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Abstract

Cognitive deficits are a core feature of schizophrenia. There is ongoing debate on whether cognition is affected by antipsychotic drugs (APDs). This study examined the effect of long-term treatment with APDs on cognition in schizophrenia. Cognitive function was assessed in 418 patients with schizophrenia on long-term treatment with APDs (215 on clozapine, 91 on risperidone and 112 on typical APDs) and 159 healthy controls using the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS). Schizophrenia symptomatology was assessed using the Positive and Negative Syndrome Scale (PANSS). We found that cognitive test scores were significantly lower in all patients compared with the healthy controls on almost all of the total and subscores of RBANS (all $P < 0.001$), except for the visuospatial/constructional index. Individuals taking clozapine showed worse immediate and delayed memory performance than those taking typical APDs (all $P < 0.01$). Moreover, individuals taking clozapine showed better language performance than those taking risperidone ($P < 0.01$). Immediate memory and delayed memory were modestly correlated with the types of APDs and the PANSS negative scores. Our results show that individuals taking clozapine performed worse in immediate and delayed memory than those taking typical APDs, but exemplified better language performance than those taking risperidone.

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**Cognitive differences in schizophrenia on long-term treatments with clozapine,
risperidone and typical antipsychotics**

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Abstract

Cognitive deficits are a core feature of schizophrenia. There is ongoing debate about whether cognition is affected by antipsychotic drugs (APDs). This study examined the effect of long-term treatment with APDs on cognition in schizophrenia. Cognitive function was assessed in 418 patients with schizophrenia on long-term treatment with APDs (215 on clozapine, 91 on risperidone, and 112 on typical APDs) and 159 healthy controls using the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS). Schizophrenia symptomatology was assessed using the Positive and Negative Syndrome Scale (PANSS). We found that cognitive test scores were significantly lower in all patient subjects compared to healthy controls on almost all of the total and subscores of RBANS (all $p < 0.001$) except for the visuospatial/constructional index. Individuals taking clozapine showed worse immediate and delayed memory performance than those taking typical APDs (all $p < 0.01$). Moreover, individuals taking clozapine showed better language performance than those taking risperidone ($p < 0.01$). Immediate memory and delayed memory were modestly correlated with the types of APDs and the PANSS negative scores. Our results show that individuals taking clozapine performed worse in immediate and delayed memory than those taking typical APDs, but exemplified better language performance than those taking risperidone.

Keywords: Schizophrenia, Cognitive deficits, Antipsychotic drugs, Treatment

Introduction

Cognition in schizophrenia is impaired across multiple domains, including memory, attention, processing speed, and executive function (Keefe and Harvey, 2012; Vyas et al., 2011). Cognitive impairment in schizophrenia is directly related to socio-vocational function, which can have a greater adverse effect on brain function than the positive or negative symptoms of schizophrenia (Velligan et al., 2000). Cognitive impairment significantly affects the acquisition of new skills, limits or prevents employment, and seriously reduces patients' quality of life (Sidlova et al., 2011; Tomida et al., 2010). Currently, the pathophysiological mechanism of cognitive deficits in patients with schizophrenia is unclear. Antipsychotic drugs (APDs) are usually prescribed to treat schizophrenia. However, the effects of APDs on cognitive deficits remain controversial for patients with schizophrenia on long-term medication (Daban et al., 2005; Keefe and Harvey, 2012; Thornton et al., 2006; Woodward et al., 2005).

Previous studies have shown that cognitive function in patients with schizophrenia could be influenced by APDs (Beninger et al., 2010; Terry and Mahadik, 2007). For example, some studies have suggested that APDs induce distinct regionalized neural responses in different brain regions that are associated with distinct cognitive functions (Beninger et al., 2010; Westerink, 2002). Moreover, some studies have shown that APDs, in particular atypical APDs, are associated with the improvement in some cognitive deficits in patients with schizophrenia, especially executive function, spatial memory, processing speed, and attention (Hill et al., 2010; Keefe et al., 2006; Meltzer and McGurk, 1999; Woodward et al., 2005). Furthermore, a meta-analytic study supported that the inherent anticholinergic property of APDs may affect long-term

memory in patients with schizophrenia (Thornton et al., 2006). An animal study also indicated that APDs had a negative effect on cognition, especially for long-term administrations (Terry and Mahadik, 2007). However, some studies did not find that APDs had a major effect on cognition in patients with schizophrenia (Daban et al., 2005; Lindenmayer et al., 1998). In addition, a few studies investigating the effects of APD treatments on language and immediate and delayed memory in patients with schizophrenia were inconclusive (Meltzer and McGurk, 1999; Minzenberg et al., 2004; Takeuchi et al., 2013). Thus, whether APDs affect cognition in patients with chronic schizophrenia, especially language and immediate and delayed memory, deserves further investigation.

A few studies have investigated the effects of clozapine on cognition in patients with schizophrenia, and have shown a mixture of beneficial, deleterious or absent effects (Hoff et al., 1996; Lindenmayer et al., 1998; Sharma et al., 2003; Thornton et al., 2006). A growing body of evidence suggests that the inherent anticholinergic properties of some APDs might limit gains or impair memory-related task performance, as well as alter central cholinergic function (Minzenberg et al., 2004; Terry and Mahadik, 2007; Thornton et al., 2006). A radioligand binding study has shown that clozapine has the highest affinity for all muscarinic M_{1-5} receptors compared to other APDs, with the highest affinity for the M_1 receptor (Bymaster et al., 2003). Although clozapine was found to have a weak partial agonist activity at the muscarinic M_1 and M_4 receptors, particularly the M_4 receptors, both *in vitro* and *in vivo* studies have indicated that clozapine functions as an antagonist at the muscarinic M_1 and M_4 receptors (Bymaster et al., 2003). Therefore, it is important to understand whether clozapine has a specific

impairment effect on cognition compared to other APDs in patients with schizophrenia during long-term medication, especially in relation to memory-related task performance.

Although risperidone is an atypical APD, it has a higher affinity and longer dissociation latency period for the D₂ receptors than other atypical APDs such as clozapine (Kapur and Seeman, 2001). These properties may contribute to risperidone's some similar effects to typical APDs in treating patients with schizophrenia (Houthoofd et al., 2008). Unlike clozapine, risperidone does not have a significant affinity with the muscarinic M₁₋₅ receptors (DeLeon et al., 2004). Risperidone has been associated with improved and clozapine with worsened memory performance in patients with schizophrenia (Houthoofd et al., 2008). Another study has shown that clozapine improved language more than risperidone (Meltzer and McGurk, 1999). However, some studies have not supported the improvement effects of clozapine on language and risperidone on memory (Buchanan et al., 1994; Stip and Lussier, 1996). Thus the effects of risperidone and clozapine on cognitive function in patients with schizophrenia deserve further investigation, especially in relation to memory and language.

In addition, compared to risperidone and typical APDs, clozapine has also been associated with substantial weight gain, increased serum triglyceride levels, and an increased risk of diabetes (Flanagan, 2008; Nasrallah, 2003). This may independently augment the risk of cognitive deficits. Therefore, it is important to understand the differences of cognitive deficits in patients with chronic schizophrenia during long-term clozapine, risperidone, and typical APDs treatment.

This study aimed to investigate whether: (1) individuals taking different APDs for chronic schizophrenia presented different cognitive deficits during long-term medication; (2) individuals taking clozapine showed worse memory performance than risperidone or other typical APDs; (3) individuals taking clozapine indicated better language performance than risperidone or other typical APDs.

Methods

Participants

A total of 418 patients with chronic schizophrenia were recruited using a cross-sectional design in Beijing Hui-Long-Guan Hospital, a Beijing City owned psychiatric hospital. The diagnosis for each patient was made by two independent and experienced psychiatrists and confirmed by the Structured Clinical Interview for DSM-IV (SCID). All patients were aged between 25 and 70 years, diagnosed with schizophrenia for at least 5 years, and were on stable doses of oral APDs for at least 6 months prior to entry into the study. The antipsychotic treatments for the patients were given by their psychiatrist. The treatments were not changed when they were recruited. Antipsychotic treatment consisted mainly of monotherapy with clozapine (n=215), risperidone (n=91), and typical APDs (n=112), including haloperidol (n=28), chlorpromazine (n=32), perphenazine (n=24), and sulpiride (n=28). “The mean dose of each antipsychotic drug used in the study were 365.3 ± 168.3 mg/day (200-700 mg/day) for clozapine, 4.9 ± 1.4 mg/day (2-7mg/day) for risperidone, 22 ± 15 mg/day (4-40 mg/day) for haloperidol, 367 ± 163 mg/day (150-700 mg/day) for chlorpromazine, 24 ± 17 mg/day (10-40 mg/day) for perphenazine and 538 ± 266 mg/day (200-1100 mg/day) for sulpiride. The detailed doses for chlorpromazine equivalents for each drug were presented in Table 2”. The

mean antipsychotic dose was converted to approximate daily mean chlorpromazine milligram equivalents for each patient using standard guidelines (Woods, 2003). Patients were hospitalized for an average of 10.7 ± 8.5 years.

One hundred and fifty nine healthy controls were recruited during the same period from the Beijing community. Psychiatric disorders in the healthy controls were ruled out with a psychiatric interview conducted by a psychiatrist.

We obtained a complete medical history, physical examination, and laboratory tests from all subjects. All healthy controls were in good physical health. All patients were free from other physical diseases, including diseases of the central nervous system, stroke, tumours, Parkinson's disease, Huntington's disease, seizure disorders, history of brain trauma, and acute and chronic infections. Neither patients nor healthy controls suffered from drug or alcohol abuse/dependence. Any subjects with a diagnosis of dementia or mild cognitive impairment (MCI) were excluded. The subjects were all from the Han Chinese population. All patients gave signed, informed consent to participate in the study, which was approved by the Institutional Review Board of the Beijing Hui-Long-Guan Hospital.

Clinical assessment

Four experienced psychiatrists, who were blind to the clinical status of patients, assessed the severity of the patients' psychopathology using the Positive and Negative Syndrome Scale (PANSS). The PANSS comprises the positive symptoms, negative symptoms, general psychopathology, and PANSS total score (Kay et al., 1987). To

ensure consistent and reliable ratings, the four psychiatrists simultaneously attended a training session for standardizing their use of the PANSS prior to the start of the study. Thereafter, they maintained an intra-class correlation coefficient of greater than 0.84 on the PANSS at repeated assessments throughout the study.

Cognitive tests

The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), used to measure cognitive function, was individually administered by trained investigators and supervised by a research psychiatrist (Duff et al., 2008). It consisted of 12 subtests used to calculate five age-adjusted index scores and a total score (Randolph et al., 1998). Test indices were: immediate memory (composed of list learning and story memory tasks); visuospatial/constructional (composed of figure copy and line orientation tasks); language (composed of picture naming and semantic fluency tasks); attention (composed of digit span and coding tasks); and delayed memory (composed of list recall, story recall, figure recall, and list recognition tasks). Our group has previously translated RBANS into Chinese and its clinical validity and test-retest reliability have already been established among controls and schizophrenia patients (Zhang et al., 2009). To ensure consistent and reliable ratings, the two clinical psychiatrists simultaneously attended a training session to standardize their use of the RBANS prior to the study. Thereafter, they maintained an intra-class correlation coefficient of 0.92 on the RBANS at repeated assessments throughout the study.

Statistical analysis

Group comparisons on demographic and clinical variables used Chi squared or Fisher

exact tests for categorical variables and analysis of variance (ANOVA) for continuous variables. Post-hoc comparisons between subgroups were made using the Tukey's honestly significant difference (HSD) procedure. For the RBANS comparisons, we also included age, gender, education, smoking, dose and duration of APDs treatment, and anti-Parkinsonian drugs as covariates in the multivariate analyses of covariance (MANCOVA). Multiple regression models were used to quantify the amount of variance in cognitive functioning explained by the psychopathological variables after controlling for several potential confounders, such as gender, age, education, and clinical variables. All statistical analyses and database manipulations were performed with SPSS version 18.0 (SPSS Inc., USA). Data were presented as mean \pm SD. All *p*-values were two-tailed at the significant level of $p < 0.05$.

Results

Demographic and clinical information

Table 1 shows no significant differences among the four examined groups in gender, age, education, body mass index (BMI), smoking, and incidence of diabetes (all $p > 0.05$). Patients taking clozapine had significantly higher triglyceride levels than risperidone and typical APDs ($p < 0.01$). Moreover, patients taking clozapine had significantly lower high density lipoprotein than typical APDs ($p < 0.01$). There were no significant differences among patients taking clozapine, risperidone, and typical APDs in fasting blood glucose, cholesterol, and low density lipoprotein. Furthermore, there were no significant differences in any PANSS scores, duration of illness, and APD dose (chlorpromazine CPZ equivalents). However, patients taking clozapine showed

significantly lower anti-Parkinsonian drugs used than risperidone and typical APDs ($p<0.001$) (Table 2).

Cognitive performance in patients with chronic schizophrenia on long-term treatment with clozapine, risperidone, and typical APDs

RBANS cognitive index scores for all subjects are summarized in Table 3. After controlling the age, education, gender, and smoking, the multivariate analysis of covariance revealed that all patients had significantly lower cognitive scores than healthy controls in almost all of the total and subscores of RBANS (all $p<0.001$), except for the visuospatial/constructional index. Furthermore, five subscores of RBANS were compared among clozapine, risperidone and typical antipsychotic treatment groups after adjustment for demographic data, clinical symptoms, antipsychotic drug dose and antiparkinsonian drugs. Immediate memory score showed 7.5% decrease in individual taking clozapine (58.3 ± 16.6) than typical APDs (62.7 ± 16.8) ($p<0.01$). Delay memory score were 7.1% decrease in individual taking clozapine (66.2 ± 19.7) than typical APDs (70.9 ± 20.4) ($p<0.01$). Language score indicated 8.4% decrease in individual taking clozapine (84.5 ± 15.6) than risperdone (78.6 ± 17.4) ($p<0.01$). Also, individuals taking risperidone showed a decreased trend than typical APDs in immediate ($p=0.071$) and delayed memory ($p=0.051$).

Associations of cognitive impairment with clinical variables in patients with chronic schizophrenia on long-term treatment with APDs

The associations of cognitive impairment with clinical psychopathological variables were further examined in patients with schizophrenia. Multivariate regression analysis showed that the following variables were independently associated with the RBANS

total scores: PANSS negative score (beta=-0.37, $t=-6.08$, $p<0.001$); PANSS general symptom score (beta=0.13, $t=2.2$, $p<0.05$); education (beta=0.15, $t=3.03$, $p<0.01$); and gender (beta=0.14, $t=-2.64$, $p<0.01$). These factors together predicted 16.4% of the variance of the RBANS total scores.

Furthermore, the subscores of RBANS were analysed separately to assess the effects of the clinical characteristics associated with cognitive impairment. Multivariate regression analyses showed that the following variables were independently associated with: (1) immediate memory: PANSS negative score (beta=-0.23, $t=-4.4$, $p<0.001$), education (beta=0.11, $t=2.17$, $p<0.05$), age (beta=-0.18, $t=-3.3$, $p<0.001$), gender (beta=0.17, $t=3.30$, $p<0.001$), and types of APDs (beta=0.18, $t=3.60$, $p<0.001$); (2) delayed memory: PANSS negative score (beta=-0.27, $t=-5.14$, $p<0.001$), gender (beta=0.14, $t=2.67$, $p<0.01$), education (beta=0.11, $t=2.09$, $p<0.05$), and types of APDs (beta=0.14, $t=2.76$, $p<0.01$); and (3) language: PANSS negative score (beta=-0.34, $t=-6.67$, $p<0.001$), and education (beta=0.15, $t=3.00$, $p<0.01$).

Discussion

This study found that all patients showed significant cognitive deficits compared to healthy controls in almost all examined cognitive domains, except for the visuospatial/constructional index. In particular, individuals taking clozapine showed worse immediate and delayed memory than typical APDs, and better language performance than risperidone.

Cognitive deficits were significantly different for patients with chronic schizophrenia during long-term treatment with clozapine, risperidone, or typical APDs. These results are supported by other studies (Beninger et al., 2010; Hill et al., 2010; Terry and Mahadik, 2007). Though this study was cross-sectional design, it was random and therefore might provide robust evidence that APDs may influence cognition in patients with chronic schizophrenia on long-term medication. Therefore, more research is required to investigate the pharmacological effects of APDs on cognition.

Interestingly, individuals taking clozapine showed 7.5% and 7.1% decrease in immediate and delayed memory than typical APDs in patients with chronic schizophrenia during long-term medication. Moreover, multivariate regression analysis showed that immediate memory and delayed memory were modestly correlated with the types of APDs. These results support that clozapine might have worse effects than typical APDs on immediate and delayed memory for patients with chronic schizophrenia during long-term medication, which is supported by human and animal studies (Addy and Levin, 2002; Goldberg et al., 1993; Pocivavsek et al., 2006). Currently, we cannot provide a reasonable explanation for these results. However, some studies have shown that the inherent anticholinergic properties of some APDs may be involved in memory impairment during long-term medication in patients with schizophrenia (Minzenberg et al., 2004; Terry and Mahadik, 2007; Thornton et al., 2006). Moreover, one study suggested that decreased activity in the central cholinergic system was involved in the pathophysiology of schizophrenia and cognitive deficits (Perry and Perry, 1995). Increasing the activity of the central cholinergic system is related to the pharmacotherapy of schizophrenia and may have beneficial effects in

improving memory-related cognitive deficits (Bymaster et al., 2003; Simosky et al., 2003). Furthermore, one study found that low doses of muscarinic antagonists such as scopolamine and atropine can lead to inattention and memory impairment (Perry and Perry, 1995). Other studies found that cognition such as immediate and working memory may be significantly improved after withdrawal of anticholinergic drugs in patients with schizophrenia (Mori et al., 2002; Desmarais et al., 2012). Clozapine has a high affinity with the muscarinic M_{1-5} receptors (Bymaster et al., 2003), and appears to function predominantly as an antagonist at the muscarinic M_1 and M_4 receptors (Bymaster et al., 2003). Taken together, these studies show that the stronger inherent anticholinergic properties of clozapine rather than typical APDs may at least partly contribute to worsened immediate and delayed memory for patients with chronic schizophrenia during long-term medication. In addition, animal studies have shown that clozapine inhibits nicotine binding at the nicotinic α_7 acetylcholine receptors and inhibits downstream catecholamine secretion (Park et al., 2001). This inhibition of the nicotinic acetylcholine receptors by clozapine and its downstream effects could lead to memory impairment (Park et al., 2001), suggesting that the potent anticholinergic properties of clozapine on the nicotinic pathway may also have a role in immediate and delayed memory impairment in patients with schizophrenia during long-term medication. Finally, compared with typical APD treatments, patients taking clozapine showed significantly increased triglyceride levels and decreased high density lipoprotein (Table 1), which may also lead to worsened immediate and delayed memory for individuals taking clozapine than typical APDs in patients with schizophrenia (Perlmutter et al., 1988; Umegaki et al., 2014).

Another finding from this study is that individuals taking clozapine showed 8.4% improvement in language performance than risperidone in patients with schizophrenia during long-term medication. This result is supported by other studies (Meltzer and McGurk, 1999; Woodward et al., 2005). This study measured cognitive function in the language domain using picture naming and semantic fluency tasks. Importantly, semantic fluency tasks are one of an important components of neuropsychological screenings for executive functioning and processing speed, which are significantly impaired cognitive domains in patients with schizophrenia (Gleissner and Elger, 2001). Therefore, this study implies that clozapine may be more effective than risperidone in improving executive functioning and processing speed in patients with schizophrenia. The fact that individuals taking clozapine showed better language than risperidone cannot be explained currently. We hypothesize that as clozapine has a significantly lower affinity with the D₂ receptor than risperidone, it may result in fewer effects of the D₂ antagonist in the fronto-striatal system (DeLeon et al., 2004). However, as this is a hypothesis, it is important to investigate the effects of the two antipsychotic drugs on the D₂ receptors with *in vivo* studies in the frontal cortex and hippocampal brain regions related to language, executive function, and processing speed (Gleissner and Elger, 2001). This may be helpful in elucidating the pharmacological effects which causes individuals taking clozapine to have better language than risperidone. It is important to point out that risperidone at 6 mg per day is the lowest dose, which produces substantial changes to negative symptoms, but does not increase extrapyramidal symptoms (EPS) (Schooler, 1994). Risperidone at dose above 6mg per day have been reported to increase EPS, which may affect cognition in patients with schizophrenia (Suzuki, et al., 2014). Therefore, different doses of risperidone could vary in the effect on cognition in

patients with schizophrenia. The dose for risperidone used in this study was almost all less than 6mg per day for patients with schizophrenia. The cognitive effects of risperidone at dose above 6 mg per day warrant further investigation.

It is worthy of noting that a number of studies have reported that clozapine has significant advantage than risperidone and typical antipsychotics for the improvement of negative symptoms (McEvoy, et al., 2006; Lewis, et al., 2006). However, this study only showed a trend of improvement for negative symptoms on clozapine than risperidone and typical antipsychotics treatments. We could not rule out that the potential bias of prescribers for clozapine group in wishing to treat the negative symptoms, which might have affected the results. Also, it is possible that the clozapine group could be more treatment resistant because of prescribing bias. This limitation should be remedied in the future investigation.

This study has some limitations. Firstly, the findings should be regarded as preliminary due to the cross-sectional study design in our patients with chronic schizophrenia. Secondly, typical APDs were not classified further due to our limited sample sizes, so we could not compare the effects of each typical APD on cognitive function with the effects of clozapine or risperidone. Thirdly, since this research is a phenomenological study, we cannot explain the real pharmacological effects of these APDs. Fourthly, we cannot completely rule out the impacts of anticholinergic drug on cognition among these examined groups, despite the appropriate management of the statistical analysis controlling for this variable. Fifthly, the dosages of antipsychotic drugs used and the co-medication antiparkinsonian used were not controlled and were chosen by the treating

physician based on individual clinical preferences. We cannot rule out the impacts of individual clinical preferences for this study.

In conclusion, during long-term APDs medication, patients with chronic schizophrenia showed significant cognitive deficits than healthy controls in almost all of the examined cognitive domains, except for the visuospatial/constructional index. Individuals taking clozapine showed worse immediate and delayed memory than typical APDs, but improved language compared with risperidone. An improved understanding of the differential effects of APDs on cognition would facilitate optimal treatment strategies to maintain or improve cognitive function in patients with schizophrenia and provide an important guide for psychiatrists and health carers to treat and care for these patients.

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Conflicts of interest

The authors have no conflicts of interest to be disclosed.

References

- Addy N, Levin ED (2002). Nicotine interactions with haloperidol, clozapine and risperidone and working memory function in rats. *Neuropsychopharmacology* **27**: 534-541.
- Beninger RJ, Baker TW, Florczynski MM, Banasikowski TJ (2010). Regional differences in the action of antipsychotic drugs: implications for cognitive effects in schizophrenic patients. *Neurotox Res* **18**: 229-243.
- Buchanan RW, Holstein C, Breier A (1994). The comparative efficacy and long-term effect of clozapine treatment on neuropsychological test performance. *Biol Psychiatry* **36**: 717-725.
- Bymaster FP, Felder CC, Tzavara E, Nomikos GG, Calligaro DO, McKinzie DL (2003). Muscarinic mechanisms of antipsychotic atypicality. *Prog Neuropsychopharmacol Biol Psychiatry* **27**: 1125-1143.
- Daban C, Amado I, Bourdel MC, Loo H, Olie JP, Poirier MF, *et al.* (2005). Cognitive dysfunctions in medicated and unmedicated patients with recent-onset schizophrenia. *J Psychiatr Res* **39**: 391-398.
- DeLeon A, Patel NC, Crismon ML (2004). Aripiprazole: a comprehensive review of its pharmacology, clinical efficacy, and tolerability. *Clin Ther* **26**: 649-666.
- Desmarais JE, Beauclair L, Margolese HC (2012). Anticholinergics in the era of atypical antipsychotics: short-term or long-term treatment? *J Psychopharmacol* **26**: 1167-1174.
- Duff K, Humphreys Clark JD, O'Bryant SE, Mold JW, Schiffer RB, Sutker PB (2008). Utility of the RBANS in detecting cognitive impairment associated with

- Alzheimer's disease: sensitivity, specificity, and positive and negative predictive powers. *Arch Clin Neuropsychol* **23**: 603-612
- Flanagan RJ (2008). Side effects of clozapine and some other psychoactive drugs. *Curr Drug Saf* **3**: 115-122.
- Gleissner U, Elger CE (2001). The hippocampal contribution to verbal fluency in patients with temporal lobe epilepsy. *Cortex* **37**: 55-63.
- Goldberg TE, Greenberg RD, Griffin SJ, Gold JM, Kleinman JE, Pickar D, *et al.* (1993). The effect of clozapine on cognition and psychiatric symptoms in patients with schizophrenia. *Br J Psychiatry* **162**: 43-48.
- Hill SK, Bishop JR, Palumbo D, Sweeney JA (2010). Effect of second-generation antipsychotics on cognition: current issues and future challenges. *Expert Rev Neurother* **10**: 43-57.
- Hoff AL, Faustman WO, Wieneke M, Espinoza S, Costa M, Wolkowitz O, *et al.* (1996). The effects of clozapine on symptom reduction, neurocognitive function, and clinical management in treatment-refractory state hospital schizophrenic inpatients. *Neuropsychopharmacology* **15**: 361-269.
- Houthoofd SAMK, Morrens M, Sabbe BGC (2008). Cognitive and psychomotor effects of risperidone in schizophrenia and schizoaffective disorder. *Clin Ther* **30**: 1565-1589.
- Kapur S, Seeman P (2001) Does fast dissociation from the dopamine D2 Receptor explain the action of atypical antipsychotics?: a new hypothesis. *Am J Psychiatry* **158**: 360-369.
- Kay SR, Fiszbein A, Opler LA (1987). The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull* **13**: 261-276.

- Keefe RSE, Harvey PD (2012). Cognitive impairment in schizophrenia. *Handb Exp Pharmacol*: 11-37
- Keefe RSE, Young CA, Rock SL, Purdon SE, Gold JM, Breier A, *et al.* (2006). One-year double-blind study of the neurocognitive efficacy of olanzapine, risperidone, and haloperidol in schizophrenia. *Schizophr Res* **81**: 1-15.
- Lewis SW, Barnes TRE, Davies L, Murray RM, Dunn G, Hayhurst KP, *et al.* (2006). Randomized controlled trial of effect of prescription of clozapine versus other second-generation antipsychotic drugs in resistant schizophrenia. *Schizophr Bull* **32**: 715-723.
- Lindenmayer JP, Iskander A, Park M, Apergi FS, Czobor P, Smith R, *et al.* (1998). Clinical and neurocognitive effects of clozapine and risperidone in treatment-refractory schizophrenic patients: a prospective study. *J Clin Psychiatry* **59**: 521-527.
- McEvoy JP, Lieberman JA, Stroup TS, Davis SM, Meltzer HY, Rosenheck RA, *et al.* (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** (4):600-610.
- Meltzer HY, McGurk SR (1999). The effects of clozapine, risperidone, and olanzapine on cognitive function in schizophrenia. *Schizophr Bull* **25**: 233-255.
- Minzenberg MJ, Poole JH, Benton C, Vinogradov S (2004). Association of anticholinergic load with impairment of complex attention and memory in schizophrenia. *Am J Psychiatry* **161**: 116-124
- Mori K, Yamashita H, Nagao M, Horiguchi J, Yamawaki S (2002). Effects of anticholinergic drug withdrawal on memory, regional cerebral blood flow and

- extrapyramidal side effects in schizophrenic patients. *Pharmacopsychiatry* **35**: 6-11.
- Nasrallah H (2003). A review of the effect of atypical antipsychotics on weight. *Psychoneuroendocrinology* **28 Suppl 1**: 83-96.
- Park T, Bae S, Choi S, Kang B, Kim K (2001). Inhibition of nicotinic acetylcholine receptors and calcium channels by clozapine in bovine adrenal chromaffin cells. *Biochem Pharmacol* **61**: 1011-1019
- Perlmutter LC, Nathan DM, Goldfinger SH, Russo PA, Yates J, Larkin M (1988). Triglyceride levels affect cognitive function in noninsulin-dependent diabetics. *J Diabet Complications* **2**: 210-213.
- Perry EK, Perry RH (1995). Acetylcholine and hallucinations: disease-related compared to drug-induced alterations in human consciousness. *Brain Cogn* **28**: 240-258.
- Pocivavsek A, Icenogle L, Levin ED (2006). Ventral hippocampal $\alpha 7$ and $\alpha 4\beta 2$ nicotinic receptor blockade and clozapine effects on memory in female rats. *Psychopharmacology* **188**: 597-604.
- Randolph C, Tierney MC, Mohr E, Chase TN (1998). The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS): preliminary clinical validity. *Journal of Clinical & Experimental Neuropsychology: J Int Neuropsychol Soc* **20**: 310-319.
- Sharma T, Hughes C, Soni W, Kumari V (2003). Cognitive effects of olanzapine and clozapine treatment in chronic schizophrenia. *Psychopharmacology* **169**: 398-403.
- Schooler NR (1994). Negative symptoms in schizophrenia: Assessment of the effect of risperidone. *J Clin Psychiatry* **55**: 22-28.

- Sidlova M, Prasko J, Jelenova D, Kovacsova A, Latalova K, Sigmundova Z, *et al.* (2011). The quality of life of patients suffering from schizophrenia--a comparison with healthy controls. *Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub* **155**: 173-180.
- Simosky JK, Stevens KE, Adler LE, Freedman R (2003). Clozapine improves deficient inhibitory auditory processing in DBA/2 mice, via a nicotinic cholinergic mechanism. *Psychopharmacology* **165**: 386-396.
- Stip E, Lussier I (1996). The effect of risperidone on cognition in patients with schizophrenia. *Can J Psychiatry* **41**: S35-40.
- Suzuki H, Gen K, Inoue Y, Hibino H, Mikami A, Matsumoto H, *et al.* (2014). The influence of switching from risperidone to paliperidone on the extrapyramidal symptoms and cognitive function in elderly patients with schizophrenia: a preliminary open-label trial. *Int J Psychiatry Clin Pract* **18**(1): 58-62.
- Takeuchi H, Suzuki T, Remington G, Bies RR, Abe T, Graff-Guerrero A, *et al.* (2013). Effects of risperidone and olanzapine dose reduction on cognitive function in stable patients with schizophrenia: an open-label, randomized, controlled, pilot study. *Schizophr Bull* **39**: 993-998.
- Terry AV, Jr., Mahalik SP (2007). Time-dependent cognitive deficits associated with first and second generation antipsychotics: cholinergic dysregulation as a potential mechanism. *J Pharmacol Exp Ther* **320**: 961-968.
- Thornton AE, Van Snellenberg JX, Sepehry AA, Honer W (2006). The impact of atypical antipsychotic medications on long-term memory dysfunction in schizophrenia spectrum disorder: a quantitative review. *J Psychopharmacol* **20**: 335-346.

- Tomida K, Takahashi N, Saito S, Maeno N, Iwamoto K, Yoshida K, *et al.* (2010). Relationship of psychopathological symptoms and cognitive function to subjective quality of life in patients with chronic schizophrenia. *Psychiatry Clin Neurosci* **64**: 62-69.
- Umegaki H, Kawamura T, Umemura T, Kawano N (2014). Factors associated with cognitive decline in older adults with type 2 diabetes mellitus during a 6-year observation. *Geriatr Gerontol Int*. In press.
- Velligan DI, Bow-Thomas CC, Mahurin RK, Miller AL, Halgunseth LC (2000). Do specific neurocognitive deficits predict specific domains of community function in schizophrenia? *J Nerv Ment Dis* **188**: 518-524.
- Vyas NS, Patel NH, Puri BK (2011). Neurobiology and phenotypic expression in early onset schizophrenia. *Early Interv Psychiatry* **5**: 3-14.
- Westerink BHC (2002). Can antipsychotic drugs be classified by their effects on a particular group of dopamine neurons in the brain? *Eur J Pharmacol* **455**: 1-18.
- Woods SW (2003). Chlorpromazine equivalent doses for the newer atypical antipsychotics. *J Clin Psychiatry* **64**: 663-667.
- Woodward ND, Purdon SE, Meltzer HY, Zald DH (2005). A meta-analysis of neuropsychological change to clozapine, olanzapine, quetiapine, and risperidone in schizophrenia. *Int J Neuropsychopharmacol* **8**: 457-472.
- Zhang BH, Tan YL, Zhang WF, Wang ZR, Yang GG, Shi C, *et al.* (2009). Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) as a Screening Test in Chinese: Reliability and Validity. *Chinese Mental Health Journal* **28**: 865-869.

Table 1 Demographic and clinical information of healthy controls, clozapine, risperidone and typical antipsychotics

	Healthy controls	Clozapine	Risperidone	Typical antipsychotics	<i>F or X²</i>	<i>p</i>
	(n=159)	(n=215)	(n=91)	(n=112)		
Gender (M/F)	132/27	182/33	79/12	95/17	1.6	0.143
Age (years)	49.1±9.3	48.6±9.4	49.5±9.6	50.3±8.0	1.4	0.245
Education (years)	9.4±3.1	9.4±4.3	9.3±2.0	8.9±2.0	0.7	0.587
BMI (kg/m ²)	25.9±3.9	24.9±3.8	24.4±3.5	24.3±4.6	1.8	0.114
Smoking (yes/no)	117/42	147/68	59/32	82/30	4.9	0.089
Diabetes (yes/no)	NA	34/181	9/82	21/91	2.7	0.512
Fast glucose (mmol/l)	NA	5.3±1.1	5.0±0.6	5.1±0.7	1.6	0.131
Cholesterol (mmol/l)	NA	4.4±1.0	4.2±0.9	4.5±1.0	1.8	0.154
Triglyceride (mmol/l)	NA	2.0±1.2 ^{**}	1.4±0.8	1.6±1.0	9.5	0.000
High density lipoprotein (mmol/l)	NA	1.2±0.3 ^{##}	1.3±0.3	1.4±0.7	7.1	0.001
Low density lipoprotein (mmol/l)	NA	2.6±0.7	2.5±0.5	2.8±0.6	2.3	0.289

Mean±SD. * indicates the comparison between clozapine and risperidone or typical antipsychotics: **p<0.01. # indicates the comparison between clozapine and typical antipsychotics: ##p<0.01.

Table 2 Characteristics of patients with chronic schizophrenia on long-term treatment with clozapine, risperidone and typical antipsychotics

	Clozapine	Risperidone	Typical antipsychotics	<i>F or X²</i>	<i>p</i>
	(n=215)	(n=91)	(n=112)		
Duration of illness (years)	25.3±9.6	26.1±9.6	26.5±8.8	0.675	0.510
Antipsychotic dose (CPZ equivalents)	428.3±142.9	419.4±116.1	409.2±184.1	0.994	0.372
Score on positive symptom scale	11.6±4.8	12.3±5.6	11.2±4.7	1.321	0.268
Score on negative symptom scale	21.3±7.0	22.9±7.9	22.8±7.4	2.370	0.095
Score on general psychopathology scale	25.0±5,8	26.0±5.9	25.4±5.1	0.964	0.382
Total PANSS score	57.8±14.4	61.1±15.2	59.5±13.0	1.851	0.158
Antiparkinsonian drugs (trihexyphenidyl) (yes/no)	18/197***	43/48	60/52	100.3	0.000

Mean±SD. * indicates the comparison between clozapine and risperidone or typical antipsychotics: ***p<0.001.

CPZ=chlorpromazine.

Table 3 The levels of cognitive function in healthy controls, clozapine, risperidone and typical antipsychotics

Cognitive index	Healthy controls (n=159)	Clozapine (n=215)	Risperidone (n=91)	Typical antipsychotics (n=112)	Main analyses F(<i>p</i> value)
Immediate memory	74.9±16.9	58.3±16.6*** ⁺⁺	59.5±17.6***	62.7±16.8***	12.4(0.000)
Visuospatial/construction	81.0±14.4	80.5±18.3	78.4±18.7	79.2±19.0	1.1(0.272)
Language	94.6±11.3	84.5±15.6*** ^{##}	78.6±17.4***	81.8±13.8***	13.4(0.000)
Attention	86.7±17.4	73.1±16.1***	73.1±20.5***	74.3±17.7***	4.3(0.005)
Delayed memory	87.5±13.9	66.2±19.7*** ⁺⁺	67.1±19.5***	70.9±20.4***	24.5(0.000)
Total RBANS scores	80.3±13.9	66.1±14.7***	65.5±16.5***	66.7±15.8***	12.1(0.000)

Mean±SD. *indicates the comparison between healthy controls with clozapine or risperidone or typical antipsychotics:

****p*<0.001. ⁺indicates the comparison between clozapine and typical antipsychotics: ⁺⁺*p*<0.01. [#]indicates the comparison

between clozapine and risperidone: ^{##}*p*<0.01.