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Ziprasidone vs clozapine in schizophrenia patients refractory to multiple antipsychotic treatments: The MOZART study ☆

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ABSTRACT

This 18-week, randomized, flexible-dose, double-blind, double-dummy trial evaluated ziprasidone as an alternative to clozapine in treatment-refractory schizophrenia patients. Patients had a DSM-IV diagnosis of schizophrenia, a history of resistance and/or intolerance to at least three acute cycles with different antipsychotics given at therapeutic doses, PANSS score ≥80, and CGI-S score ≥4. Patients were randomized to ziprasidone (80–160 mg/day, $n=73$) or clozapine (250–600 mg/day, $n=74$). On the primary ITT-LOCF analysis, baseline-to-endpoint decreases in PANSS total scores were similar in the ziprasidone (-25.0 ± 22.0, 95% CI -30.2 to -19.8) and clozapine (-24.5 ± 22.5, 95% CI -29.7 to -19.2) groups. A progressive and significant reduction from baseline in PANSS total score was observed from day 11 in both study arms. There were also significant improvements on PANSS subscales, CGI-S, CG-I, CDSS, and GAF, without between-drug differences. The two treatment groups had similar rates of early discontinuations due to AEs. AEs were mostly of similar mild-moderate severity in the two groups. There were also no detrimental effects on prolactin, renal and liver function, hematology, and cardiovascular parameters. However, ziprasidone but not clozapine showed a significant reduction of SAS and AIMS scores. Moreover, when compared with clozapine, ziprasidone also had a more favorable metabolic profile, with significant endpoint differences in weight, fasting glucose, total cholesterol, LDL cholesterol, and triglycerides. In conclusion, this trial indicates that both ziprasidone and clozapine, having comparable efficacy coupled with satisfactory general safety and tolerability, may be regarded as valuable options for the short-term treatment of difficult-to-treat schizophrenia patients with a history of multiple resistance and/or intolerance to antipsychotics. The more favorable metabolic profile of ziprasidone may represent an added value that could guide clinicians, at least in the presence of patients at high risk for metabolic disorders.

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1. Introduction

Approximately 20% to 35% of patients with schizophrenia who receive an adequate trial fail to respond to prescribed antipsychotics (Conley and Kelly, 2001; Elkis, 2007; Essock et al., 1996; Lerner et al., 2004). Others cannot tolerate treatment at therapeutic dosages (Conley and Kelly, 2001). Continued psychosis, the common result of these two clinically different processes (Elkis, 2007; Sacchetti et al., 2004; Taylor and Duncan-McConnell, 2000), causes persistent disability (Lindenmayer, 2000) and imposes a substantial socio-economic burden (McEvoy, 2007; Revicki, 2000).

Clozapine is the gold standard therapy for treatment-refractory schizophrenia (Chakos et al., 2001; Elkis, 2007; Moncrieff, 2003; Taylor and Duncan-McConnell, 2000). In the past decade, several double-blind comparisons have reported the acute (4–18 week) efficacy of clozapine to be comparable (Bitter et al., 2004; Bondolfi et al., 1998; Breier et al., 1999; Conley et al., 2003; Meyer-Lindenberg et al., 1997; Tollefson et al., 2001; Volavka et al., 2002) or greater (Azorin et al., 2001) than other second-generation antipsychotics. The recent Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Phase 2 study (McEvoy et al., 2006) found clozapine more effective than switching to a different second-generation antipsychotic in patients with schizophrenia who failed to improve after initial treatment with an atypical antipsychotic.

Although ziprasidone proved effective and well-tolerated in controlled trials in schizophrenia (Kane, 2003; Simpson et al., 2004; Simpson et al., 2005), little data exists in treatment-resistant or treatment-intolerant patients. In one small open-label study of patients with inadequate response to at least 6-months of clozapine, additional ziprasidone was effective in most patients (Ziegenbein et al., 2005). In another comparative trial in treatment-resistant patients, ziprasidone showed comparable efficacy to chlorpromazine on positive symptoms, but greater efficacy against negative symptoms (Kane et al., 2006). Moreover, ziprasidone was better with respect to prolactin levels and weight gain. In an open-label, single-arm extension study (Loebel et al., 2007) limited to those treatment-resistant patients who responded to ziprasidone or chlorpromazine during the initial double-blind study, the novel antipsychotic proved to be both effective in maintaining symptom control and well-tolerated over 1 year.

The current double-blind, flexible-dose study compared efficacy and safety of ziprasidone and clozapine in severely ill patients with schizophrenia and a history of resistance and/or intolerance to multiple cycles with antipsychotic medications. A recent paper has separately reported cognitive effects of clozapine and ziprasidone from this study (Harvey et al., 2008).

2. Methods

2.1. Study design

The MOZART (Monitoring Oral Ziprasidone As Rescue Therapy) trial involved antipsychotic-resistant and/or intolerant patients with schizophrenia at 23 Italian departments of mental health. The study comprised three periods: a 1- to 7-day screening period, including wash-out from previous antipsychotic drugs; a randomized, 18-week (±3 days), double-blind, double-dummy, treatment period (reported here and in Harvey et al., 2008); and an open-label, 1-year extension period for patients who responded to ziprasidone (reported separately). Ethical review boards responsible for study sites approved the protocol and all participants gave written, informed consent before entering the study.

Decisions about eligibility for the study, clinical assessments, and completion of case report forms were carried out by investigators who had previous experience of protocol procedures, were specifically trained at investigator meetings, and demonstrated valid inter-rater reliability in the Diagnostic and Statistical Manual of Mental Disorders, Fourth edition (DSM-IV) diagnosis of schizophrenia (American Psychiatric Association, 1994) and use of the selected battery of rating scales.

2.2. Inclusion and exclusion criteria

The trial enrolled men and women aged ≥18 who had sufficient understanding and willingness to participate in all study procedures.

2.2.1. Inclusion criteria

Patients were required to have a DSM-IV diagnosis of schizophrenia (295×), and to be resistant and/or intolerant to at least three acute cycles with different antipsychotic treatments in the previous 5 years. Treatment resistance and/or intolerance were defined retrospectively by the investigator, utilizing a detailed clinical interview for the current episode and all the medical records concerning previous episodes. Operationally, resistance to an antipsychotic was defined as a failure to experience an acceptable clinical improvement after completion of a 6-week trial at doses within the therapeutic range proposed by the manufacturer. In turn, intolerance was defined as the inability to achieve and/or maintain a therapeutic dosage of an antipsychotic treatment for at least 6 weeks due to emergence of severe, untreatable side effects.

At baseline, patients were also required to have scores ≥4 on the Clinical Global Impression Severity (CGI-S) scale (Guy 1976) and ≥80 on the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987, 1988).

2.2.2. Exclusion criteria

Key exclusion criteria included: current DSM-IV Axis I comorbid disorders; concomitant acute or unstable physical illnesses; clinically significant abnormal laboratory test values; (abnormal decrease of lymphocytes [<0.8 × lower normal limit], abnormal increase of basophils [>1.2 × upper normal limit], abnormal increase of eosinophils [>1.2 × upper normal limit], abnormal increase of monocytes [>1.2 × upper normal limit], abnormal decrease of high-density lipoprotein cholesterol [HDL-C; <0.8 × lower normal limit], abnormal increase of low-density lipoprotein cholesterol [LDL-C; >1.2 × upper normal limit], abnormal increase of triglycerides [>1.3 × upper normal limit], abnormal increase of prolactin [>1.1 × upper normal limit]); a QTc interval (Bazett correction) >500 ms; a positive urine screen for substances of abuse; any contraindication to ziprasidone or clozapine; and treatment with the investigational drugs during the previous 3 months. Female patients of childbearing potential not using contraception were

also excluded. Patients whose first-generation depot antipsychotic medication had been discontinued were eligible only if they had received their last depot injection at least 2 weeks or one treatment cycle prior to the screening visit.

2.3. Treatment

Patients first completed a 1- to 7-day screening period where excluded concomitant psychotropic medications and oral antipsychotics were discontinued. Prior to receiving study medication, patients were treated with a 3-day placebo run-in period (Harvey et al., 2008), with a possible restriction to 12 h when symptoms of psychosis worsened.

Eligible patients were randomized (1:1 ratio) on a centralized basis to receive 18 weeks of either ziprasidone or clozapine. Ziprasidone was initiated at 80 mg/day (dosed b.i.d.) for the first 3 days and flexibly dosed (80–160 mg/day) thereafter. Clozapine was initiated at 25 mg/day, titrated to 300 mg/day over 10 days and maintained at this dose for 1 week; thereafter, patients were flexibly dosed (250–600 mg/day). When flexible doses were allowed, investigators were free to change the dosage weekly by one or two levels (one level of ziprasidone = 20 mg; one level of clozapine = 50 mg), based on their clinical judgment.

The only concomitant psychotropic medications permitted were benzodiazepines and anticholinergic agents for control of extrapyramidal symptoms (EPS) and propranolol for the management of akathisia.

2.4. Efficacy evaluations

Efficacy was evaluated using the following: PANSS (total, positive, negative, and general psychopathology subscales) and CGI-S completed at baseline, and weekly thereafter; Clinical Global Impression Improvement (CGI-I) scale (Guy, 1976) administered at each post-baseline study visit; Calgary Depression Scale for Schizophrenia (CDSS), (Addington et al., 1990, 1992), and Global Assessment of Functioning (GAF) scale (American Psychiatric Association, 1994), and Drug Attitude Inventory-10 (DAI-10) scale (Awad and Hogan, 1994) completed at baseline, months 2 and 3, and study endpoint.

2.5. Safety evaluations

The severity, duration, and possible relation to study drug of all observed or volunteered adverse events (AEs) were recorded.

Movement disorders were evaluated with the Simpson–Angus Scale (SAS) (Simpson and Angus, 1970), the Barnes Akathisia Scale (BAS) (Barnes, 1989), and Abnormal Involuntary Movement Scale (AIMS) (Guy, 1976). SAS and BAS were measured at baseline, week 1, months 2 and 3, and study endpoint. AIMS was evaluated at baseline and endpoint.

Laboratory tests were performed at screening and at the end of the study. Hematologic monitoring consistent with clozapine requirements was performed on all patients.

Vital signs were obtained at the screening, baseline, and at each study visit. All patients underwent electrocardiographic (ECG) evaluations at screening, visit 1, at months 2 and 3, and at the end of the study.

2.6. Statistical methods

The endpoint change from baseline in PANSS total score was the primary efficacy measure and was used for the determination of the sample size. Secondary efficacy measures were the endpoint change from baseline in PANSS positive, negative and general psychopathology subscales, CGI-S, CGI-I, CDSS, GAF, and DAI-10 as well as response rates based on $\geq$20%, $\geq$30% and $\geq$40% improvements in PANSS total scores. Total PANSS change from baseline at any scheduled visit was used as a secondary efficacy measure.

The study was designed as an "equivalence" trial of ziprasidone and clozapine. The margin of clinical equivalence (Δ) was set, a priori, at 13.5 points on the PANSS total score, the largest difference that would yield an effect size (0.45, with an SD = 30) considered clinically acceptable. On this basis, and at an α level of 5% and an 80% power, enrollment of 65 subjects in each group was considered sufficient.

Four populations were considered in the statistical analysis: (a) intent-to-treat (ITT) population, defined as all randomized patients who took at least one dose of medication and had a baseline and at least one valid post-baseline PANSS measurement; (b) per-protocol population (PP), which comprised all ITT patients who had at least an 80% compliance with the study drug and who did not take excluded concomitant medications; (c) completer population, comprising all ITT patients who completed the study; and (d) safety population, comprising all patients who received at least one dose of the study medication.

A blind review document summarizing major and minor protocol violations was produced and discussed with the clinical team before breaking the blind.

For primary and secondary efficacy variables, an analysis of covariance (ANCOVA) model was used, with treatment, center, and baseline score as covariates.

The 95% confidence interval (CI), based on the difference in least square (LS) means, was used to demonstrate equivalence.

PANSS total score changes from baseline were evaluated in ITT and PP populations with both last observation carried forward (LOCF) and observed cases (OC) analyses. The proportion of responders (i.e., patients with a $\geq$20%, 30%, or 40% improvement in PANSS total score from baseline) was analyzed using the Cochran–Mantel–Haenszel method. The time course of improvement on the PANSS total score was assessed with a mixed-model, repeated-measures post hoc analysis of variance, with terms for treatment, site, visit, and visit $\times$ treatment interaction. An unstructured covariance matrix was fitted to the within-patient repeated measures.

Safety data were reported with descriptive statistics or frequency tables, as appropriate. Changes from baseline of SAS, BAS, and AIMS scores, QTc interval, weight, and laboratory parameters in the two treatment arms were analyzed using analysis of variance (ANOVA) or ANCOVA models with, when required, the rank transformed change from baseline to endpoint.

3. Results

3.1. Patient characteristics and disposition

Of 162 patients screened, 147 were randomized and 146 (73 in each group) received at least one dose of study drug

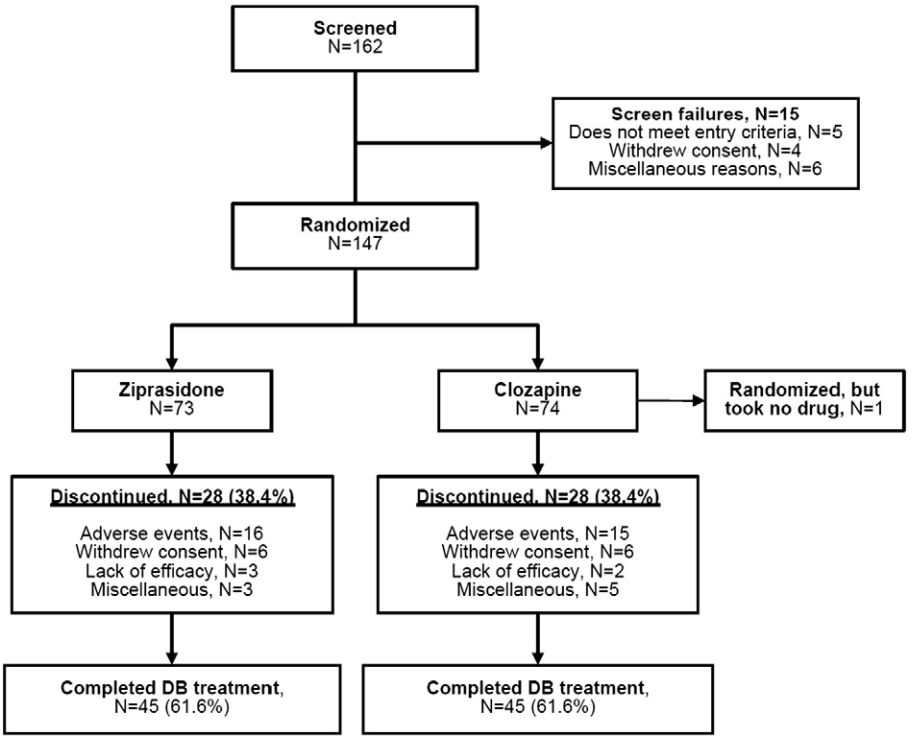

Fig. 1. Patient disposition.

(Fig. 1). There were no significant differences between groups in baseline key demographic, psychopathological, and clinical characteristics. Also the rates of patients satisfying the criteria for treatment resistance, intolerance, or both in at least three cycles with different antipsychotics were similar in the two treatment arms (Table 1).

Early discontinuation (Fig. 1) occurred in 28 patients (38.4%) in each group, mainly due to AEs (16 ziprasidone and 15 clozapine patients, respectively).

Table 1
Demographic and clinical characteristics of patient sample at baseline.

	Ziprasidone ($n=73$)	Clozapine ($n=73$)
Male, *n* (%)	52 (71.2)	49 (67.1)
Age, years, mean ± SD	41.6 ± 10.2	38.3 ± 11.2
Weight, kg, mean ± SD (range)	81.7 ± 17.1 (54–136)	83.0 ± 18.1 (45–130)
Duration of illness, years, mean (range)	13.4 (0–38.1)	14.1 (0–47.3)
Historical causes of refractoriness in different treatment cycles		
Resistance only	28 (38.4)	30 (41.1)
Intolerance only	15 (20.5)	8 (11.0)
Both resistance and intolerance	30 (41.1)	35 (47.9)
Clinical measures, mean ± SD		
PANSS score		
Total	108.5 ± 18.2	106.6 ± 17.0
Negative subscale	29.1 ± 7.5	27.2 ± 7.1
Positive subscale	23.6 ± 6.5	24.0 ± 6.4
General psychopathology subscale	55.7 ± 11.4	55.3 ± 10.4
CGI-S score	5.2 ± 0.7	5.2 ± 0.7
CDSS score	8.3 ± 5.4	7.8 ± 5.7
GAF score	40.6 ± 15.0	41.8 ± 13.0
DAI-10 score	2.9 ± 4.5	1.3 ± 5.1

3.2. Dosing

Mean (±SD) daily doses in the ITT population were 130 ± 24 mg for ziprasidone and 346 ± 61 mg for clozapine. Among completers, the mean daily doses at study endpoint were 137 ± 26 mg for ziprasidone and 365 ± 83 mg for clozapine. Median duration of treatment was 129 days for both treatment arms.

3.3. Efficacy

Table 2 shows data from both the ITT-LOCF and OC populations. Statistical comparisons between ziprasidone and clozapine groups were only conducted for the LOCF cohort. OC data showed similar trends.

3.3.1. Panss

Endpoint PANSS total score changes from baseline (ITT-LOCF) were similar (Table 2) in the ziprasidone (−25.0 ± 22.0, 95% CI −30.2 to −19.8) and clozapine (−24.5 ± 22.5, 95% CI −29.7 to −19.2) groups. A progressive decrease from baseline (Fig. 2) was observed from visit 1 (day 11) onward in both the treatment arms ($p<0.001$, except $p=0.003$ in the clozapine group at day 11). No significant between-group difference was observed at endpoint. The baseline to endpoint effect size was 1.41 for ziprasidone and 1.38 for clozapine. The ziprasidone–clozapine difference in adjusted means was equal to 0.59, with the 95% bilateral CI ranging between −6.42 and 7.59. Similar results were obtained in the PP-LOCF sample.

The rates of patients with a baseline-to-endpoint reduction in PANSS total score ≥20%, 30%, or 40% were similar in the two treatment arms when the ITT sample was considered (Table 2). Also the proportion of responders in the completer population

Table 2
Primary and secondary efficacy outcomes: baseline-to-endpoint change for ziprasidone and clozapine based on ITT population (LOCF and OC analyses).

	Ziprasidone ($n=71$)	Clozapine ($n=73$)
PANSS total score		
Baseline mean (±SD)	108.5±18.2	106.6±17.0
Mean (±SD) change (LOCF)	−25.0±22.0*, [a]	−36.2±16.7*
Mean (±SD) change (OC)	−36.0±16.7*	−34.3±19.7*
PANSS positive subscale score		
Baseline mean (±SD)	23.6±6.5	24.0±6.4
Mean (±SD) change (LOCF)	−6.0±7.8*, [a]	−7.0±7.2*, [a]
Mean (±SD) change (OC)	−10.0±6.1*	−9.7±6.1*
PANSS negative subscale score		
Baseline mean (±SD)	29.1±7.5	27.2±7.1
Mean (±SD) change (LOCF)	−7.6±6.7*, [a]	−6.1±6.5*, [a]
Mean (±SD) change (OC)	−10.5±6.2*	−8.5±5.9*
PANSS general psychopathology subscale score		
Baseline mean (±SD)	55.7±11.4	55.3±10.4
Mean (±SD) change (LOCF)	−11.3±11.4*, [a]	−11.4±12.8*, [a]
Mean (±SD) change (OC)	−15.7±10.3*	−16.2±12.3*
CGI-S score		
Baseline mean (±SD)	5.2±0.7	5.2±0.7
Mean (±SD) change (LOCF)	−0.6±0.9*, [a]	−0.6±0.9*, [a]
Mean (±SD) change (OC)	−1.0±0.8*	−0.9±0.9*
CGI-I score		
ITT-LOCF-endpoint	3.2±1.5 [b]	3.3±1.3 [b]
ITT-OC-endpoint	2.4±1.0	2.7±1.0
CDSS score		
Baseline mean (±SD)	8.3±5.4	7.8±5.7
Mean (±SD) change (LOCF)	−3.1±5.3*, [a]	−2.1±5.1*, [a]
Mean (±SD) change (OC)	−4.6±5.1*	−3.2±5.2*
GAF score		
Baseline mean (±SD)	40.6±15.0	41.8±13.0
Mean (±SD) change (LOCF)	8.3±13.9*, [a]	7.2±10.8*, [a]
Mean (±SD) change (OC)	12.4±13.9*	10.6±11.5*
DAI 10 score		
Baseline mean (±SD)	2.9±4.5	1.3±5.1
Mean (±SD) change (LOCF)	1.8±5.6**, [a]	1.6±5.7**, [a]
Mean (±SD) change (OC)	3.2±5.4*	3.1±5.8*
Response rates based on percent improvement in PANSS total score:		
>20% improvement (LOCF)	67.6%	54.8%
>30% improvement (LOCF)	35.2%	30.1%
>40% improvement (LOCF)	15.5%	16.4%
>20% improvement (OC)	97.8***	77.8%
>30% improvement (OC)	51.1%	44.4%
>40% improvement (OC)	13.3%	15.6%

*$p<0.001$ vs baseline.
**$p<0.05$ vs baseline.
***$p<0.05$ vs clozapine.
[a] ANCOVA of ITT-LOCF change scores at endpoint found no significant differences in improvement for ziprasidone versus clozapine.
[b] Difference at endpoint was non-significant.

failed to differentiate the two treatments, with the unique exception of a higher frequency ($p=0.007$) of patients with a PANSS total score improvement of 20% or more in the ziprasidone group (97.8%) compared to the clozapine group (77.8%).

Both treatments caused significant improvement ($p<0.001$) from baseline to endpoint (ITT-LOCF) in PANSS positive, negative, and general psychopathology subscales, with no significant differences between the arms (Table 2).

3.3.2. CGI-S and CGI-I

A significant endpoint improvement from baseline in CGI-S scores (ITT-LOCF) was observed in both the ziprasidone and clozapine groups, with no between-drug difference (Table 2). Throughout the study period, a significant CGI-S improvement from baseline was detected at each visit, except at day 11 in the clozapine group.

Endpoint CGI-I scores demonstrated equivalent improvements in the two treatments groups. The endpoint rates of ziprasidone and clozapine patients classified as "much/very much improved" at CGI-I overlapped both in the ITT (ziprasidone = 40.8%; clozapine = 32.9%) and the completer (ziprasidone = 62.2%; clozapine = 51.1%) populations.

3.3.3. Cdss

LOCF analysis showed progressive, significant CDSS improvement from baseline throughout the study with both the study drugs. The endpoint decreases in CDSS scores were not significantly different between the two groups (Table 2).

Among patients with clinically significant depressive symptoms at baseline (CDSS score ≥5), mean endpoint improvement in CDSS was similar in the ziprasidone and the clozapine arms (−7.1±1.6 vs −5.4±1.1; $p=0.17$).

3.3.4. Gaf

LOCF results showed a progressive and significant GAF improvement from baseline throughout the study in both treatment groups. No evidence of significant differences between ziprasidone and clozapine arms emerged at endpoint (Table 2).

3.3.5. Dai-10

LOCF results showed a progressive and significant DAI-10 improvement from baseline throughout the study in both treatment groups (except at day 11 in the clozapine group). No significant difference between groups was found at endpoint (Table 2).

3.3.6. Efficacy in the treatment-refractory subgroup

A post hoc ANCOVA performed on patients enrolled due to resistance to at least three different antipsychotics, regardless of whether they were also intolerant in other cycles, confirmed the results valid for the total sample: ziprasidone ($n=57$) had comparable efficacy to clozapine ($n=65$) on LS-mean change in PANSS total (−26.1±2.7 vs −22.9±2.8; $p=0.36$), and on all secondary efficacy measures.

3.4. Safety and tolerability

3.4.1. Adverse events

Fifty-two ziprasidone (71%) and 58 (79.5%) clozapine patients experienced treatment-emergent AEs during the study. Most AEs were mild to moderate. Among the most frequently reported treatment-related AEs (Table 3), insomnia was more common in the ziprasidone group, while salivation, tachycardia, dizziness, and somnolence were over-represented in the clozapine group.

A total of 204 AEs were judged to be treatment-related, 59 in the ziprasidone and 145 in the clozapine group. Treatment-related AEs were responsible for 7 and 13 premature discontinuations in the ziprasidone and clozapine groups, respectively.

3.4.2. Movement disorders

The two treatments were associated with modest endpoint improvement of baseline SAS, BAS, and AIMS scores (Table 4). All the changes were significant in the ziprasidone group while only the reduction of the initial BAS score reached the level of

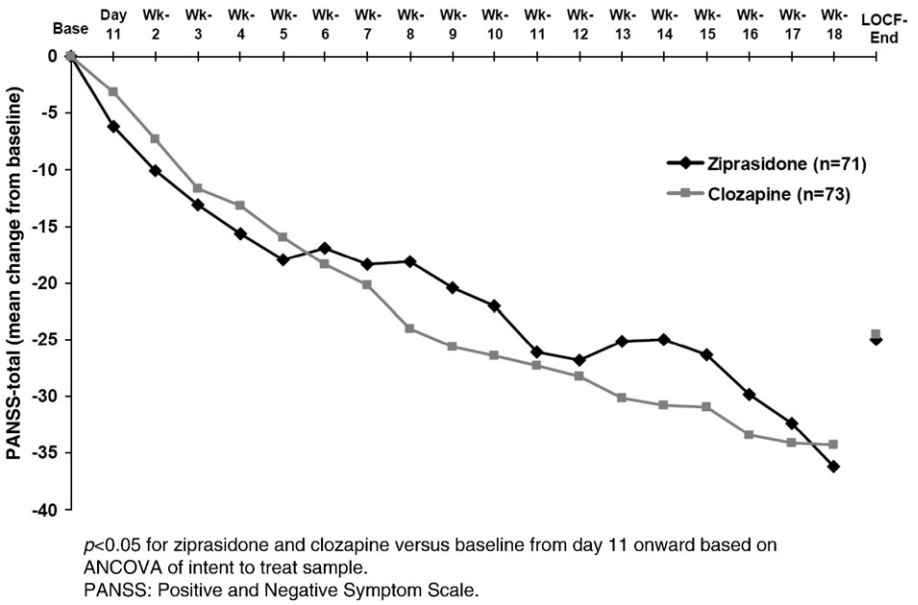

Fig. 2. Mean change from baseline in PANSS total score (ITT population).

statistical significance in the clozapine group. No significant between-drug differences were observed.

3.4.3. Metabolic indices

3.4.3.1. Body weight. At endpoint, clozapine patients experienced a weight gain from baseline of 0.8 ± 4.6 kg, while ziprasidone patients decreased by 2.6 ± 4.7 kg at endpoint, with a significant between-group difference ($p<0.001$).

3.4.3.2. Serum lipid profile. Median changes from baseline to endpoint in fasting total cholesterol, LDL-C, and triglycerides significantly favored ziprasidone (Fig. 3).

3.4.3.3. Glucose metabolism. Median baseline fasting glucose levels (Fig. 3) of ziprasidone (96 mg/dL) and clozapine (89 mg/dL) patients were unchanged (ziprasidone) and increased by 6 mg/dL (clozapine group). The between-arm difference was significant ($p=0.003$).

3.4.4. Other clinical laboratory tests

Treatment was associated with a comparable reduction, at endpoint, in median prolactin levels for ziprasidone (−5.0 ng/mL) and clozapine (−6.5 ng/mL). No detrimental effects for either drug were observed with regard to hematology, renal and liver functions, and electrolytes.

Table 3
Most frequently reported individual treatment-related adverse events (incidence ≥10% of total patients).

	Ziprasidone($n=73$)	Clozapine($n=73$)
Increased salivation	0%	28.8%
Tachycardia	2.7%	28.8%
Dizziness	4.1%	9.6%
Headache	6.8%	4.1%
Nausea	6.8%	8.2%
Somnolence	4.1%	23.3%
Insomnia	9.6%	2.7%
Any adverse event	71.2%	79.5%

3.4.5. Cardiovascular parameters

3.4.5.1. Vital signs. There were no significant changes in systolic or diastolic blood pressure during treatment; the increases of heart rate with clozapine (+8.0 b.p.m.) and ziprasidone (+2.0 b.p.m.) were not significantly different.

3.4.5.2. QTc Interval. No significant treatment-emergent ECG abnormalities were observed. Mean QTc change was not significantly different in ziprasidone (+6.0 ± 43.3 ms) and clozapine (−3.6 ± 39.3 ms) groups. Three patients (4.5%) in the ziprasidone group and 10 (14.1%) in the clozapine group had QTc values ≤450 ms at screening and >450 ms at endpoint. Only one clozapine patient had a QTc value ≤500 ms at screening and >500 ms at endpoint.

Table 4
Treatment-emergent changes in abnormal movement scales.

	Ziprasidone	Clozapine
Simpson–Angus Scale	($n=62$)	($n=72$)
Baseline, mean ± SD	0.47 ± 0.5	0.31 ± 0.4
Change score, mean [95% CI]	−0.21 [−0.30 to −0.12] **	−0.06 [−0.14 to 0.02]
Barnes Akathisia Scale	($n=67$)	($n=72$)
Baseline, mean ± SD	0.75 ± 1.1	0.54 ± 0.9
Change score, mean [95% CI]	−0.37 [−0.64 to −0.11] *	−0.22 [−0.44 to 0.01]*
Abnormal Involuntary Movement Scale	($n=66$)	($n=73$)
Baseline, mean ± SD	0.28 ± 0.4	0.21 ± 0.4
Change score, mean [95% CI]	0.15 [−0.08 to −0.22]**	−0.08 [−0.18 to 0.03]

*$p<0.05$ vs baseline; **$p<0.001$ vs baseline.

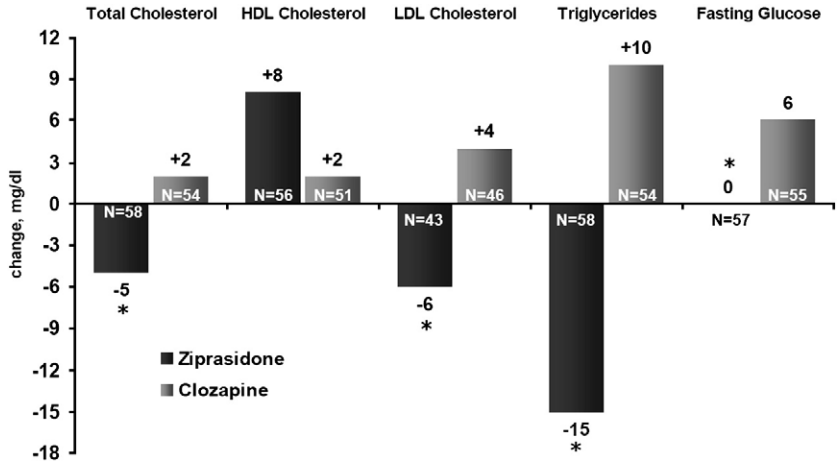

Fig. 3. Median change from baseline to LOCF-endpoint in lipid parameters and fasting glucose. *$p<0.05$ (between-group). Normalized data are shown.

3.5. Concomitant medications

A total of 93 patients, 49 (67.1%) in the ziprasidone group and 44 (60.3%) in the clozapine group, took concomitant medications for movement disorders during the study. Hypnotics and anxiolytics were taken by 86 patients, 47 (64.4%) in the ziprasidone group and 39 (53.4%) in the clozapine group.

4. Discussion

This first randomized, double-blind, comparison of ziprasidone and clozapine involved schizophrenia patients with a history of multiple refractoriness to antipsychotic treatments and a higher illness severity (baseline scores: PANSS total, ~107; CGI-S, 5.2) than typically reported in previous trials of treatment-refractory individuals.

Overall, the study demonstrates that, in this special population, ziprasidone and clozapine are similarly effective and safe, although with drug-specific differences in their potential to induce some AEs.

Several strands of evidence support the conclusion that ziprasidone and clozapine have a satisfactory and equivalent efficacy. First, both drugs produced a significant baseline-to-endpoint reduction in PANSS total score, the primary outcome measure, with close overlap of endpoint effect sizes and an adjusted mean ziprasidone–clozapine difference of 0.59. Interestingly, the effect sizes observed in the current study fell in the range (0.96–1.71) reported in three previous studies of clozapine in treatment-refractory patients (Azorin et al., 2001; Bitter et al., 2004; Tollefson et al., 2001). Second, the temporal course of total PANSS improvement was comparable between the two treatment arms. Third, the two investigational drugs were associated with relevant improvements in all components of the large battery of secondary efficacy measures we selected, thus suggesting for both the medications an efficacy that is generalized to all the domains of psychopathology rather than confined to a specific symptom cluster. Fourth, a separate, post hoc analysis of cases enrolled due to lack of response in at least three previous adequate trials with different antipsychotics, demonstrated a comparable ziprasidone–clozapine efficacy in strictly treatment-resistant patients. Fifth, the results based on PP-LOCF data replicated closely those of the ITT-LOCF population.

The results on severity of AEs, incidence of early discontinuations due to AEs, and effects on prolactin, renal and liver functions, hematology, and cardiovascular parameters coherently underline that ziprasidone and clozapine share enough global safety and tolerability profiles in refractory schizophrenia patients. However, together with these relevant similarities, the safety and tolerability profiles of the two drugs nonetheless displayed some differences. In particular, ziprasidone was more associated with insomnia while clozapine had higher rates of somnolence, salivation, dizziness, and tachycardia. Furthermore, parkinsonian symptoms and abnormal involuntary movements improved significantly only in the ziprasidone group. Finally, as expected according to current literature on this issue (Henderson et al., 2005; Lamberti et al., 2006; Lieberman et al., 2005; Montes et al., 2007; Weiden et al., 2008), ziprasidone exhibited a significantly more favorable metabolic profile compared to clozapine.

Plausibly, ziprasidone–clozapine differences in the incidence of AEs and the improvement of movement disorders may have little clinical impact: indeed, the AEs were generally not severe and the endpoint reduction of baseline SAS and AIMS scores was mild. Furthermore, the frequent concomitant use of benzodiazepines and anticholinergic agents renders hypotheses of a differential effect of the investigational drugs on parkinsonian symptoms and abnormal involuntary movements largely untestable.

Conversely, one should consider the advantage of ziprasidone over clozapine in most metabolic indices, if confirmed, as more relevant. Indeed, people with schizophrenia suffer in overt excess, among other physical illnesses, from obesity, diabetes, dyslipidemias, metabolic syndrome, coronary heart disease, and cerebrovascular accidents (Chuang et al., 2008; Leucht et al., 2007; Marder et al., 2004; McEvoy et al., 2005; Meyer et al., 2008; Millar, 2008; Nasrallah, 2008; Newcomer, 2005; Sacchetti et al., 2008; Sharif, 2008). Many causal and facilitating factors contribute to this dramatic picture. Familial, possibly genetic predisposition, intrinsic metabolic disadvantages, persistent unhealthy lifestyles, poor interest and adherence to wellness plans, reduced inclination to request medical help, barriers to an easy use of health care

facilities, common lack of recognition and under-treatment of physical illnesses by physicians, and inequalities in the therapies certainly play a relevant contribute (Chuang et al., 2008; Felker et al., 1996; Gough and O'Donovan, 2005; Koranyi, 1979; Leucht et al., 2007; Lin et al., 2007; McCreadie and Scottish Schizophrenia Lifestyle Group, 2003; Millar, 2008; Nasrallah, 2008; Newcomer, 2005). Evidence of high rates of metabolic disturbances in schizophrenia patients studied before the advent of the era of antipsychotics or at their first, drug-naïve episode suggest an involvement of schizophrenia independent from contamination of these medications (Kohen, 2004; Ryan et al., 2003, 2004; Spelman et al., 2007; Thakore, 2004), although few negative results also exist (Arranz et al., 2004; Sengupta et al., 2008). However, many typical and atypical antipsychotics unquestionably may induce, with drug-specific differences, obesity, diabetes, dyslipidemias, and metabolic syndrome (Baptista et al., 2008; De Hert et al., 2008; Haupt, 2006; Henderson, 2005; Leucht et al., 2009; Lieberman et al., 2005; Lindenmayer et al., 2003; Meyer et al., 2008; Nasrallah, 2008; Newcomer, 2005, 2007; Sacchetti et al., 2008; Sharif, 2008). Therefore, antipsychotics with neutral or, better, favorable metabolic effects should be numbered among the options at the disposition of the clinician for the control of these disabling, potentially life-threatening accidents. In particular, antipsychotics with safe metabolic profiles and demonstrated effectiveness in schizophrenia refractory patients are likely to represent a plausible first-line strategy whenever psychosis precludes active participation of the patients.

Nonetheless we acknowledge that the study has some inherent limitations. First, analogous with previous trials (Azorin et al., 2001; Bitter et al., 2004; Bondolfi et al., 1998; Tollefson et al., 2001), the definitions of resistance and intolerance were retrospective, without the prospective confirmation of a treatment during a lead-in period. The risk of biased recruitment due to lack of objective sources of information was however reduced: Italian psychiatric departments supply continuity of care to individuals within a defined catchment area and, therefore, the participating centers were able to screen well-known patients and to have immediate access to all clinical records.

Furthermore, as in other studies involving refractory patients (Azorin et al., 2001; Bondolfi et al., 1998; Tollefson et al., 2001), the interval between the last exposure to antipsychotics, both depot and oral, and the first administration of study medications was insufficient for the drugs to clear the system. This short period of wash-out due to the severity of psychotic symptoms implies that clinical improvements may not be completely attributable to study drugs. While this is a possibility, it must be stressed that previous antipsychotic therapies had, by definition, to be unsuccessful and thus it appears unlikely that they may have played a major influence in early reductions of psychopathology during the trial.

Also, and once again in common with other trials (Bitter et al., 2004; Bondolfi et al., 1998), the recruitment did not distinguish between resistant and intolerant patients, although the two causes of treatment failure reflect different reasons and suggest different solutions (Sacchetti et al., 2004; Taylor and Duncan-McConnell, 2000). Resistant patients require antipsychotics with an efficacy superior to that of preceding treatments while intolerant individuals are in need of medications with a safety and tolerability profile improved enough to permit the attainment and maintenance of fully therapeutic doses. Therefore, inclusion of both resistant and intolerant patients precludes determination of whether ziprasidone, clozapine, or both the drugs are preferentially or equally indicated in resistant or intolerant people. Nevertheless, the comparable distribution of the causes of treatment refractoriness in the two arms and the full replication of the efficacy results from the global sample by patients with a history of only resistance, suggest that ziprasidone and clozapine are indicated in refractory patients, irrespective of the fact that they are resistant, intolerant, or both.

Finally, the mean dosage of clozapine (346 mg/day), while within the therapeutic range, is perhaps lower than recommended for some patients in clinical practice. This finding may be attributable to the flexible-dose regimen encouraging investigators to maintain the lowest dosage that achieved acceptable efficacy while minimizing the risk of emergent AEs. The use in other clozapine flexible-dose trials (Bitter et al., 2004, Bondolfi et al., 1998; McEvoy et al., 2006, Tollefson et al., 2001) of mean lower daily doses of clozapine than those in the current study is compatible with this interpretation. Common evidence, in our sample population, of significant improvements from the early, low-dose phases of treatment could have plausibly further facilitated non-aggressive management.

5. Conclusion

This double-blind, flexible-dose study supports the conclusion that both ziprasidone and clozapine, having comparable efficacy coupled with satisfactory general safety and tolerability, may be regarded as valuable options for the short-term management of difficult-to-treat schizophrenia patients with a history of multiple resistance and/or intolerance to antipsychotics.

The more favorable metabolic profile of ziprasidone may represent an added value that could guide clinicians toward treatment choice, at least in the presence of high-risk individuals. If and when confirmed in the long-term, metabolic differences could promote a preference for ziprasidone over clozapine for the maintenance treatment of otherwise refractory patients with schizophrenia.

Role of the funding source

Pfizer Inc supported this research. This was an industry-sponsored clinical trial which proceeded following consultation with the authors. The sponsor of the trial turned over the data of the final report to the first author who interpreted the results.

Contributors

Prof. Sacchetti participated in the design of the trial, provided overall scientific supervision, acted as the principal investigator, supervised the conduct of the research, interpreted the results, and drafted and edited the manuscript.

Dr. Galluzzo was the co-principal investigator of the trial, supervised the assessment of the patients, contributed to the interpretation of the results, and managed the literature searches.

Dr. Valsecchi participated in the supervision of clinical data, and contributed to the interpretation of the results.

Dr. Romeo designed the trial, selected the principal investigator, in conjunction with Dr. Gorini, and contributed to the analyses of the data and writing of the report.

Dr. Gorini worked with Dr. Romeo on all aspects of the trial from Pfizer, Italy.

Dr. Warrington contributed to interpretation of the results and the development of the manuscript.

Conflict of interest

In the past 5 years Professor Emilio Sacchetti has received funding for consultancy, research, advisory board membership, and sponsored lectures from Abbott, AstraZeneca, Boehringer Inghelheim, Bristol-Meyers Squibb, Dainippon Sumitomo Pharma, Eli Lilly, GlaxoSmithKline, Innova Farma, Italfarmaco, Janssen-Cilag, Lundbeck, Pfizer, Sanofi-Aventis, and Wyeth Lederle; he is not a shareholder in any of these corporations.

In the past 5 years Dr. Alessandro Galluzzo has received funding for research and sponsored lectures from AstraZeneca, Boehringer Inghelheim, Bristol-Meyers Squibb, Eli Lilly, Janssen-Cilag, and Pfizer; he is not a shareholder in any of these corporations.

In the past 5 years Dr. Paolo Valsecchi has received funding for research and sponsored lectures from AstraZeneca, Boehringer Inghelheim, Bristol-Meyers Squibb, Eli Lilly, Janssen-Cilag, and Pfizer; he is not a shareholder in any of these corporations.

Dr. Fabio Romeo was a full-time employee of Pfizer, Italy at the time of the study.

Dr. Barbara Gorini is a full-time employee of Pfizer, Italy.

Dr. Lewis Warrington was a full-time employee of Pfizer, Inc at the time of the study.

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References

Addington, D., Addington, J., Schissel, B., 1990. A depression rating scale for schizophrenics. Schizophr. Res. 3, 247–251.

Addington, D., Addington, J., Maticka-Tyndale, E., Joyce, J., 1992. Reliability and validity of a depression rating scale for schizophrenics. Schizophr. Res. 6, 201–208.

American Psychiatric Association, 1994. Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), Fourth Edition. American Psychiatric Association, Washington, DC.

Arranz, B., Rosel, P., Ramirez, N., Duenas, R., Fernandez, P., Sanchez, J.M., Navarro, M.A., San, L., 2004. Insulin resistance and increased leptin concentration in noncompliant schizophrenia patient but not in antipsychotic-naïve first-episode schizophrenia patients. J. Clin. Psychiatry 65, 1335–1342.

Awad, A.G., Hogan, T.P., 1994. Subjective response to neuroleptics and the quality of life: implications for treatment outcome. Acta Psychiatr. Scand., Suppl. 380, 27–32.

Azorin, J.M., Spiegel, R., Remington, G., Vanelle, J.M., Pere, J.J., Giguere, M., Bourdeix, I., 2001. A double-blind comparative study of clozapine and risperidone in the management of severe chronic schizophrenia. Am. J. Psychiatry 158, 1305–1313.

Baptista, T., ElFakih, Y., Uzcátegui, E., Sandia, I., Tálamo, E., Araujo de Baptista, E., Beaulieu, S., 2008. Pharmacological management of atypical antipsychotic-induced weight gain. CNS Drugs 22 (6), 477–495.

Barnes, T.R., 1989. A rating scale for drug-induced akathisia. Br. J. Psychiatry 154, 672–676.

Bitter, I., Dossenbach, M.R., Brook, S., Feldman, P.D., Metcalfe, S., Gagiano, C.A., Furedi, J., Bartko, G., Janka, Z., Banki, C.M., Kovacs, G., Breier, A., 2004. Olanzapine versus clozapine in treatment-resistant or treatment-intolerant schizophrenia. Prog. Neuro-psychopharmacol. Biol. Psychiatry 28, 173–180.

Bondolfi, G., Dufour, H., Patris, M., May, J.P., Billeter, U., Eap, C.B., Baumann, P., Risperidone Study Group, 1998. Risperidone versus clozapine in treatment-resistant chronic schizophrenia: a randomized double-blind study. Am. J. Psychiatry 155, 499–504.

Breier, A.F., Malhotra, A.K., Su, T.P., Pinals, D.A., Elman, I., Adler, C.M., Lafargue, R.T., Clifton, A., Pickar, D., 1999. Clozapine and risperidone in chronic schizophrenia: effects on symptoms, parkinsonian side effects, and neuroendocrine response. Am. J. Psychiatry 156, 294–298.

Chakos, M., Lieberman, J., Hoffman, E., Bradford, D., Sheitman, B., 2001. Effectiveness of second-generation antipsychotics in patients with treatment-resistant schizophrenia: a review and meta-analysis of randomized trials. Am. J. Psychiatry 158, 518–526.

Chuang, H.T., Mansell, C., Patten, S.B., 2008. Lifestyle characteristics of psychiatric outpatients. Can. J. Psychiatry 53 (4), 260–266.

Conley, R.R., Kelly, D.L., 2001. Management of treatment resistance in schizophrenia. Biol. Psychiatry 50, 898–911.

Conley, R.R., Kelly, D.L., Richardson, C.M., Tamminga, C.A., Carpenter Jr., W.T., 2003. The efficacy of high-dose olanzapine versus clozapine in treatment-resistant schizophrenia: a double-blind crossover study. J. Clin. Psychopharmacol. 23, 668–671.

De Hert, M., Schreurs, V., Sweers, K., Van Eyck, D., Hanssens, L., Šinko, S., Wampers, M., Scheen, A., Peuskens, J., van Winkel, R., 2008. Typical and atypical antipsychotics differentially affect long-term incidence rates of the metabolic syndrome in first-episode patients with schizophrenia: a retrospective chart review. Schizophr. Res. 101, 295–303.

Elkis, H., 2007. Treatment-resistant schizophrenia. Psychiatr. Clin. North Am. 30, 511–533.

Essock, S.M., Hargreaves, W.A., Dohm, F.A., Goethe, J., Carver, L., Hipshman, L., 1996. Clozapine eligibility among state hospital patients. Schizophr. Bull. 22, 15–25.

Felker, B., Yazel, J.J., Short, D., 1996. Mortality and medical comorbidity among psychiatric patients: a review. Psychiatr. Serv. 47, 1356–1363.

Gough, S.C., O'Donovan, M.C., 2005. Clustering of metabolic comorbidity in schizophrenia: a generic contribution? J. Psychopharmacol. 19 (suppl 6), 47–55.

Guy, W., 1976. ECDEU Assessment Manual for Psychopharmacology. . US Dept of Health, Education and Welfare. National Institute of Mental Health, Washington, DC, pp. 76–338.

Harvey, P.D., Sacchetti, E., Galluzzo, A., Romeo, F., Gorini, B., Bilder, R.M., Loebel, A.D., 2008. A randomized double-blind comparison of ziprasidone vs. clozapine for cognition in patients with schizophrenia selected for resistance or intolerance to previous treatment. Schizophr. Res. 105, 138–143.

Haupt, D.W., 2006. Differential metabolic effect of antipsychotic treatments. Eur. Neuropsychopharmacol. 16 (supp 3), s149–s155.

Henderson, D.C., 2005. Schizophrenia and comorbid metabolic disorders. J. Clin. Psychiatry 66 (suppl.6), 11–20.

Henderson, D.C., Nguyen, D.D., Copeland, P.M., Hayden, D.L., Borba, C.P., Louie, P.M., Freudenreich, O., Evins, E., Cather, C., Goff, D.C., 2005. Clozapine, diabetes mellitus, hyperlipidemia, and cardiovascular risks and mortality: results of a 10-years naturalistic study. J. Clin. Psychiatry 66, 1116–1121.

Kane, J.M., 2003. Oral ziprasidone in the treatment of schizophrenia: a review of short-term trials. J. Clin. Psychiatry 64 (Suppl 19), 19–25.

Kane, J.M., Khanna, S., Rajadhyaksha, S., Giller, E., 2006. Efficacy and tolerability of ziprasidone in patients with treatment-resistant schizophrenia. Int. Clin. Psychopharmacol. 21, 21–28.

Kay, S.R., Fiszbein, A., Opler, L.A., 1987. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr. Bull. 13, 261–276.

Kay, S.R., Opler, L.A., Lindenmayer, J.P., 1988. Reliability and validity of the positive and negative syndrome scale for schizophrenics. Psychiatry Res. 23, 99–110.

Kohen, D., 2004. Diabetes mellitus and schizophrenia: historical perspective. Br. J. Psychiatry 184 (suppl.47), s64–s66.

Koranyi, E.K., 1979. Morbidity and rate of undiagnosed physical illnesses in a psychiatric clinic population. Arch. Gen. Psychiatry 36, 414–419.

Lamberti, J.S., Olson, D., Crilly, J.F., Olivares, T., Williams, G.C., Tu, X., Tang, W., Wiener, K., Dvorin, S., Dietz, M.B., 2006. Prevalence of the metabolic syndrome among patients receiving clozapine. Am. J. Psychiatry 163, 1273–1276.

Lerner, V., Libov, I., Kotler, M., Strous, R.D., 2004. Combination of "atypical" antipsychotic medication in the management of treatment-resistant schizophrenia and schizoaffective disorder. Prog. Neuro-psychopharmacol. Biol. Psychiatry 28, 89–98.

Leucht, S., Burkard, T., Henderson, J., Maj, M., Sartorius, N., 2007. Physical illness and schizophrenia: a review of literature. Acta Psychiatr. Scand. 116, 317–333.

Leucht, S., Corves, C., Arbter, D., Engel, R.R., Li, C., Davis, J.M., 2009. Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis. Lancet 373, 31–41.

Lieberman, J.A., Stroup, T.S., McEvoy, J.P., Swartz, M.S., Rosenheck, R.A., Perkins, D.O., Keefe, R.S., Davis, S.M., Davis, C.E., Lebowitz, B.D., Severe, J., Hsiao, J.K., 2005. Effectiveness of antipsychotic drugs in patients with schizophrenia. N. Engl. J. Med. 353, 1209–1223.

Lin, H.C., Chen, C.S., Liu, T.C., Tsai, S.-Y., Lee, H.-C., 2007. Lack of care for diabetes among schizophrenia patients. Schizophr. Res. 89, 353–354.

Lindenmayer, J.P., 2000. Treatment refractory schizophrenia. Psychiatr. Q. 71, 373–384.

Lindenmayer, J.P., Czobor, P., Volavka, J., Citrome, L., Sheitman, B., McEvoy, J.P., Cooper, T.B., Chakos, M., Lieberman, J.A., 2003. Changes in glucose and cholesterol levels in patients with schizophrenia treated with typical or atypical antipsychotics. Am. J. Psychiatry 160, 290–296.

Loebel, A.D., Khanna, S., Rajadhyakska, S., Siu, C.O., Giller, E., Potkin, S.G., 2007. Ziprasidone in treatment-resistant schizophrenia: a 52-week, open-label continuation study. J. Clin. Psychiatry 68, 1333–1338.

Marder, S.R., Essock, S.M., Miller, A.L., Buchanan, R.W., Casey, D.E., Davis, J.M., Kane, J.M., Lieberman, J.A., Schooler, N.R., Covel, N., Stroup, S., Weissman, E.M., Wirshing, D.A., Hall, C.S., Pogach, L., Pi-Sunyer, X., Bigger, J.T., Friedman, A., Kleinberg, D., Yevich, S.J., Davis, B., Shon, S., 2004. Physical health monitoring of patients with schizophrenia. Am. J. Psychiatry 161, 1334–1349.

McCreadie, R.G., Scottish Schizophrenia Lifestyle Group, 2003. Diet, smoking and cardiovascular risk in people with schizophrenia: descriptive study. Br. J. Psychiatry 183, 534–539.

McEvoy, J.P., 2007. The cost of schizophrenia. J. Clin. Psychiatry 68 (suppl 14), 4–7.

McEvoy, J.P., Meyer, J.M., Goff, D.C., Nasrallah, H.A., Davis, S.M., Sullivan, L., Meltzer, H.Y., Hsiao, J., Stroup, T.S., Lieberman, J.A., 2005. Prevalence of the metabolic syndrome in patients with schizophrenia: baseline results from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) schizophrenia trial and comparison with national estimates from NHANES III. Schizophr. Res. 80, 19–32.

McEvoy, J.P., Lieberman, J.A., Stroup, T.S., Davis, S.M., Meltzer, H.Y., Rosenheck, R.A., Swartz, M.S., Perkins, D.O., Keefe, R.S., Davis, C.E., Severe, J., Hsiao, J.K., 2006. 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 163, 600–610.

Meyer, J.M., Davis, V.G., Goff, D.C., McEvoy, J.P., Nasrallah, H.A., Davis, S.M., Rosenheck, R.A., Daumit, G.L., Hsiao, J., Swartz, M.S., Stroup, T.S., Lieberman, J.A., 2008. Change in metabolic syndrome parameters with antipsychotic treatment in the CATIE schizophrenia trial: prospective data from phase 1. Schizophr. Res. 101, 273–286.

Meyer-Lindenberg, A., Gruppe, H., Bauer, U., Lis, S., Krieger, S., Gallhofer, B., 1997. Improvement of cognitive function in schizophrenic patients receiving clozapine or zotepine: results from a double-blind study. Pharmacopsychiatry 30, 35–42.

Millar, H., 2008. Management of physical health in schizophrenia: a stepping stone to treatment success. Eur. Neuropsychopharmacol. 18, s121–s128.

Moncrieff, J., 2003. Clozapine v. conventional antipsychotic drugs for treatment-resistant schizophrenia: a re-examination. Br. J. Psychiatry 183, 161–166.

Montes, J.M., Rodriguez, J.L., Balbo, E., Sopelana, P., Martin, E., Soto, J.A., Delgado, J.F., Diez, T., Villardaga, I., 2007. Improvement in antipsychotic-related metabolic disturbances in patients with schizophrenia switched to ziprasidone. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 31, 383–388.

Nasrallah, H.A., 2008. Atypical antipsychotic-induced metabolic side effect: insights from receptor-binding profiles. Mol. Psychiatry 13, 27–35.

Newcomer, J.W., 2005. Second-generation (atypical) antispychotics and metabolic effects. A comprehensive literature review. CNS Drugs 19 (suppl.1), 1–93.

Newcomer, J.W., 2007. Metabolic considerations in the use of antipsychotic medications: a review of recent evidence. J. Clin. Psychiatry 68 (suppl 1), 20–27.

Revicki, D.A., 2000. The new atypical antipsychotics: a review of pharmacoeconomic studies. Expert Opin. Pharmacother. 1, 249–260.

Ryan, M.C., Collins, P., Thakore, J.H., 2003. Impaired fasting glucose and elevation of cortisol elevation in drug-naïve first episode schizophrenia. Am. J. Psychiatry 160, 284–289.

Ryan, M.C., Flanagan, S., Kinsella, U., Keeling, F., Thakore, J.H., 2004. The effects of atypical antipsychotics on visceral fat distribution in first episode, drug-naïve patients with schizophrenia. Life Sci. 74, 1999–2008.

Sacchetti, E., Panariello, A., Regini, C., Valsecchi, P., 2004. Quetiapine in hospitalized patients with schizophrenia refractory to treatment with first-generation antipsychotics: a 4-week, flexible-dose, single-blind, exploratory, pilot trial. Schizophr. Res. 69, 325–331.

Sacchetti, E., Valsecchi, P., Parrinello, G., QUERISOLA Group, 2008. A randomized, flexible-dose, quasi naturalistic comparison of quetiapine, risperidone, and olanzapine in the short-term treatment of schizophrenia: the QUERISOLA trial. Schizophr. Res. 98, 55–65.

Sengupta, S., Parrilla-Escobar, M.A., Klink, R., Fathalli, F., Ng, K.Y., Stip, E., Baptista, T., Malla, A., Joober, R., 2008. Are metabolic indices different between drug-naïve first-episode psychosis patients and healthy controls? Schizophr. Res. 102, 329–336.

Sharif, Z., 2008. Side effects as influencers of treatment outcome. J. Clin. Psychiatry 69 (suppl 3), 38–43.

Simpson, G.M., Angus, J.W., 1970. A rating scale for extrapyramidal side effects. Acta Psychiatr. Scand., Suppl. 212, 11–19.

Simpson, G.M., Glick, I.D., Weiden, P.J., Romano, S.J., Siu, C.O., 2004. Randomized, controlled, double-blind multicenter comparison of the efficacy and tolerability of ziprasidone and olanzapine in acutely ill inpatients with schizophrenia or schizoaffective disorder. Am. J. Psychiatry 161, 1837–1847.

Simpson, G.M., Weiden, P., Pigott, T., Murray, S., Siu, C.O., Romano, S.J., 2005. Six-month, blinded, multicenter continuation study of ziprasidone versus olanzapine in schizophrenia. Am. J. Psychiatry 162, 1535–1538.

Spelman, L.M., Walsh, P.I., Sharifi, N., Collins, P., Thakore, J.H., 2007. Impaired glucose tolerance in first-episode drug-naïve patients with schizophrenia. Diabet. Med. 24, 481–485.

Taylor, D.M., Duncan-McConnell, D., 2000. Refractory schizophrenia and atypical antipsychotics. J. Psychopharmacol. 14, 409–418.

Thakore, J.H., 2004. Metabolic disturbance in first-episode. Br. J. Psychiatry 184 (suppl.47), s76–s79.

Tollefson, G.D., Birkett, M.A., Kiesler, G.M., Wood, A.J., 2001. Double-blind comparison of olanzapine versus clozapine in schizophrenic patients clinically eligible for treatment with clozapine. Biol. Psychiatry 49, 52–63.

Volavka, J., Czobor, P., Sheitman, B., Lindenmayer, J.P., Citrome, L., McEvoy, J.P., Cooper, T.B., Chakos, M., Lieberman, J.A., 2002. Clozapine, olanzapine, risperidone, and haloperidol in the treatment of patients with chronic schizophrenia and schizoaffective disorder. Am. J. Psychiatry 159, 255–262.

Weiden, P.J., Newcomer, J.W., Loebel, A.D., Yang, R., Lebovitz, H.E., 2008. Long-term changes in weight and plasma lipids during maintenance treatment with ziprasidone. Neuropsychopharmacology 33, 985–994.

Ziegenbein, M., Kropp, S., Kuenzel, H.E., 2005. Combination of clozapine and ziprasidone in treatment-resistant schizophrenia: an open clinical study. Clin. Neuropharmacol. 28, 220–224.