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VARIOUS EFFECTS OF ANTIPSYCHOTICS ON P50 SENSORY GATING IN CHINESE SCHIZOPHRENIA PATIENTS: A META-ANALYSIS

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SUMMARY

***Background**: The aim of this study was to conduct a meta-analysis so we could evaluate the impact of antipsychotics on the P50 ratio in Chinese schizophrenia patients.*

***Methods**: Data were collected from the following databases: PubMed, China Biological Medicine Database, China National Knowledge Infrastructure, Cochrane Library and Elsevier Science Direct, with the latest report up to May 2011. An effect size with a 95% confidence interval (CI) was used to assess the strength of various effects of antipsychotics on P50 ratio in the patients.*

***Results**: A total of six studies including 315 and 285 schizophrenia patients at the baseline and endpoint, respectively. Overall, no significant effect of these medicines on the P50 ratio was found (overall effect z=1.03, p=0.30; heterogeneity: Chi^2=2.81, df=8, p=0.95, I^2=0%). In subgroup analysis by drug, we did not find any significant effects on P50 ratio in either first-generation antipsychotics (effect z=0.92, p=0.36; heterogeneity: Chi^2=0.00, df=1, p=0.98, I^2=0%) or second-generation antipsychotics (effect z=0.55, p=0.58; heterogeneity: Chi^2=2.38, df=5, p=0.79, I^2=0%).*

***Conclusion**: Our meta-analysis suggests that neither the first-generation nor the second-generation antipsychotics had any significant effects on P50 ratio in Chinese patients with schizophrenia.*

Key words: *schizophrenia - P50 - sensory gating - antipsychotics - meta-analysis*

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INTRODUCTION

Schizophrenia is a severe mental illness characterrized by significant impairment of cognitive, social, and psychological functioning (Ross et al. 2006). It has been suggested that defects in one or more basic neurophysiological mechanisms might account for such symptoms (Potter et al. 2006). Schizophrenia patients have a deficit in gating the response to extraneous sensory stimuli (sensory gating); hence, they are flooded by sensory input that they then have trouble organizing (Turetsky et al. 2007). P50 is an electroencephalogram (EEG) event-related potential (ERP) waveform occurring at 50 ms (P50) used to assess sensory gating (de Wilde et al. 2007).

The P50 is an early positive component of the auditory averaged response, which is recorded at the vertex 50 ms after a click stimulus that can be elicited by the paired click paradigm (Patterson et al. 2008). In this paradigm, when using a paired click paradigm with a 500-ms interval, a reduced P50 response after the second (test) stimulus compared with the P50 response after the first (conditioning) stimulus is expected. The most commonly used sensory gating index is the P50 ratio (Potter et al. 2006), or the amplitude of the P50 to the second stimulus divided by the amplitude of the P50 to the first stimulus (S2/S1).

Numerous studies have reported a P50 sensory gating abnormality in schizophrenia (L. Su et al. 2010). Furthermore, several meta-analyses have shown that schizophrenia patients have a higher P50 ratio than controls (Bramon et al. 2004, de Wilde et al. 2007, Patterson et al. 2008). A meta-analysis of P50 studies in schizophrenia carried out by de Wilde et al. (2007) had estimated the average effect size to be 1.28 (SD=0.72) when comparing the schizophrenia proband with healthy control subjects. In 2004, a meta-analysis was published (Bramon et al. 2004) showing a P50 gating deficit in patients with schizophrenia across 21 studies. In this study, the P50 ratio had a large effect size (Cohen's d=1.56, 95% CI=1.06-2.05) in schizophrenia patients. Recently, in 2010, we carried out a meta-analysis in Chinese schizophrenia patients also showing average effect size to be 1.22 (95% CI=0.95-1.49) (Su et al. 2010).

But the effects of medication on the P50 ratio were not clear from these previous studies. Conventional antipsychotic medication or first-generation antipsychotics (FGAs) do not significantly remedy the P50 gating deficit in schizophrenia patients, regardless of the magnitude of the clinical response (Adler et al. 2004, Becker et al. 2004, Light et al. 2000). It has been found that clozapine may improve P50 suppression in schizophrenia patients (Adler et al. 2004, Nagamoto et al. 1996). Results from cross-sectional studies, prone to selection bias, showed that patients treated with second-generation antipsychotics (SGAs) had better P50 ratios than patients treated with FGAs (Light et al. 2000, Yee et al. 1998). However, findings from several other studies suggest that there is not a significant differential effect of SGAs versus FGAs on the P50 sensory gating index in schizophrenia (Adler et al. 2004, Arango et al.

2003). And recently, Hong et al. (2009) and Sanchez-Morla et al. (2009) found that atypical antipsychotics had no significant impact on the P50 ratio in schizophrenia. Due to the small sample sizes and non-randomized non-blind design in most of these studies, type II error cannot be ruled out in the studies with negative findings.

Meta-analysis is a statistical procedure for combining the results of several studies to produce a single estimate of the major effect with enhanced precision (Egger et al. 1997b). It has come to play an important role in psychiatric disorders because of rapid increases in the number and size of datasets. In a meta-regression analysis of the relationship between medication and P50 ratio, Bramon et al. (2004) found no significant effect of antipsychotics on the P50 ratio, but they did not divide antipsychotics into conventional and SGA groups. Meanwhile, a high heterogeneity in effect size was found in this study, but the authors could not detect the predictors of this heterogeneity. In addition, this meta-analysis study failed to include any publications in the Chinese language. China has the largest population of any country in the world (with one-fifth of the world's population). As clinical trials are beginning to move away from wealthy countries to less wealthy countries, the proportion of clinical trials conducted in China is growing steadily (Wang 2010). Some studies have been conducted again in China to compare the medication effect on the P50 ratio (Liu et al. 2010, Yang et al. 2010, Hong et al. 2009, Wang et al. 2008, Su et al. 2011, Chen et al. 2006). Therefore, we performed a meta-analysis of all related literatures to evaluate medication effects on the P50 ratio in Chinese schizophrenia patients of a more homogeneous population.

METHODS

Literature search and inclusion criteria

Search strategy and selection criteria data were identified by electronic searches of PubMed (January 1978 to May 2011), the Chinese 'MEDLINE' China Biological Medicine Database (Chen et al. 1999) (CBM-disc 1979 to May 2011), China National Knowledge Infrastructure (CNKI 1996 to May 2011), Cochrane Library and Elsevier Science Direct (1978 to May 2011), with the terms "China", "Chinese", "Han", "P50", "sensory gating", "schizophrenia", "schizophrenic" and "psychosis". References in the relevant identified articles were hand-searched. The inclusion criteria were limited to the effects of medication on the P50 ratio in schizophrenia. Studies were done in mainland China. Only papers published in English or Chinese were included. There was no time limit for the studies.

To be included in our study articles had to meet the following inclusion criteria: (1) containing a description of ERPs elicited in patients with an ICD-9, ICD-10, DSM-III, DSM-III R or DSM-IV diagnosis of schizophrenia with an auditory paired click paradigm; (2) containing a description of P50 ratio before and after antipsychotic treatment so that estimates of the group difference effect size could be calculated; and (3) containing a description of sample size of each condition before and after antipsychotic treatment. Finally, studies were included if effect sizes could not be computed directly from the published central tendency and variance statistics, but could be derived from statistical analyses (Hozo et al. 2005)

Data analysis

When a study reported P50 gating for several patient samples (for example, schizophrenia patients on typical vs. atypical medications), each medicine was considered as an independent study and the effect sizes were calculated separately (Wolf 1986) since the ratios could be quite different. Subgroup analysis was performed by collecting summaries for subsets of studies with different characteristics grouped by the types of antipsychotics. Effect size measures were used to assess the strength of the relationship between P50 gating ratios before and after treatment, its practical importance and meaningfulness, and to complement traditional statistical tests, which provide a summary index of statistical significance. As effect size measure, the absolute value of Cohen's d was obtained by dividing the P50 ratio differences by the pooled standard deviation following the modified formula popularized (Wolf 1986, Hunter & Schmidt 2004).

Forest plots display the results of the meta-analyses in graphical format. These graphs represent the variation between the results of the various studies and an estimate of the overall effect size of all the studies together considering the data available for each study included in the meta-analysis (Lewis & Clarke 2001). The overall estimate from the meta-analysis and its CI is displayed at the bottom of the plot, represented as a diamond. Homogeneity between the trials was analyzed using Cochran's Q test (Higgins et al. 2003). I^2 describes the percentage of total variation across studies that is due to heterogeneity rather than chance, and ranges between 0% (no inconsistency) and 100% (high heterogeneity), with values of 25%, 50% and 75% suggested as low, moderate and high heterogeneity (Higgins et al. 2003). Statistically significant results are more likely to be published than studies with non-significant results. Therefore, the presence of publication bias was assessed informally by visual inspections of funnel plots, which represent a plot of a study's precision (1/standard error) against effect size. The visual assessments were corroborated by their corresponding statistical analogue by Egger's test (Egger et al. 1997a).

Meta-analyses were carried out using Stata V. 9.1 (Stata, College Station, TX, USA) and RevMan 5.1 (Review Manager (RevMan) (computer program), Version 5.1, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration 2011).

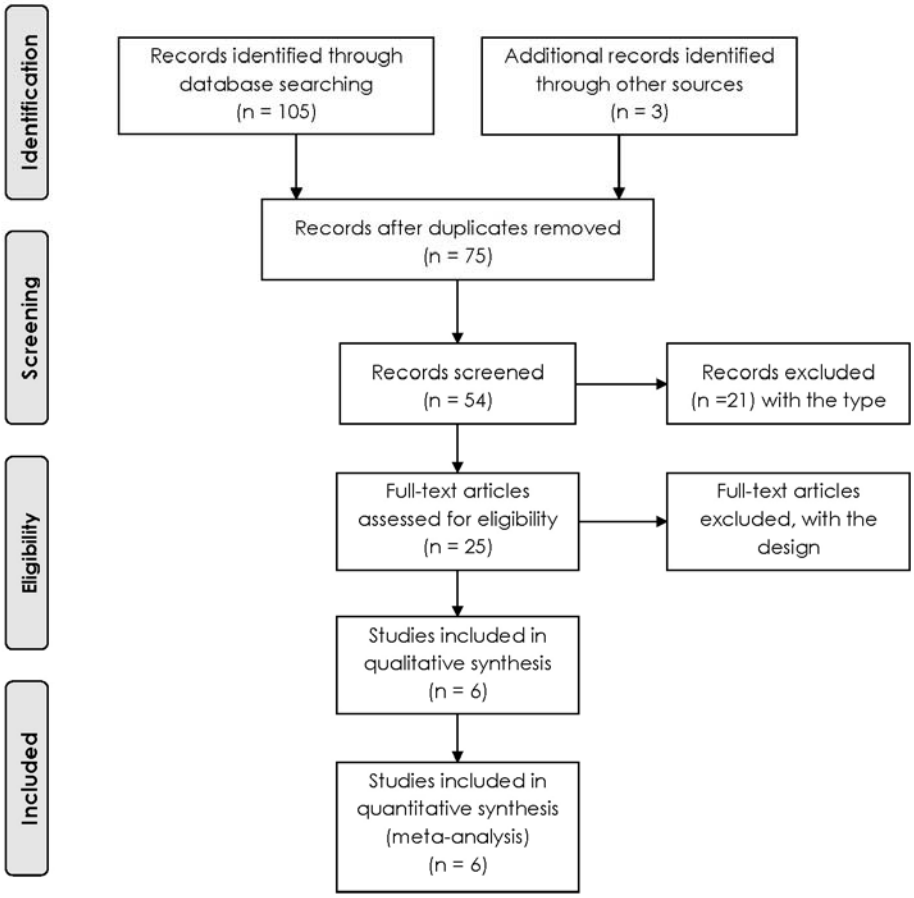
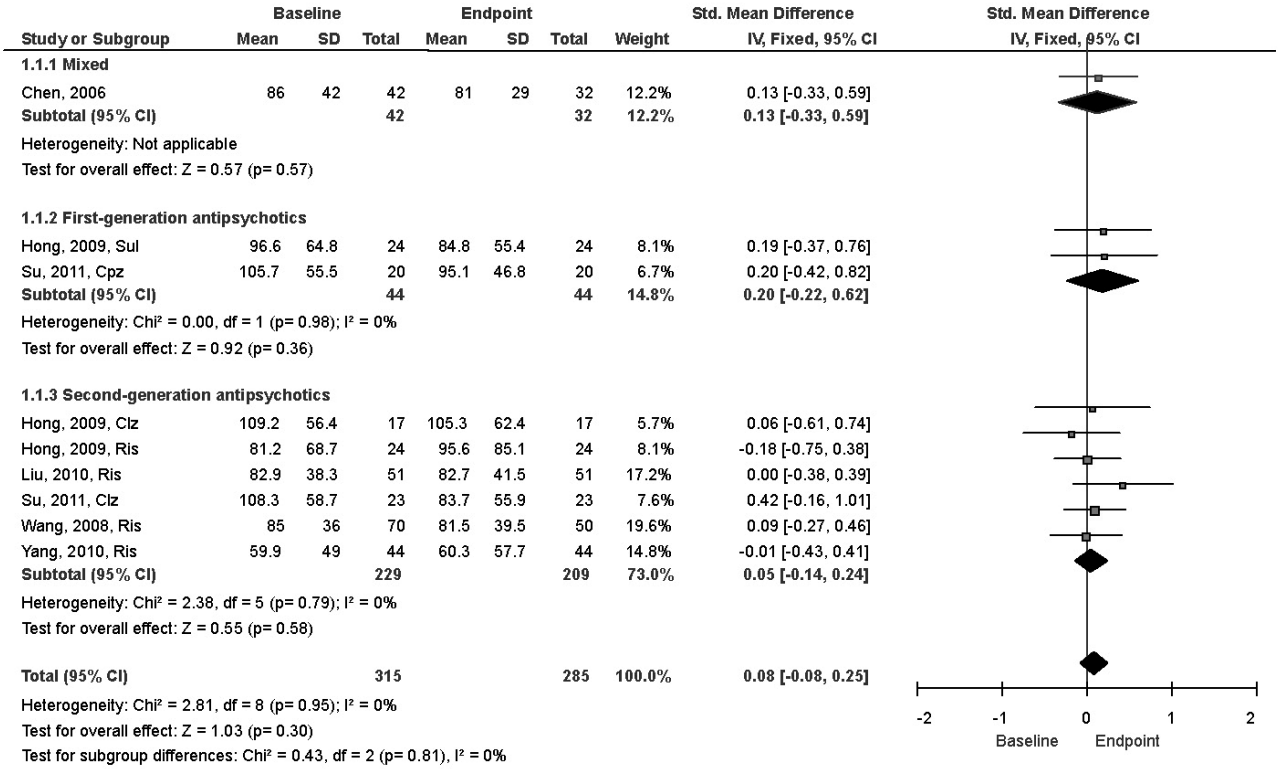


Figure 1. Flow diagram of meta-analysis of P50 ratios in Chinese schizophrenia patients



Figue 2. Comparison by meta-analysis of P50 ratios in Chinese schizophrenia patients before and after treatment with various antipsychotics

RESULTS

Figure 1 presents P50 sensory gating data from 108 studies of schizophrenia patients reported in the literature from all databases and hand-searching. In conclusion, for 6 of these studies, mean P50 ratios were available for both before (n=315) and after (n=285) treatment in schizophrenia patients in the same study, and six of these reported the standard deviations required for the meta-analysis. Along with each study citation, Table 1 provides demographic data, including number of subjects studied, age and sex, subject characteristics including PANSS score, treatment time and medications taken. One study only reported that patients were treated with several medications (Chen et al. 2006); three studies reported the change of P50 ratio in patients treated with risperidone (Ris) (Liu et al. 2010, Yang et al. 2010, Wang et al. 2008); one study compared the difference in effects on P50 ratio in patients treated with chlorpromazine (Cpz) and clozapine (Clz) (L Su et al. 2011); and one study compared effects from sulpiride (Sul), Ris and Clz (Hong et al. 2009).

Comparison of before and after treatment in schizophrenia patients by meta-analysis

Along with the demographic data and methods, Table 1 presents the mean P50 gating ratio and standard deviation reported from each literature study for schizophrenia patients. P50 gating ratios for the schizophrenia patients range at baseline from 60 to 109%, with a range of 60 to 106% at endpoints. Figure 2 shows the results of the meta-analysis. This plot presents mean differences and interval estimates for the studies used in the meta-analysis, and also provides a visual representation of the heterogeneity among the results of the studies. There was no statistically significant heterogeneity in our analysis (heterogeneity: Chi^2=2.81, df=8, p=0.95, I^2=0%), so a fixed effect model was used and the SMD was 0.08 (95% CI -0.08 to 0.25, Test for overall effect: z=1.03, p=0.30).

Subgroup analysis

For subgroup analysis, there was no statistically significant heterogeneity in subgroups (test for subgroup differences: Chi^2=0.43, df=2, p=0.81, I^2=0%) as shown in Figure 2. Neither the first (effect z=0.92, p=0.36;

Table 1. P50 ratio studies of Chinese schizophrenia patients cited in the literature

Authors, year	Scz n male, n female	Scz × age Mean (S.D.)	Scz P50 ratio (S.D.) at baseline	Scz P50 ratio (S.D.) at endpoint
Liu, 2010	36 m, 15 f	29 (6)	82.9(38.3)	82.7(41.5)
Chen, 2006	39 m, 27 f	28 (6)	86.0(42.0)	81.0(29.0)
Su, 2011	31 m, 25 f	30 (6)	Cpz:105.7(55.5) Clz: 108.3(58.7)	Cpz: 95.1(46.8) Clz: 83.7(55.9
Hong, 2009	50 m, 15 f	26 (7)	Sul: 96.6(64.8) Clz: 109.2(56.4) Ris: 81.2(68.7)	Sul: 84.8(55.4) Clz: 105.3(62.4) Ris: 95.6(85.1)
Wang, 2008	56 m, 14 f	28(7)	85(36)	81.5(39.5)
Yang, 2010	30m, 34 f	35(10)	59.9(49)	60.3(57.7)

Authors, year	Medication types and dose	Treatment time	Scz PANSS score at baseline and at endpoint
Liu, 2010	Ris: flexible-dose, mean dose 4.4 mg/d	4-6 weeks	Mean total score 70 at baseline, nr at endpoint
Chen, 2006	Mixed medication: Cpz-equivalent dose 345mg/d	12 weeks	Mean total score 111.5, nr at endpoint
Su, 2011	Cpz: mean dos 389mg/d Clz: mean dos 345mg/d	8 weeks	PANSS total score in Cpz group =78.2(9.0) and Clz group =83.2(12.6), neither nr at endpoint
Hong, 2009	Sul: mean dose 848mg/d Clz: mean dose 269 mg/d Ris: mean dose 3.76 mg/d	6 weeks	Scz PANSS score at baseline and at endpoint = 83.8 and 43.1, respectively
Wang, 2008	Ris: mean dose 3.8mg/d	2 months	Scz PANSS score at baseline and at endpoint = 69.7 and 40.3, respectively
Yang, 2010	Ris: flexibledose, no report of mean dose	8 weeks	PANSS total score in each patient ≥60 at baseline, but the mean scores were not reported neither at baseline or endpoints

*: abbreviations: not reported (nr), schizophrenia (Scz), chlorpromazine (Cpz), clozapine (Clz), risperidone (Ris), Sulpiride (Sul)

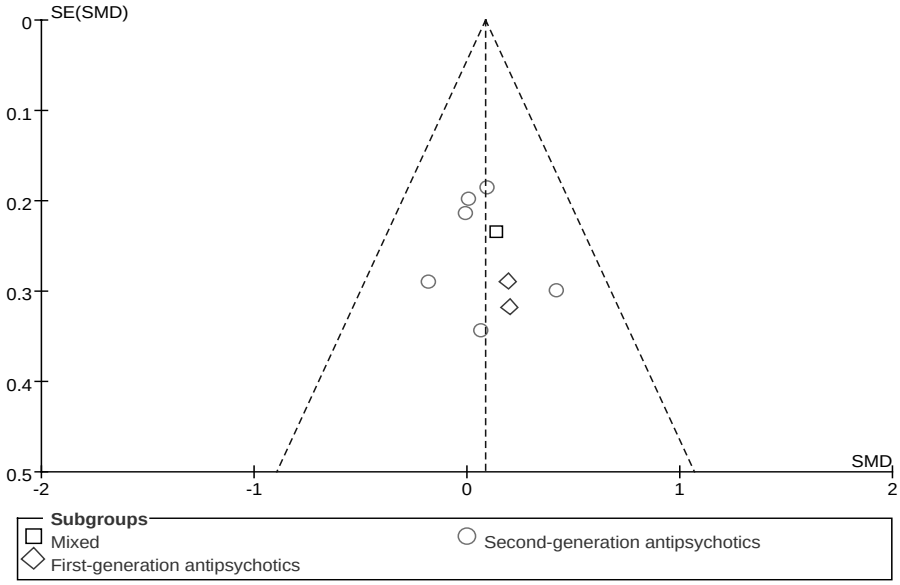


Figure 3. Funnel plot in meta-analysis of P50 ratios in Chinese schizophrenia patients

heterogeneity: Chi^2=0.00, df = 1, p=0.98, I^2=0%) nor the second generation (effect z=0.55, p=0.58; heterogeneity: Chi^2=2.38, df=5, p=0.79, I^2=0%) antipsychotics had any significant effect on P50 ratio in Chinese schizophrenia patients.

Publication bias

A funnel plot based on all six studies did not indicate publication bias as shown in Figure 3. Nor did formal tests (Egger's test t=0.86, p=0.42). In summary, there is no evidence for publication bias, and the estimated effect size found from the fixed effects model is realistic.

The overall conclusion from this analysis is that antipsychotic medication did not influence P50 ratio significantly based on the evidence from published studies.

DISCUSSION

The results of this meta-analysis indicate that second-generation antipsychotics, including clozapine and risperidone, were not significantly superior to first-generation for the treatment of sensory gating impairments in Chinese schizophrenia patients. What is more, the medication by time effect for the P50 measure of sensory gating was not significant. The results of our meta-analysis were similar to the findings of Bramon et al. (2004) which showed no significant effect of antipsychotics upon the P50 ratio in the Caucasian population by meta-regression analysis.

Previous studies suggested that first-generation antipsychotic medications do not remedy sensory gating deficits (P50 ratio) in schizophrenia patients (Adler et al. 2004, Arango et al. 2003, Nagamoto et al. 1996). However, the effects of these antipsychotics on the P50 ratio are still controversial. It has recently been reported that haloperidol improved disrupted P50 suppression deficits in healthy individuals expressing high P50 gating levels (Csomor et al. 2008). However, to what extent results in healthy subjects can be extrapolated to patients with schizophrenia is not clear. Further, it has been suggested that a dysfunction in both serotonin and dopamine neurotransmission may, in part, be responsible for the gating deficits observed in schizophrenia (Mann et al. 2008), which would explain why conventional antipsychotics have no effect on sensory gating in schizophrenia patients.

Unexpectedly, our meta-analysis failed to find any beneficial effects of second-generation antipsychotics. The various drugs, including clozapine, had no effect on the P50 ratio when compared to patients with schizophrenia treated with first-generation antipsychotics in previous research (Adler et al. 2004, Becker et al. 2004, Light et al. 2000, Nagamoto et al. 1996). Our meta-analysis showed that the effect of clozapine on the P50 ratio was not significant.

In previous longitudinal studies, clozapine has been shown to improve P50 suppression in a group of treatment-resistant patients (Nagamoto et al. 1996, Nagamoto et al. 1999). We think that the reasons are as follows. First, the beneficial effect of clozapine on P50 suppression was observed in treatment-resistant patients. Second, the previous studies that found clozapine to be associated with normal P50 suppression in patients with schizophrenia were not randomized studies (Adler et al. 2004, Becker et al. 2004). Moreover, two recent longitudinal studies of patients initiating clozapine treatment showed that sensory gating did normalize with this treatment (Nagamoto et al. 1996, Nagamoto et al. 1999).

The effects of other second-generation antipsychotics on P50 gating remain unknown. One previous study showed a beneficial effect of second-generation antipsychotics on the P50 ratio (Light et al. 2000), which

suggested that patients treated with second-generation antipsychotics, but not conventional antipsychotics, have normal P50 suppression. However, another randomized, longitudinal design study (Arango et al. 2003) did not repeat the findings of the former study - which was a cross-sectional study. Risperidone (Yee et al. 1998) has been associated with improvements in sensory gating in cross-sectional studies. In addition, it has been reported that olanzapine improves P50 suppression in healthy controls (Carroll et al. 2004). However, in a randomized double-blind trial, olanzapine did not show any differential effect as compared to haloperidol (Arango et al. 2003). Likewise, our meta-analysis suggests that neither first-generation antipsychotics nor second-generation antipsychotics (i.e., clozapine and risperidone) are related to a normalized P50 ratio.

Our results support another longitudinal study which found that there were no differences in baseline or endpoint P50 gating in patients who received clozapine, risperidone or first-generation antipsychotics (Hong et al. 2009). Furthermore, another recent study found that second-generation antipsychotics (including clozapine, risperidone, olanzapine and aripiprazole) were not related to more normal sensory gating in this population of patients with chronic schizophrenia (Sanchez-Morla et al. 2009). Our meta-analysis supports the two recent longitudinal design studies that showed negative results. Moreover, our meta-analysis achieved a different goal in evaluation of the targeted effect; our results may more strongly support the evidence that P50 sensory gating deficit is independent of antipsychotic treatment.

LIMITATIONS

There were several limitations to our study. First, methodological differences in P50 recording and measurements (Fuerst et al. 2007, Patterson et al. 2008) may have resulted in the disagreement found in the effects of clozapine on the P50 ratio. But there is no heterogeneity among the different studies. Second, various types of publication bias may arise during publication of the primary studies (Naylor 1997) and the bias toward the publication of positive results (Turner et al. 2008). However, upon inclusion of six studies, we found no publication bias for the P50 ratio, and most of the studies found negative results. Third, a meta-analysis cannot overcome certain limitations of the literatures. For example, not all samples in the primary studies were randomized. Therefore, our results may be indirectly subject to selection bias. In addition, the patients were not matched for some illness variables (age, gender and PANSS, et al) although these potential confounders were controlled for in the statistical analysis. Last, it should be noted that our results may be limited by the small sample size (N=6) and the short duration of treatment.

CONCLUSION

In conclusion, we did not find a differential impact of first- or second-generation antipsychotics on P50 gating. Clozapine and risperidone, contrary to the findings of some previous studies, were not associated with more normal sensory gating in Chinese population. P50 suppression deficits in schizophrenia patients are persistent and found in both acutely ill and more stable schizophrenia outpatients, and both predominantly positive-symptom and negative-symptom patients (Turetsky et al. 2007). So, the P50 ratio could be viewed as a promising candidate endophenotype for schizophrenia due to the evidence currently available. Longitudinal and randomized studies are needed to further explore other effects on the P50 ratio. If P50 sensory gating will be used in the future to guide drug development, then much more research is needed to understand and validate the clinical significance of the gating impairment (Potter et al. 2006).

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