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Regular Article

Cognitive function and social abilities in patients with schizophrenia: Relationship with atypical antipsychotics

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Abstract Although atypical antipsychotics have been associated with improvements in cognitive function in schizophrenia, the neurochemical basis for such effects is not well understood. Candidate neurotransmitter systems primarily involve dopamine and serotonin. The current study explored this issue by examining the cognitive abilities, social function and quality of life in patients with schizophrenia who were medicated with atypical antipsychotics. Comparisons were done for matched schizophrenia patients who were on antipsychotics with (i) an affinity for multiple receptors (olanzapine, clozapine, quetiapine) versus those that have preferential affinity for dopamine receptors (risperidone, amisulpride); and patients on medication with (ii) a high affinity for serotonin (5HT-2A) receptors (risperidone, olanzapine, clozapine) versus those with a low (or no) affinity for 5HT-2A receptors (quetiapine, amisulpride). No differences emerged between groups on any cognitive or social variable when the groups were compared for the dopaminergic properties of antipsychotic medication. By contrast, differences did emerge when patients were compared on the 5HT-2A affinity of their antipsychotic medications. Patients on low 5HT-2A-affinity antipsychotics exhibited a better performance on a measure of selective attention and adjustment to living. These findings accord with the notion that serotonergic mechanisms are important determinants of both the cognitive and the social effects of the atypical antipsychotics.

Key words 5HT-2A, atypical antipsychotics, cognition, dopamine, schizophrenia, serotonin, social function.

INTRODUCTION

The emergence of the atypical antipsychotics as the front-line treatment for schizophrenia has brought more than just the hope that positive and negative symptoms will be successfully treated. There is the hope that the cognitive deficits, which are also a feature of the disorder, may be addressed. Such deficits, commonly involving aspects of memory, attention and executive function,[1] can be a severe hindrance to the quality of life and social/occupational functioning of many patients.[2–4]

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Studies have found that the most widely used atypical antipsychotics, olanzapine, clozapine, risperidone, quetiapine and amisulpride, all have an influence on cognitive function in schizophrenia, and this influence is mostly a positive one.[5–7] Nevertheless, it remains unclear precisely how these medications exert their cognitive effects, and an understanding of the biochemical mechanisms involved remains an important goal for researchers and clinicians alike. Candidate neurotransmitter systems primarily include dopamine and serotonin (5HT-2A).

Dopaminergic effects

The atypical antipsychotics all exert an influence on the dopaminergic system, and it is well established that this system plays a role in cognitive processes.[8–14] It is therefore plausible that antipsychotic action at this neurotransmitter site may underlie the cognitive effects of

these medications. The influence of dopamine on cognitive function is believed to be mediated by several dopaminergic subtypes that are represented in the prefrontal cortex, including D1, D2, D4 and D5.[15] The atypical antipsychotics all have an antagonistic (blocking) effect on dopaminergic receptors, yet they differ in their antagonistic potential (expressed as Ki nm). While risperidone and amisulpride have strong affinities (and hence greater antagonistic potential) for all dopamine receptor subtypes (e.g. risperidone receptor affinity for D2 is 3 Ki nm, amisulpride is 2.8 Ki nm), clozapine, olanzapine and quetiapine do not. In contrast, the latter compounds have less affinity to dopamine receptors (e.g. clozapine affinity for D2 receptors is 126 Ki nm; olanzapine, 112 Ki nm; quetiapine, 160 Ki nm) and their antagonistic effects are much more widespread: involving multiple receptor types.[16–18] The distinction between the dopamine-focused antipsychotic compounds and those that act on multiple receptors provides the opportunity to contrast the cognitive effects of these groups of medications. This will clarify the contribution of the dopaminergic system in the cognitive action of the atypical antipsychotics.

Serotonergic effects

Another potential mechanism of action for the cognitive effects of the atypical antipsychotics is the serotonergic system. Indeed, unequivocal evidence indicates that serotonin plays an important role in cognitive function and this influence mainly involves 5HT-2A receptors, although other receptors may also play a role.[19,20] Some authors suggest that atypical antipsychotics influence cognitive function by antagonizing 5HT-2A receptors, which leads to an increase in prefrontal dopamine turnover and a consequent improvement of the cognitive functions that are mediated by the prefrontal cortex.[21]

Studies with schizophrenia patient have also supported this hypothesis. Poyurovsky *et al.* gave 30 patients a daily dose of a drug that has 5HT-2A antagonist properties (mianserin) and found an improvement on a neuropsychological battery after 4 weeks.[22] Potkin *et al*. found that another 5HT-2A antagonist (M100907) decreased errors on the Wisconsin Card Sorting Test.[23] Finally, a 5HT-2A agonist (psilocybin) was found to impair performance on a continuous performance test in healthy volunteers.[24] The evidence therefore suggests that 5HT-2A antagonism enhances cognitive function, while agonism impairs it.

With regard to the atypical antipsychotics, these do not exert a uniform effect on 5HT-2A receptors, rather, they can be divided into two groups according to their affinity to 5HT-2A receptors.[25] Those that have a high affinity for 5HT-2A (affinity constant: risperidone [0.6], olanzapine [4], clozapine [12]) and those that have low or no affinity for 5HT-2A (quetiapine [220], amisulpride [infinity]).[26] If antagonism of 5HT-2A receptors were an important determinant of the cognitive effects of the atypical antipsychotics, then we would expect a difference in cognitive function between patients taking high-5HT-2A-affinity antipsychotics and those taking low- or no-5HT-2A-affinity antipsychotics.

These two neurotransmitter systems therefore provide potential candidates to explain the cognitive effects of the atypical antipsychotics. The ideal methodology for exploring this issue is to do a longitudinal follow-up study to track changes over time for patients on their respective medications. These types of studies are, however, prone to a number of extraneous problem variables such as patient drop-out, medication changes and test–retest reliability issues for some cognitive tests. Another approach that minimizes such problems is to use cross-sectional methodology where patients who are matched on demographic variables, psychopathology and premorbid IQ are compared on cognitive measures at a particular time point. This approach is useful in providing a snapshot of cognitive function in schizophrenia and how patients, on different medication regimens, are fairing.

The aims of the current study are as follows.

(1) To compare the cognitive abilities, social function and quality of life of patients with schizophrenia who are on atypical antipsychotics that have (i) an affinity for multiple receptors (olanzapine, clozapine, quetiapine) versus those that have preferential affinity for dopamine receptors (risperidone, amisulpride); and (ii) a high affinity for 5HT-2A receptors (risperidone, olanzapine, clozapine) versus those that have a low (or no) affinity for 5HT-2A receptors (quetiapine, amisulpride). Small numbers precluded comparisons between each individual medication group.

(2) To explore associations between the neurochemical properties of the atypical antipsychotics and social function and quality of life in schizophrenia.

METHODS

Patients

Thirty patients (25 male; five female) with a DSM-IV diagnosis of schizophrenia, were recruited from inpatient ($n = 5$) and outpatient ($n = 25$) units in East Yorkshire, UK. All gave informed consent to participate in the study. None of the patients had a history of neurological disease, head injury, substance or alcohol abuse. The average age of the patients was 38 ± 7.8 years (range 22–52 years), with a mean length of illness of

Table 1. Medication summary

Antipsychotic	*n*	Mean daily dose per medication group (mg)	Mean percentage of maximum dose	Mean no. months on medication
Olanzapine	8	12	62	25
Risperidone	5	4	25	24
Clozapine	8	350	38	44
Quetiapine	5	350	46	26
Amisulpride	4	500	41	8

Table 2. Group split according to dopamine

	Multiple receptor group	Preferential dopamine group	*P*
Age (years)	39.19	35.77	0.28
Premorbid IQ	98.19	98.55	0.95
Length of illness (months)	159.52	117.33	0.17
Months on medication	32.81	17.55	0.08
% max dose	49.38	33.61	0.08
BPRS total score	10.14	10.44	0.88

BPRS, Brief Psychiatric Rating Scale.

Table 3. Group split according to 5HT-2A

	High affinity	Low affinity	*P*
Age (years)	37.47	39.77	0.47
Premorbid IQ	94.91	106.22	0.05
Length of illness (months)	141.81	158.66	0.56
Months on medication	32.43	18.44	0.11
% max dose	44.92	44.00	0.92
BPRS total score	10.19	10.33	0.94

BPRS, Brief Psychiatric Rating Scale; 5HT-2A, serotonin.

12 ± 6 years (range, 2 months–25 years). Symptom type and severity was assessed with the Brief Psychiatric Scale (BPRS),[27] which gave a mean total score of 10.2 ± 4.6 (range, 3–22). When the BPRS score was broken down according to four symptom dimensions,[28] the ratings were: thinking disturbance, mean 3.6 ± 2.5, range 0–9; withdrawal/retardation, mean 1.8 ± 1.8, range 0–6; hostility/suspiciousness, mean, 1.6 ± 1.4, range 0–4; and anxiety/depression, mean 4.9 ± 3.0, range 1–12. The National Adult Reading Test (NART[29]) was used to assess premorbid IQ.

To investigate associations between medication levels and neuropsychological test performance, antipsychotic dosages were converted to the percentage of maximum dose (PMD) according to the British National Formulary.[30] This is a novel yet reliable method of comparing antipsychotic potency and avoids some of the problems of using chlorpromazine equivalents as a method of investigating dose equivalence.[31] Table 1 provides a summary of patient medication type and dosage and mean PMD for each medication group. Demographics with regard to dopamine, and 5HT-2A affinity are given in Tables 2,3.

Procedure

Measures of cognitive function

The neurocognitive battery was chosen to provide a comprehensive investigation of cognitive ability; short-term memory, working memory, attention (sustained, selective and divided) and executive function. Where possible the emphasis was on tests with strong ecologic validity.

Digit span. This test is considered to reflect short-term verbal memory and requires a subject to repeat an increasing sequence of numbers.[32]

Digit span reversed. This test uses the same procedure as the digit span (DS) test except that the sequence of numbers has to be repeated in reverse order. This test requires the manipulation (reversal) of items that are held in short-term working memory.[32]

Test of Everyday Attention. This battery of tests is designed to measure attentional abilities in an everyday setting using naturalistic tasks.[33] Because it would take a whole hour to administer the whole battery, three subtests were chosen that we felt were representative of the key components of attention: (i) sustained attention (this refers to the ability to sustain attention to repetitive stimuli), the Test of Everyday Attention (TEA) subtest that measured this ability involved counting sequences of bleeps played on an audiotape; (ii) selective attention (this refers to the ability to attend to target stimuli in the presence of powerful distracters), this subtest involved counting bleeps of a certain pitch, while ignoring bleeps of a different pitch; and (iii) divided attention (this concerns the ability to respond to more than one task at the same time), the TEA subtest of this ability involves an auditory counting task and a visual search task that have to be performed simultaneously.

Behavioral Assessment of the Dysexecutive Syndrome. This battery of tests assesses executive skills using naturalistic tasks, such as searching for a key, planning a route around a zoo, and organizing several tasks within a time limit.[34] It is sensitive to problems such as an inability to co-ordinate and guide lower level processes such as memory and attention, the planning, initiation and sequencing of behavior, and the inhibition of behavior that is inconsistent with a specific goal.

Other measures

Multinomah Community Ability Scale. This scale is designed to measure the level of social functioning of chronically mentally ill patients living in the community.[35] It is designed to be completed by someone with a detailed knowledge of the patient and is based on a likert scale scoring system. It poses questions about a number of different domains of social function, although an abridged version of this scale was used in the current study which included the modules *adjustment to living* (section 2, 3 questions) and *social competence* (section 3, 5 items). For patients who were not living in the community at the time of the study (5/30), the staff member who completed the scale was asked to judge the social abilities of the patients from what they had observed on the unit, and what they knew about how well the patient coped on home visits.

Quality of Life Self-Assessment Inventory. This scale contains a 100-item inventory divided into 11 domains: housing, environment, knowledge and education, contacts, dependence, inner experiences, mental health, physical health, leisure, work, and religion.[36] Patients are asked to circle the items that they judge unsatisfactory at present (e.g. size of housing, friendships). The higher the number of items circled, the lower is judged their quality of life.

RESULTS

Student's *t*-tests were used to compare the patients in terms of the dopaminergic and serotonergic profile of their antipsychotic medication. No differences emerged on any of the demographic, neuropsychological or social variables when the groups were compared in terms of the dopaminergic properties of their antipsychotic medication. A single difference did emerge on the BPRS Hostility/Suspiciousness dimension with the preferential dopamine affinity group scoring higher than the multiple receptor group (2.4 vs 1.2: $t_{28} = -2.31$, $P = 0.028$).

By contrast, several differences in cognitive performance emerged when the patients were split in terms of the 5HT-2A affinity of their antipsychotic medications. The patients on low-5HT-2A-affinity antipsychotics (amisulpride, quetiapine) achieved significantly better scores on the digit span test, the TEA elevator counting test and the TEA elevator counting with distraction test. In addition, they also scored more highly on the adjustment to living subscale from the Multinomah questionnaire (Table 4).

Although the high- and low-affinity groups were matched for age, duration of illness, number of months on medication and symptom variables, the patients on low-5HT-2A-affinity antipsychotics had significantly greater IQ than the high-5HT-2A-affinity group (106 vs 95: $t_{28} = -2.07$, $P = 0.047$). To consider the possibility that premorbid IQ differences could account for the differences in cognitive and social performance, a MANOVA was performed with premorbid IQ as a covariate. The group difference on the digit span test ($P = 0.092$) and the TEA elevator counting task ($P = 0.13$) were no longer significant, although the group differences remained on the TEA elevator counting with distraction test ($P = 0.048$), and the adjustment to living

Table 4. Cognitive and social measures according to 5HT-2A affinity (mean ± SD)

Domain of function	Test/measure	5HT-2A affinity High ($n = 21$)	5HT-2A affinity Low ($n = 9$)	*t*-tests *t*	*t*-tests *P*	*t*-tests Effect size (d)
Short-term memory	Digit span forward	5.5 ± 1.0	6.5 ± 0.8	–2.49	0.02	1.02
Working memory	Digit span backward	4.0 ± 1.1	4.6 ± 1.9	–1.16	0.25	0.48
Sustained attention	TEA Elevator counting	5.4 ± 1.9	6.7 ± 0.6	–2.82	0.01	1.16
Selective attention	TEA Elevator counting with distraction	4.0 ± 2.7	7.0 ± 2.5	–2.75	0.01	1.13
Divided attention	Telephone search while counting	7.2 ± 12.0	6.3 ± 9.8	0.19	0.84	0.08
Executive function	BADS total score	15.0 ± 3.6	15.8 ± 2.0	–0.64	0.52	0.26
Quality of life	Self-assessment inventory	11.7 ± 9.5	17.2 ± 12.1	–1.28	0.21	0.53
Social function	Multinomah scale total	27.9 ± 7.1	31.1 ± 5.0	–1.21	0.23	0.49
	Multinomah scale adjustment to living	11.5 ± 3.1	13.8 ± 1.2	–2.87	0.01	1.18
	Multinomah scale social competence	16.3 ± 4.4	17.2 ± 4.2	–0.50	0.62	0.20

BADS, Behavioural Assessment of the Dysexecutive Syndrome; 5HT-2A, serotonin; TEA, Test of Everyday Attention.

subscale of the Multinomah questionnaire ($P = 0.035$). It is also important to note that universally the patients on low-5HT-2A-affinity antipsychotics had higher mean scores on all the cognitive and social variables than the high-5HT-2A-affinity group. In addition, they achieved a higher score on the quality of life measure, indicative of a greater awareness of circumstantial problems.

DISCUSSION

The current study reports that schizophrenic patients taking atypical antipsychotics with little or no affinity to 5HT-2A receptors (amisulpride, quetiapine) performed better on a test of sustained attention and a measure of social functioning than those on high-5HT-2A-affinity antipsychotics (risperidone, olanzapine, clozapine). In addition, a perusal of the mean scores on each measure indicates a universally superior performance of the low-5HT-2A-affinity group. By contrast, splitting the patient group in terms of the dopaminergic properties of the antipsychotics yielded no group differences. These findings suggests that 5HT-2A affinity plays an important role in the cognitive effects of the atypical antipsychotics, and that low or no affinity is more beneficial for cognition and social function than high affinity.

At first glance this finding appears contradictory to research suggesting that compounds with an antagonistic effect on 5HT-2A are beneficial for cognitive function.[22] If this were indeed the case then patients medicated on compounds with the most antagonistic potential for 5HT-2A receptors, would display superior cognitive abilities than those who were on medications with little or no antagonistic potential. Nevertheless, the findings of the current study are consistent with a recent report that found that over an 18-month period, patients on low-5HT-2A-affinity antipsychotics improved on measures of short-term memory, recognition memory and thinking time on a planning task.[26] In contrast, patients on high-5HT-2A-affinity antipsychotics had no change on measures of digit span, but did suffer a decrement in performance on recognition memory tests and thinking time in a planning task (i.e. they became slower with repeated testing). In addition, Wagner *et al.* reported that the atypical antipsychotic amisulpride (which is devoid of 5HT-2A affinity) was as effective at alleviating cognitive deficits as olanzapine (high 5HT-2A affinity).[5] Although this finding in itself does not suggest a cognitive advantage of atypical antipsychotics with no affinity for 5HT-2A receptors, Wagner *et al.* did note stronger effects of amisulpride on attention and executive function and suggested that a similar study with higher statistical power might demonstrate an advantage of amisulpride over risperidone.[5] Certainly, the assertion that serotonin activation impairs learning and memory whereas reduced serotonergic function enhances these processes needs reconsideration.[37]

In addition, our finding of enhanced social abilities for the low-5HT-2A-affinity group suggests that serotonergic mechanisms are important for successful functioning in a social environment. However, it is likely that these superior social abilities are reflective of the cognitive differences between groups, because we found significant associations between several of our measures of cognitive function and social abilities. In addition, the link between cognition and social functioning is well-established in the literature.[2]

Clearly, our findings can be considered only tentative at this stage because it remains difficult to precisely define the neurochemical basis for the cognitive effects of the atypical antipsychotics. Part of the problem stems from the fact that the atypical antipsychotics act on a number of neurotransmitters simultaneously, and so they may exert a combined effect on the brain and behavior that is not seen in more selective compounds, such as those used in animal studies. Indeed, the role of serotonergic–cholinergic interactions in the mediation of cognitive behavior has been considered,[20,38] as have the interactions between norepinephrine, dopamine, serotonin and the cholinergic system.[19,39,40] In addition, all the atypical antipsychotics except amisulpride exert sedative side-effects,[41] and these must be considered in the light of their purported cognitive effects.

Furthermore, paradigmatic differences between studies further limit the general conclusions that can be drawn from this issue. These include the serotonin-altering compound (global manipulation/depletion or specific subtype manipulation/depletion); temporal factors in compound administration (before, during or after testing); the type of subject (rat, patient, or healthy control); the cognitive tests administered (which are rarely the same across studies); and the length of the study.

One limitation of this study relates to its cross-sectional rather than longitudinal design. Because we did not take baseline measures on all variables, the equivalence of the groups was not established. It is therefore possible that the group differences we observed were related to baseline differences rather than medication differences. We do not, however, feel that this is the case because the groups were matched on a variety of relevant variables including: age, duration of illness, number of months on medication, percentage of maximum dose of medication and symptom variables. The patients were also from similar socioeconomic backgrounds. We did find a difference in premorbid IQ between groups, but this was controlled in analyses. We therefore make the assumption that the groups were equivalent at baseline because they did not differ on any variables that could have had an influence on their cognitive status. In conclusion, our study findings accord with the wider literature indicating that serotonergic mechanisms are important determinants of the cognitive and social effects of the atypical antipsychotics.

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