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ORIGINAL RESEARCH

Efficacy of olanzapine in comparison with clozapine for treatment-resistant schizophrenia: evidence from a systematic review and meta-analyses

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Introduction. Clozapine is considered the gold standard for the treatment of patients with treatment-resistant schizophrenia (TRS); however, randomized controlled trials (RCT) of olanzapine showed efficacy similar to clozapine in patients with TRS.

Methods. A systematic review was conducted comparing clozapine with olanzapine in patients with TRS. Meta-analyses were performed for single outcome measures. Response to treatment was measured by the percentage of responders, or mean change or endpoint values of psychotic symptoms scales. Effect sizes were shown as relative risks (RR), or standardized mean differences, with 95% confidence intervals.

Findings. Seven RCT were included, comprising 648 patients. Five meta-analyses were performed. Olanzapine and clozapine had similar effects on dropout rates (RR = 0.93, $CI_{95\%}$ = 0.77–1.12), PANSS total endpoints (SMD = 0.21, $CI_{95\%}$ = –0.04–0.46), and PANSS total mean changes (SMD = 0.08, $CI_{95\%}$ = –0.01–0.027). Clozapine was superior to olanzapine for PANSS positive (SMD = 0.51, $CI_{95\%}$ = 0.17–0.86) and negative (SMD = 0.50, $CI_{95\%}$ = 0.16–0.85) subscales. There was a trend toward high doses of olanzapine producing higher effect sizes for this drug.

Conclusions. The results of this study suggest that clozapine is significantly more efficacious than olanzapine in improving positive and negative symptoms in TRS patients.

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Key words: clozapine, olanzapine, treatment-resistant schizophrenia, meta-analysis, systematic review, schizophrenia.

FOCUS POINTS

- Clozapine is the gold standard antipsychotic for treatment-resistant schizophrenia (TRS).
- Olanzapine emerged as a very efficacious antipsychotic, and some studies have demonstrated its efficacy also in TRS.
- Olanzapine, particularly in higher dosages, might be considered as an alternative to clozapine in TRS; however, most robust evidence still supports clozapine as the gold standard.

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Introduction

Antipsychotics are the mainstay of treatment of schizophrenia.[1] However 20–30% of patients do not respond appropriately to conventional or second generation antipsychotics (SGAs)[2] and are considered treatment-resistant, or refractory, presenting persistent psychotic symptoms and chronically disability.[3] This represents a significant socioeconomic impact.[4]

Clozapine is the gold standard for treatment-resistant schizophrenia (TRS) patients,[5] based on its well established efficacy when compared with first generation antipsychotics (FGAs).[6–12] Nevertheless, serious adverse events, and precautions associated to clozapine use, might limit its use for up to 5% of patients with schizophrenia.[13] Data comparing clozapine to other SGAs are still controversial,[14] in spite of recent guidelines emphasizing the recommendation of clozapine for TRS patients.[15]

In a meta-analysis published in 2001,[7] clozapine had a greater overall effect size when compared with other SGAs in TRS patients, but the difference was small in two trials that compared clozapine with risperidone.[16,17] Data obtained from other meta-analyses with patients with schizophrenia, regardless of refractoriness status,[18,19] suggest that clozapine was superior just to zotepine and risperidone, whereas olanzapine was superior to risperidone, quetiapine, and aripiprazole, with no difference when compared with clozapine or amisulpride.

A large pragmatic trial conducted in the UK showed that clozapine led to greater improvement in Positive and Negative Syndrome Scale (PANSS) scores than other SGAs.[20] In the second phase of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE), both clozapine and olanzapine were equally effective in reducing total PANSS scores,[21] but olanzapine was more effective in terms of discontinuation rates.[21] In addition, in a meta-analysis comparing the effectiveness of SGAs except clozapine, olanzapine was superior to all other SGAs.[22]

Findings suggesting similar efficacy between clozapine and other SGAs, particularly olanzapine, might have been partially driven by dose issues.[14] Clozapine in higher doses might produce better effects than at lower doses,[23,24] and it is possible that the same dose-response relationship might occur with olanzapine in TRS patients, as suggested by one RCT,[25] although no clear dose-response pattern has been found for olanzapine in non-TRS patients.[26,27] In addition, metabolic adverse events might limit the use of high doses of olanzapine.[28]

Based on the evidence that shows a comparable efficacy of clozapine and olanzapine, but not other SGAs, in patients with TRS, further assessment is needed. Therefore, in the present study, we show the results of a systematic review and meta analyses that assess and test such evidence supporting the use of olanzapine in patients with TRS, as an alternative to clozapine.

Methods

A systematic review of the literature was performed to identify all prospective, randomized, double-blind, controlled trials that have compared SGAs with clozapine in patients with schizophrenia according to the criteria in the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV),[29] aged 18 years or older, who were considered treatment-resistant (i.e., have failed to respond to at least one prior antipsychotic with appropriate dose and duration of treatment). Crossover studies were included if it was possible to extract data just from the first part of the study. For the present article, only the studies comparing olanzapine with clozapine were included.

Efficacy outcomes were as follows: (a) mean scores at the endpoint of the trial, or mean changes from baseline to endpoint, on PANSS,[30] Brief Psychiatric Rating Scale (BPRS),[31] Clinical Global Improvement (CGI),[32] or any other rating scale; (b) proportion of patients with no clinically significant response, as defined by each study; and (c) dropout rates.

An electronic database search was conducted assessing studies that were published until December 2009. The search had no restriction for language, but only articles published in English were analyzed. The following databases were assessed: PUBMED, MEDLINE, EMBASE, Current Contents, BIOSIS, Derwent Drug File, International Pharmaceutical Abstracts, Evidence Based Medical Journals, PsycInfo, Cochrane's Central Register of Controlled Trials (CCRCT), and Database of Systematic Reviews. The combination of terms related to clozapine, second generation antipsychotics, and treatment resistant schizophrenia were searched in titles, abstracts, and keywords using the Boolean operator AND. The complete list of terms that were used in the search is listed in Table 1. Only clinical trials or trials with clozapine or other SGAs as investigational drugs were searched. Reference lists of relevant articles and book chapters were also hand searched.

Two reviewers (J.S. and I.T.) independently inspected all reports of identified studies, based on the titles and abstracts. All potentially eligible studies were then fully assessed to decide by consensus whether these studies met the inclusion criteria. Any disagreement was solved by consensus. The risk of bias was assessed following recommendations from the *Cochrane Handbook for*

Table 1. *List of search terms*

Clozapine	Clozapine or clozaril or leponex or denzapin or zaponex
Second generation antipsychotics	Atypical antipsychotic agent or second generation or antipsychotics or amissulpride or aripiprazole or asenapine or bifuprenox or iloperidone or olanzapine or paliperidone or quetiapine or remoxipride or risperidone or sertindole or sulpiride or ziprasidone or ziprazidone or zotepine
Treatment-resistant schizophrenia	Therapy resistant or therapy refractory or treatment resistant or treatment refractory or resistant schizophrenia or refractory schizophrenia or treatment-resistant schizophrenia or treatment resistant schizophrenia or treatment-refractory schizophrenia

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Systematic Review Interventions (CHSRI).[33] Data resulting from intention-to-treat analyses were carefully separated from data from completers ("as observed"). For dichotomous outcomes, the total number of patients and the number of patients who met the response criteria were recorded. For continuous outcomes, the scores and respective standard deviations (SD) were recorded.

Data were analyzed using the Comprehensive Meta-Analysis software.[34] All analyses were performed for single outcome measures if at least 3 studies could be pooled together. For dichotomous outcomes, the relative risk (RR) with a 95% confidence interval (CI) was calculated. For continuous outcomes, the standard mean difference (SMD), with a 95% CI, was calculated. The fixed-effect model method was employed for all analysis. Heterogeneity of studies was assessed using the Q-test as well as I^2. The overall statistical significance (p) and Z scores were also calculated.

For publication bias, funnel plots were used, but since they are limited to detect small effects,[35] they were constructed only if more than 10 studies could be pooled. A sensitivity analysis was conducted; studies with patients who were intolerant to the prior antipsychotic treatment, in addition to the truly refractory patients based on prior lack of efficacy, were excluded. Meta-regressions were conducted using olanzapine doses as moderators of the effect size. In order to establish a standardized comparison, clozapine and olanzapine doses were calculated in terms of dose equivalents of chlorpromazine.[36,37]

Findings

The original search yielded 248 articles. Of those, 83 were selected as potentially eligible to be included, and 10 articles compared SGAs to clozapine.[6,25,38–45] In addition, one study was added by hand searching.[17] (See Figure 1.) Seven studies compared clozapine with olanzapine, and therefore are included in the current analyses (Table 2).[25,39–42,44,45] All these studies were short term (8–28 weeks), parallel group trials, except for one crossover study.[40] Less than 20% of patients were representatives of developing countries. Analysis included 648 patients with schizophrenia and 29 patients with schizoaffective disorder. The mean age ranged from 34 to 40.8 years old, with a mean duration of illness ranging from 7.1 to 15.8 years and the mean number of hospitalizations ranging from 6 to 11. Most studies reported no data regarding the use of concomitant medication, although the use of hypnotic-sedative agents was permitted in all trials. Refractoriness was defined by failure to one[39,42] or two[25,40,41,45] prior antipsychotics, but two trials

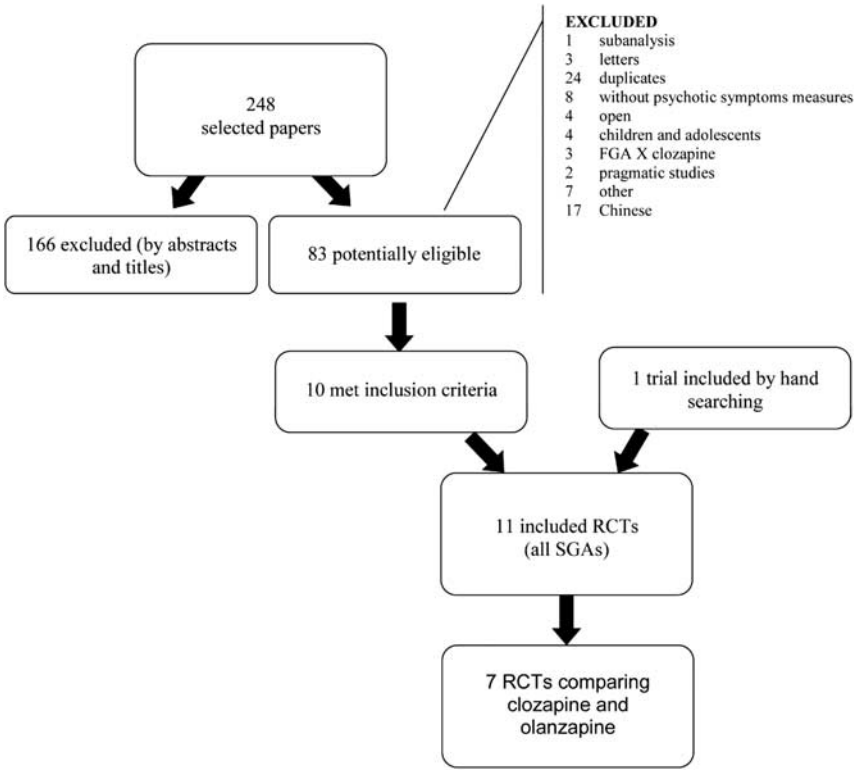

Figure 1. Included and excluded studies.

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Table 2. *Characteristics of included studies*

Study	Year	Design	Weeks	N[1]	# of prior AP	Subset of intolerant[2] patients	Age[3]
Meltzer *et al.*[25]	2008	Parallel	24	40	2	N	36.8 (10)
Tollefson *et al.*[44]	2001	Parallel	18	176	2	N	38.6 (10.6)
Volavka *et al.*[45]	2002	Parallel	14	157	1	N	40.8 (9.2)
Conley *et al.*[40]	2003	Crossover	16	13	2	N	37.5 (9)
Bitter *et al.*[39]	2003	Parallel	18	150	1	Y	37.6 (SD NA)
Moresco *et al.*[41]	2004	Parallel	8	23	2	N	37.6 (9.4)
Naber *et al.*[42]	2005	Parallel	28	108	1	Y	34 (10.6)

SA = schizoaffective disorder patients, AP = antipsychotics, NA = not available, SD = standard deviation, N = No, Y = Yes, USA = United States of America.

1. Randomized patients.
2. Patients who were intolerant to their prior antipsychotic regimen.
3. Mean (SD).

Table 3. *Clozapine and olanzapine final mean doses (mg/D)*[1]

Study	Clozapine	Olanzapine
Meltzer *et al.*[25]	564 (243)	33.6 (11.2)
Tollefson *et al.*[44]	303.6 (108.7)	20.5 (2.8)
Volavka *et al.*[45]	526.6 (140.3)	30.4 (6.6)
Conley *et al.*[40]	450[2]	50[2]
Bitter *et al.*[39]	216.2 (107.9)	17.2 (4.8)
Moresco *et al.*[41]	325.4 (9.7)[3]	18.3 (0.5)[3]
Naber *et al.*[42]	209 (91)	16.2 (4.8)

1. ITT.
2. Fixed dose.
3. Completers.

also included an unidentified subset of patients who were intolerant to their previous antipsychotic regimen.[39,42] Two trials specifically compared clozapine to a high dose of olanzapine,[25,40] but in all other trials, the mean doses of olanzapine were relatively high (Table 3). With only one exception,[40] all studies were sponsored by pharmaceutical companies, which is an important bias. No meta-analyses pooled more than 10 studies, and therefore no funnel plots were constructed.

For five outcome measures, it was possible to pool results from at least three studies (Table 4). Meta-analyses did not detect differences between clozapine and olanzapine in terms of dropout rates (ITT) (RR = 0.93, $CI_{95\%}$ = 0.77–1.12, Figure 2), in terms of the total PANSS endpoint (SMD = 0.21, $CI_{95\%}$ = –0.04–0.46, Figure 3), or in mean changes of the total PANSS (ITT) (SMD = 0.08, $CI_{95\%}$ = –0.01–0.027, Figure 4). For dropout rates and total PANSS endpoint meta-analyses, a sensitivity analysis was done that excluded studies with a subset of intolerant patients,[39,42] and this did not change the results.

However, in the analysis of endpoints of PANSS positive and negative subscales, clozapine was superior to olanzapine (respectively, SMD = 0.51, $CI_{95\%}$ = 0.17–0.86, Figure 5; and SMD = 0.50, $CI_{95\%}$ = 0.16–0.85, Figure 6). No heterogeneity was found in any of the meta-analyses. Meta-regression analyses did not show any significant result.

Discussion

The results of the present meta-analyses showed that there were no significant differences between olanzapine and clozapine in patients with TRS, as measured by dropout rates or total PANSS scale. However, this similarity should be interpreted with caution, taking into consideration that clozapine was superior to olanzapine in terms of efficacy on both positive and negative symptoms.

The dose issue is particularly important in the interpretation of this present review of results. In fact, two studies[25,40] showed an important impact toward better olanzapine results, and that might be related to the mean olanzapine dose, which was considerably higher than the usual dose in both studies (33.6 ± 11.2 and 30.4 ± 6.6, respectively). In all studies comparing clozapine to olanzapine, the olanzapine dose was higher than the standard doses commonly used in clinical practice, with a mean final dose ranging from 16.2 ± 4.8[42] to 33.6 ± 1.2.[25] Additionally, in at least two studies,[39,42] the mean final dose of clozapine was considered to be subtherapeutic (216.2 ± 107.9 and 209 ± 91, respectively). One of the industry-sponsored trials that was included in this review[44] compared a moderate dose of clozapine (303.6 ± 108) with a high

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Table 4. *Single outcome metanalysis*

Outcome	Number of pooled studies	Results
Dropout rates (ITT)	6	RR = 0.93, $CI_{95\%}$ = 0.77–1.12
PANSS total—endpoints	4	SMD = 0.21, $CI_{95\%}$ = –0.04–0.46
PANSS total—mean change (ITT)	3	SMD = 0.08, $CI_{95\%}$ = –0.01–0.027
PANSS Positive Symptoms Subscale—endpoints	3	SMD = 0.51, $CI_{95\%}$ = 0.17–0.86
PANSS Negative Symptoms Subscale—endpoints	3	SMD = 0.50, $CI_{95\%}$ = 0.16–0.85

PANSS = Positive and Negative Symptoms Scale; ITT = Intention to treat analysis; RR = relative risk; SMD = standardized mean difference; CI = confidence interval.

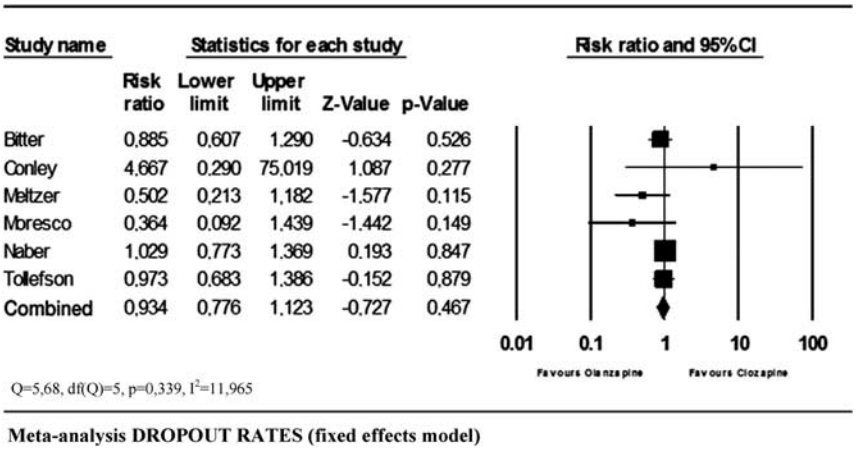

Figure 2. Dropout rates (ITT).

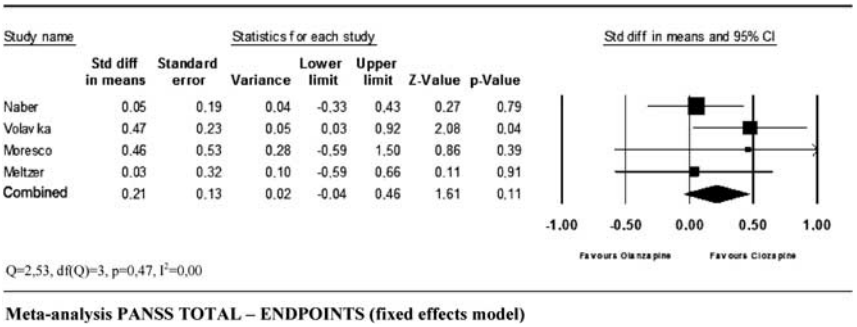

Figure 3. Panss total – endpoints.

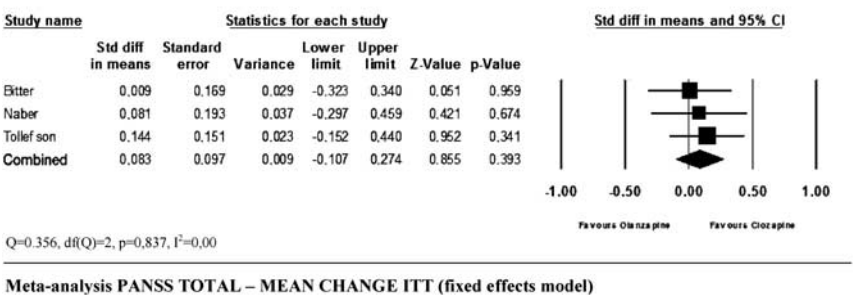

Figure 4. Panss total – mean change (ITT).

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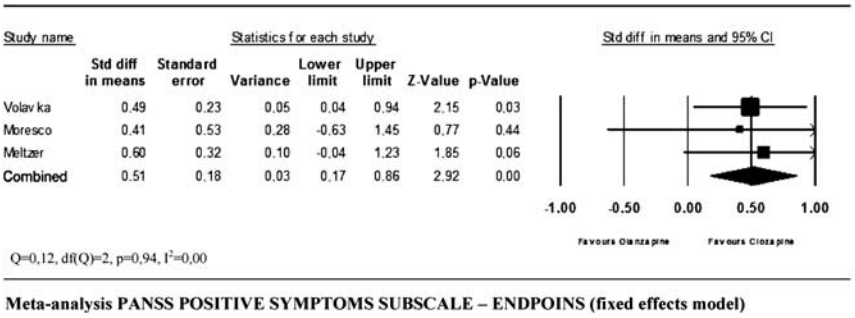

Figure 5. Panss positive symptoms subscale – endpoints.

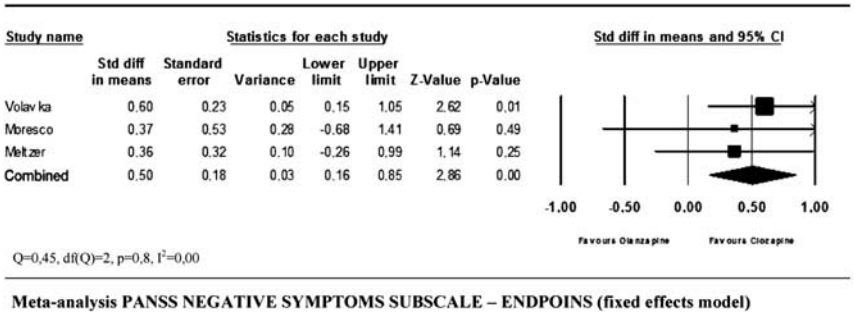

Figure 6. Panss negative symptoms subscale - endpoints.

dose of olanzapine (20.5 ± 2.8), raising the issue of sponsorship bias. The hypothesis that a high dose of olanzapine can positively influence its efficacy in patients with TRS had already been previously observed in noncontrolled settings,[46–53] in spite of the evidence showing a lack of a clear dose-response pattern for non-TRS patients.[26,27]

This is important, as several studies have reported a similar efficacy between clozapine and olanzapine in the last decade. For example, clozapine was found to have similar efficacy to olanzapine, according to PANSS total score and PANSS positive subscale, in a meta-analysis that included 78 studies with 13,558 patients.[19] Additionally, in the case of pragmatic trials, such as the second phase of the CATIE trial, which compared olanzapine, risperidone, and quetiapine, with clozapine, no statistically significant difference was observed between clozapine, with a final mean dose of 332.1 ± 156.9, and olanzapine, with a final mean dose of 23.4 ± 7.9, both in terms of time for discontinuation due to any reason and due to lack of efficacy.[21] However, the relationship between such results and treatment resistance is unclear, since both studies included a nonselected population of schizophrenia patients.

Adverse events and safety-related outcomes of clozapine or olanzapine in TRS patients were not focused on in this review, but should be taken into consideration while assessing the results. The use of SGAs is generally associated with impaired glucose metabolism, diabetes mellitus, weight gain, and dyslipidemia, with olanzapine presenting a higher risk when compared to most SGAs.[28] Therefore high dose olanzapine might represent a higher risk of metabolic adverse events. Although the evidence regarding a dose-response correlation between olanzapine concentration and weight gain is conflicting,[54,55] one RCT that was included in the present review, which specifically addressed high dose olanzapine in TRS patients, showed a significantly higher risk of weight gain and increase in body mass index (BMI) for olanzapine-treated patients when compared with clozapine, at 6 months but not 6 weeks, which also raises the issue of time effects when assessing metabolic adverse events.[25]

The present study has the following limitations: (a) Data from the PANSS General Psychopathology Sub-Scale was not available in most studies, which hindered additional analysis regarding differential effects of clozapine and olanzapine in other important general psychopathological symptoms; (b) two studies[42] made no appropriate distinction between truly refractory and intolerant patients, although sensitivity analysis that was conducted excluding these studies showed no important impact in the overall results; (c) two trials included a small subset of schizoaffective patients,[25,45] although significant heterogeneity was not found due to these studies; (d) non-English

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language articles were not included in the present review (however, in a meta-analysis that compared clozapine with FGAs, such criteria showed no effect on the final results)[9]; and (e) difficulties inherent in research on schizophrenia, such as the lack of homogeneity of a refractory schizophrenia criteria, variability in terms of doses and titration schemes, small sample sizes, and relatively short periods of observation. To our knowledge, this is the first systematic review and meta-analysis that evaluated the efficacy of olanzapine in comparison with a well-established drug (i.e., clozapine) in treatment-resistant schizophrenia.

Conclusions

The results of this study suggest that clozapine is significantly more efficacious than olanzapine in improving positive and negative symptoms in TRS patients.

Disclosures

Juliano S. Souza was an employee at Abbott Laboratories. Monica Kayo has acted as a consultant for Abbott, Aché, Apsen, Glaxo-Smithkline, Janssen-Cilag, Novartis, and União Química; she received a research grant from Roche and travel support from Eli Lilly. Ivson Tassell has received research honoraria from Janssen-Cilag. Camila Bertini Martins has no conflicts of interest to declare. Helio Elkis has acted as a consultant for, received travel support from, was member of the speaker's bureau for, and received research grants from Astra-Zeneca, Eli Lilly, Janssen-Cilag, Lundbeck, Moksha 8, Novartis, Organon, Pfizer, Roche, and Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP).

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