Comparison of the Efficacy and Acceptability of Atypical Antipsychotic Drugs: a Meta-Analysis of Randomized, Placebo-Controlled Trials

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Abstract

Knowing the clinical differences of olanzapine, quetiapine, and risperidone would be of benefit for choosing an atypical antipsychotic drug. In order to compare their efficacy and acceptability, we conducted a meta-analysis of published, randomized, placebo-controlled trials by comparing the response and dropout rates of an atypical antipsychotic drug group and those of a placebo group. After a comprehensive search of study reports, the response and dropout rates of patients treated with an atypical antipsychotic drug and those treated with placebo were extracted on the intention-to-treat basis. The effect size with 95 per cent confidence interval (CI) of pooled data comparing the response and dropout rates of an atypical antipsychotic drug group and those of a placebo group were calculated by using the Peto method. The response-rate effect sizes (95% CIs) of olanzapine, quetiapine, and risperidone were 1.75 (1.06 to 2.89), 1.71 (1.20 to 2.42), and 3.28 (1.98 to 5.44), respectively. The dropout-rate effect sizes (95% CIs) of olanzapine, quetiapine, and risperidone were 0.55 (0.35 to 0.88), 0.65 (0.46 to 0.91), and 0.39 (0.24 to 0.62), respectively. In conclusion, olanzapine, quetiapine, and risperidone are more effective and more acceptable than placebo in treating schizophrenic patients. However, they are not different from each other in the respect of efficacy and acceptability. The cost of these agents should play an important role in choosing an atypical antipsychotic drug.

Key word : Antipsychotic Drugs, Olanzapine, Quetiapine, Risperidone, Randomized-Controlled Trial, Meta-Analysis

Antipsychotic drugs are the mainstay of treatment for schizophrenic patients. The discovery of conventional antipsychotic drugs in the1950's has been considered a major progress in psychiatry. The use of these drugs, for example, chlorpromazine, haloperidol, can relieve psychotic symptoms, decreases the schizophrenic patients' need for hospitalization, and makes outpatient services for schizophrenic patients possible. So far, conventional antipsychotic drugs have been the standard treatment for schizophrenic patients.

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Although conventional antipsychotic drugs have been widely accepted as the standard treatment for schizophrenia, their limitations have been of concern. Firstly, due to a variety of mechanisms of action, conventional antipsychotic drugs cause several adverse effects, such as, extrapyramidal side effects, sedation, orthostatic hypotension, and anti-muscarinic side effects. Secondly, at least 20 per cent-30 per cent of schizophrenic patients do not respond or only partially respond to conventional antipsychotic drugs. Lastly, although conventional antipsychotic drugs are effective for positive symptoms (e.g., delusions, hallucinations), they are only partially effective for negative symptoms (e.g. blunted affect, social withdrawal).

Owing to those limitations of conventional antipsychotic drugs, several attempts have been made to find out a better antipsychotic drug. Atypical antipsychotic drugs, e.g., clozapine, olanzapine, quetiapine, risperidone, available in the 1990's represent a significant advance in therapeutics for schizophrenia. Kerwin (1994) defined an atypical antipsychotic drug as an antipsychotic drug with low propensity both to induce extrapyramidal side effects and to increase serum prolactin level[1]. It has been suggested that they are effective for treating both positive and negative symptoms and are well tolerated[2]. However, clozapine is different from other atypical antipsychotic drugs in several respects, e.g. its effectiveness for treatment-resistant schizophrenia and its propensity to induce agranulocytosis. The differences among olanzapine, quetiapine, and risperidone have not been made clear.

Due to the several advantages of olanzapine, quetiapine, and risperidone, it is likely that physicians will prescribe these agents more and more. Knowing the clinical differences of these agents would be of benefit for choosing an atypical antipsychotic drug. However, there has been no study with head-to-head comparison of these three agents.

Meta-analysis is a method for synthesis data obtained from similar studies. In carrying out a meta-analysis, comparison of atypical antipsychotic drugs with a placebo should be a reliable strategy since the effects of a placebo on patients are not different from study to study. After knowing the effect size of an atypical antipsychotic drug in comparison to a placebo, the differences among atypical antipsychotic drugs can be known.

In order to compare the efficacy and acceptability of olanzapine, quetiapine, and risperidone, we conducted a meta-analysis of published, randomized, placebo-controlled trials carried out on adult schizophrenic patients. Since response and dropout rates represent the efficacy and acceptability of a treatment, respectively, we compared the response and dropout rates of each atypical antipsychotic drug group and those of the placebo group.

MATERIAL AND METHOD

We started performing MEDLINE search from 1966 to March 1998 by using the following strategy: (olanzapine or quetiapine or risperidone) and placebo and schizophrenia. After that, the search was limited to only randomized controlled trials. Finally, only papers presenting data relevant to the response and dropout rates of adult psychotic patients were taken into consideration. Owing to the failure of electronic searches to detect all relevant references, we also examined the reference lists of identified papers but found no more published papers. Since multiple publications from single studies can lead to bias in several ways[3], we selected only one paper presenting the best details of each trial.

In each study, the response and dropout rates of patients treated with an atypical antipsychotic drug and those treated with a placebo were extracted on the intention-to-treat basis. The number of patients randomized to each treatment group was considered as the total number of patients.

For the trials in which several fixed doses of atypical antipsychotic drugs were given, only the patients' data treated with the recommended doses were included in the analysis. The recommended doses were as follows: i) 5-15 mg/day of olanzapine, ii) 150-750 mg/day of quetiapine, and iii) 2-16 mg/day of risperidone.

The Odds Ratio with 95 per cent confidence interval (CI) was computed for each rate comparison[4,5]. The effect size with 95 per cent CI of pooled data comparing the response and dropout rates of the atypical antipsychotic drug group and those of the placebo group were calculated by using the Peto method[6]. The heterogeneity of pooled data were also assessed by using the Chi-square test.

Regarding the interpretation, the response-rate effect size higher than 1 was considered to be favourable for the atypical antipsychotic drug. The dropout-rate effect size lower than 1 was considered

to be favourable for the atypical antipsychotic drugs. The p-value of Chi-square test that was higher than 0.05 indicated the homogeneity of pooled data.

RESULTS

This meta-analysis included the data of 2 olanzapine trials[7,8], 4 quetiapine trials[9-12], and 3 risperidone trials[13-15]. The total number of patients given olanzapine, quetiapine, and risperidone was 248, 457, and 360, respectively. Four hundred and twenty-four patients were given placebo. All patients met the DSM-III-R diagnostic criteria for schizophrenia[16]. The study duration of all trials, except one, was between 6 and 8 weeks. Table 1 shows the characteristics of each study.

Table 2 shows the response rates, the response-rate Odds Ratios (95% CIs), and the res-

Table 1. Characteristics of the trials included in the meta-analysis of response and dropout rates between atypical antipsychotic drugs and placebo.

Author	Study duration (weeks)	Treatment allocation[a]	Measure of response[b]	Definition of response[b]
Beasley et al 1996a	6	Placebo (68) O 5.0 mg/d (65) O 10.0 mg/d (64) O 15.0 mg/d (69) H 15.0 mg/d (69)	BPRS (0-6)	BPRS decreased ≥ 40%
Beasley et al 1996b	6	Placebo (50) O 1.0 mg/d (52) O 10.0 mg/d (50)	BPRS (0-6)	BPRS decreased ≥ 40%
Fabre et al 1995	3	Placebo (4) Q 250 mg/d (8)	BPRS (1-7)	BPRS decreased ≥ 30%
Borison et al 1996	6	Placebo (55) Q 307 mg/d (54)	CGI	CGI rated as improved
Arvanitis et al 1997	6	Placebo (51) Q 75 mg/d (53) Q 150 mg/d (48) Q 300 mg/d (52) Q 600 mg/d (51) Q 750 mg/d (54) H 12 mg/d (52)	BPRS (1-7)	BPRS decreased ≥ 30%
Small et al 1997	6	Placebo (96) Q 209 mg/d (94) Q 360 mg/d (96)	BPRS (0-6)	BPRS decreased ≥ 30%
Borison et al 1992	6	Placebo (12) R 2-10 mg/d (12) H 4-20 mg/d (12)	BPRS (0-6)	BPRS decreased ≥ 20%
Chouinard et al 1993	8	Placebo (22) R 2 mg/d (24) R 6 mg/d (22) R 10 mg/d (22) R 16 mg/d (24) H 20 mg/d (21)	PANSS	PANSS decreased ≥ 20%
Marder & Meibach 1994	8	Placebo (66) R 2 mg/d (63) R 6 mg/d (64) R 10 mg/d (65) R 16 mg/d (64) H 20 mg/d (66)	PANSS	PANSS decreased ≥ 20%

[a] H = haloperidol; O = olanzapine; Q = quetiapine; R = risperidone.
[b] BPRS = Brief Psychiatric Rating Scale; CGI = Clinical Global Impression Scale; PANSS = Positive and Negative Syndrome Scale for Schizophrenia.

ponse-rate effect sizes (95% CIs). In comparison to placebo, the response-rate effect sizes (95% CIs) of olanzapine, quetiapine, and risperidone were 1.75 (1.06 to 2.89), 1.71 (1.20 to 2.42), and 3.28 (1.98 to 5.44), respectively.

Table 3 shows the dropout rates, the dropout-rate Odds Ratios (95% CIs), and the dropout-rate effect sizes (95% CIs). In comparison to placebo, the dropout-rate effect sizes (95% CIs) of olanzapine, quetiapine, and risperidone were 0.55 (0.35 to 0.88), 0.65 (0.46 to 0.91), and 0.39 (0.24 to 0.62), respectively.

It is of interest to note that all p-values of the Chi-square test were higher than 0.05 which indicated that the pooled data were not significantly heterogeneous (see Table 2 and Table 3).

Table 2. The response rate, the response-rate odd ratio (95% CI) of each comparison, and the efficacy effect size (95% CI) of each pooled data.

Author	Treatment[a]	Response rate of treatment group	Response rate of placebo group	Response-rate odd ratio (95% CI)
Beasley et al 1996a	O vs Placebo	79/198	21/68	1.47 (0.83 to 2.59)
Beasley et al 1996b	O vs Placebo	12/50	4/50	3.25 (1.12 to 9.42)
Effect size (Chi-square = 1.67, df = 1, p = 0.20)		91/248	25/118	1.75 (1.06 to 2.69)
Fabre et al 1995	Q vs Placebo	8/8	2/4	27.11 (1.24 to 591.99)
Borison et al 1996	Q vs Placebo	15/54	13/55	1.24 (0.53 to 2.92)
Arvanitis et al 1997	Q vs Placebo	100/205	18/51	1.72 (0.93 to 3.17)
Small et al 1997	Q vs Placebo	98/190	35/96	1.76 (1.08 to 2.88)
Effect size (Chi-square = 3.64, df = 3, p = 0.30)		219/457	68/206	1.71 (1.20 to 2.42)
Borison et al 1992	R vs Placebo	7/12	0/12	14.97 (2.67 to 83.87)
Chouinard et al 1993	R vs Placebo	30/92	2/22	3.17 (1.13 to 8.89)
Marder & Meibach 1994	R vs Placebo	77/256	7/66	2.74 (1.48 to 5.06)
Effect size (Chi-square = 3.32, df = 2, p = 0.19)		114/360	9/100	3.28 (1.98 to 5.44)

O = olanzapine; Q = quetiapine; R = risperidone.

Table 3. The dropout rate, the dropout-rate odd ratio (95% CI) of each comparison, and the acceptability effect size (95% CI) of each pooled data.

Author	Treatment[a]	Dropout rate of treatment group	Dropout rate of placebo group	Dropout-rate odd ratio (95% CI)
Beasley et al 1996a	O vs Placebo	111/198	40/68	0.62 (0.35 to 1.09)
Beasley et al 1996b	O vs Placebo	31/50	40/50	0.42 (0.18 to 0.99)
Effect size (Chi-square = 0.55, df = 1, p = 0.46)		142/248	86/118	0.55 (0.35 to 0.88)
Fabre et al 1995	Q vs Placebo	0/8	1/4	0.05 (0.00 to 3.18)
Borison et al 1996	Q vs Placebo	26/54	33/55	0.62 (0.29 to 1.32)
Arvanitis et al 1997	Q vs Placebo	107/205	35/51	0.52 (0.28 to 0.95)
Small et al 1997	Q vs Placebo	102/190	57/96	0.79 (0.49 to 1.30)
Effect size (Chi-square = 2.66, df = 3, p = 0.45)		235/457	126/206	0.65 (0.46 to 0.91)
Borison et al 1992	R vs Placebo	NA	NA	
Chouinard et al 1993	R vs Placebo	36/92	16/22	0.26 (0.10 to 0.66)
Marder & Meibach 1994	R vs Placebo	122/256	45/66	0.44 (0.26 to 0.76)
Effect size (Chi-square = 0.91, df = 1, p = 0.34)		158/348	61/88	0.39 (0.24 to 0.62)

O = olanzapine; Q = quetiapine; R = risperidone.

DISCUSSION

Regarding the response-rate effect sizes of three agents, the lower ends of 95 per cent CIs that were higher than 1 suggest the significant superiority of olanzapine, quetiapine, and risperidone to placebo. However, the overlap of these 95 per cent CIs indicates the nonsignificant difference of efficacy among them.

Regarding the dropout-rate effect sizes of three agents, the upper ends of 95 per cent CIs were lower than 1. These results suggest that olanzapine, quetiapine, and risperidone are significantly more acceptable than placebo. Similar to their efficacy, the overlap of these 95 per cent CIs indicates the nonsignificant difference of acceptability among them.

The findings of this meta-analysis should be helpful for choosing an atypical antipsychotic drug for a schizophrenic patient. Since olanzapine, quetiapine, and risperidone are not different in the respect of efficacy and acceptability, the cost of these agents should play an important role in choosing an atypical antipsychotic drug. Prescribing the least expensive atypical antipsychotic drug should be of economical benefit without losing the therapeutic effects. The other issue that should be taken into account in choosing an atypcial antipsychotic drug is the individual preference, especially, the acceptable side effects. Although all three atypical antipsychotic drugs are well tolerated, their side-effect profiles are a bit different. For example, as weight gain is a prevalent adverse effect of olanzapine, dry mouth and dizziness are prevalent ones of quetiapine. A prevalent adverse effect of risperidone appears to be dizziness.

Some limitations should be considered in interpreting the results of this analysis. Firstly, since the patients included in this meta-analysis were general adult schizophrenic patients, the results should not be generalized to schizophrenic patients with special characteristics, for example, treatment-resistant schizophrenia, late-onset schizophrenia. Secondly, those results obtained from the trials with a study duration of 3-8 weeks. Therefore, this meta-analysis does not determine the long-term outcome of those three agents. Thirdly, the results of a study of 3 weeks' duration[9] may slightly distort the effect sizes of quetiapine-treated group. Although some patients in this study responded to the treatment, the duration of the study seems to be too short to investigate the real effects of an antipsychotic drug. However, because of the small sample size, the results of this 3-week study only had a small effect on the effect sizes of the quetiapine-treated group. Lastly, patients' responses to atypical antipsychotic drugs may be an individual issue. In some schizophrenic patients, a particular atypical antipsychotic drug may be more effective than others without any known explanation.

In conclusion, olanzapine, quetiapine, and risperidone are more effective and more acceptable than placebo in treating schizophrenic patients. However, they are not different from each other in the respect of efficacy and acceptability. The cost of these agents should play an important role in choosing an atypical antipsychotic drug.

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REFERENCES

1. Kerwin RW. The new atypical antipsychotics. Br J Psychiatry 1994;164:141-8.
2. Stahl SM. What makes an antipsychotic atypical? J Clin Psychiatry 1998;59:403-4.
3. Huston P, Moher D. Redundancy, disaggregation, and the integration of medical research. Lancet 1996;347:1024-6.
4. Fleiss JL. Confidential intervals for the odds ratio in case-control studies: the state of the art. J Chron Dis 1979; 32: 69-77.
5. Fleiss JL. Statistical methods for rates and proportions. 2nd ed. New York: Wiley, 1981.
6. Yusuf S, Peto R, Lewis J, Collins R, Sleight P. Beta blockade during and after myocardial infarction: an overview of the randomized trials. Prog Cardiovas Dis 1985; 5: 335-71.
7. Beasley Jr CM, Tollefson G, Tran P, et al. Olanzapine versus placebo and haloperidol: acute phase results of the North American double-blind olanzapine trial. Neuropsychopharmacol 1996; 14: 111-23.
8. Beasley Jr CM, Sanger T, Satterlee W, et al. Olanzapine versus placebo: results of a double-blind,

fixed-dose olanzapine trial. Psychopharmacol 1996; 124: 159-67.
9. Fabre LF, Arvanitis L, Pultz J, Jones VM, Malick JB, Slotnick VB. ICI 204,636, a novel, atypical antipsychotic - early indication of safety and efficacy in patients with chronic and subchronic schizophrenia. Clin Therapeutics 1995; 17: 366-78.
10. Borison RL, Arvanitis LA, Miller BG, Study Group. ICI 204,636, an atypical antipsychotic - efficacy and safety in a multicenter, placebo-controlled trial in patients with schizophrenia. J Clin Psychopharmacol 1996; 16: 158-69.
11. Arvanitis LA, Miller BG, the Seroquel Trial 13 Study Group. Multiple fixed doses of "Seroquel" (quetiapine) in patients with acute exacerbation of schizophrenia: a comparison with haloperidol and placebo. Biol Psychiatry 1997; 42: 233-46.
12. Small JG, Hirsch SR, Arvanitis LA, Miller BG, Link CGG, and the Seroquel Study Group. Quetiapine in patients with schizophrenia. A high- and low-dose double-blind comparison with placebo. Arch Gen Psychiatry 1997; 54: 549-57.
13. Borison RL, Pathiraja AP, Diamond BI, Meibach RC. Risperidone: clinical safety and efficacy in schizophrenia. Psychopharmacol Bull 1992; 28: 213-8.
14. Chouinard G, Jones B, Remington G, et al. A Canadian multicenter placebo-controlled study of fixed doses of risperidone and haloperidol in the treatment of chronic schizophrenic patients. J Clin Psychopharmacol 1993; 13: 25-40.
15. Marder SR, Meibach RC. Risperidone in the treatment of schizophrenia. Am J Psychiatry 1994; 151: 825-35.
16. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 3rd revised ed. Washington, DC: American Psychiatric Press, 1987.

การเปรียบเทียบประสิทธิภาพและการยอมรับยารักษาโรคจิตชนิดผิดพวก : มหวิเคราะห์ของการทดลองชนิดสุ่มตัวอย่างที่มีการควบคุมด้วยยาหลอก

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การทราบถึงความแตกต่างทางคลินิกของ olanzapine, quetiapine และ risperidone เป็นสิ่งที่มีประโยชน์ต่อการเลือกยารักษาโรคจิตชนิดผิดพวก ในการเปรียบเทียบประสิทธิภาพและการยอมรับยาดังกล่าว, ผู้นิพนธ์ได้ทำมหวิเคราะห์ของการทดลองชนิดสุ่มตัวอย่างที่มีการควบคุมด้วยยาหลอกโดยการเปรียบเทียบอัตราการตอบสนองและการออกจากการวิจัยของกลุ่มที่ได้รับยารักษาโรคจิตชนิดผิดพวกแต่ละตัวกับอัตราดังกล่าวของกลุ่มที่ได้รับยาหลอก หลังจากได้ค้นหาบทความอย่างครอบคลุมแล้ว อัตราการตอบสนองและการออกจากการวิจัยของผู้ป่วยที่ได้รับการรักษาด้วยยารักษาโรคจิตชนิดผิดพวกและอัตราดังกล่าวของผู้ป่วยที่ได้รับยาหลอกได้ถูกสกัดด้วยวิธี intention-to-treat ในการเปรียบเทียบอัตราการตอบสนองและการออกจากการวิจัยของกลุ่มที่ได้รับยารักษาโรคจิตชนิดผิดพวกและอัตราดังกล่าวของกลุ่มที่ได้รับยาลวง effect size และ 95% confidence interval (95% CI) ของข้อมูลรวมถูกคำนวณโดยวิธีการของ Peto ในด้านประสิทธิภาพ effect sizes (95% CIs) ของอัตราการตอบสนองของ olanzapine, quetiapine และ risperidone เท่ากับ 1.75 (1.06 ถึง 2.89), 1.71 (1.20 ถึง 2.42) และ 3.28 (1.98 ถึง 5.44) ตามลำดับในด้านการยอมรับ effect sizes (95% CIs) ของอัตราการออกจากการวิจัยของ olanzapine, quetiapine และ risperidone เท่ากับ 0.55 (0.35 ถึง 0.88), 0.65 (0.46 ถึง 0.91) และ 0.39 (0.24 ถึง 0.62) ตามลำดับ โดยสรุป olanzapine, quetiapine และ risperidone มีประสิทธิภาพและการยอมรับสูงกว่ายาหลอกในการรักษาผู้ป่วยโรคจิตเภท อย่างไรก็ตาม ยาดังกล่าวไม่แตกต่างกันในด้านประสิทธิภาพและการยอมรับ ค่าใช้จ่ายของยาน่าจะเป็นปัจจัยสำคัญในการเลือกยารักษาโรคจิตชนิดผิดพวก

คำสำคัญ : ยารักษาโรคจิต, โอแวนซาพีน, คิวทิอะพีน, ริสเพอริโดน, มหวิเคราะห์, การทดลองสุ่มตัวอย่างที่มีการควบคุมด้วยยาหลอก

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