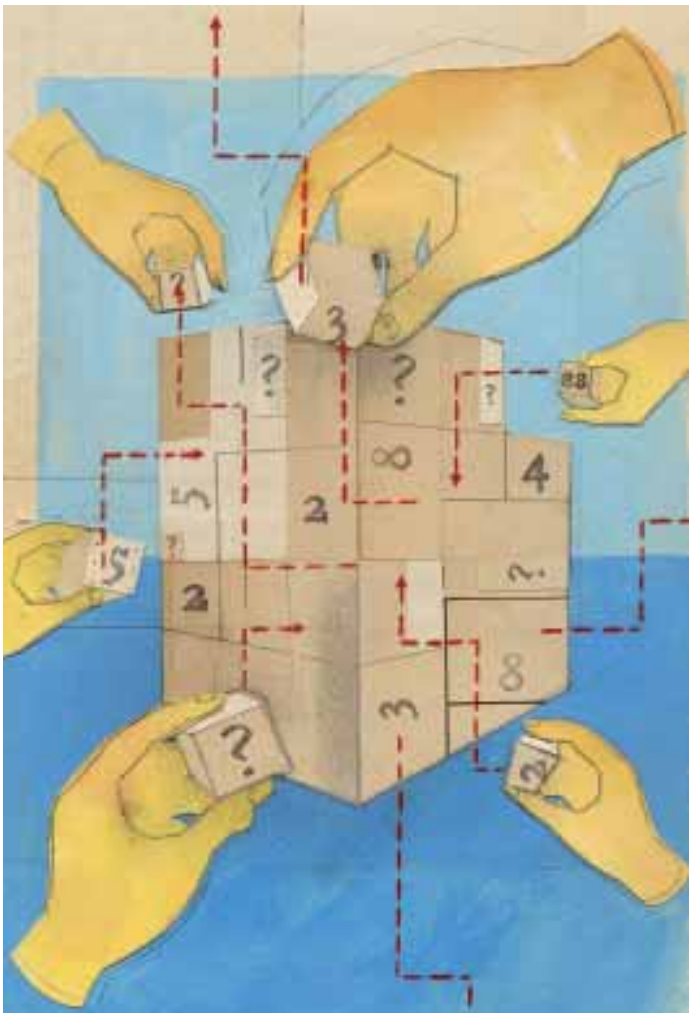
Current PSYCHIATRY

Antipsychotics equivalent? CUtLASS renews the debate

Is UK trial the final word, or another piece of the puzzle?



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When treating chronic psychotic disorders, U.S. psychiatrists generally prefer second-generation antipsychotics (SGAs) to first-generation antipsychotics (FGAs) because of widely held views[1,2] that SGAs:

- are more effective for negative and cognitive symptoms
- produce fewer troublesome side effects
- help patients realize a better quality of life.

These beliefs have been challenged by two large-scale, government-supported studies: the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) in the United States[3-6] and more recently the Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS) from the United Kingdom.[7,8]

CATIE and CUtLASS data suggest that the SGA advantage has been exaggerated, if in fact such an advantage exists. Other CURRENT PSYCHIATRY articles for the clinical practitioner have discussed the CATIE findings.[9-11] This article addresses the CUtLASS results in the context of the trial's methodology, using information from the primary publications[7,8] and technical report.[12]

Table 1

Summary of CUtLASS trial design and results

Band 1

- **1-year study** comparing FGAs with SGAs in 14 community psychiatric services in the United Kingdom
- **227 patients** with mean illness duration of 14 years and mean PANSS score of 72 (moderately ill); 99% were receiving antipsychotics at enrollment
- **Found** FGAs and SGAs equal in overall effectiveness and quality of life, with no significant difference in side effects

Band 2

- **1-year study** comparing clozapine with other SGAs in 136 patients with treatment-resistant schizophrenia
- **Found** clozapine significantly more effective (P <0.02) than other SGAs in reducing symptoms but not in improving quality of life (P = 0.08)

CUtLASS: Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study
FGA: First-generation antipsychotic
PANSS: Positive and Negative Syndrome Scale
SGA: Second-generation antipsychotic

CUtLASS STUDY

Design. CUtLASS included 2 "bands" (*Table 1*):

- Band 1 compared the clinical usefulness and cost effectiveness of FGAs and SGAs in treating schizophrenia[7]
- Band 2 compared the effectiveness of clozapine versus other SGAs in treating refractory schizophrenia.[8]

CUtLASS Band 1 was not as extensive in scope as CATIE, and its design had some important differences (*Table 2, page 60*). Patients were referred for participation because their psychiatrists were considering a change in antipsychotic medication to address adverse effects or inadequate response. Fewer patients were recruited than expected—40% of the planned sample during 30 months of recruitment—but researchers considered the size sufficient to compare the effectiveness of FGAs and SGAs.

Patients were randomly assigned to treatment with an antipsychotic class, either:

- an FGA (1 of 11 options—including 5 depot formulations—chosen by the treating clinician)
- or an SGA (risperidone, olanzapine, quetiapine, or amisulpride, also chosen by the clinician).

Physicians and patients were not blinded to the medications used. They could choose medications within patients' assigned classes and switch as needed in ways that mimicked clinical practice. Trained assessors, who were blinded to the medications being used, evaluated the patients after 12, 26, and 52 weeks.

Quality of life was the primary outcome measure.[13] Secondary measures included symptoms, side effects, patient satisfaction, and cost of care.

Band 1 results. Patients assigned to the SGA or FGA classes showed no significant differences in quality of life measures or schizophrenia symptoms. If anything, the findings slightly favored the FGAs.

Patient satisfaction and overall cost of care were similar, and rates of extrapyramidal symp-

Table 2

Comparing designs of the CUtLASS and CATIE schizophrenia trials

	CUtLASS	CATIE
Trial duration	12 months	18 months
Clinical sites	14 (United Kingdom)	57 (United States)
Number of subjects	227	1,460
Gender and age	68% male; mean age 41	74% male; mean age 41
Mental illness duration (mean)	14 years	16 years
Diagnosis	75% schizophrenia	100% schizophrenia
First-episode patients included?	Yes (13% of sample)	No
% of patients receiving antipsychotics at enrollment	99%	74%
Baseline antipsychotic	82% FGAs; 40% depot	15% FGAs; <5% depot
Baseline PANSS score (mean)	72.2	75.7
Baseline EPS scores	Low	Low
Antipsychotic options in randomization	2 classes (SGA or FGA) (50% of subjects assigned to an FGA)	4 SGAs, 1 FGA (20% of subjects assigned to an FGA)
% of subjects given sulpiride	49%	0%
Administration methodology	Medication blinded to raters but not to patients and physicians	Medication blinded to patients and physicians
Primary outcome	Quality of life	Discontinuation of medication
Long-acting antipsychotic option?	Yes	No
Antipsychotic switching	All patients switched agents; 49% changed antipsychotic class	15% stayed on same agent

CATIE: Clinical Antipsychotic Trials of Intervention Effectiveness
CUtLASS: Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study
EPS: Extrapyramidal symptom
FGA: First-generation antipsychotic
PANSS: Positive and Negative Syndrome Scale
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toms (EPS), tardive dyskinesia, and akathisia did not differ significantly.

Clozapine comparison. In CUtLASS band 2, a different sample of 136 schizophrenia patients who had responded poorly to ≥2 antipsychotics was randomly assigned to clozapine or one of the above four SGAs. During the 1-year comparison trial, clozapine:

- was found to be significantly more effective (P=0.01) in managing patients' symptoms, as measured by total Positive and Negative Syndrome Scale (PANSS) score
- showed a trend (P=0.08) towards providing these treatment-resistant patients with a better quality of life.[8]

Table 3

'Flies in the ointment' of the CUtLASS trial design

Who was studied	• Recruited patients were at low risk for EPS • A greater number of treatment-refractory patients was assigned to the SGA arm, compared with the FGA arm
What was compared	• SGA class vs FGA class (including sulpiride) • Oral SGAs vs oral or depot FGAs
Other issues	• Greater initial switching of medication class in the SGA group in relatively stable, moderately ill patients; adverse effects of such switching were seen early (at the 12-week assessment) • Substantial contamination (43% of patients in the FGA class were receiving SGAs at 52 weeks, but results were calculated [intent-to-treat analysis] as if the patients were receiving FGAs)

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COMPARING CATIE, CUtLASS DATA

The CUtLASS findings are not identical to those of CATIE phase 1[14] but are remarkably similar: no differences in effectiveness were seen between FGAs and SGA when treating patients with chronic schizophrenia.[15,16]

CUtLASS investigators concluded that "in people with schizophrenia whose medication is changed for clinical reasons, there is no disadvantage across 1 year in terms of quality of life, symptoms, or associated costs of care in using FGAs rather than nonclozapine SGAs."[7]

By confirming CATIE's results, is CUtLASS the final word on antipsychotic treatment of chronic schizophrenia? Or is it just another piece of the puzzle? CATIE and CUtLASS add much to our knowledge, but methodologic "flies in the ointment" plague all clinical trials. We must consider potential biases and confounding factors to properly interpret and apply their findings.

Although the CUtLASS trial was well-constructed and executed, its conclusions—like those of CATIE—merit careful scrutiny. Its patient recruitment methods and study design involved choices and compromises that are appropriate to evaluate[17,18] as we weigh CUtLASS' contribution to the SGA/FGA debate (*Table 3*).

WHO WAS STUDIED?

Selection questions. CUtLASS researchers had problems recruiting patients for their study, in part because clinicians were reluctant to expose their patients to a 50% probability of being assigned to an FGA. Only 40% of the targeted sample was recruited, and participating clinicians referred only 20% to 37% of their eligible patients to the study.[12] Thus, one could ask:

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- Were enrolled subjects truly representative of the population from which they were drawn?
- Or did selection bias result in a disproportionate inclusion of individuals with certain characteristics?

Is it possible, for example, that clinicians preferentially referred medication-noncompliant patients to CUtLASS because they believed the benefits of depot FGAs—such as more assured adherence—would compensate for the potential benefits of SGAs—better efficacy/tolerability?[19]

Treatment resistance. Although patients were randomly assigned to FGAs or SGAs, a significantly greater proportion of those whose antipsychotics were being changed because of treatment resistance were assigned to receive SGAs. Treatment resistance was one reason that 88% of subjects in the SGA arm were referred to the trial, compared with 70% of subjects in the FGA arm (P <0.01).[12] The extent to which this differential assignment may have biased results against SGAs is unclear.

Do results apply to US practice if 49% of FGA patients took sulpiride, which is not available here?

EPS risk. CUtLASS-1 patients had been ill a mean of 14 years and had low baseline EPS rates despite receiving long-term antipsychotics (primarily FGAs). Even so, FGAs and SGAs showed similar rates of akathisia and other EPS. Thus—as with the CATIE results—the extent to which CUtLASS-1 findings may apply beyond chronic schizophrenia patients at relatively low risk for EPS is unclear.[11,17]

Impact of switching. Although patients were referred to CUtLASS because of adverse effects or inadequate response to one or more antipsychotics, they were only moderately ill (mean PANSS total score 72)[20] and probably were deriving some benefit from their baseline antipsychotics. Before randomization, 82% of patients were receiving an FGA and 19% an SGA. Consequently, a far larger percentage of patients in the SGA group had to switch to a different medication class as the trial began.

As observed in CATIE, switching antipsychotics often has short-term negative consequences for patients,[21] although switching classes (as in CUtLASS) may have had a different impact than switching individual antipsychotics (as in CATIE). If unequal antipsychotic switching rates in the two arms differentially affected patients' quality of life, we would expect to see this effect emerge at the 12-week assessment, which is precisely where the greatest difference in Quality of Life Scale (QLS)[13] scores appeared.

The mean QLS score for patients in the SGA arm was 2.6 points lower than in the FGA group at 12 weeks. This difference disappeared and, in fact, reversed at 26 weeks, but this 12-week effect had a strong impact on results of the 52-week intent-to-treat analysis. CUtLASS—like CATIE—might exemplify the risks of switching patients from treatment with partially effective antipsychotics.[22]

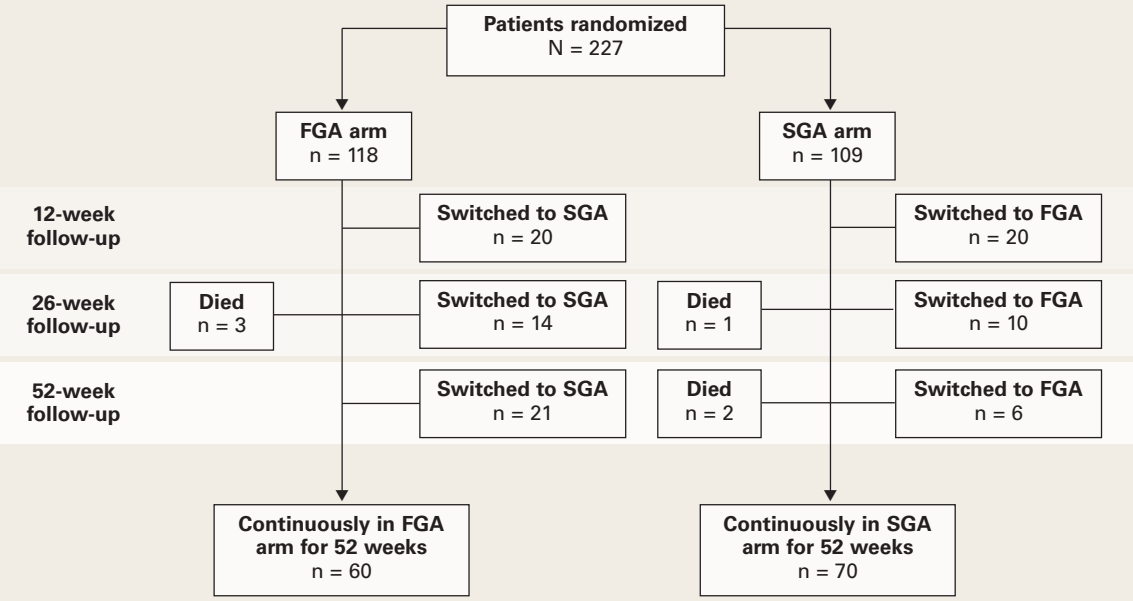
WHAT WAS COMPARED?

Classes vs individual drugs. The decision in CUtLASS-1 to compare antipsychotic classes rather than individual agents makes it difficult to interpret its findings. Antipsychotics are not homogeneous; clear differences exist within both the SGA and FGA classes in terms of individual agents' efficacy and tolerability, and each SGA has a reasonably well-established and different side-effect profile.[23]

Sulpiride was the most commonly used FGA in CUtLASS-1 (by 49% of FGA patients). Sulpiride has some unusual attributes—such as lower EPS liability—and is not available in the United States. Thus, including this agent might have affected how applicable CUtLASS findings are to clinical practice in the United States.

Figure

CUtLASS-1: Did switching rate affect trial outcome?



The high rate of cross-class medication switching in CUtLASS-1 may have weakened the study's conclusion that virtually no difference in effectiveness exists between first- and second-generation antipsychotics. At the 52-week assessment, 51 of 118 patients (43%) in the intent-to-treat FGA group were receiving SGAs instead. Not shown in the figure is that 4 of the total 55 patients who switched from FGAs to SGAs had switched back to FGAs by the 52-week assessment.

CUtLASS: Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study
FGA: First-generation antipsychotic
SGA: Second-generation antipsychotic
Source: Adapted from reference 7, figure 1

Oral vs depot delivery. Individuals assigned to an FGA could receive either oral or long-acting depot medication, whereas those assigned to an SGA could receive only oral medication. At baseline, 84 of 227 CUtLASS-1 participants were receiving a depot antipsychotic, which was discontinued during randomization in 72 patients. During the 1-year study, the number of patients receiving a depot antipsychotic tripled from 12 to 35, suggesting the usefulness of long-acting agents in this population.[19]

Cross-class switching. Although participating physicians and their patients were urged to stay within assigned antipsychotic classes at least for the first 12 weeks and ideally for 1 year, a high rate of cross-class switching occurred (*Figure*). At the 52-week assessment, 51 of 118 patients (43%) in the intent-to-treat FGA group were receiving SGAs instead.

The CUtLASS authors' assert that the trial refutes the hypothesis that using SGAs is superior to using FGAs in improving quality of life. This conclusion is difficult to justify when so

Table 4

Clinical 'pearls' from the CUtLASS trial data

- **Avoiding EPS** may be the key to "atypical" benefits; if the EPS difference between FGAs and SGAs is eliminated, no significant differences in effectiveness may remain
- **Clozapine** remains the most effective antipsychotic for patients with treatment-resistant schizophrenia
- **Long-acting** antipsychotics, by promoting adherence, may improve patient outcomes

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many patients assigned to the FGA class actually were receiving SGAs. The conclusion is further weakened if differential switching rates put SGAs at a disadvantage in the first 12 weeks of the trial.

A more accurate conclusion of the intent-to-treat comparison appears in the technical report: "There was no statistically significant difference in terms of quality of life or symptoms over 1 year in *commencing* [italics added] conventional antipsychotic drugs rather than new atypical drugs."[12]

CLINICAL IMPLICATIONS

Notwithstanding these cautionary notes, CUtLASS-1 findings add to the questions raised by CATIE about the relative effectiveness of SGAs and FGAs. At a minimum, the data indicate that the SGA advantage has been overstated or oversimplified and that FGAs may be suitable options for meeting the needs of some patients with psychosis (particularly those at low risk for EPS).

Depot antipsychotics. CUtLASS also suggests a wider role for long-acting antipsychotics in chronic psychotic disorders, beyond treating patients with severe nonadherence.[19,23] The number of patients receiving long-acting agents tripled over the 1-year study.[12]

Clozapine. Both CATIE and CUtLASS-2 confirmed clozapine's superior efficacy for patients with treatment-resistant psychotic illness (*Table 4*). CUtLASS-2 also reaffirmed the challenges of clozapine's metabolic and other side effects, such as sedation, hypotension, and hypersalivation.

All-cause discontinuation was significantly higher (P <0.05) in patients taking clozapine (73%) than in those taking other SGAs (52%). Even so, clozapine-group patients achieved significantly greater symptom reduction and tended toward a higher quality of life than other SGA-group patients.

Overview. In conclusion, one can reasonably conclude from analyzing the CATIE and CUtLASS data that:

- FGA-SGA differences are not as great as previously thought.
- Substantial differences exist among agents within both antipsychotic classes, particularly in side effect profiles.
- Neither study disproves the following presumed benefit of SGAs: that compared with FGAs, SGAs provide an equivalent antipsychotic effect and pose a lower risk of problems related to unmitigated dopamine blockade—such as EPS, dysphoria, bradyphrenia, neuroleptic-induced deficit syndrome, and tardive dyskinesia.[11]
- To use antipsychotics effectively and optimize individual treatment, consider the CATIE and CUtLASS trials in the contexts of their designs and the results of other studies of patients with chronic schizophrenia.

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Consider the CUtLASS finding of no differences between SGAs and FGAs in the context of the study's population and design. FGAs may be suitable options, particularly for patients at low risk for extrapyramidal symptoms. Clozapine remains the most effective SGA for refractory schizophrenia. Long-acting antipsychotics may offer wider benefits for many patients with chronic psychotic illness.

Bottom Line

Related resource

- Heres S, Davis J, Maino K, et al. Why olanzapine beats risperidone, risperidone beats quetiapine, and quetiapine beats olanzapine: An exploratory analysis of head-head comparison studies of second-generation antipsychotics. *Am J Psychiatry* 2006;163:185-94.

DRUG BRAND NAMES

Clozapine • Clozaril
Olanzapine • Zyprexa
Quetiapine • Seroquel
Risperidone • Risperdal

DISCLOSURE

The authors report no financial relationship with any company whose products are mentioned in this article or with manufacturers of competing products.

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