido/impotence compared with risperidone (OR = 1.38), amisulpride (OR = 1.50), clozapine (OR = 1.39), oral typical antipsychotics (OR = 1.71) and depot typical antipsychotics (OR = 1.37). No difference was observed between olanzapine and quetiapine.

Weight gain occurred in all treatment cohorts over the first 12 months and mean increases ranged from 1.7 kg in the quetiapine group to the largest mean gain of 4.2 kg in the olanzapine group. Regression analysis showed that there was significantly less weight gain in the risperidone, quetiapine and oral typical antipsychotic cohorts compared with olanzapine. No significant differences in weight change were found between olanzapine and clozapine, amisulpride and depot typical antipsychotics.

4.3 Sexual Dysfunction Trials: the First-Time Neuroleptic-Treated and the 12-Month Analysis Trials (Intercontinental) and the Tardive Dyskinesia and Sexual Dysfunction Trials (Pan European)

In the first-time treated patient trial, data from 570 patients were analysed. In as early as 3 months after antipsychotic initiation differences between treatment groups on neuroleptic-related loss of libido and sexual dysfunction existed, which became statistically significant at 6 months. Olanzapine showed the lowest prevalence of neuroleptic-induced sexual difficulties.[32]

In the 12-month analysis trial, the proportion of patients reporting sexual dysfunction during the 12-month period was highest for haloperidol (71.1%), risperidone (67.8%), quetiapine (60.2%)

and olanzapine (55.7%). When compared with the olanzapine group the odds of a patient reporting problems were greater with risperidone (OR = 2.92; 95% CI 1.63, 2.49) and haloperidol (OR = 2.47; 95% CI 1.61, 3.77). Based on patient perception, the odds of emergent sexual dysfunction during 12 months of therapy was lower for olanzapine (13%) and quetiapine (22.9%) than with patients on haloperidol (30.9%) or risperidone (27.8%).[33]

5. ZODIAC

The main objective of ZODIAC[2,34] was to compare the rate of non-suicide mortality of patients initiating ziprasidone with those patients initiating olanzapine. Table V summarizes the main description of ZODIAC and the main outcomes.

6. Discussion

So, what have we learned from these recent effectiveness studies of antipsychotics? Efficacy studies have already demonstrated that clozapine is uniquely effective in refractory schizophrenia[35] and that olanzapine has some efficacy advantages over other drugs.[36] We also knew that clozapine and olanzapine were particularly and relatively more likely to cause metabolic adverse effects.[37] It was also accepted that SGAs generally caused less frequent and severe EPS (including TD) than FGAs.[38,39] What more was uncovered? What assumptions were challenged?

6.1 CATIE

In the CATIE programme, clozapine's unique effectiveness in resistant schizophrenia was confirmed, while olanzapine's improved outcomes compared with risperidone, quetiapine and ziprasidone were also noted, supporting findings from some prior efficacy studies.[36,40,41] Intriguingly, no advantage was seen in people changing antipsychotics compared with those staying on the original drug. Clozapine, olanzapine and quetiapine seemed particularly prone to cause metabolic adverse effects.

Despite these expected findings, results from CATIE, the apparently equal effectiveness and better cost-effectiveness of perphenazine have provoked strong reactions and extensive discussions among clinicians, academics, patients and policy makers. CATIE apparently did not support the hypothesis that SGAs are treatments of choice in schizophrenia. Instead the study supported the view that FGA and SGAs have similar therapeutic effect with diverse side effect profiles. Perhaps most importantly, at the end of the 18-month study, 74% of patients in phase 1 were not taking the same drug they started with, which tells us that switching or discontinuation in the maintenance phase of schizophrenia is the rule rather than the exception.[42]

6.1.1 Adverse Outcomes: Metabolic Considerations

Individuals with schizophrenia and affective disorders have an increased risk of death from medical causes and up to a 20% shorter lifespan compared with the general population.[43] More than two-thirds of patients with schizophrenia compared with half in the general population die of coronary heart disease.[43] One of the clearest and most compelling messages from CATIE is the issue of metabolic side effects. Except for clozapine, olanzapine clearly caused the heaviest burden of metabolic side effects.[8]

Table V. Description and main outcomes of the ZODIAC trial[a]

Trial	No. of participants	Drugs involved	Description	Outcome measures	Main outcomes
ZODIAC[34]	18 240	Ziprasidone Olanzapine	Patients were randomly assigned to treatment with either ziprasidone or olanzapine and received the medication in an unblinded fashion. No further interventions were made. Patients were then followed up for 1 y	Non-suicide mortality	This randomized, unblinded trial found no difference in non-suicide mortality between ziprasidone and olanzapine cohorts. This study was not designed to identify the risk of rare events like torsade de pointes

a Worldwide: US, Brazil, Sweden, Latin America, East Asia, Central and Eastern Europe. Industry sponsored.

The risks of metabolic syndrome need to be assessed in line with the issue of mortality and schizophrenia, and the role of antipsychotic therapy on mortality. Hogan et al.[44] conducted a large population-based cohort study (the FIN11 study). Data for the study conducted in Finland, included 66 881 patients and data were collected from 1996 to 2006. The primary outcome measure was all-cause mortality with secondary outcomes of mortality as death due to suicide and ischaemic heart disease. These authors concluded that long-term use of antipsychotics is associated with a reduction in mortality among patients with schizophrenia compared with no or short-term use.[44] Clozapine was the most effective in terms of preventing death among patients with schizophrenia.[44] However, overall life expectancy for patients with schizophrenia was not shown to be further decreased with the increased use of atypical antipsychotics.[44] None of the antipsychotics had an effect on mortality due to ischaemic heart disease.[44]

6.1.2 Tardive Dyskinesia

CATIE was not designed to maximize detection of EPS. There was no wash-out phase at the start of CATIE, not even for anti-parkinsonian medication, which may have further diminished differences in EPS.[45] More patients discontinued perphenazine because of EPS than with SGAs but the excess was modest.[7] Patients with TD were excluded from the perphenazine arm, making a true comparison of relative risk of TD onset impossible. The length of drug exposure may have also been too short to assess its true long-term toxicity, as highlighted by Casey ''It is a major error to conclude that perphenazine offers the same benefit-risk ratio as the atypical agent when the efficacy is compared to the acute EPS and tardive dyskinesia risk.''[46] CATIE does not contradict the evidence that strongly suggests a lower risk of TD with SGAs.[47] Some authors have suggested that lower doses of FGAs will reduce the incidence of TD. However, a study that evaluated the 12-month incidence of TD in first-episode patients prescribed a very low dose of haloperidol (mean dose = 1.67 mg/day) concluded that the incidence of TD was at least as high as in other samples treated with standard doses of conventional antipsychotics and unacceptably high for clinical use.[48]

6.1.3 Limitations of CATIE

Kraemer and colleagues, summed up the study limitations rather coarsely: ''Too many drugs, too many strata, too many sites with inadequate numbers of subjects, too many outcome measures and too many statistical tests.''[49]

If we start with the study population, the mean time since first treatment was 24 years and mean time since first treatment with an antipsychotic was 14 years. This population is thus perhaps more representative of poor or partial responders.[50] Once enrolled, clinicians knew that there was a second and third phase of the trial; therefore, discontinuing medication in the first phase could have been influenced to some extent by the availability (and the explicit or implicit desire to recruit subjects) of a second and third phase.[50]

In terms of medication, in phase 1 of the trial, patients could have been randomized to the medication they had previously been taken. Of patients in phase 1 of CATIE, 15% were randomly assigned to the medication they had previously been receiving prior to the study. Patients assigned to risperidone or olanzapine who had been receiving those medicines prior to the study remained on their medication significantly longer than other patients. When these patients were removed from the intention-to-treat analysis, the overall test of the comparison of treatments was not statistically significant regarding the primary outcome measure of all-cause discontinuation.[51]

The mean modal doses prescribed during phase 1 were 20.1 mg/day for olanzapine, 20.8 mg/day for perphenazine, 543.4 mg/day for quetiapine and 3.9 mg/day for risperidone. During phase 2E the trial the doses were 332.1 mg/day for clozapine, 23.4 mg/day for olanzapine, 642.9 mg/day for quetiapine and 4.8 mg/day for risperidone.[4,5] These mean doses are not considered equivalent: the olanzapine dose is above the licensed dose of 20 mg/day, while the quetiapine and risperidone doses are modest in comparison (at least when the

maximum doses are considered). More recently, however, the optimal dose of quetiapine has been suggested as being between 300 and 400 mg/day[52] and, similarly, a review was unable to support the use of high dose (>800 mg/day) quetiapine.[53] In addition, there is probably no particular advantage for higher doses of olanzapine compared with, for example, 10 mg/day.[54] In respect to dose then, the relatively higher doses of olanzapine might have added nothing to its effectiveness but added significant burden to adverse effects.

6.2 CUtLASS

The results of CUtLASS 1 rejected the hypothesis that SGAs are superior to FGAs in terms of improvement in Quality of Life Scale (QLS) scores. CUtLASS 2 showed that commencing clozapine in treatment-resistant patients led to significantly more improvement in symptoms but not QLS over 1 year compared with commencing one of the other SGAs. The results also show there is no evidence to suggest SGAs are more cost effective than FGAs, and that clozapine is associated with higher costs and higher quality-adjusted life-years (QALYs) than other SGAs for the 12-month period following a change in therapy.

6.2.1 Limitations of CUtLASS

Sulpiride, a selective dopamine D_2 receptor blocker, is thought to pose less of a risk of EPS compared with other FGAs, which may be why it was chosen more often in CUtLASS compared with previous efficacy trials (haloperidol is most often used). Its presence in the FGA arm itself may pose a bias (as it is considered to have SGA properties); however, results from a systematic review have not supported this SGA property or superior efficacy.[55] When clozapine was used in CUtLASS 2, the mean doses were low and no clozapine levels were done to ensure the dose was at an effective therapeutic level.

In terms of the patient population, QLS scores were not well balanced at baseline. The proposed effect size of 5 points in the QLS may have been unrealistically large. The results of randomization were known to the clinician and participant, which may have led to bias.

6.3 SOHO

One of the most outstanding strengths of the SOHO trial was its high retention rate: at 12 months the retention rate was around 85%, whereas the expected drop-out rate would be around one-third.[56] Patients were also allowed to remain in the study even if they changed medication at any point. Broadly speaking, SOHO suggested relatively better effectiveness for clozapine and olanzapine compared with other SGAs and FGAs and reduced rates of TD for SGAs compared with FGAs. As in CATIE, quetiapine suffered somewhat compared with some other antipsychotics in respect to effectiveness.

6.3.1 Limitations of SOHO

SOHO allowed clinicians to select the treatment and therefore a bias in assignment of patients to groups could not be controlled for and confounding by indication is a real possibility. Direct comparisons between medication groups are therefore not entirely appropriate as clinicians would choose the medication they felt would provide maximum benefit. Over-sampling of the olanzapine cohort was included in the study because the main objective of the study was to compare olanzapine with other antipsychotics. Although this may not be representative of the outpatient population setting, it does allow for precise estimates of outcome compared with olanzapine.

When reviewing SOHO trial results chronologically, one would expect 12, 24 and 36 months' results that continue to report the primary outcomes of Clinical Global Impressions (CGI) scale and EuroQol-5 Dimension; and continue to use the Pan European population as they did in the baseline and 6-month study. However, we are left with publications from the intercontinental study and several other reports with measures such as remission, recovery and relapse. One is left with the feeling of too many publications from the same population and publications that vary slightly from the main aim set out originally by

SOHO (e.g. there was a polypharmacy arm that was ultimately not reported on).

6.4 ZODIAC

The ZODIAC study showed that there was no difference in all-cause mortality between ziprasidone and olanzapine. Admission to hospital was more likely with ziprasidone than with olanzapine.

6.4.1 Limitations of ZODIAC

Ziprasidone is associated with a risk of QTc prolongation. The study was not designed to examine the risks of rare cardiac events such as torsade de pointes. The fact that there was no difference in all-cause mortality may go some way to increasing ziprasidone's use especially as it has a low risk of metabolic syndrome. ZODIAC also indicated that the relatively more adverse metabolic effects of olanzapine do not, at least in the short term, cause more cardiovascular mortality than the metabolically neutral ziprasidone.

7. Conclusion

Clozapine is the most effective antipsychotic, followed by olanzapine and then by all other SGAs and modest doses of FGAs. We do not believe CATIE, CUtLASS, SOHO or ZODIAC provide 'new found' effectiveness or tolerability of FGAs. The biggest surprise from the results of these large pragmatic studies is how surprised the field has been by the results.[57] There has never been acceptance by governing bodies of the superiority of SGAs other than for clozapine.

We could not recommend non-clozapine SGAs over FGAs on the basis that SGAs have efficacy for primary negative symptoms or cognitive impairment. We would, however, recommend the use of SGAs over FGAs (even at modest doses of the latter) because the lower risk of extrapyramidal effects and TD.

Should we start using the cheapest AP? More studies are needed to add to the limited body of evidence that compares the cost effectiveness of antipsychotics.[58] As the earlier SGAs lose patent protection and the drug costs become less of an issue, the pharmacoeconomic debate will probably not focus on drug cost.

Should we change the way we use clozapine? Clozapine remains unique in its effects in the treatment-resistant population. Patients who fail to respond to two antipsychotics should be offered clozapine. We could also probably say that one of the antipsychotics should be an SGA[58] and that data also support the notion that one of the drugs should be olanzapine.[59]

What type of trial may give us more conclusive answers? Swartz and colleagues[60] assessed and outlined eight principles for a practical clinical trial to maximize its impact on clinical decision making:

- questions posed should be straightforward and relevant;
- trials should be carried out in real-world settings to ensure results can be generalized;
- study should be sufficiently powered to detect small to moderate outcomes;
- randomization should be used;
- there should be clinical uncertainty of the outcome;
- outcomes should be simple and meaningful;
- assessments and treatments should reflect best clinical practice;
- subject and investigator burden should be minimized.

On the surface, recent real-world trials seemed not to have added new information to that available before they were conducted; clozapine is superior and other antipsychotics are more or less equal apart from the drugs' side effect profiles. Often though, clinical trial results are not about 'ground-breaking discoveries' but rather adding layer upon layer to our knowledge and experience as clinicians. No one study can adequately answer the complex question of optimizing pharmacological treatment of schizophrenia. These trials have provided additional important factors to consider when choosing the very best therapy for patients and may thus be considered valuable and worthwhile (even cost effective) when one considers outcomes and costs of conducting these studies. They have reminded us of: the importance of TD and metabolic syndrome, the slight advantages olanzapine may have, that most pa-

tients will switch their medication, and the need for new and novel therapies especially to address cognitive and negative symptoms.

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Correspondence: Prof. *David M. Taylor,* Pharmacy Department, South London and Maudsley NHS Foundation Trust, Denmark Hill, London SE5 8AZ, UK.
E-mail: David.Taylor@slam.nhs.uk