LEADING ARTICLE

CNS Drugs 2009; 23 (8): 649-659
1172-7047/09/0008-0649/$49.95/0

The CATIE and CUtLASS Studies in Schizophrenia

Results and Implications for Clinicians

Dieter Naber and *Martin Lambert*

Department of Psychiatry and Psychotherapy, Centre for Psychosocial Medicine, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

Abstract

Numerous double-blind studies have compared second-generation antipsychotics (SGAs) with first-generation antipsychotics (FGAs), with most finding better efficacy and tolerability for SGAs. However, these 'efficacy trials' were generally short term and included only highly selected patients. Mostly because of weight gain and other metabolic effects of the SGAs, as well as their high acquisition price, the debate on the (cost) effectiveness of the SGAs led to two pragmatic clinical trials with no sponsorship by industry. Both trials had broad inclusion criteria and long follow-up, and tried to mimic clinical routine: CATIE (Clinical Antipsychotic Trials of Intervention Effectiveness) and CUtLASS (Cost Utility of the Latest Antipsychotic drugs in Schizophrenia Study).

1493 patients participated in CATIE, an 18-month, double-blind trial comparing the SGAs olanzapine, quetiapine, risperidone and ziprasidone with the FGA perphenazine. If efficacy or tolerability was insufficient, patients were re-randomized to a medication other than the one they previously received. Improvement of psychopathology and of quality of life was only moderate. Overall, 74% of patients discontinued study medication before 18 months, and the median time to discontinuation was 4.6 months. Aside from olanzapine (time to discontinuation 9.2 months), the other SGAs did not differ from each other or from perphenazine. Except for adverse effects as a reason for discontinuation, differences between the SGAs and the FGA were minimal. In CUtLASS, a 12-month open-label trial, 277 patients were randomized to receive an FGA or a SGA. Again, efficacy was rather similar between the two groups, with only limited improvement of psychopathology and quality of life. The authors of both trials concluded that SGAs do not markedly differ from FGAs regarding compliance, quality of life and effectiveness.

The methodological problems of both trials have been discussed extensively. Patients had psychotic symptoms that were moderate in severity and were at least partially treatment resistant. The marginal improvement observed indicated that this population might not be appropriate to detect differences between FGAs and SGAs. Specific issues of CATIE include the exclusion of patients with tardive dyskinesia in the perphenazine arm and the high discontinuation rate. In CUtLASS, the concept of including 13 different

FGAs and four SGAs in the respective classes was problematic. It is of interest that the most widely prescribed drug was sulpiride – of the FGAs, this is probably the 'most atypical' drug. Aside from the finding that the advantages of the SGAs are not as strong as early trials and marketing suggested or promised, the trials do not provide much helpful information regarding everyday practice. For tardive dyskinesia, no conclusions at all can be drawn. Similarly, methodological problems inhibited the detection of the other major advantage of the SGAs, i.e. the improved subjective well-being/quality of life while receiving these agents. It is well known that patients' and doctors' perspectives differ markedly, and the Quality of Life Scale (QLS), an expert-rated scale used in both trials, might not be sensitive enough to detect the subjective advantages reported by the majority of patients in other trials.

CATIE and CUtLASS suggest that SGAs do not live up to all the previous expectations. However, even if most of these advantages are debatable, the lower risk of tardive dyskinesia and the better subjective effects should be strong enough reasons to favour these drugs. There is no single antipsychotic that is best for every schizophrenia patient, as individual responses differ markedly. For successfully individualized treatment, a multitude of antipsychotic options are needed.

The development of second-generation (atypical) antipsychotics (SGAs) has markedly increased the hopes of psychiatrists, patients and their relatives for a better pharmacological treatment of schizophrenia, and thereby for a better prognosis for this serious psychiatric illness. For a long time, clozapine was the only SGA available; in the 1990s, the new SGAs amisulpride, olanzapine, quetiapine, risperidone, sertindole, ziprasidone and zotepine followed. Most of these drugs do not fulfil the original, although mostly informal, definition of atypicality (antipsychotic efficacy without the typical motor adverse effects); at higher doses they induce, to different degrees, extrapyramidal symptoms (EPS). Atypicality was found to be dimensional, not categorical, and that was one of the reasons why this term was replaced by 'SGA'.[1] However, this distinction is also pseudo-categorical and the difficulty of defining SGAs versus first-generation antipsychotics (FGAs) should be kept in mind in the discussion about potential differences between these two classes of drugs.

With these new antipsychotics, success criteria became more ambitious and included a more thorough consideration of negative and cognitive symptoms, both of which are of major relevance for long-term prognosis. The most important change since the early 1990s is the long overdue consideration of the patients' perspective. The (subjective) well-being/quality of life under antipsychotic treatment had been largely neglected or was of very limited scientific relevance, respectively. It might not be a coincidence that scientific interest in the subjective effects of antipsychotic drugs started with the availability of the SGAs, perhaps induced by the clinical experience that, in addition to the reduced motor symptoms, many patients reported less dysphoria or anhedonia, which might be the reason why most patients prefer the SGAs over the FGAs.[2,3]

Numerous double-blind, controlled studies have compared SGAs with FGAs, most often favouring SGAs, i.e. greater symptom reduction (particularly for negative, cognitive and affective symptoms) and better tolerability (notably regarding motor adverse effects). In reaction to these positive studies, most international evidence-based guidelines advocate first-line use of SGAs,[4-8] supported by several meta-analyses showing advantages of some, but not all, SGAs.[9-13] However, meta-analyses were not consistent, and the rather high dosage of haloperidol, which was most often used as the comparator drug, was, according

to Geddes et al.,[14] the major reason for the misleading positive trials, although the later review by Davis et al.[9] did not find a dose effect. It was hypothesized that comparing FGAs in a low dosage with SGAs would result in a very similar clinical profile. Other issues in the discussion about the advantages of the SGAs are weight gain and the metabolic syndrome, which increase the risk for diabetes mellitus and cardiovascular disease, and are induced by some of the new SGAs more often than by FGAs. These issues (together with the high price of the new SGAs) led to two pragmatic clinical trials: the US CATIE (Clinical Antipsychotic Trials of Intervention Effectiveness)[15] and the UK CUtLASS (Cost Utility of the Latest Antipsychotic drugs in Schizophrenia Study).[16] These trials were designed and conducted to investigate the clinical advantages and cost effectiveness of the new SGAs, with no sponsorship by industry. Both trials had broad inclusion criteria and long follow-up, and tried to mimic routine clinical practice.

1. CATIE

1.1 Methods

The CATIE schizophrenia study, sponsored by the US National Institute of Mental Health (NIMH), was a randomized, double-blind, controlled study designed to evaluate the effectiveness of antipsychotic treatment of schizophrenia in 'real-world' patients.[15] The study, including 57 sites in the US, was conducted to provide data generalizable to the average outpatient with schizophrenia: 1493 patients underwent randomization and 1460 were included in the analysis.

The mean (±SD) age of the patients was 41 ± 11 years, and they had been treated with antipsychotics for 14 ± 11 years. They had moderate levels of psychotic symptoms (total Positive and Negative Syndrome Scale [PANSS][17] score of 76 ± 18) despite previous treatment with mostly SGAs (at baseline 55% were taking one or more of the SGAs under study), indicating that many of these patients were at least partially treatment resistant.

In phase I of the trial, patients were randomized to receive up to 18 months of treatment with one of the SGAs (olanzapine mean dosage of 20.1 mg/day, n = 336; quetiapine 543.2 mg/day, n = 337; risperidone 3.9 mg/day, n = 341; ziprasidone 112.8 mg/day, n = 185) or a so-called 'representative' FGA (perphenazine 20.8 mg/day, n = 261). One important issue was the exclusion of patients with tardive dyskinesia (15% of the population) from the perphenazine group. Ziprasidone became available as a treatment arm only after 40% of the CATIE participants had already been enrolled.

If patients discontinued treatment for any reason, they were offered the option of participation in phase II, where they were re-randomized to a medication other than the one they previously received. If the first drug was ineffective, patients were assigned to the clozapine randomization pathway (n = 99),[18] which involved randomization to open-label clozapine, or blinded olanzapine, quetiapine or risperidone. If intolerability was the reason for discontinuation, patients were randomly assigned to blinded ziprasidone, olanzapine, quetiapine or risperidone (n = 444).[19] Another double-blind study investigated patients who discontinued perphenazine: they were switched to olanzapine, quetiapine or risperidone.[20]

If patients discontinued phase II early, they were offered participation in phase III, where they could choose from the following open-label treatments: aripiprazole, clozapine, fluphenazine, olanzapine, perphenazine, quetiapine, risperidone or ziprasidone, or a combination of two of these antipsychotics.

1.2 Results

Only a minority of patients in each group remained on the assigned drug treatment for the duration of this study: 74% discontinued the study medication before 18 months (olanzapine 64%, perphenazine 75%, quetiapine 82%, risperidone 74% and ziprasidone 79%). Median time to discontinuation was 4.6 months overall; aside from olanzapine (9.2 months), the other SGAs differed neither from each other nor from the FGA perphenazine group in terms of efficacy

(not effectiveness) or extrapyramidal adverse effects. Overall improvement on the PANSS was very modest; even the drug performing best showed only a little over 10% improvement of the PANSS total score. Moreover, there was no evidence that the SGAs were better for cognitive symptoms.[21] Times to discontinuation because of intolerable adverse effects or EPS of the treatments were not significantly different between drugs. Across treatment groups, reasons for discontinuation were patient's decision (30%), followed by lack of efficacy (24%), intolerability (15%) and other reasons (6%). Among those who stopped medication due to intolerability, 4% was due to weight gain/metabolic effects, 4% because of motor symptoms, 2% due to sedation and 5% attributable to other reasons. Patients assigned to olanzapine had the longest time to discontinuation as a result of inadequate efficacy, the longest successful treatment time and the fewest hospitalizations as a result of exacerbation of schizophrenia. Olanzapine was associated with more discontinuation for weight gain or metabolic effects, and perphenazine with more discontinuation for EPS.

Quality of life, measured with the Quality of Life Scale (QLS) scale,[22] was only moderately improved for the one-third of patients (n = 455 of 1493) who reached the primary QLS analysis endpoint of 12 months. Although individually significant changes from baseline were found for several of the drugs, overall there were no significant differences between the different groups in terms of quality of life.[23] No subjective data were documented.

Regarding cost, analysis included medications plus health services used. Quality-adjusted life-years (QALYs) were assessed on the basis of PANSS and adverse effect rating scale scores. Average total healthcare costs were 20–30% lower for perphenazine than for SGAs, and there were no significant differences between treatments in terms of QALYs.[24]

Data from the phase II switching trials are difficult to summarize because of their complexity. Clozapine (open-label trial, weekly therapeutic contacts to monitor white blood cell count) was more effective than the new SGAs. Data on the differences between these new SGAs were dependent on previous treatment and other variables, and give some relevant information on the usefulness of switching between SGAs, which was urgently needed.

2. CUtLASS

2.1 Methods

CUtLASS 1[16] compared FGAs with SGAs other than clozapine, and CUtLASS 2[25] compared SGAs with clozapine in open-label (i.e. not-masked to patients and clinicians, raters were blind) randomized trials. Primary outcome was quality of life at 1 year, and symptoms were the main secondary outcome.

In CUtLASS 1,[16] 227 people with schizophrenia, mostly outpatients, were assessed by their clinical team for medication review because of poor response or adverse effects. They were randomized to either a FGA or SGA other than clozapine (amisulpride, olanzapine, quetiapine or risperidone). The choice of individual drug within each class was made by the clinician in advance of randomization.

The mean (±SD) age of the patients was 41 ± 11 years, and the duration of illness was 19 ± 11 years. Eighty percent of patients were being treated with a FGA when referred into the trial. Psychopathology was moderate, with a PANSS total score of 73 ± 17 points, which was similar to CATIE[15] (76 ± 18). Drugs prescribed in the FGA arm (n = 118) were mostly sulpiride (n = 58; mean daily dose 813 mg), followed by trifluoperazine (n = 21; 12 mg); only eight patients were treated with haloperidol (22 mg). Drugs prescribed in the SGA arm were amisulpride (n = 13; 610 mg), olanzapine (n = 50; 15 mg), quetiapine (n = 23; 450 mg) and risperidone (n = 22; 5 mg). If a treatment change was required, the psychiatrist was instructed to initiate an alternative from the same class. Adjunctive medication was allowed, but antipsychotic polypharmacy was discouraged.

The CUtLASS 2 trial[25] was of similar design and compared clozapine with other SGAs in

136 patients who had not responded well to two or more previous drugs.

To determine the relative costs and value of treatment with FGAs versus SGAs, the authors conducted a cost-effectiveness acceptability analysis.[26] The health measure for the economic evaluation was the QALY, calculated from the health status reported by all patients enrolled in the trial, using the European Quality of Life (EuroQoL) EQ-5D.[27]

2.2 Results

The rate of follow-up interview was 81% at 1 year (FGAs 85%; SGAs 78%). Numerous patients switched, both within the group of FGAs or SGAs as well as across the treatment groups: 55 of 118 patients (47%) switched from FGAs to SGAs, and 36 of 109 (33%) from SGAs to FGAs. More patients randomized to receive an SGA than an FGA remained in the allocated treatment arm for the whole year (65% [71/109] vs 54% [64/118]).

Improvement was rather limited; the PANSS total score reduction was 8.3 points in the FGA group and 5.1 in the SGA group. Similarly small was the increase in QLS points, with no advantage for SGAs in terms of QLS over 1 year (FGAs from 43 ± 22 to 53 ± 21 points, SGAs from 44 ± 20 to 51 ± 20).

There were also no differences between groups in terms of global assessment, Calgary depression score[28] or motor symptoms. Patients' attitudes and subjective experiences were assessed with the Drug Attitude Inventory (DAI);[29] they reported no clear preference for either class of drug.

Results of CUtLASS 2 showed that there was a significant advantage for clozapine in symptom improvements over 1 year; moreover, patients significantly preferred this drug.[25]

Regarding cost effectiveness, the authors found that FGAs had lower costs and higher QALYs than SGAs.[26] However, they used the EQ-5D, which consists of five domains that are not particularly schizophrenia specific, such as mobility or pain/distress. It is hard to explain why 28% of patients receiving FGAs had problems with mobility, compared with 41% of patients receiving SGAs.

3. Conclusions from CATIE and CUtLASS

In wide agreement, the authors of both studies concluded that, with the possible exception of clozapine, SGAs do not markedly differ from FGAs with regard to compliance, quality of life and effectiveness.

4. Methodological Problems of CATIE and CUtLASS

There is no doubt that CATIE and CUtLASS are important studies in terms of their design, number of patients and duration of illness. While most previous studies addressed 'pure' efficacy and safety, CATIE and CUtLASS focused on real-world 'effectiveness', combining measures of efficacy, tolerability and adherence. Thus, they addressed different questions with different designs compared with the usual double-blind trials. They applied broader inclusion criteria, they allowed more concomitant medications, and in CUtLASS the doctors could choose among different FGAs and SGAs and ultimately even switch between groups. Problems of replicating the findings of efficacy studies in effectiveness studies are well known from other medical fields. For example, statins markedly lower cholesterol levels, but documented differences in mortality are only a few percentage points.[30,31]

Nevertheless, the results of CATIE and CUtLASS were surprising because they contradict the data from most double-blind trials that compared FGAs and SGAs and had the usual restrictions of registration trials (i.e. inclusion and exclusion criteria, dosage, duration of treatment), and also the clinical experience of many doctors. Most psychiatrists working in the field before the arrival of the SGAs remember well the clearly visible effects of contemporary antipsychotic treatment, easily recognisable by a multitude of motor symptoms in most patients. When the new SGAs entered the market with the promise and hope that these 'clozapine-like compounds without agranulocytosis' would

increase compliance and improve long-term prognosis, it was soon realised that compliance was only moderately increased and that medication adherence does not depend only on efficacy and tolerability. Nevertheless, the finding of no relevant differences between FGAs and SGAs was not expected, and there are obvious methodological problems of CATIE and CUtLASS that go beyond 'efficacy versus effectiveness'.[32-38]

Patients might have been negatively selected with a long duration of illness and, despite rather long treatment, only limited scope for improvement of psychopathology. For these at least partially therapy-resistant patients, after 13–14 years of previously unsuccessful pharmacological treatment, an average PANSS total score of approximately 70 points is possibly the best on which they can be stabilized. The ''unrealistic expectations'', mentioned by the authors of CATIE and CUtLASS, of the effectiveness of SGAs (and FGAs) in possibly treatment-resistant patients is a severe design problem in both studies.

If stabilization on the new medication with the lowest possible (subjective) adverse effect profile had been the main outcome measure of the two studies, findings and conclusions might have been different. Studies of the impact of duration of illness or of previous treatment on the efficacy of antipsychotic drugs are limited. However, numerous trials in young or first-episode schizophrenia patients[39,40] have found better efficacy and an elevated risk of motor adverse effects in these patients compared with patients with more chronic disease, indicating that the populations in CATIE and CUtLASS might not be the most sensitive to detect differences between FGAs and SGAs.

To choose comparators other than haloperidol (perphenazine in CATIE; sulpiride in approximately 50% of the patients in CUtLASS:), which may be less prone to EPS, was important, but in most industrialized countries haloperidol is the most frequently used antipsychotic, not perphenazine or sulpiride (even in the UK). Therefore, the studies did not reflect current standard care as is appropriate for effectiveness studies.

The positive outcome for clozapine, still the gold standard for most clinicians, is not surprising. However, this positive outcome might be related to the fact that many treatment-resistant patients refused to enter the clozapine arm and were therefore assigned to the other SGAs. Moreover, open-label treatment and also the weekly contact because of the white blood cell count and their impact on the therapeutic alliance have to be considered as a potential source of positive bias.

4.1 Additional Methodological Problems of CATIE

Furthermore, the extremely high discontinuation rate of patients in CATIE made all outcomes except for dropout very difficult to interpret. In our opinion, even the best statistical method cannot account for an overall discontinuation rate of 74%. This number appears high but is not surprising, as patients were not actually dropping out of the study. Rather, they were switching from one drug to the next. It is certainly relevant that only 40% of patients were treated with the maximal dosage, although only 15% discontinued because of tolerability problems. It may be that the study protocol encouraged patients and their clinicians to switch agents too early by raising hopes that a new drug would produce better results than the one initially assigned. The issue of expectations in such cases could have been paramount, but it remains unclear why 24% of patients were discontinued due to inefficacy, especially because the final PANSS score of 75 points showed that patients did not deteriorate after switching to the new antipsychotic.

Another issue is the difficulty of understanding the reasons for discontinuation. Switching is a common practice, but certainly not well investigated yet. Although the findings of the switching studies[18-20] are of great value, it would have been very helpful to know how often the patient, the relative, the psychiatrist or all of them switched either because of inefficacy or intolerability. The rather limited differentiation between lack of efficacy, reduced tolerability or patients' wish barely reflects the multitude of factors influencing medication discontinuation or switching,

respectively. This important issue has already been comprehensively criticised.[38]

Dosages are another issue of concern. The range of dosages of olanzapine (7.5–30 mg/day) used in the study was considerably broader than used in practice, with the mean dosage of 20.3 mg/day considerably higher than the 15 mg/day that is used for most patients with schizophrenia. The dosages for the other three SGAs were much more in line with the recommended clinical dosage, although quetiapine is nowadays used mostly in a higher dosage. Of relevance might also be the different percentages of patients who were randomized to the drug with which they had already been pre-treated: 23% for olanzapine, 18% for risperidone and 5% for quetiapine.

Another problem described by Glick[33] was the blinding and administration of treatments. Although treatment was blinded, the required dosing of the medications differed. Quetiapine and ziprasidone were taken twice daily while perphenazine, olanzapine and risperidone could be taken once a day. Thus, rather than designating the same medication schedule for all patients, using a placebo when necessary, half of those receiving perphenazine, olanzapine or risperidone were assigned to once-daily regimens and half to twice-daily regimens.

4.2 Additional Methodological Problems of CUtLASS

The major advantage of the SGAs, not used in CATIE, but somewhat utilized in CUtLASS, is certainly their heterogeneity. Due to their largely different receptor-binding profiles, SGAs differ in tolerability, if not in efficacy, and offer far more possibilities for individualizing treatment by taking into account individual attitudes towards and experiences of adverse effects than FGAs, for which only low versus middle versus high antipsychotic potency can be distinguished. In CUtLASS, doctors had the choice among four SGAs, but there was not a lot of information on how the decision to use a specific drug was made. As a result, the majority of patients in the FGA group received sulpiride and unequal numbers of patients were assigned to the various drugs within each class. Sulpiride, a benzamide that has been on the market for >25 years, is not widely used in the UK but was the most frequently used drug in the FGA arm. One reason might be that this drug is probably the 'most atypical' FGA; it provides a good example of the difficulties of classifying heterogeneous compounds into one class. As mentioned in the introduction, the differentiation between FGAs and SGAs is pseudo-categorical and therefore problematic. The non-random selection of drugs within each class, the large number of drugs and the small numbers of patients per group treated with the different drugs preclude any pair-wise comparison within or between drug classes. Together with the problem of 'blindness' in an open-label trial, the frequent switching between and within groups is in keeping with the intent-to-treat principle, but it blurs any difference between SGAs and FGAs.

5. Two Major Advantages of Second-Generation Antipsychotics Not Considered in CATIE and CUtLASS

Two recent non-regulatory open-label trials, conducted in 'real-world conditions' similar to CATIE and CUtLASS, are the observational, non-randomized European SOHO (Schizophrenia Outpatient Health Outcomes) study[41] and the randomized EUFEST (EUropean First-Episode Schizophrenia Trial).[42] Both studies investigated a less chronically ill population and had much higher retention rates compared with CATIE and CUtLASS, and found some relevant advantages of SGAs over FGAs.

Patients in SOHO were a mean (±SD) age of 42 ± 14 years, had a duration of illness of 7.6 ± 1.7 years and a baseline Clinical Global Impression (CGI)[43] score of 4.4 ± 1.0.[41] Data from 2 years' antipsychotic treatment ($n = 2960$) indicated that patients treated with SGAs (retention rate 71% vs 66% with FGAs) had a higher chance of reaching remission (odds ratio of 2.5) than those receiving FGAs. Moreover, patients' subjective well-being increased significantly more with SGAs compared with FGAs.[41]

In EUFEST (n = 498), patients were a mean (±SD) age of 26 ± 6 years, had positive symptoms of 2 years' maximum duration and had received antipsychotic treatment for ≤2 weeks (33% were drug naïve).[42] The PANSS total score was 89 ± 21 at baseline, and patients showed an improvement of 35 points after 12 months. The improvement in CGI score was similar to that measured in SOHO, from 4.8 ± 0.8 at baseline to 2.3–3.0, depending on the treatment. SGAs were compared with a low dosage of haloperidol (3.0 ± 1.2 mg/day). Most patients responded well to both haloperidol and SGAs, with no differences in symptom reduction. However, there were significant differences in the CGI and the Global Assessment of Functioning (GAF)[44] scores, with greatest improvements seen with amisulpride and olanzapine, and least improvements with quetiapine and haloperidol. Moreover, relevant differences were found favouring SGAs with regard to retention rate (amisulpride 60%, olanzapine 67%, quetiapine 47% and ziprasidone 55% vs haloperidol 28%) and motor adverse effects.[42]

Probably, the two most relevant advantages of SGAs versus FGAs are the better subjective effects and a reduced risk of tardive dyskinesia. Most clinicians with long expertise in the use of FGAs agree that a large majority of patients strongly prefer the SGAs over the FGAs. One example is the survey by Karow et al.,[3] where 61 'experts by experience' (i.e. schizophrenia patients who had been treated with SGAs for 2 years and before or afterwards with FGAs for 1 year) described marked differences, not in efficacy on positive symptoms, but on negative and affective symptoms, and also better tolerability regarding motor and sexual adverse effects. The findings by Voruganti et al.,[45] who compared haloperidol and SGAs in an open-label trial, are similar. Quality of life was assessed by self-rating as well as by expert-rating scales, and 'only' the patients detected a difference in favour of the SGAs.

It is well known that patient-rated and observer-rated quality of life is at best only moderately related. Unlike subjective measures, which are sensitive to depressive symptoms and anxiety, objective quality-of-life measures such as the QLS developed by Heinrichs et al.,[22] which was applied in CATIE and CUtLASS, are more strongly related to the presence and degree of negative symptoms. Using the QLS for patients who have chronic schizophrenia with a high degree of negative symptoms and only a small improvement over time would therefore bias a sample towards non-significant differences between two comparison groups. Scores on the Subjective Well-being under Neuroleptics (SWN) instrument,[46] developed to measure the subjective effects of antipsychotics, were found not to be strongly related to QLS scores at the beginning of antipsychotic treatment (r = 0.4–0.5), but after 9–12 months, correlations increased up to 0.6–0.7.[47] Several studies indicate that improvement of the SWN score is a much more powerful predictor than improvement of psychopathology in terms of compliance and enduring symptomatic remission.[41,48] Data on the predictive power of QLS scores are not available yet.

In the debate about the benefits of SGAs, the argument of an excessively high dosage of the comparator in double-blind trials is often used. It is justified for the older trials, but most of the more recent trials have used haloperidol in moderate dosages.[49,50] Moreover, the landmark study by Zimbroff et al.,[51] in which three dosages of haloperidol were compared with three dosages of sertindole (plus placebo), has shown that haloperidol 5 mg/day was not effective enough and that the sometimes suggested low dosages of haloperidol might be too low.

One final issue is tardive dyskinesia, which was very much neglected in both trials. In CATIE, patients with tardive dyskinesia were excluded from the perphenazine arm, but nevertheless patients treated with the FGA had the highest discontinuation rate due to motor symptoms. There was no wash-out phase at the start of CATIE, not even for antiparkinson medication. Many patients may have received antiparkinson medication from the start (the exact numbers were never published) and were thus receiving 'prophylactic antiparkinson medication', which may have further diminished differences in EPS. As Casey[32] wrote in his critique of CATIE,

"Since evaluations involving the perphenazine group were thus limited to patients without tardive dyskinesia, a true comparison among treatment groups of tardive dyskinesia onset or worsening of existing cases with perphenazine versus the other antipsychotics is not possible. … 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." One can add that in no way do the CATIE and CUtLASS studies contradict the current evidence, which indicates a lower risk of tardive dyskinesia with SGAs.[52] Regarding the suggested advantages of SGAs in low dosage, there are data that even 2–3 mg/day of haloperidol is associated with a high risk of tardive dyskinesia.[53] Even if most of the other previously reported advantages of the SGAs are debatable, the lower risk of tardive dyskinesia might be a strong enough reason to favour these drugs. The ethical or clinical question is rather how many dollars or euros are justifiably spent to save patients from tardive dyskinesia.[54]

6. Clinical Implications of CATIE and CUtLASS

Aside from the information that the advantages of SGAs are not as strong as early trials and marketing suggested or promised, the trials do not provide much help to the psychiatrist looking for the right antipsychotic drug for his/her individual patient. Studies certainly do not provide a definite answer as to which antipsychotic is most effective, and there is, not surprisingly, no antipsychotic that is best for every patient with schizophrenia.

We still need more information on what to do when drugs are not effective or not tolerable or if the patient does not want to take them. If these problems arise, how long should we wait before we switch the antipsychotic, before we offer the patient a depot treatment (more SGAs in this formulation are needed), or before we combine antipsychotics? As Meltzer and Bobo[34] suggest, "Best treatment balances efficacy, prevention of disease progression and medication side effects; achievable outcomes need to be tailored to individual cases and may vary from merely symptom improvement to full remission; and not every patient experiences every drug side effect. Therefore, it is vital to have a variety of treatment options." Most relevant in this regard are the CATIE switching trials.[18-20] The complex data from the trials indicate again that patients differ markedly not only in psychopathology, but also in the effects of psychopharmacology. They have different expectations, attitudes and apprehensions regarding wanted and unwanted effects of antipsychotic treatment. Sedation might be a severe adverse effect for some patients, but rather pleasant for others. For a successfully individualized treatment, the patient and the different antipsychotic options have to be very well known. Close monitoring and careful listening to the patient are essential, particularly in the first weeks or months of antipsychotic treatment, to create a therapeutic alliance that will hopefully result in a better outcome.

7. Conclusions

Two of the authors of CATIE and CUtLASS, Lewis and Lieberman,[55] conclude in their editorial 'CATIE and CUtLASS: Can we handle the truth?': "…that first-generation drugs, if carefully prescribed, are as good as most second-generation drugs in many if not most patients with established schizophrenia." [We could ask: Which truth? Did only these two studies find the truth?] Aside from the dubious pseudo-categorization of FGAs versus SGAs, which the reader of this article must also be aware of, we think that this conclusion goes much too far and does not fairly consider the literature, clinical experience and the opinion of two important groups: patients and their relatives/partners. While the first SGAs have already lost patent protection (others will become generic in the near future), the mostly pharmacoeconomic debate on the differences between FGAs and SGAs will probably fade away. We conclude that the advantages of the SGAs are doubtful regarding some success criteria (such as effects on negative or cognitive symptoms) but, aside from their heterogeneity and the consequent increased

potential to address individual patients' problems, the better subjective well-being or quality of life experienced by many (most?) patients and the reduced risk of tardive dyskinesia of at least some SGAs are two strong arguments to restrict the use of, at least, the high-potency FGAs.

Acknowledgements

The authors gratefully acknowledge the careful reading and helpful comments of Dr Stefan Leucht. No sources of funding were used to assist in the preparation of this review. Dr Naber has received honoraria from and/or acted as a consultant for AstraZeneca, Eli Lilly, Janssen-Cilag and Pfizer. Dr Lambert has received honoraria from and/or acted as a consultant for AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Janssen-Cilag and Pfizer.

References

1. Tandon R, Belmaker RH, Gattaz WF, et al. World Psychiatric Association Pharmacopsychiatry Section statement on comparative effectiveness of antipsychotics in the treatment of schizophrenia. Schizophr Res 2008; 100: 20-38
2. Naber D. Subjective effects of antipsychotic treatment. Acta Psychiatr Scand 2005; 111: 81-3
3. Karow A, Schindler D, Naber D. What would the patient choose? Subjective comparison of atypical and typical neuroleptics. Pharmacopsychiatry 2006; 39: 47-51
4. American Psychiatric Association. Practice guideline for the treatment of patients with schizophrenia (second Compendium). Arlington (VA): APA, 2004: 249-440
5. Falkai P, Wobrock T, Lieberman J, et al. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of schizophrenia. Part 1: acute treatment of schizophrenia. World J Biol Psychiatry 2005; 6: 132-91
6. Lehman AF, Kreyenbuhl J, Buchanan RW, et al. The Schizophrenia Patient Outcomes Research Team (PORT): updated treatment recommendations 2003. Schizophr Bull 2004; 30: 193-217
7. National Institute for Clinical Excellence (NICE). Schizophrenia: core interventions in the treatment and management of schizophrenia in primary and secondary care. Clinical Guideline 1, National Collaborating Centre for Mental Health. London: NICE, 2002
8. Royal Australian and New Zealand College of Psychiatrists Clinical Practice Guidelines Team for the Treatment of Schizophrenia and Related Disorders. Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for the treatment of schizophrenia and related disorders. Aust N Z J Psychiatry 2005; 39: 1-30
9. Davis JM, Chen N, Glick ID. A meta-analysis of the efficacy of second-generation antipsychotics. Arch Gen Psychiatry 2003; 60: 553-64
10. Dolder CR, Lacro JP, Dunn LB, et al. Antipsychotic medication adherence: is there a difference between typical and atypical agents? Am J Psychiatry 2002; 159: 103-8
11. Leucht S, Wahlbeck K, Hamann J, et al. New generation antipsychotics versus low-potency conventional antipsychotics: a systematic review and meta-analysis. Lancet 2003; 361: 1581-9
12. Leucht S, Barnes T, Kissling W, et al. Relapse prevention in schizophrenia with new-generation antipychotics: a systematic review and exploratory meta-analysis of randomized, controlled trials. Am J Psychiatry 2003; 160: 1209-22
13. Woodward ND, Scot EP, Meltzer HY, et al. A meta-analysis of neuropsychological change to clozapine, olanzapine, quetiapine, and risperidone in schizophrenia. Int J Neuropsychopharmacology 2005; 8: 457-72
14. Geddes J, Freemantle N, Harrison P. Atypical antipsychotics in the treatment of schizophrenia: systematic overview and meta-regression analysis. BMJ 2000; 321: 1371-6
15. Lieberman JA, Stroup TS, McEvoy JP, et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N Engl J Med 2005; 353: 1209-23
16. Jones PB, Barnes TR, Davies L, et al. Randomized controlled trial of the effect on quality of life of second- vs first-generation antipsychotic drugs in schizophrenia: Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS 1). Arch Gen Psychiatry 2006; 63: 1079-87
17. Kay SR, Fiszbein A, Opler LA. The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. Schizophr Bull 1987; 13: 261-76
18. McEvoy JP, Lieberman JA, Stroup TS, et al. Effectiveness of clozapine versus olanzapine, quetiapine, and risperidone in patients with chronic schizophrenia who did not respond to prior atypical antipsychotic treatment. Am J Psychiatry 2006; 163: 600-10
19. Stroup TS, Lieberman JA, McEvoy JP, et al. Effectiveness of olanzapine, quetiapine, risperidone, and ziprasidone in patients with chronic schizophrenia following discontinuation of a previous atypical antipsychotic. Am J Psychiatry 2006; 163: 611-22
20. Stroup TS, Lieberman JA, McEvoy JP, et al. Effectiveness of olanzapine, quetiapine, and risperidone in patients with chronic schizophrenia after discontinuing perphenazine: a CATIE study. Am J Psychiatry 2007; 164: 415-27
21. Keefe RS, Bilder RM, Davis SM, et al. Neurocognitive effects of antipsychotic medications in patients with chronic schizophrenia in the CATIE trial. Arch Gen Psychiatry 2007; 64: 633-47
22. Heinrichs DW, Hanlon TE, Carpenter WT. The Quality of Life Scale: an instrument for rating the schizophrenic deficit syndrome. Schizophr Bull 1984; 10: 398-9
23. Swartz MS, Perkins DO, Stroup TS, et al. Effects of antipsychotic medications on psychosocial functioning in patients with chronic schizophrenia: findings from the NIMH CATIE study. Am J Psychiatry 2007; 164: 428-36
24. Rosenheck AR, Leslie DL, Sindelar J, et al. Cost-effectiveness of second-generation antipsychotics and perphenazine in a randomized trial of treatment for chronic schizophrenia. Am J Psychiatry 2006; 163: 2080-9
25. Lewis SW, Barnes TRE, Davies L, et al. Randomized controlled trial of effect of prescription of clozapine versus other second-generation antipsychotic drugs in resistant schizophrenia. Schizophr Bull 2006; 32: 715-23

26. Davies LM, Lewis S, Jones PB, et al. Cost-effectiveness of first- v. second-generation antipsychotic drugs: results from a randomised controlled trial in schizophrenia responding poorly to previous therapy. Br J Psychiatry 2007; 191: 14-22
27. Kind P. The EuroQoL instrument: an index of health related quality of life. In: Spilker B, editor. Quality of life and pharmacoeconomics in clinical trials. 2nd ed. Philadelphia (PA): Lippincott-Raven, 1996
28. Addington D, Addington J, Schissel B. A depression rating scale for schizophrenics. Schizophr Res 1990; 3: 247-51
29. Hogan TP, Awad AG, Eastwood R. A self-report scale predictive of drug compliance in schizophrenics: reliability and discriminative validity. Psychol Med 1983; 13: 177-83
30. Edwards JE, Moore RA. Statins in hypercholesterolaemia: a dose-specific meta-analysis of lipid changes in randomised, double-blind trials. BMC Fam Pract 2003; 4: 18
31. Baigent C, Keech A, Kearney PM, et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet 2005 Oct 8; 366 (9493): 1267-78
32. Casey DE. Implications of the CATIE trial on treatment: extrapyramidal symptoms. CNS Spectr 2006; 11 Suppl. 7: 25-31
33. Glick ID. Understanding the results of CATIE in the context of the field. CNS Spectr 2006; 11 Suppl. 7: 40-7
34. Meltzer HY, Bobo WV. Interpreting the efficacy findings in the CATIE study: what clinicians should know. CNS Spectr 2006; 11 Suppl. 7: 14-24
35. Meyer JM. Strategies for the long-term treatment of schizophrenia: real-world lessons from the CATIE trial. J Clin Psychiatry 2007; 68 Suppl. 1: 28-33
36. Möller HJ. Do effectiveness (''real world'') studies on antipsychotics tell us the real truth? Eur Arch Psychiatry Clin Neurosci 2008; 258: 257-70
37. Nasrallah HA. The roles of efficacy, safety, and tolerability in antipsychotic effectiveness: practical implications of the CATIE schizophrenia trial. J Clin Psychiatry 2007; 68 Suppl. 1: 5-12
38. Weiden PJ. Discontinuing and switching antipsychotic medications: understanding the CATIE schizophrenia trial. J Clin Psychiatry 2007; 68 Suppl. 1: 12-9
39. McEvoy JP, Hogarty GE, Steingard S. Optimal dose of neuroleptic in acute schizophrenia: a controlled study of the neuroleptic threshold and higher haloperidol dose. Arch Gen Psychiatry 1991; 48: 739-45
40. Remington G, Kapur S, Zipursky RB. Pharmacotherapy of first-episode schizophrenia. Br J Psychiatry Suppl 1998; 172: 66-70
41. Lambert M, Schimmelmann BG, Naber D, et al. Prediction of remission as a combination of symptomatic and functional remission and adequate subjective well-being in 2,960 patients with schizophrenia. J Clin Psychiatry 2006; 67 (11): 1690-7
42. Kahn RS, Fleischhacker WW, Boter H, et al. Effectiveness of antipsychotic drugs in first-episode schizophrenia and schizophreniform disorder: an open randomised clinical trial. Lancet 2008; 371: 1085-97
43. National Institute of Mental Health. 12-CGI: Clinical Global Impressions. In: Guy W, Bonato RR, editors. Manual for the ECDEU assessment battery. 2nd rev. ed. Chevy Chase (MD): NIHM, 1970: 12-1-6
44. Endicott J, Spitzer RL, Fleiss JL, et al. The global assessment scale: a procedure for measuring overall severity of psychiatric disturbance. Arch Gen Psychiatry 1976; 33 (6): 766-71
45. Voruganti L, Cortese L, Oyewumi L, et al. Comparative evaluation of conventional and novel antipsychotic drugs with reference to their subjective tolerability, side-effect profile and impact on quality of life. Schizophr Res 2000; 43: 135-45
46. Naber D, Moritz S, Lambert M, et al. Improvement of schizophrenic patients' subjective well-being under atypical antipsychotic drugs. Schizophr Res 2001; 50: 79-88
47. Wehmeier PM, Kluge M, Schacht A, et al. Correlation of physician and patient rated quality of life during antipsychotic treatment in outpatients with schizophrenia. Schizophr Res 2007; 91: 178-86
48. de Haan L, van Nimwegen L, van Amelsvoort T, et al. Improvement of subjective well-being and enduring symptomatic remission: a 5-year follow-up of first episode schizophrenia. Pharmacopsychiatry 2008; 41: 125-8
49. Rabinowitz J, Lichtenberg P, Kaplan Z, et al. Rehospitalization rates of chronically ill schizophrenic patients discharged on a regimen of risperidone, olanzapine, or conventional antipsychotics. Am J Psychiatry 2001; 158: 266-9
50. Schooler NR, Keith SJ, Severe JB, et al. Relapse and rehospitalisation during maintenance treatment of schizophrenia. Arch Gen Psychiatry 1997; 54: 453-63
51. Zimbroff DL, Kane JM, Tamminga CA, et al. Controlled dose-response study of sertindole and haloperidol in the treatment of schizophrenia. Am J Psychiatry 1997; 154: 782-91
52. Correll CU, Leucht S, Kane JM. Lower risk for tardive dyskinesia associated with second-generation antipsychotics: a systematic review of 1-year studies. Am J Psychiatry 2004; 161: 414-25
53. Oosthuizen PP, Emsley RA, Maritz JS, et al. Incidence of tardive dyskinesia in first-episode psychosis patients treated with low-dose haloperidol. J Clin Psychiatry 2003; 64 (9): 1075-80
54. Rosenheck RA. Evaluating the cost-effectiveness of reduced tardive dyskinesia with second-generation antipsychotics. Br J Psychiatry 2007; 191: 238-45
55. Lewis S, Lieberman J. CATIE and CUtLASS: can we handle the truth? Br J Psychiatry 2008; 192: 161-3

Correspondence: Prof. Dr *Dieter Naber*, Department of Psychiatry and Psychotherapy, University Medical Center Hamburg-Eppendorf, Martinistrasse 52, 20246 Hamburg, Germany.
E-mail: naber@uke.uni-hamburg.de