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Clinical Research

Attentional and emotional functioning in schizophrenia patients treated with conventional and atypical antipsychotic drugs

Authors' Contribution:
A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

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Summary

Background: Effectiveness of antipsychotics in treating emotional and cognitive deficits in schizophrenia still remains controversial. The aim of our study was to assess emotional and cognitive functioning in schizophrenic inpatients currently treated with typical antipsychotics (perphenazine, perazine, fluphenazine, and haloperidol) and in another group of schizophrenic inpatients currently on atypical antipsychotics (olanzapine, risperidone, amisulpride, and quetiapine).

Material/Methods: One hundred patients with DSM-IV schizophrenia or schizoaffective disorders (39 treated using typical antipsychotics and 61 treated with atypical antipsychotics) under naturalistic treatment conditions, and 50 healthy controls were given the following: Test of Everyday Attention, Facial Emotion Recognition Test, Facial Memory Recognition Test, and "Reading the mind in the eyes" Test.

Results: Patients with a diagnosis of schizophrenia revealed the following deficits: facial emotion perception, empathy /theory of mind, visual selective attention/speed, attentional switching, and auditory-verbal working memory. Our results show a significant difference between schizophrenic and healthy controls in all tasks, with schizophrenic patients performing worse than controls. Interestingly, our patients on atypical neuroleptics performed similarly compared to schizophrenic patients treated with conventional neuroleptics on all tasks provided. There were some significant relationships between emotional and cognitive deficits and clinical variables.

Conclusions: Our findings remain consistent with other recent studies in which atypical antipsychotics did not show a clear advantage over typical antipsychotics on both emotional and cognitive functioning.

key words: emotion perception • cognition • empathy • attention • chronic schizophrenia • atypical antipsychotic • typical antipsychotics

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BACKGROUND

"Atypical" antipsychotic drugs represent a second generation of antipsychotic drugs, with a significantly lower incidence of extrapyramidal side-effects (EPS) than "conventional" first generation antipsychotic drugs. Most atypical antipsychotic drugs possess a strong affinity for serotonin 5-HT2 receptors and relatively weak affinity for the dopamine D2 receptor [1]. Some clinical studies suggest that atypical antipsychotic drugs bring about improvement in cognitive symptoms, and that such improvement appears to be correlated with improvement of negative symptoms. This cognitive enhancement may be mediated by increases in dopamine and acetylcholine in prefrontal dorsolateral regions, and in those parts of the hippocampus associated with the acquisition and consolidation of new information [2–4].

Several studies have evaluated the beneficial effect of atypical antipsychotic drugs on emotional and cognitive functions in schizophrenia [5–7].

Guilera et al. presented a meta-analysis of 18 independent studies (N=1808) with the aim of exploring whether patients treated with atypical antipsychotic drugs obtain better results on cognitive functioning than those treated with conventional antipsychotic drugs [8]. Their results showed a mild improvement in the global cognitive index of patients treated with atypical antipsychotic drugs. These minor benefits were observed particularly in speed of processing and learning tasks. These effects are somewhat lower than those found in the meta-analysis of Woodward et al. [7], who concluded that patients receiving atypical antipsychotic drugs performed moderately better on neuropsychological tests than those treated with conventional antipsychotic drugs.

By contrast, conventional antipsychotic drugs provide modest-to-moderate improvements in multiple cognitive domains [9]; specifically, some improvement in attention was recorded [10]. Moreover, treatment of EPS with anticholinergic drugs can impair memory. However, many of these studies comparing the effectiveness of conventional versus atypical antipsychotic drugs have been sponsored by the pharmaceutical industry, thus the effects of atypical antipsychotic drugs on cognitive and emotional function remain controversial [8].

Recent findings from CATIE (Clinical Antipsychotic Trials for Intervention Effectiveness), EUFEST (European First-Episode Schizophrenia Trial), CUTLASS (Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study), TEOSS (Treatment of Early Onset Schizophrenia Spectrum Disorders) and other antipsychotic trials have suggested that neurocognitive improvements in patients treated with conventional or atypical antipsychotic drugs are minimal – neither class of drug is inferior to the other. Some benefit in patients with first-episode psychosis may be associated with symptom reduction, but most of the cognitive enhancement may have a practice effect, supplemented by the expectation of benefit [11–13].

Research on the influence of antipsychotic drug treatment on emotion recognition has produced inconsistent results. Hempel et al. reviewed the effects of antipsychotic medication on facial affect recognition in schizophrenia according

to 8 studies [14]. No substantial improvement was observed after treatment with either typical or atypical antipsychotic drugs. Facial affect recognition was not related to neuropsychological functioning, and it was unclear whether improvement of symptom severity was related to performance on facial affect recognition tasks. A growing body of evidence suggests that deficits in emotion perception are not significantly improved with atypical antipsychotic medication [15–18].

The aim of our study was to assess emotional and cognitive functioning in schizophrenia patients currently treated with conventional or atypical antipsychotic drugs.

The objectives of the study were:
1. to determine the extent and nature of emotional and attentional deficits in these patients; and
2. to evaluate the relationship of such deficits to patients' age, sex, education, current mood, duration of illness, severity of psychopathology (means of Scale for the Assessment of Negative Symptoms [SANS], Scale for the Assessment Positive Symptoms [SAPS] and Beck Depression Inventory [BDI]), and medication type and dose.

MATERIAL AND METHODS

The study was approved by the Ethics Committee of the Lublin University Medical School, and all participants gave written informed consent. A total of 150 persons aged ≤60 years were studied (Table 1). Study participants were 100 partially remitted schizophrenia inpatients diagnosed according to DSM-IV criteria on the basis of clinical interview from Lublin University Psychiatric Hospital, and 50 healthy volunteers (controls). Thirty-nine patients were treated using conventional antipsychotic drugs (perphenazine, perazine, fluphenazine, haloperidol) and 61 were treated with atypical antipsychotic drugs (olanzapine, risperidone, amisulpride, clozapine and quetiapine).

All patients were clinically stable after 4 weeks of antipsychotic treatment, and aged between 18–60 years. Duration of illness was between 4 and 41 years, and number of psychiatric admissions was 1 to 16. The mean daily dose in chlorpromazine equivalents (CPZE) was 394 (202) mg in patients treated with conventional antipsychotic drugs, and 422 (227) mg in patients on atypical antipsychotic drugs (Table 1). Patients were assessed with the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1983) and the Scale for the Assessment Positive Symptoms (SAPS) [20] by a trained rater (AT) (Table 1).

All 150 subjects completed the Beck Depression Inventory (BDI) [21], an instrument for self-rating of symptoms of depression (Table 1).

Patients and controls were matched with regard to their age and sex. Fifty controls (mean age 29.6 [11.5] years) with no history of psychiatric illness were recruited from the non-professional staff at Lublin University Medical School, and Lublin Psychiatric Hospital also participated in the study.

All subjects were right-handed [22]. Exclusion criteria for all subjects included the presence of a neurological disorder (eg, epilepsy, dementia), and either habitual drug or

alcohol abuse. Subjects who had difficulties with vision (including poor acuity and lack of correction) and severe hearing problems were also excluded. Four schizophrenia patients who volunteered to take part in the study were not included in the final sample – either they were unable to complete the full set of tests because of akathisia or agitation, or they were discharged before completing the 3 experimental sessions.

The Test of Everyday Attention (TEA)

The Test of Everyday Attention (TEA) is based on ecologically plausible activities such as searching maps, looking through telephone directories, and listening to lottery number broadcasts. This test provides norm-referenced scores on tests that are sensitive to selective attention, sustained attention and attentional switching.

For study purposes, 3 subtests were used:
1. Visual selective attention – map search task. Subjects search a map for 2 minutes.
2. Auditory selective attention – elevator counting with distraction task. Subjects count how many times they hear a tone, while ignoring a distracting tone of a higher note.
3. Sustained visual attention – visual elevator task. Subjects count each elevator door, imagining that it represents a floor. Both accuracy and timing are assessed [23].

Short Recognition Memory Test for Faces (SRMT)

This is a forced-choice recognition memory test. It consists of 25 unfamiliar grey-scale male faces, which are presented at a rate of 1 every 3 seconds (timed by stop watch). The subject is required to respond "yes" or "no" to each item, depending on whether the face is judged to be pleasant or not. Recognition memory is assessed immediately after the presentation of the stimuli using a 2-choice format, each stimulus item being paired with 1 distracter item. The number of correct choices for each subtest was recorded [24].

Facial Expression Recognition Test (FERT)

Facial Expression Recognition Test (FERT) is a computerized task based on 25 facial expressions from a standardized series [25]. Subjects view prototypical facial expressions of the 6 basic emotions (fear, disgust, anger, surprise, happiness, sadness) and neutral facial expressions. They judge the emotion displayed by each facial expression.

"Reading the mind in the eyes" Test ("Eyes test")

"Reading the mind in the eyes" Test ("Eyes test") is a measure of adult "metalizing". It assesses how well the subject can put themselves into the mind of another person and empathies with their mental state. Subjects see 36 photographs of the eye region of unknown faces, and choose which of 2 words best describes what the person in the photo is thinking or feeling [26].

Balanced Emotional Empathy Scale (BEES)

The full-length (30 item) BEES was used. When completing the scale, subjects were asked to state the extent to which they agreed or disagreed with 30 statements (examples: Unhappy movie endings haunt me for hours afterward; I cannot feel much sorrow for those who are responsible for their own misery) using a 9-point agreement-disagreement scale [27].

Analysis

A repeated-measures analysis of variance was employed to determine the main effects of subject group and interactions between these factors. Post-hoc Tukey tests were then employed to examine specific differences in performance between groups. The influence of independent variables (eg, years of education) and mean Beck Depression Inventory (BDI) score on performance of experimental tasks was controlled by analyses of covariance (ANCOVAs). Finally, Pearson correlations were performed between mean accuracy scores and clinical variables (eg, SANS and SAPS score, BDI, antipsychotic dose, illness duration, and number of hospitalizations).

RESULTS

All analyses were carried out utilizing SPSS software (Table 1).

Patients versus controls

The Independent Samples T-test was used to compare test performance of patients versus controls – controls outperformed patients to a highly statistically significant degree (p<0.001) in all tests.

Analysis of variance (ANOVA) indicated that the 3 groups differed significantly in years of education (F=8.02; df=2.147; p<0.001) and severity of depressive symptoms on Beck Depression Inventory (BDI) (F=29.07; df=2.147; p<0.001).

Post-hoc Tukey multiple comparison procedures failed to find statistically significant differences in test performance between the 2 patient groups: (TEA Sc/ Sa mean difference =1.14; p=0.43; SRMT Sc/Sa mean difference =0.36; p=0.82; FERT Sc/Sa mean difference =0.91; p=0.48; Eyes test Sc/ Sa mean difference =2.27; p=0.89; BEES Sc/Sa mean difference =4.83; p=0.59).

Apparently data analysis in our sample might suggest prescribing bias.

Our patients treated on atypical antipsychotic drugs appeared to be less severely ill (lower mean scores on both SANS and SAPS) and less depressed (lower mean BDI score). Furthermore, they were younger and presented with lower numbers of admissions and shorter illness duration. They outperformed the conventional treated patients on every test. Despite their clinical and demographic advantages, the better performance of atypical antipsychotic treated patients was not statistically superior to the performance of patients treated with conventional antipsychotics.

Relationship between emotional perception and independent variables

The influence of education, mood (mean BDI score) and neutral perceptual control task score (SRMT) on emotional perception was evaluated using ANCOVA. The only

Med Sci Monit, 2012; 18(1): CR44-49

Kucharska-Pietura K et al – Attentional and emotional functioning in schizophrenia...

Table 1. Demographic information and clinical data for each subject group: schizophrenia patients on conventional antipsychotics (Sc), schizophrenia patients on atypical antipsychotics (Sa) and healthy controls (N).

Variable	Sc M ±SD	Sa M ±SD	N M ±SD	F	P=
Age (in years)	33.33±15.0	29.27±12.8	29.66±11.5	1.29	0.27
Education (in years)	11.51±2.2	12.65±2.9	13.76±2.5	8.02	**0.000**
Duration of illness (in years)	10.17±9.8	7.60±9.8	–	–	–
Number of admissions	6.35±5.6	3.95±4.5	–	–	–
CPZE, mg/day	394.10±201.9	422.13±227.6	–	–	–
SAPS	40.35±23.2	38.63±18.5	–	–	–
SANS	63.89±23.0	55.85±18.9	–	–	–
BDI	19.07±11.9	15.27±11.5	3.97±3.6	29.70	**0.000**
TEA	27.0±11.1	29.56±11.0	52.1±7.8	89.5	**0.000**
Memory Face Recognition (SRMT)	20.25±3.5	20.62±3.2	22.77±2.0	9.86	**0.000**
Facial affect recognition (FERT)	15.76±4.7	16.68±4.5	21.84±1.8	34.03	**0.000**
Eyes test	17.74±5.6	20.01±5.5	25.68±4.5	28.42	**0.000**
BEES	29.23±24.81	24.39±25.56	40.80±21.88	6.47	**0.000**

Table 2. ANCOVA tests of between-subjects effects for emotion processing experiment.

ANCOVA	FERT	Eyes Test
Source	F (d.f.1)	F (d.f.1)
Education (in years)	3.01	0.82
BDI	0.18	0.10
Neutral perceptual control test (SRMT)	10.76**	5.62*
Group (d.f.2)	14.13***	14.28***

* P<0.05; ** P<0.01; ***P<0.001.

significant covariate was neutral task performance. However, when this was taken into account the effect of group on performance remained highly significant (Table 2).

Analysis of Pearson correlations in patients on both conventional and atypical antipsychotics showed statistically significant correlations between mean FERT score and mean scores on the SAPS (Sc r=–0.45; p=0.004; Sa r=–0.27; p=0.03), SANS (Sc r=–0.62; p=0.001; Sa r=–0.32; p=0.01), number of admissions (Sc r=–0.66; p=0.001; Sa r=–0.37; p=0.003), illness duration (Sc r=–0.59; p=0.001; Sa r=–0.37; p=0.003), and subject age (Sc r=–0.67; p=0.001; Sa r=–0.38; p=0.002).

Regarding the "Reading the mind in the eyes" test in schizophrenia patients on conventional antipsychotic drugs, Pearson correlations analyses showed statistically significant correlations between score and frequency of admissions (r=–0.40; p=0.01), illness duration (r=–0.48; p=0.002) and age (r=–0.38; p=0.016). In the patient group on atypical antipsychotic drugs no significant correlations were found.

BEES

Analysis of covariance (mean score as dependent variable), the type of antipsychotic FGA or SGA as a fixed factor were carried out, with years of education and mean score of BDI as covariates. The effect of group upon performance on this test remained highly significant (F=5.40; df=2.148; P=0.005) after controlling for these covariates.

Pearson correlations analyses showed statistically significant correlations between mean test score and mean SANS score (r=–0.27; P=0.036) in patients treated with atypical antipsychotic drugs.

SRMT

The effect of group upon performance on SRMT did not remain significant (F=1.56; df=2.148; P=0.21) after controlling for years of education and mean score of BDI as covariates. The analysis showed that both covariates appeared significant (education F=4.37; df=1; P=0.04; BDI F=9.52; df=1; P=0.002).

TEA

The effect of group upon performance on TEA remained highly significant (F=47.28; df=2.147; P=0.001) after controlling for years of education and mean score of BDI as covariates. Again, both covariates were significant (education F=4.19; df=1; P=0.04; BDI F=7.13; df=1; P=0.008).

Analyses of Pearson correlations in the patient group treated using conventional antipsychotics revealed statistically significant correlations between mean TEA score and mean scores of SAPS (r=–0.51; p=0.004), SANS r=–0.45; p=0.001), and numbers of admissions r=–0.31; p=0.001), illness duration (r=–0.50; p=0.001), as well as age of examined subjects r=–0.58; p=0.001). In the patient group treated using atypical antipsychotic drugs, analysis of Pearson correlations showed statistically significant correlations between mean TEA score and numbers of admissions (r=–0.31; p=0.014) and illness duration (r=–0.32; p=0.012).

DISCUSSION

Our results show significant differences between patients and healthy controls in all tasks (apart from the Short Recognition Memory Test for Faces) after controlling for covariates, with schizophrenia patients performing worse than controls.

Schizophrenia patients have difficulty in recognizing emotions, empathizing with others and "putting themselves into someone else shoes" (theory of mind), and demonstrate deficits in understanding social instructions [28–31]. It has been argued that conventional antipsychotic drugs possess the capacity to restore emotional and cognitive deficits in schizophrenia [5,7,10,32].

ANCOVA results in this study did not show significant impairment in processing facial information *per se* in schizophrenia patients; however, they confirmed the presence of deficits in perception of emotions in schizophrenia. Moreover, other significantly deeper deficits were shown in the scope of reading "the state of mind" of other people (theory of mind) and at the emotional empathy level in schizophrenia patients, in comparison with the group of healthy controls. Furthermore, the schizophrenia patients demonstrated deficits in attention function, in particular selective and sustained attention and switching attention.

The results of this study confirmed neither the positive effect of atypical antipsychotics nor the negative influence of conventional antipsychotic drugs on emotional and attentional functions in schizophrenia. Thus, the type of the antipsychotic drug used in the study (typical versus atypical) seems not to have a substantial effect on improvement or deterioration in emotional and cognitive domains. The emotional and attentional deficits remained dependent on the evaluated variables, particularly on exacerbation of illness symptoms, number of hospitalizations, illness duration and on the age of the people examined (ie, general severity effects).

The results of our study are in agreement with those of Selva-Vera et al. [33], who found no greater cognitive enhancement over 2 years in patients taking atypical antipsychotic drugs, compared to those treated with conventional antipsychotic drugs.

Interestingly, recent prominent studies assessing the effect of antipsychotic drugs on restoring emotional functioning in schizophrenia have shown no statistically significant improvement [14,15,17,18], which agrees with the results of our study.

However, the cross-sectional design of our study allowed us to conduct only one-time evaluation of emotional and attentional functioning. Prospective, randomized comparison trials of well matched patients would be necessary to settle the issue. To date it seems that most of the evidence points in the same direction, in that it is not possible to demonstrate cognitive or attentional advantages for patients treated with atypical antipsychotic drugs. This is the case even when controlling for prescribing biases. Finally, these results are consistent with those from large randomized pragmatic trials, which have repeatedly demonstrated that (with the exception of EPSE for most exemplars) the claimed advantages for atypical antipsychotic drugs are more apparent than real.

CONCLUSIONS

1. Patients with a diagnosis of schizophrenia compared with healthy people demonstrated the following deficits:
a. Facial emotion perception,
b. Empathy/theory of mind,
c. Attention (visual selective attention/speed, and attentional switching).
2. There was no difference between the performance of atypical and conventional treated patient groups, even when controlling for the prescription of atypical antipsychotic drugs to younger, less severely ill patients.

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