Amisulpride and olanzapine followed by open-label treatment with clozapine in first-episode schizophrenia and schizophreniform disorder (OPTiMiSE): a three-phase switching study

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Summary

Background No established treatment algorithm exists for patients with schizophrenia. Whether switching antipsychotics or early use of clozapine improves outcome in (first-episode) schizophrenia is unknown.

Methods This three-phase study was done in 27 centres, consisting of general hospitals and psychiatric specialty clinics, in 14 European countries and Israel. Patients aged 18–40 years who met criteria of the DSM-IV for schizophrenia, schizophreniform disorder, or schizoaffective disorder were treated for 4 weeks with up to 800 mg/day amisulpride orally in an open-label design (phase 1). Patients who did not meet symptomatic remission criteria at 4 weeks were randomly assigned to continue amisulpride or switch to olanzapine (≤20 mg/day) during a 6-week double-blind phase, with patients and staff masked to treatment allocation (phase 2). Randomisation was done online by a randomisation website; the application implemented stratification by site and sex, and applied the minimisation method for randomisation. Patients who were not in remission at 10 weeks were given clozapine (≤900 mg/day) for an additional 12 weeks in an open-label design (phase 3). The primary outcome was the number of patients who achieved symptomatic remission at the final visits of phases 1, 2, and 3, measured by intention-to-treat analysis. Data were analysed with a generalised linear mixed model, with a logistic link and binomial error distribution. This trial is registered with ClinicalTrials.gov, number NCT01248195, and closed to accrual.

Findings Between May 26, 2011, and May 15, 2016, we recruited 481 participants who signed informed consent. Of the 446 patients in the intention-to-treat sample, 371 (83%) completed open-label amisulpride treatment, and 250 (56%) achieved remission after phase 1. 93 patients who were not in remission continued to the 6-week double-blind switching trial, with 72 (77%) patients completing the trial (39 on olanzapine and 33 on amisulpride); 15 (45%) patients on amisulpride versus 17 (44%) on olanzapine achieved remission (p=0·87). Of the 40 patients who were not in remission after 10 weeks of treatment, 28 (70%) started on clozapine; 18 (64%) patients completed the 12-week treatment, and five (28%) achieved remission. The number of serious adverse events did not differ between the treatment arms in phase 2: one patient on olanzapine was admitted to hospital because of an epileptic seizure, and one patient on amisulpride was admitted to hospital twice because of exacerbations of psychotic symptoms. Over the course of the trial, two serious suicide attempts were reported.

Interpretation For most patients in the early stages of schizophrenia, symptomatic remission can be achieved using a simple treatment algorithm comprising the sequential administration of amisulpride and clozapine. Since switching to olanzapine did not improve outcome, clozapine should be used after patients fail a single antipsychotic trial—not until two antipsychotics have been tried, as is the current recommendation.

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Introduction

Although effective antipsychotic medications have been available for more than half a century, the application and implementation of these treatments is far from optimum. No established treatment algorithm exists for the use of antipsychotics in schizophrenia. In clinical practice, when a patient has not responded to the initial treatment, they are often switched from one antipsychotic medication to another; however, there is surprisingly little evidence that this treatment switch improves clinical outcomes. One of the most relevant questions in the treatment of the early phase of schizophrenia—and essential to any treatment algorithm—is whether switching to another antipsychotic improves outcome when a patient has not responded to the initial treatment is clinically useful. Another aspect that has often been omitted from

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See Online for appendix

Research in context

Evidence before this study

No established treatment algorithm exists for patients with schizophrenia. Fundamental questions about the treatment of the disorder, such as whether switching antipsychotics improves outcome, remain unaddressed. We searched PubMed from the start of database inception until October, 2017, for randomised trials in which patients with schizophrenia, schizophreniform, or schizoaffective disorder (any diagnostic criteria) had been treated prospectively with a first antipsychotic drug, and individuals who had no response were subsequently randomly assigned to either switching the antipsychotic or another pharmacological strategy. Search terms were, "schizophreni* AND (antipsychot* OR neurolept* OR drug OR treat*) AND (switch* OR alternative* OR consecutive* OR subsequent OR shift OR change) AND (nonrespon* OR not respon* OR fail OR resistant* OR refract* OR ineffect*)", and article types were clinical trials or randomised controlled trials. No restriction was placed on language. 14 reports on ten studies met the inclusion criteria for our search. The only study with an appropriate design studied switching patients who did not respond to risperidone to olanzapine versus maintaining them on risperidone, with a slightly better outcome for switching. No available studies were restricted to patients with first-episode schizophrenia.

Added value of this study

This is the first study, to our knowledge, examining the relevance of switching antipsychotic medication in patients with first-episode schizophrenia who have not responded to their initial course of treatment. The results suggest that in the large majority of patients in the early stages of schizophrenia, symptomatic remission can be achieved using a simple treatment algorithm comprising the sequential administration of amisulpride and clozapine. Since switching to olanzapine did not improve outcome, clozapine should be used after patients fail a single antipsychotic trial.

Implications of all the available evidence

The current guideline that clozapine should only be used after patients fail treatment with two different antipsychotics might need to be adapted. Our data indicate that clozapine should be used after schizophrenia patients fail to remit to a single antipsychotic, thus shortening the time until patients receive the most effective antipsychotic, possibly improving long-term outcome.

treatment studies in schizophrenia is a clinically relevant outcome measure. Generally, response to treatment has been defined as a reduction in the Positive and Negative Syndrome Scale (PANSS) total score by more than 20%, but remission has been argued to be a more stringent outcome, analogous to cancer treatment and reflecting an almost complete absence of the psychotic symptoms of schizophrenia.[1] This measure is clinically relevant and useful as an outcome in clinical trials.[2,3]

In a previous trial, we found that amisulpride and olanzapine had similar efficacies in the treatment of first-episode schizophrenia,[4] despite their different receptor binding profiles.[5–8] These results are consistent with those of meta-analyses[9–11] comparing the efficacy of antipsychotics in the treatment of schizophrenia. In treatment algorithms, given equal effectiveness, one would choose to initiate treatment with medication with the fewest toxic effects. Although both drugs have multiple side-effects, in the case of amisulpride, these side-effects are mostly limited to extrapyramidal symptoms and hyperprolactinaemia (although QTc prolongation can occur at higher doses), whereas side-effects associated with olanzapine increase the risk of cardiovascular complications and are therefore more serious in the long term than those associated with amisulpride.[9] Relevant for the implementation of the study results is that amisulpride is not licensed in the USA and in some European countries.

For most patients with schizophrenia who do not respond to antipsychotic medication, the intervention best supported by evidence is treatment with clozapine.[12] Current guidelines recommend clozapine be offered to patients who have not responded to two different antipsychotics, given at adequate doses for at least 6 weeks each. A first-episode patient could therefore receive clozapine within 12 weeks after the start of treatment; however, in clinical practice, the interval between the onset of treatment and the initiation of clozapine can be as long as 10–12 years.[13]

The present study aimed to address two key issues: whether switching to another antipsychotic is effective for first-episode patients who do not respond to their first trial of antipsychotic medication, and whether earlier treatment with clozapine improves outcome in patients who have not remitted after 10 weeks of antipsychotic treatment.

Methods

Study design

This study comprised a combination of treatment designs: the first phase was an open-label, single-treatment arm; the second phase was a randomised, double-blind design; and the third phase was an open-label, single-treatment arm. The study was done in 27 centres located in 14 European countries (Austria, Belgium, Bulgaria, Czech Republic, Denmark, France, Germany, Italy, the Netherlands, Poland, Romania, Spain, Switzerland, and the UK) and Israel, consisting of general hospitals and psychiatric specialty clinics.

Each country obtained ethics approval. The trial complied with the Declaration of Helsinki.[14] The University Medical Center Utrecht, Netherlands, monitored the trial according

to Good Clinical Practice and International Conference on Harmonization guidelines.[15]

Patients

Patients were recruited at the participating hospitals from nearby health-care facilities and through public advertisements. Eligible patients were aged 18–40 years and met criteria of the DSM-IV for schizophrenia, schizophreniform disorder, or schizoaffective disorder; diagnoses were confirmed by the Mini International Neuropsychiatric Interview plus.[16] Female patients of childbearing potential were required to use a proper method of contraception (such as the use of oral contraceptives and approved contraceptive devices). Patients were excluded if the time between the onset of psychosis and study entry exceeded 2 years; any antipsychotic medication had been used for more than 2 weeks in the previous year or for a total of 6 weeks or more in their lifetime; they had a known intolerance to one of the study drugs; they met any of the contra-indications for any of the study drugs as mentioned in the (local) package insert texts; they were coercively treated or represented by a legal guardian, or both, or under legal custody; or, they were pregnant or breastfeeding. All study participants provided written informed consent.

Randomisation and masking

For treatment allocation of patients participating in phase 2, a randomisation table was generated by the Data Management department of the Julius Center, University Medical Center Utrecht, Netherlands, using VB.Net with access to an SQL Server backend database. Study medication was packaged in line with this randomisation table, using sequentially numbered kits. Randomisation was done online by a randomisation website, also developed by the Julius Center, which provided the applicable kit number correlated with a specific kit containing all medication for the individual patient. The application implemented stratification by site and sex, and applied the minimisation method for randomisation.

The data management group was not involved in patient recruitment, which was done at each participating centre. The complete study teams at each centre and patients were masked to treatment allocation. Masking was achieved by overencapsulating two 2·5 mg olanzapine tablets or one 200 mg amisulpride tablet into one capsule, using the same manufacturing process to ensure that appearance, shape, smell, mass, and taste of the opaque capsules were indistinguishable. Olanzapine and amisulpride were purchased commercially and overencapsulated by Piramal Healthcare UK, Morpeth.

Blood samples were taken by local study teams at the beginning and end of each treatment phase to test proteomic, immune, and genetics parameters. Additionally, patients who had remitted were randomly assigned to a specific psycho-social intervention versus treatment as usual with the goal to improve adherence. The results from these studies are not yet available and will be reported separately. MRI and magnetic resonance spectroscopy assessments were conducted in a subsample of participants.[17]

Procedures

After patients signed informed consent, the screening visit was done, during which eligibility was assessed and baseline data collected. Baseline data were obtained, including demographics, diagnoses, present treatment setting, psychopathology (PANSS), severity of illness (Clinical Global Impression; CGI), depression (Calgary Depression Scale for Schizophrenia; CDSS), personal and social functioning (Personal and Social Performance scale; PSP), subjective wellbeing (Subjective Wellbeing under Neuroleptic use; SWN), adverse effects (Udvalg for Kliniske Undersogelser; UKU), and alcohol and drug use.

The study design is described in detail by Leucht and colleagues,[18] including references for the scales used. Briefly, the trial was divided into three treatment phases; patients were eligible for participation in the subsequent phase if they did not meet criteria of symptomatic remission at the end of the previous phase. Symptomatic remission was defined according to the criteria of Andreasen: eight specific symptoms rated by the PANSS (items P1, P2, P3, N1, N4, N6, G5, and G9) are, at the most, only mildly present (maximum rating of 3), meaning that they do not interfere with daily life functioning.[15] However, in contrast with the Andreasen criteria, the minimum duration of symptom severity (6 months) was not applied.[1] All patients started with a 4-week open-label treatment with amisulpride (200–800 mg/day orally; phase 1). At the start of phase 2, individuals who were not in remission from phase 1 were randomly assigned 1:1 to double-blind flexible dose treatment with olanzapine (5–20 mg/day orally) or amisulpride (200–800 mg/day orally). Individuals who were not in remission in phase 2 continued into 12-week open-label treatment with oral clozapine 100–900 mg/day (phase 3). Unused pills and empty pill boxes were returned to the study centres and counted, and blood levels were assessed to measure medication compliance.

Data were collected after weeks 1, 2, 4, 6, 8, and 10–22, for most or all of the efficacy, safety, and tolerability outcomes. Weight, abdominal circumference, and height were measured and an electrocardiogram was done as per the amisulpride summary of product characteristics. Patients who did not meet remission criteria after completion of phase 3 returned for a follow-up visit 48 weeks after baseline (26 weeks after the final phase 3 visit), in which PANSS was assessed and rehospitalisation data were collected. For all patients who started phase 1, a follow-up visit at 74 weeks post baseline was scheduled to assess symptom severity and the current clinical diagnosis, and to collect data on admissions to hospital.

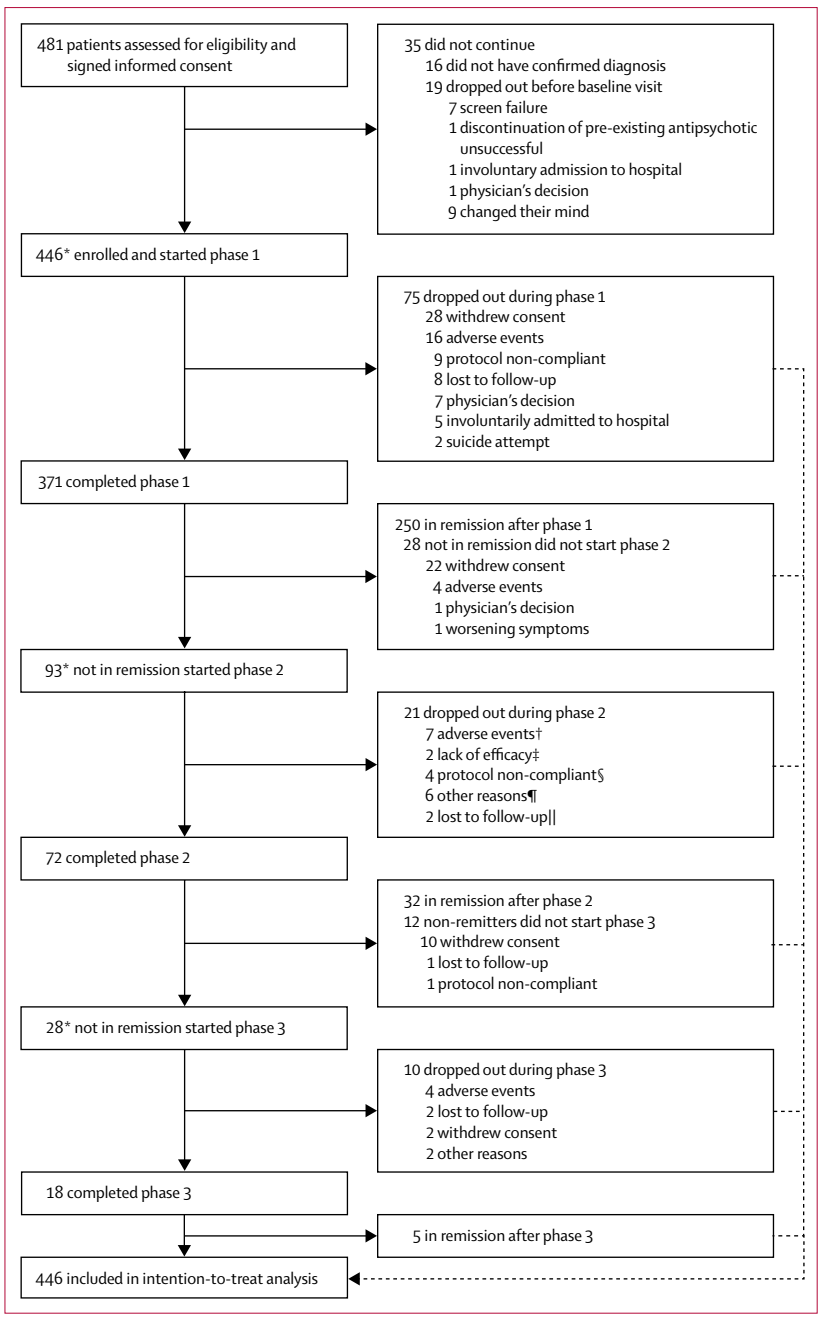

Figure 1: **Trial profile**
*Assessed for primary endpoints.†Six in amisulpride group and one in olanzapine group. ‡One in amisulpride group and one in olanzapine group. §All in amisulpride group. ¶Three in amisulpride group and three in olanzapine group. ||All in olanzapine group.

Outcomes

The primary outcome was the number of patients who achieved symptomatic remission at the final visits of phase 1 (after 4 weeks of open treatment with amisulpride), phase 2 (after 6 weeks of double-blind treatment with amisulpride or olanzapine), and phase 3 (after 12 weeks of open-label treatment with clozapine). If remission criteria were met, the patient had completed the trial. If remission criteria were not met, the patient progressed to the next phase of treatment. All raters were certified through a standardised PANSS training and examination, provided by the sponsor. Halfway through the study, an inter-rater reliability assessment was done at all sites (intraclass correlation coefficient=0·82).

The main secondary outcome measure was a comparison between amisulpride and olanzapine on all-cause treatment discontinuation. Other secondary outcomes include the severity and improvement scores of the CGI, levels of depression (CDSS), personal and social functioning (PSP), and subjective wellbeing (SWN). Safety outcomes include the UKU side-effects rating scale and weight gain. We studied whether earlier treatment with clozapine would improve outcome in first-episode schizophrenia. Remission to clozapine after 22 weeks of treatment was used as the outcome measure.

Frequency and severity of adverse events were recorded at each visit (ie, weeks 1, 2, 4, 6, 8, and 10–22).

Statistical analysis

Data from the EUFEST study[4] showed that about 40% of patients on amisulpride were in symptomatic remission within 4 weeks; however, halfway through the current study, almost 60% of phase 1 patients met remission criteria. On the basis of these data, we adjusted our power analysis such that we expected 50% of the 4-week individuals who had no response and stayed on amisulpride to be in symptomatic remission after another 6 weeks of treatment (10 weeks from treatment initiation). If the percentage of patients in remission increased from 50% to 70% as a result of switching to olanzapine (which was an estimation, as no previous studies exist on this topic), the two treatment groups had to contain 90 patients each to obtain a statistical power of 0·79 with a type-I error rate of 0·05. We considered that the proportion of dropouts would be approximately 30% and the proportion of remissions would be 60% (both observations after 250 patients had been enrolled into the study); thus, at least 487 patients had to be included at baseline, taking into account a dropout of 30% during phase 2 (observation in first 50 phase 2 patients).

Remission, assessed at the final visit of each phase, was first summarised as patient counts and percentages. Subsequently, remission at each visit was analysed using a generalised linear mixed model (GLMM), with a logistic link and binomial error distribution. Proportion of patients in remission data are presented back-transformed from a logistic scale. Visit number was included as a categorical variable and the baseline PANSS score as a continuous covariate. In this way, all visits contributed to the estimate of the between-patient variance, thereby making the estimate of remission at the final visit more robust while accounting for dropout. For phase 2, a comparison was made between the amisulpride and olanzapine groups, by including the treatment group as a factor in the GLMM. The cumulative

proportion of patients in remission over all three study phases was calculated using the number of patients in remission at the last visit of each phase (ie, the individuals in remission who completed the phase). We used the conservative assumption that dropouts within a phase did not reach remission throughout the study. Patients eligible for the next study phase, but not continuing into that phase, were assumed not to be different from patients who continued. To assess the proportion of dropouts over time, a Kaplan-Meier curve was used. Follow-up time was defined as the number of weeks between the date of the baseline visit and the date of the last visit of a patient. Patients who did not progress to a next phase because they were in remission were censored. Side-effects were summarised per visit and per phase, and expressed as percentages. Missing values were not imputed, as the GLMM analysis incorporates all available measurements, assuming that patients with available measurements are representative for all patients, including the patients with missing values. For side-effects, we assumed that missing values indicated absence of side-effects. All quantitative scores, including the PANSS, were summarised as mean (SD), and differences between groups were assessed by use of a t test. Dichotomous variables were expressed as counts and percentages, and differences between groups were assessed by use of χ^2 tests. Differences between groups in proportions were calculated, and 95% CIs were calculated according to Wilson's method. In all analyses, the criterion for statistical significance was $p<0{\cdot}05$. SPSS version 25 was used for all analyses. A data safety monitoring board oversaw the study.

This trial is registered with ClinicalTrials.gov, number NCT01248195.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Participants were recruited between May 26, 2011, and May 15, 2016, when the project end date was reached. The final study visit took place on Nov 1, 2017. The trial profile is shown in figure 1.481 patients were assessed for eligibility and signed the informed consent. In 16 (3%) patients, the diagnosis could not be confirmed. Another 19 (4%) patients dropped out before the baseline visit for various reasons (figure 1). 446 (93%) patients met diagnostic criteria and initiated the first phase: open-label treatment with amisulpride (200–800 mg/day). Baseline characteristics for the intention-to-treat (ITT) sample (n=446) are given in table 1, as are the subgroups of patients who continued into the subsequent treatment phase 2 (n=93) and phase 3 (n=28).

Of the 446 patients in the ITT sample who initiated the open-label amisulpride treatment phase, 371 (83%) completed the 4-week treatment. Of the individuals who completed treatment, 250 (67%) patients met remission

	Phase 1 (n=446)	Phase 2 (n=93)	Phase 3 (n=28)
Age, years	26·0 (6·0)	25·2 (5·4)	26·3 (6·5)
Sex			
Women	134 (30%)	23 (25%)	7 (25%)
Men	312 (70%)	70 (75%)	21 (75%)
Race			
White	386 (87%)	86 (92%)	27 (96%)
Other	60 (13%)	7 (8%)	1 (4%)
Education, years*	12·3 (3·0)	11·9 (2·7)	11·4 (2·4)
Living status			
Independently	83 (19%)	20 (22%)	8 (29%)
Living with assistance	363 (81%)	73 (78%)	20 (71%)
Employment status			
Employed or student	185 (41%)	33 (35%)	10 (36%)
Unemployed	261 (59%)	60 (65%)	18 (64%)
Disease type			
Schizophreniform disorder†	190 (43%)	28 (30%)	8 (29%)
Schizoaffective disorder†	27 (6%)	2 (2%)	2 (7%)
Schizophrenia†	229 (51%)	63 (68%)	18 (64%)
Comorbid major depressive disorder†	34/429 (8%)	9/91 (10%)	3 (11%)
Suicidality†	55/429 (13%)	10/91 (11%)	17 (18%)
Substance abuse or dependence in the past 12 months†	75/429 (17%)	9/91 (10%)	1 (4%)
Type of care at baseline			
Inpatient	276 (62%)	53 (57%)	17 (61%)
Outpatient	170 (38%)	40 (43%)	18 (64%)
Duration of untreated psychosis, months	6·3 (6·2)	8·4 (7·3)	8·0 (6·5)
Antipsychotic naïve	187 (42%)	54 (58%)	13 (45%)
Clinical scores			
PANSS total score‡	78·2 (18·7)	85·7 (16·4)	89·0 (16·8)
PANSS Positive Subscale‡	20·2 (5·5)	21·7 (5·1)	21·5 (4·6)
PANSS Negative Subscale‡	19·4 (7·1)	22·4 (7·0)	23·3 (6·8)
PANSS General Subscale‡	38·6 (9·8)	41·6 (9·3)	44·1 (10·1)
CGI severity§	4·5 (0·9)	4·7 (0·8)	4·7 (0·9)
Depression score¶	13·5 (4·6)	14·2 (4·8)	14·6 (4·4)
BMI	23·4 (5·0)	23·9 (4·3)	25·0 (2·6)
Overweight (BMI ≥25)	119/436 (27%)	25/82 (30%)	11/20 (55%)
Abdominal circumference, cm	83·3 (12·4)	84·1 (10·5)	86·8 (8·5)

Data are mean (SD), n (%), or n/N (%). Baseline is visit 2, at which study medication is initiated. Denominators change because of incomplete data. PANSS=Positive and Negative Syndrome Scale. CGI=clinical global impression. BMI=body-mass index (measured as kg/m²). *Years in school from age 6 years onwards. †According to the Mini International Neuropsychiatric Interview 5 plus. Suicidality includes medium to high suicide risk. ‡Theoretical scores range from 30 to 210 (total scale), 7 to 49 (positive scale), 7 to 49 (negative scale), and 16 to 112 (general psychopathology scale). High scores indicate severe psychopathology. §Theoretical scores range from 1 to 7; high scores indicate increased severity of illness. ¶According to the Calgary Depression Scale for Schizophrenia. Theoretical scores range from 0 to 27; high scores indicate increased depression.

Table 1: **Characteristics of patient samples at the start of each treatment phase**

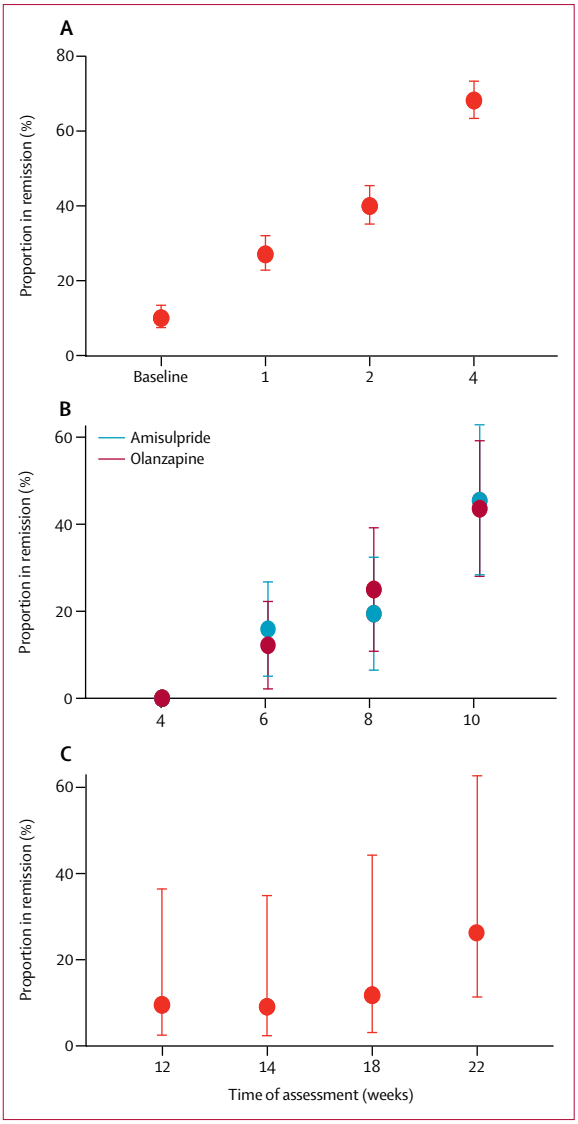

Figure 2: **Proportion of patients in remission during phases 1, 2, and 3**
Data are proportions, estimated by a logistic mixed model, with 95% CIs. This model provides symmetric error bars on the logistic scale, which turn asymmetric after back-transformation to the linear scale. The proportion of patients in remission during (A) phase 1 (4-week, open-label treatment with amisulpride), (B) phase 2 (6-week, double-blind treatment with amisulpride or olanzapine), and (C) phase 3 (12-week, open-label treatment with clozapine). The proportion of patients in remission increased over time during each individual phase, indistinctively for amisulpride and olanzapine in phase 2.

criteria at the end of phase 1. Within the whole ITT sample (n=446), 250 (56%) patients achieved remission, when patients without a known remission status at the end of phase 1 were categorised as individuals who were not in remission. The proportion of patients who achieved remission over the course of phase 1 is shown in figure 2A. Symptom scores and changes in weight are shown in table 2, alongside sexual dysfunction and extrapyramidal symptoms.

We found no significant differences in sex between those who were in remission and those who were not (70 [30%] men *vs* 29 [24%] women, p=0·20), but they did differ in age (26·3 years [SD 6·3] *vs* 24·5 years [5·4], p=0·0044); duration of the current psychotic episode (6·0 months [6·0] *vs* 7·7 months [7·0], p=0·025), and age at onset (25·9 years [6·3] *vs* 23·8 years [5·4], p=0·0009; data not shown).

The mean amisulpride dose at the end of phase 1 was 490·4 mg/day (SD 207·4); it was 463·8 mg/day (196·0) in the individuals who were in remission and 535·2 mg/day (209·2; p=0·001) in the individuals who were not in remission (table 3). Individuals who were in remission were more likely to have a diagnosis of schizophreniform disorder (44% *vs* 33% for individuals who were not in remission, p=0·044) and less likely to have a diagnosis of schizophrenia (52% *vs* 71% for individuals who were not in remission, p=0·0005). No differences in alcohol dependency or substance abuse were found (data not shown).

Of the 121 individuals who were not in remission at the end of phase 1, 93 (77%) continued to phase 2, at which time they were randomly assigned 1:1 to 6 weeks of continued treatment with amisulpride (n=47) or switched to 6 weeks of treatment with olanzapine (n=46). 28 individuals who were not in remission from phase 1 decided not to continue into phase 2 for various reasons (figure 1); this subgroup had a shorter duration of illness (5·6 months [SD 5·3]) than those who initiated phase 2 treatment (8·4 months [7·3], p=0·040), but we found no significant differences in sex, age, diagnosis, or alcohol or substance abuse. Baseline characteristics of the 93 patients for the two treatment groups are shown in table 4.

Of the 93 patients randomly assigned to treatment, 72 (77%) completed phase 2: 33 taking amisulpride versus 39 taking olanzapine. At the end of phase 2, 32 (44%) patients met remission criteria. Within the ITT sample, 32 (34%) of 93 patients achieved remission. The proportion of patients who achieved remission per treatment group over the phase 2 visits are depicted in figure 2B. We found no significant difference in the proportion of patients who achieved remission between the two treatment groups: 15 (45%) achieved remission in the amisulpride group versus 17 (44%) in the olanzapine group (p=0·87). Symptom scores and changes in weight are shown in table 2. The mean dose of amisulpride at the end of phase 2 was 590·9 mg/day (SD 236·1), with the mean dose for individuals who were in remission recorded as 586·7 mg/day (220·0) and that for individuals who were not in remission recorded as 600·0 mg/day (237·6; p=0·87). The mean dose of olanzapine at the end of phase 2 was 15·6 mg/day (6·5), with the mean dose for individuals who were in remission recorded as 14·4 mg/day (5·6), and for individuals who were not in remission recorded as 17·5 mg/day (6·3; p=0·12; table 3).

A logistic generalised linear model was used to analyse the remission data using all three repeated

	Phase 1	Phase 2		Phase 3
	Amisulpride (n=371)	Amisulpride (n=33)	Olanzapine (n=39)	Clozapine (n=18)
PANSS total score change from baseline*	−19·1 (17·9)	−10·1 (19·9)	−6·1 (13·9)	−18·4 (21·7)
PANSS Positive Subscale change from baseline*	−7·1 (5·7)	−2·8 (6·0)	−1·1 (4·2)	−5·5 (5·8)
PANSS Negative Subscale change from baseline*	−3·2 (5·6)	−3·7 (6·8	−1·8 (5·1)	−4·5 (5·1)
PANSS General Subscale change from baseline*	−8·8 (9·6)	−3·7 (10·3)	−3·3 (8·1)	−8·4 (12·2)
CGI severity change from baseline†	−1·1 (1·1)	−0·33 (1·1)	−0·26 (0·9)	NA
Sexual side-effects ‡				
Men	107 (29%)	2 (6%)	8 (21%)	6 (33%)
Women	61 (16%)	5 (15%)	6 (15%)	3 (17%)
Extrapyramidal symptoms‡				
Dystonia	58 (16%)	1 (3%)	4 (10%)	3 (17%)
Rigidity	83 (22%)	3 (9%)	9 (23%)	4 (22%)
Tremor	92 (25%)	3 (9%)	10 (26%)	3 (17%)
Akathisia	105 (28%)	1 (3%)	5 (13%)	0
Weight change from baseline, kg	2·5 (4·0)	2·7 (2·9)	4·2 (3·6)	4·8 (5·5)
Weight gain (≥7% from baseline)	70 (19%)	5 (15%)	10 (26%)	8 (44%)
Abdominal circumference change from baseline, cm	2·1 (4·7)	1·4 (2·7)	4·2 (5·0)	3·5 (5·9)

Data are n (%) or mean (SD). Baseline for phase 1 is visit 2, at which study medication is initiated. Baselines for phases 2 and 3 are the first visits of these phases (ie, visit 5 for phase 2 and visit 8 for phase 3). Denominators change because of incomplete data. PANSS=Positive and Negative Syndrome Scale. CGI=Clinical Global Impression. NA=not assessed. *Theoretical scores range from 30 to 210 (total scale), 7 to 49 (positive scale), 7 to 49 (negative scale), and 16 to 112 (general psychopathology scale). High scores indicate severe psychopathology. †Theoretical scores range from 1 to 7; higher scores indicate greater severity of illness. ‡Any symptoms scored on the Udvalg for Kliniske Undersøgelser questionnaire during the respective phase (ie, men: increased or decreased libido, orgastic dysfunction, gynaecomastia, or erectile or ejaculatory dysfunction [six items]; women: increased or decreased libido, orgastic dysfunction, menorrhagia, amenorrhoea, galactorrhoea, or dry vagina [seven items]). An extensive list of adverse events is reported in the appendix.

Table 2: **Symptom severity and side-effects per treatment phase**

PANSS assessments, adjusting for the PANSS score at the start of phase 2 (week 4; phase 2 baseline). The odds ratio for meeting remission criteria at the end of phase 2 for amisulpride relative to olanzapine was 1·07 (95% CI 0·38 to 2·96). Using a linear mixed model, PANSS scores at the end of phase 2 were compared between treatment groups, again adjusting for the PANSS score at the start of phase 2 (phase 2 baseline). The reduction in PANSS score was not significantly different between treatments; the phase 2 baseline-corrected difference for amisulpride relative to olanzapine was −3·24 (95% CI −10·07 to 3·60, p=0·35).

The number of dropouts did not differ significantly between the two treatment groups. 14 (30%) patients randomly assigned to amisulpride dropped out versus seven (15%) randomly assigned to olanzapine (95% CI −2·5 to 30·7, p=0·093). Patients treated with olanzapine gained significantly more weight than patients treated with amisulpride: 4·40 kg (SD 3·65) versus 2·29 kg (3·07; p=0·021). The two treatment groups did not otherwise differ in the number of side-effects, corrected for phase 2 baseline assessments.

Of the 40 phase 2 individuals who were not in remission, 12 (30%) patients decided not to continue to the 12-week open-label phase 3 (figure 1). A further ten patients dropped out during phase 3 (36% dropout), leaving 18 patients who completed the clozapine treatment. Of the patients who completed treatment, five (28%) met remission criteria (figure 2C). Within the ITT sample, which classified dropouts as not meeting remission criteria, five (18%) of 28 patients achieved remission.

	Phase 1	Phase 2		Phase 3
	Amisulpride, mg/day	Amisulpride, mg/day (n=44)	Olanzapine, mg/day (n=43)	Clozapine, mg/day
Intention-to-treat sample	490·4 (207·4)	590·9 (236·1)	15·6 (6·5)	279·0 (130·2)
Completers only	488·0 (203·4)	593·9 (226·3)	16·2 (6·1)	307·0 (137·1)
Dropouts only	511·4 (240·4)	581·8 (275·0)	10·0 (8·2)	207·1 (78·7)

Data are mean (SD). Mean dose is based on the dose of each individual patient at the last visit of the applicable phase (eg, for phase 1 completers, the dose at visit 5 [end of phase 1] is used; for a phase 2 dropout, the dose at the last visit before dropping out is used).

Table 3: **Mean doses of study medication used during the three phases of the trial**

Despite the low proportion of patients who achieved remission, patients showed symptom improvement during clozapine treatment, as shown in figure 3. The individuals who completed phase 3 improved by 24·9 points on the PANSS score relative to study baseline (visit 2, p<0·0001) and 18·4 points relative to the phase 3 baseline (at week 10, p=0·0023). The mean dose of clozapine at the end of phase 3 was 279·0 mg/day (SD 130·2); for individuals who were in remission the mean dose was 280·0 mg/day (115·1), and for individuals

	Amisulpride (n=47)	Olanzapine (n=46)
Age, years	24·9 (5·4)	24·6 (5·5)
Women	11 (23%)	12 (26%)
White	43 (91%)	43 (93%)
Education, years*	12·4 (2·9)	11·4 (2·3)
Living independently	11 (23%)	9 (20%)
Employed or student	17 (36%)	16 (35%)
Schizophreniform disorder†	15 (32%)	14 (30%)
Schizoaffective disorder†	1 (2%)	2 (4%)
Schizophrenia†	35 (74%)	30 (65%)
Comorbid Major Depressive Disorder†	5 (11%)	4 (9%)
Suicidality‡	6 (13%)	8 (17%)
Substance abuse or dependence, or both, in the past 12 months†	1 (2%)	2 (4%)
Inpatient status	27 (57%)	26 (57%)
Duration of untreated psychosis, months	9·5 (7·8)	7·2 (6·6)
PANSS total score§	79·1 (16·2)	75·2 (16·2)
PANSS Positive Subscale§	18·2 (5·1)	17·0 (5·1)
PANSS Negative Subscale§	22·5 (6·8)	20·9 (6·5)
PANSS General Subscale§	38·4 (9·1)	37·2 (9·4)

Data are n (%) or mean (SD). Baseline is visit 2, at which study medication is initiated, except for the PANSS scores. PANSS=Positive and Negative Syndrome Scale. *Years in school from 6 years of age onwards. †According to the Mini International Neuropsychiatric Interview 5 plus. ‡Suicidality includes medium to high suicide risk. §Theoretical scores range from 30 to 210 (total scale), 7 to 49 (positive scale), 7 to 49 (negative scale), and 16 to 112 (general psychopathology scale). High scores indicate severe psychopathology.

Table 4: **Baseline characteristics of patients included in phase 2, according to randomised treatment group**

who were not in remission the mean dose was 317·3 mg/day (146·7, p=0·62). Clozapine blood concentration was assessed at the end of phase 3. Individuals who were in remission (n=5) had a mean clozapine blood concentration of 321 ng/mL (SD 226), and individuals who were not in remission (n=13) had a mean clozapine concentration of 350 ng/mL (SD 391).

Of the 446 patients who initiated the first treatment phase, 287 (64%) patients met remission criteria at one of the three treatment phases, after a maximum of 20 treatment weeks. The cumulative remission based on the individuals who completed the three phases was 76%. A decline in the mean total PANSS scores over the course of each individual treatment phase is shown in figure 3. The Kaplan-Meier curve for dropout over time is shown in the appendix. After 22 weeks of follow-up, the proportion still under study (censoring for remission) was 65%. The mean doses of amisulpride, olanzapine, and clozapine in the three treatment phases are given in table 4; for dropouts, the dose at the last visit has been used. The use of concomitant medication in each phase is shown in the appendix.

An extensive report of all side-effects is provided in the appendix. The number of serious adverse events did not differ between the treatment groups in phase 2: one patient randomly assigned to olanzapine was admitted to hospital because of an epileptic seizure, and one patient randomly assigned to amisulpride was admitted to hospital twice during phase 2 because of exacerbations of psychotic symptoms. Over the course of the trial, two serious suicide attempts were reported in phase 1. One resulted in the only death during the trial, 7 days after discontinuing amisulpride. The other attempt was during amisulpride treatment.

For patients who did not meet remission criteria after completion of phase 3, a follow-up visit was scheduled 48 weeks post baseline (26 weeks after the final phase 3 visit). Of the 11 individuals who were not in remission at the end of phase 3, eight patients returned for this visit. The mean total PANSS score was 70·5 (SD 22·3, range 40–104). Three patients met remission criteria during this visit. None of the patients were readmitted to hospital after the end of phase 3.

For all patients who entered phase 1, a follow-up visit was scheduled 74 weeks post baseline. This visit was conducted for 167 patients. At this visit, 13 (8%) patients were diagnosed with schizophreniform disorder, 22 (13%) with schizoaffective disorder, 123 (74%) with schizophrenia, and nine (5%) received other diagnoses (eg, psychosis not otherwise specified, bipolar disorder, or unspecified non-organic psychosis). PANSS data were available for 140 patients; the mean total PANSS score was 50·2 (SD 15·0, range 30–105). 95 patients (57%) met remission criteria. 17 (10%) of 140 patients were admitted to hospital at least once after the most recent study visit.

Discussion

Switching from amisulpride to olanzapine in first-episode schizophrenia did not improve clinical outcome. Of the 93 patients who were randomly assigned to phase 2 treatment, an almost equal proportion (45%) achieved remission whether they continued treatment with amisulpride or switched to olanzapine. Moreover, the clinical outcome in the two groups was also similar when this was defined in terms of symptomatic improvement (as a continuous variable). These data suggest that if a patient does not achieve remission on their first antipsychotic drug, switching to a different drug is no more effective than remaining on the same medication and waiting to see if remission is achieved at a later stage.

To our knowledge, this is the first study to examine the effects of switching antipsychotics in patients with (first-episode) schizophrenia who do not respond to their initial antipsychotic treatment (response has been defined differently in the various studies; we used remission in the current study). With the exception of one study,[19] all previous studies were conducted in the later, chronic stage of the illness. Moreover, the single study that did address first-episode schizophrenia did not assess whether switching was more effective than staying on the original treatment (for review see Leucht and colleagues[18]). Agid and colleagues[19] compared risperidone

and olanzapine in 287 patients with first-episode schizophrenia in a non-randomised, open design. Response was defined as much improved or better on the CGI. Patients who did not meet response criteria after 4 weeks were switched to the other antipsychotic; thus switching versus staying on the first medication was not examined. Clozapine was given when no response to both antipsychotics was reported. In that study,[19] 75% of patients met response criteria after 4 weeks, with more responding to olanzapine (115 [82%] of 140 patients) than to risperidone (69 [66%] of 104 patients). In the second phase of the study, responses dropped to 17%, with olanzapine again doing better than risperidone. Important differences to the present study were that the first antipsychotic was selected by the treating clinician, the definition of response was less stringent, and switching was open. Whether data were analysed on the basis of only the individuals who completed the phase, or whether an ITT analysis was done, is also unclear.

The only double-blind study[20] that compared switching versus continuation in individuals who had no response was done in patients with chronic schizophrenia (aged around 42 years). Response in the first 2 weeks was defined as a reduction in total PANSS scores of at least 20%. This corresponds to a lesser degree of clinical improvement than the symptomatic remission criterion used in the present study. Patients who did not respond to a 2-week open trial with risperidone (2–6 mg/day) were randomly assigned to either continuing on risperidone or switching to olanzapine (10–20 mg/day). Switching resulted in a small but significantly greater reduction in total PANSS scores after 4 weeks (p=0·020).

In the current study, after 10 weeks of treatment, most of the patients were either in symptomatic remission or had dropped out, leaving only 28 (6%) of the initial 446 patients eligible for switching to clozapine. Although only five patients treated with clozapine reached remission, a substantial symptomatic improvement was reported in the sample overall, with an average reduction in total PANSS scores of more than 18 points. These results suggest that providing clozapine early in the treatment of patients with first-episode schizophrenia might result in clinical improvement, even if this is short of full symptomatic remission. Moreover, because we followed up patients on clozapine for only 12 weeks, and the full treatment response might take several months, remission might have improved further had we followed up the patients for longer.[21]

Symptomatic remission was high: after only 4 weeks of open treatment with amisulpride, 56% of all 446 patients had reached remission, even when assuming that all dropouts were not in remission. The proportion of patients who achieved remission increased to 67% when the analysis was restricted to patients who completed the initial 4-week treatment period. This proportion is impressive for two reasons: it corresponds to clinical remission and not just a numerical reduction of symptoms on a rating scale; and remission was achieved after only 4 weeks of treatment. Our results therefore suggest that most patients show a clinically meaningful improvement after only a few weeks of treatment, which is corroborated by the reduction in the CGI scale. An additional 6 weeks of treatment led to a further 45% of patients (in both groups) achieving remission; however, because this was on the basis of a smaller sample (because of the high initial number of remissions and dropouts between phases), the total remission in individuals who completed was calculated from baseline at the end of phase 2 and was 65%. Additional treatment with clozapine increased the cumulative remission to 76%, again assuming all dropouts did not achieve remission. This indicates that for most patients with first episode of schizophrenia, a rapid and almost complete symptomatic recovery can be expected with antipsychotic treatment. This high and rapid symptomatic response is consistent with results reported in other studies in first-episode schizophrenia.[22,23] Nevertheless, some patients with first-episode schizophrenia will respond only after continuous treatment lasting up to 8 weeks.[24] Finally, we restricted our sample to patients with a duration of illness less than 2 years, reflecting the early stage of schizophrenia in Europe. Whether our data can be extrapolated to patients who have gone untreated for much longer before their first antipsychotic exposure, as often is the case in other areas of the world, remains open for debate.

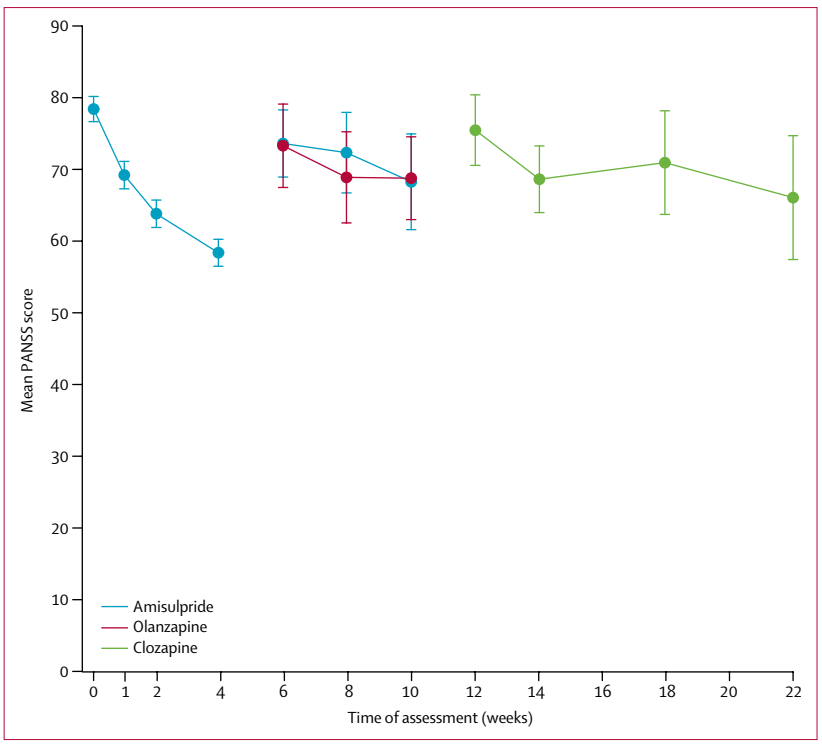

Figure 3: **Positive and Negative Syndrome Scale (PANSS) scores per visit for phases 1, 2, and 3**
Data are presented as mean and 95% CIs. Mean PANSS scores decrease during each individual treatment phase.

The doses of antipsychotics used are consistent with those generally administered in first-episode schizophrenia; the mean dose of amisulpride given was 591 mg/day, olanzapine 15·6 mg/day, and clozapine 279 mg/day (with blood levels a little under 350 ng/L). Crucially, the doses in those who were in remission and those who were not were similar, with doses in those individuals who were not in remission numerically higher in all phases for all drugs, suggesting that non-remission was not attributable to underdosing. Similarly, although the clozapine dose given was low (280–300 mg/day), blood concentrations in the individuals who were not in remission were adequate (>350 ng/L), so the low remission is unlikely to be related to inadequate dosing. Moreover, the clozapine dose was similar to that given in the first-episode study by Lieberman and colleagues,[21] in which 80% of patients on clozapine reached remission.

Side-effects were as expected: amisulpride was associated with extrapyramidal side-effects and those related to increased prolactin levels; and olanzapine and clozapine induced substantial weight gain, even over the relatively short 6-week and 12-week periods of treatment, respectively. In phase 2, side-effects were more prominent in the patients on olanzapine than patients on amisulpride: this result might have been because those intolerant to amisulpride had dropped out in the earlier phase or had developed tolerance. All drugs were associated with a substantial gain in weight over the course of treatment, although it was most pronounced in patients who were treated with olanzapine and clozapine.

The results should be viewed in the context of the study's limitations. The sample in the second, randomised phase was relatively modest, comprising 93 patients—below that in our projected power sample size calculation. This was more the result of the proportion of remissions compared with dropouts in phase 1, which was less than 17%. However, the proportions of remissions in the amisulpride and olanzapine groups were similar, suggesting a larger sample size might not have changed the results. Additionally, both the initial treatment with amisulpride and the subsequent one with clozapine were open label. This might have increased the proportion of remissions in both phases. We thought the initial treatment should be pragmatic, reflecting clinical reality as much as possible; whereas the comparison between two drugs in phase 2 needed to be as unbiased as possible, and therefore double blind. A comparison between continuation with amisulpride and switching to clozapine in phase 3 could be argued to be of interest; however, the current design could not address that question. Whether clozapine has an added benefit over continuation with amisulpride after 10 weeks of its use needs further study. Although a 4-week trial could be argued to be too short to decide whether or not to switch treatments, a 2015 meta-analysis suggests this period is sufficient.[25] Finally, although our results show that most patients with first-episode schizophrenia reach remission within a few months of treatment, those who do not stay in remission remain a major challenge in the treatment of schizophrenia.[26]

Current guidelines recommend that clozapine should be offered to patients who have not responded to treatment with two different antipsychotics. However, if the likelihood of non-response to one antipsychotic given for a sufficient length of time is similar to that with two courses of different antipsychotics, it might be feasible to define non-response (operationalised as failure to achieve symptomatic remission) on the basis of a single course of antipsychotic treatment, as long as it is given for long enough. Adopting a simpler treatment algorithm with one course of antipsychotic treatment would allow these patients to be identified earlier and reduce the delay before they can be treated with clozapine.

In summary, our results suggest that switching antipsychotics in minimally treated patients with first-episode schizophrenia does not improve outcome in those who are not in symptomatic remission after their first antipsychotic regimen. Although switching to clozapine early in the treatment did not markedly improve the proportion of patients who achieved remission, it did result in a substantial improvement in symptoms, albeit that many first-episode patients did not tolerate the side-effects associated with its treatment.

Through the use of an algorithm of treatment with a single antipsychotic for up to 10 weeks and subsequent use of clozapine in individuals who were not in remission, remission can be achieved within 22 weeks for more than three-quarters of first-episode patients who complete treatment and for almost two-thirds of patients who initiate treatment. Although these results need to be replicated and broadened (by use of different antipsychotics), they suggest that achievement of remission in the early stages of schizophrenia is possible in most patients using a simple treatment algorithm of sequential use of amisulpride and clozapine.

Contributors

RSK, SK, IES, IWvR, SL, SH, and WWF designed the study. RSK and SK obtained funding. RSK supervised the study. MJCE, RSK, and IWR analysed and interpreted the data. RSK, IWvR, and MJCE drafted the report. RSK, IWvR, SL, PM, SWL, ML, CA, PD, RD, CMD-C, SH, DR, MW, SG, BG, WWF, and IES participated in the collection of data. All authors participated in the critical revision of the Article and approved the final Article.

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RSK declares personal fees for consultancy from Alkermes, Minerva Neuroscience, Gedeon Richter, and Otsuka; and personal (speaker) fees from Otsuka/Lundbeck. SL declares fees for consulting from LB Pharma, Lundbeck, Otsuka, Teva, and Gedeon Richter; and fees for lectures from Janssen, Eli Lilly, Lundbeck, Otsuka, Sanofi, and Servier. SWL declares personal fees from Otsuka. CA declares grants, personal fees, and other fees from Janssen-Cilag, Lundbeck, Otsuka, Acadia, Abbott, Amgen, AstraZeneca, Bristol-Myers Squibb, Caja Navarra, Cibersam, Fundación Alicia Koplowitz, Forum, Instituto de Salud Carlos III, Gedeon Richter, Merck, Ministerio de Ciencia e Innovación, Ministerio de Sanidad, Ministerio de Economía y Competitividad, Mutua Madrileña, Pfizer, Roche, Servier, Shire, Schering Plough, Sumitomo

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