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Cognitive effectiveness of olanzapine and risperidone in first-episode psychosis

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Background
Cognitive impairment in schizophrenia-spectrum disorders is highly prevalent and notably influences functional outcomes.

Aims
To characterise the cognitive effectiveness of second-generation antipsychotic drugs.

Method
One hundred consecutive and previously unmedicated patients with first-episode schizophrenia-spectrum disorders were admitted. Seventy-seven completed baseline, 1-month and 6-month psychopathological and neuropsychological assessments. Patients were randomised to risperidone or olanzapine treatment. Four final treatment allocation groups were defined since patients continued treatment in their normal setting: risperidone, olanzapine, mixed and no-antipsychotic groups.

Results
There were no differences in cognitive effectiveness between the four treatment groups. Reliable change index methods demonstrated that nearly a half of patients showed an improvement in Global Cognitive Score at the 6-month assessment. Improvement on the neuropsychological tests ranged from 17 to 54%.

A strong predictor of cognitive response was poor performance on baseline neuropsychological tests; response was moderately influenced by a low premorbid scholastic performance and IQ.

Conclusions
Cognitive improvement related to second-generation antipsychotic drugs appeared within the first 4 weeks of treatment and persisted at 6 months irrespective of treatment group. Greater cognitive dysfunction at baseline and lower premorbid cognitive background predicted cognitive improvement in our sample.

Declaration of interest
None.

Cognitive impairment is a prevalent feature in patients with schizophrenia[1–5] that greatly influences functional outcomes.[6,7] Both global deficit and impairments in attention, memory and executive functions are commonly found in schizophrenia.

A renewed interest in the amelioration of cognitive deficits of schizophrenia arose with the new antipsychotic drugs. Earlier reviews suggested that first-generation antipsychotic drugs did not improve cognitive performance in schizophrenia,[8–13] although studies concluded that low doses of typical antipsychotics seem to have favourable cognitive effects.[14–18] Moreover, two recent contributions reduce the strength of the argument for cognitive efficacy of antipsychotic drugs. First, the CATIE study concluded that the cognitive improvement related to either first- or second-generation antipsychotics was significant, but smaller than previously reported.[17] Second, it was recently suggested that part of this improvement in patients with first-episode schizophrenia was similar to the practice effect observed in healthy controls.[19]

The present study was a naturalistic, randomly assigned and non-commercially funded study aimed at assessing the cognitive outcome at 6 months in a sample of drug-naive patients with first-episode psychosis. The primary goal was to compare cognitive function between four treatment conditions: patients receiving either risperidone or olanzapine; patients who changed their initial atypical antipsychotic; and patients who did not receive antipsychotics in the last 3 months of the study. As a secondary goal, this study aimed to investigate individual prognostic indicators of a good cognitive response irrespective of treatment group.

Method

Participants

A total of 100 consecutive, drug-naive patients with first-episode psychosis were evaluated. Inclusion criteria were:

(a) patients aged 16–65 years

(b) an acute episode at study intake that met DSM–IV–TR[20] criteria for schizophrenia and other psychotic disorders

(c) no previous exposure to antipsychotics

(d) provided written informed consent and able to take part in neuropsychological assessment.

Patients with a history of serious medical or neurological disease, head injury, intellectual disability or drug dependence were excluded from the study.

All study aims and procedures were fully explained to participants and their families before they signed a written consent form; the study was approved by the institutional review board.

Study design and procedures

This was a longitudinal and naturalistic study, which comprised comprehensive psychopathological and neuropsychological assessments at three points: baseline, 1-month and 6-month follow-up. All patients underwent the Comprehensive Assessment of Symptoms and History interview.[21] A DSM–IV–TR diagnosis was reached by clinical consensus between the two senior researchers (M.J.C. and V.P.).

Two psychiatrists (E.G.J. and M.S.C.) assessed the psychopathological and cognitive status of patients in such a way that each was masked to the assessment of the other and to the treatment received by patients. Good interrater reliability coefficients for psychopathological assessments ($\kappa = 0.80–0.98$) were achieved by the two psychiatrists.

Once baseline assessments were completed on the first day of admission, participants were randomly assigned to receive either risperidone ($n = 56$) or olanzapine ($n = 44$) treatment. Patients initially received a low dose (2.5 mg for risperidone, 5 mg for

olanzapine), which was gradually titrated up while active symptoms were present. Patients were followed in their natural treatment environment and treatment decisions after initial randomisation were made by treating psychiatrists.

Of the 100 patients, 23 withdrew during the course of the study (11 and 12 individuals at 1-month and 6-month assessments respectively) (Fig. 1). Final drug allocation groups were as follows: risperidone group, $n=29$; olanzapine group, $n=22$; mixed group (those patients who needed to change their initial antipsychotic to another atypical antipsychotic), $n=16$; and no-antipsychotic group (those patients who did not receive antipsychotic drugs in the last 3 months of follow-up), $n=10$.

Doses of the atypical antipsychotics were transformed to chlorpromazine equivalents (mg).[22] Patients received either biperidene or benzodiazepines if needed by indication of the treating psychiatrists.

Drug adherence was assured by collecting information independently from patients, families and the attending psychiatrist at every point of assessment. Surveillance by close relatives is one of most accurate methods of measuring adherence.[23]

Neuropsychological assessment

Participants were assessed by means of a comprehensive neuropsychological battery measuring attention, executive function, information processing, and memory. Neuropsychological tests included: Verbal Fluency[24] (number of animals evoked in 1 min); Trail Making Test – form B[24] (number of seconds to complete the task); Wechsler Memory Scale (WMS);[25] and four tasks of the COGLAB computerised neuropsychological battery:[26,27] a reaction time task (that included Redundancy-Associated Deficit (RAD), a vigilance and span of apprehension task (Asarnow's test, which included Total Hits and Total False Alarms), a visual backward masking task (iconic memory test), and the Wisconsin Card Sorting Test (WCST; Perseverative Errors and Total Trials).

Exploratory factor analyses of the 14 cognitive measures at each assessment point were done to obtain a Global Cognitive Score (GCS) and to normalise different scales of measurements. Exploratory factor analyses resulted in four factors (eigenvalue =1), although an inspection of the three Scree test plots revealed that only one factor achieved the greater percentage of explained variance. Thus, reduction to a one-factor solution was carried out and baseline, 1-month and 6-month GCS variables were saved. Oblimin rotation was chosen to allow factors to be correlated, as it occurs usually among cognitive measures.[28]

General IQ was ascertained by means of the Spanish version of a non-verbal IQ test (TONI-2 Test).[29]

Statistical analysis

To compare demographic and clinical characteristics between groups, one-way repeated measures ANOVA and chi-squared test were applied. Logarithmic transformation or *z*-transformations were applied to non-normally distributed variables.

Testing occasion was the within-group factor (baseline, 1 month and 6 months) and treatment assignment was the between-group factor (risperidone, olanzapine, mixed and no-antipsychotic groups). Repeated measures ANCOVA was also performed for each cognitive variable using baseline neuropsychological assessments, biperidene and antipsychotic mean doses (chlorpromazine equivalents in mg) as covariates. Tukey's Honestly Significant Difference test was performed for *post hoc* analysis between diagnostic groups.

We also calculated two forms of the reliable change index (RCI),[30] which is a group of statistical techniques used in many areas of medicine to help determine when an individual's performance on a neuropsychological test has changed from a previous assessment with the same test. The index provides

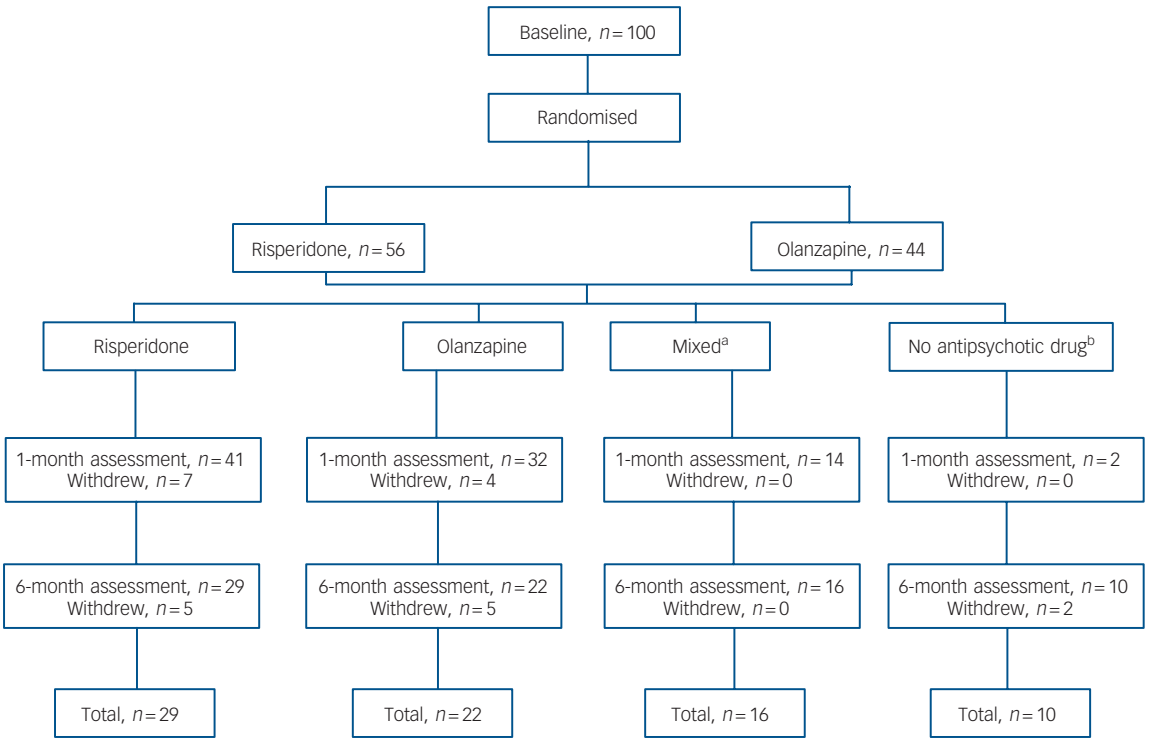

Fig. 1 Flow of participants through the study.

a. Patients who needed to change their initial antipsychotic to another.
b. Patients who did not receive antipsychotic drugs in the last 3 months of follow-up.

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information about whether people have changed sufficiently that the change is unlikely to be due to simple measurement unreliability. Formulas for RCI–simple (RCI–s) and RCI–practice (RCI–p) are shown in the online supplement to this paper.

Results

Demographic and clinical characteristics of treatment groups

No differences in clinical or epidemiological variables at baseline were found between those patients who withdrew ($n=23$, 23%) and those who completed the study ($n=77$, 77%) except for years of education ($t=2.36$, d.f. = 98, $P<0.020$) (Table 1). The subsequent results refer to those who completed the three assessments ($n=77$).

The four treatment groups did not differ in most epidemiological, clinical and diagnostic variables. However, the risperidone group had significantly higher scores for psychotic syndrome than the olanzapine group; the no-antipsychotic group had significantly higher scores than the risperidone group for depressive syndrome; and the risperidone and mixed groups showed significantly higher scores for disorganisation syndrome than the olanzapine group at baseline (online Table DS1). Patients in the risperidone group received higher antipsychotic doses at 6-month but not at 1-month assessment and they were treated more often with anticholinergic drugs (37.93%) than either the mixed (18.75%) or olanzapine and no-antipsychotic groups (0%) (Table 2).

Neuropsychological test results

No significant main effects on neuropsychological tests and on the GCS were found for any of the four groups. Cognitive performance showed significant improvement over time on most neuropsychological tests irrespective of the treatment group, with the exception of performance on three tasks: reaction time, RAD and Asarnow Total False Alarms (Table 3). The mixed group showed greater improvement than the other three groups on WMS Associated Learning (group × time interaction: $F=2.63$, d.f. = 3.63, $P=0.044$).

After including antipsychotic and biperidene doses at the 6-month point with baseline neuropsychological results as covariates on repeated measures ANCOVA analyses, most effects for time vanished. Only the effects for time on WCST Total Trials ($F=6.29$, d.f. = 1, $P=0.015$) and Asarnow Total Hits ($F=12.47$, d.f. = 1, $P=0.001$) remained statistically significant.

The significant findings of both ANOVA and ANCOVA did not exceed the required P-value level of the Bonferroni correction ($P=0.003$, for 16 sets of repeated measures of ANOVA or ANCOVA), except for Asarnow Total Hits.

Reliable change index scores

Reliable change indices for the whole sample demonstrated great variation in individual patterns over time across neuropsychological tests, although both indices (simple and practice) showed similar scores. Specifically, the percentages of patients who improved on neuropsychological tests and GCS ranged from 17.33% on Asarnow False Alarms to 54.54% on Verbal Fluency (Table 3).

The RCI–s and RCI–p results for the GCS demonstrated that 35 (47.29%) and 33 (45.83%) patients respectively showed a statistically meaningful improvement (or reliable improvement) and that 39 (52.70%) and 38 (52.77%) patients respectively displayed a lower change than expected at 6-month follow-up. However, there were no individual patients performing below their own baseline performance at the 6-month assessment on any cognitive measures.

Reliable worsening and stable patterns should be interpreted with caution since they do not represent patients definitively

Table 1 Demographic, clinical and pharmacological characteristics of the sample at baseline

	Risperidone ($n=29$)	Olanzapine ($n=22$)	Mixed ($n=16$)	No antipsychotic drug ($n=10$)	Total ($n=77$)	Statistic (P)
Gender						
Male	22	16	9	6	53	$\chi^2=2.37$ (0.5)
Female	7	6	7	4	24	
Age, years: mean (s.d.)	26.7 (7.44)	32.73 (11.8)	30.13 (10.86)	34.10 (8.86)	30.09 (10)	$F=2.27$ (0.087)[a]
Age at onset, years: mean (s.d.)	24.99 (7.57)	31.5 (11.8)	26.63 (9.17)	29.89 (9.93)	27.83 (9.78)	$F=2.16$ (0.099)[a]
Duration of illness, years: mean (s.d.)	0.84 (1.47)	0.61 (0.9)	1.74 (3.12)	2.10 (3.65)	1.13 (2.2)	$F=1.67$ (0.179)[a]
Years of education, mean (s.d.)	13.83 (3.52)	15 (4.61)	12.38 (4.36)	14.30 (3.23)	13.92 (4.04)	$F=1.35$ (0.263)[a]
Parents' years of education, mean (s.d.)	8.83 (3.38)	7.76 (2.27)	7.03 (1.81)	8.20 (3.73)	8.07 (2.90)	$F=1.46$ (0.233)[a]
Scholastic performance,[b] n (%)						
Excellent	3 (10)	1 (5)	0	1 (10)	5 (6)	$\chi^2=13.56$ (0.330)
Good	3 (10)	4 (18)	2 (13)	3 (30)	12 (16)	
Medium	12 (41)	10 (45)	4 (25)	4 (40)	30 (39)	
Low	8 (28)	6 (27)	10 (63)	1 (10)	25 (32)	
Failing	3 (10)	1 (5)	0	1 (10)	5 (6)	
GAF–P, mean (s.d.)	76.07 (17.71)	80.14 (12.54)	73.94 (21.45)	82.30 (17.04)	77.60 (17.11)	$F=0.72$; (0.540)[a]
Current IQ (TONI-2), mean (s.d.)	96.9 (17.85)	92.5 (18.94)	96.06 (18.35)	99.10 (20.74)	95.75 (18.41)	$F=0.37$; (0.776)[a]
DSM–IV–TR diagnosis, n (%)						
Schizophrenia	16 (55)	6 (27)	7 (44)	4 (40)	33 (43)	$\chi^2=21.47$; (0.122)
Schizoaffective disorder	1 (3)	1 (5)	2 (13)	2 (20)	6 (8)	
Brief psychotic disorder	6 (21)	7 (32)	4 (25)	1 (10)	18 (23)	
Schizophreniform disorder	6 (21)	3 (14)	3 (19)	0	12 (16)	
Delusional disorder	0	4 (19)	0	2 (20)	6 (8)	
Atypical psychosis	0	1 (5)	0	1 (10)	2 (3)	
Benzodiazepines, n (%)	22 (76)	16 (73)	13 (81)	9 (90)	60 (78)	

GAF–P, Global Assessment of Functioning over the past year.
a. One-way ANOVA.
b. Mean educational qualifications, assessed on a 10-point scale by patients and their families, where: excellent is 10, good is 8–9, medium is 6–7, low is 5, failing is <5.

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Table 2 Clinical and pharmacological characteristics of the sample at 1-month and 6-month assessment

	Risperidone ($n = 29$)	Olanzapine ($n = 22$)	Mixed ($n = 16$)	No antipsychotic drug ($n = 10$)	Total ($n = 77$)	Statistic (P)
1-month assessment						
Chlorpromazine equivalent dose, mg: mean (s.d.)	303.44 (136.23)	215.90 (96.83)	290.62 (174.13)	227.50 (134.08)	265.90 (138.30)	$F = 2.19$ (0.096)[a]
Biperidene						
Dose, mg: mean (s.d.)	3.33 (1.15)	0	0	0	3.33 (1.15)	$F = 1.60$ (0.195)[a]
Patients, *n* (%)	3 (10)	0	0	0	3 (4)	
Benzodiazepines, *n* (%)	29 (100)	17 (77)	16 (100)	9 (90)	71 (92)	
6-month assessment						
DSM–IV–TR diagnosis, *n* (%)						
Schizophrenia	23 (79)	10 (45)	10 (63)	4 (40)	47 (61)	$\chi^2 = 26.12$ (0.097)
Schizoaffective disorder	2 (7)	2 (9)	3 (19)	2 (20)	9 (12)	
Acute psychosis	3 (10)	5 (23)	2 (13)	1 (10)	11 (14)	
Schizophreniform disorder	1 (3)	1 (5)	1 (6)	0	3 (4)	
Delusional disorder	0	4 (18)	0	2 (20)	6 (8)	
Atypical psychosis	0	0	0	1 (10)	0	
Chlorpromazine equivalent dose, mg: mean (s.d.)	212.93 (143.24)	145.45 (72.22)	288.09 (334.14)	0	206.28 (190.06)	$F = 6.04$ (0.001)[a,b]
Biperidene						
Dose, mg: mean (s.d.)	3.63 (0.81)	0	4 (0)	0	3.71 (0.72)	$F = 5.02$ (0.003)[a,c]
Patients, *n* (%)	11 (38)	0	3 (19)	0	14 (18)	
Benzodiazepines, *n* (%)	26 (90)	21 (95)	14 (88)	0	71 (92)	

a. One-way ANOVA.
b. Risperidone>no antipsychotic drug; mixed>no antipsychotic drug.
c. Risperidone>olanzapine, no antipsychotic drug.

Table 3 Reliable change index (95%) simple and practice frequencies for each neuropsychological test

Cognitive test	Patients, *n* RCI–s/RCI–p	Worsening, *n* (%) RCI–s/RCI–p	Stable, *n* (%) RCI–s/RCI–p	Improvement, *n* (%) RCI–s/RCI–p
Verbal fluency[a]	77/77	35 (45.45)/39 (50.64)	0 (0)/0 (0)	42 (54.54)/38 (49.35)
Trail Making Test–B[a]	77/77	50 (64.93)/48 (62.33)	2 (2.59)/1 (1.29)	25 (32.46)/28 (36.36)
Wechsler Memory Scale				
Total	76/76	40 (52.63)37 (46.68)	0 (0)/1 (1.31)	36 (47.36)/38 (50.00)
Logical memory	77/77	35 (45.45)/41 (53.24)	5 (6.49/1 (1/29)	37 (48.05)/35 (45.45)
Digital memory	77/77	36 (46.75/45 (58.44)	0 (0)/0 (0)	41 (53.24)/32 (41.55)
Visual reproduction	77/77	41 (53.24)/40 (51.94)	1 (1.29)/2 (2.59)	35 (45.45)/35 (45.45)
Paired associated learning	77/77	44 (57.14)/37 (48.05)	1 (1.29)/2 (2.59)	32 (41.55)/38 (49.35)
COGLAB[a]				
Reaction time	77/75	45 (58.44)/39 (52.00)	2 (2.59)/1 (1.33)	30 (38.96)/35 (46.66)
RAD (reaction time)	77/75	40 (51.94)/39 (52.00)	4 (5.19)/1 (1.33)	33 (42.85)/35 (46.66)
Backward Masking Total	75/73	44 (58.66)/37 (50.68)	2 (2.66)/3 (4.10)	29 (38.66)/33 (45.20)
WCST Perseverative Errors	76/74	44 (57.89)/37 (50.00)	4 (5.26)1 (1.35)	28 (36.84)/36 (48.64)
WCST Total Trials	76/74	50 (65.78)/40 (54.05)	3 (3.94)/0 (0)	23 (30.26)/34 (45.94)
Asarnow Total Hits	75/73	45 (60.00)/41 (56.16)	2 (2.66)/1 (1.36)	28 (37.33)/31 (42.46)
Asarnow Total False Alarms	75/73	49 (65.33)/28 (38.35)	13 (17.33)/0 (0)	13 (17.33)/45 (61.64)
Global Cognitive Score[b]	74/72	39 (52.70)/38 (52.77)	0 (0)/1 (1.38)	35 (47.29)/33 (45.83)

RCI–s, reliable change index, simple; RCI–p, reliable change index, practice; RAD, Redundancy-Associated Deficit; WCST, Wisconsin Card Sorting Test..
a. *z*-transformation.
b. Factorial transformation.

showing a deteriorating outcome, rather those patients who did not reach significant statistical changes as shown in online Fig. DS1.

To characterise the cognitive improvement of our patients, two sets of stepwise regression procedures were set for demographic and clinical variables in which the indices of neuropsychological tests and of GCS were introduced as 'dummy' dependent variables (improvement *v.* stable and no-improvement patients) (see footnote of online Table DS2 for a description of variables entered into the regression analyses). Moreover, in order to gain greater insight into patients' cognitive performance, it was necessary to account for both ceiling effects of cognitive measures and for patients' performance within normal ranges on neuropsychological tests by including baseline performance on each test and baseline GCS together with the above demographic and clinical variables for both RCI–s and RCI–p.

Patients with a cognitive response were strongly influenced by poor performance on neuropsychological tests at baseline (online Table DS2). The premorbid scholastic performance and current IQ were moderate predictors of cognitive improvement; high baseline psychopathological scores (disorganisation and psychotic syndrome scores), treatment variables (lower 6-month chlorpromazine equivalent doses) and 6-month DSM–IV–TR diagnosis were slight, but also significant predictors. Treatment status was not included in these patients' profiles in the regression analyses.

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Discussion

In the present study, we followed the treatment effects of atypical antipsychotic drugs on neurocognitive performance in a drug-naive patient sample with first-episode schizophrenia-spectrum disorders over 6 months in a naturalistic setting.

Three main conclusions can be drawn from this study. First, no differences in cognitive effectiveness were found between the four treatment groups. Second, 30% of the total sample showed an improvement in GCS at 6 months and showed improvement on the 14 neuropsychological tests ranging from 17 to 54%. Finally, the clinical profile at the individual level was strongly influenced by poor cognitive performance at baseline and moderately influenced by low premorbid scholastic performance and low IQ. Female gender, young age and low antipsychotic doses at the 6-month assessment also contributed marginally to a better cognitive improvement profile at the individual level.

Levels of cognitive impairment and rates of global cognitive improvement in our patients were in keeping with previous studies at initial disease presentation.[31–34] Our results can also be applied to non-drug-naive patients with first-episode psychosis since no differences were evident between studies comparing drug-naive and non-naive patients in first-episode psychosis.[35,36]

It is usually taken for granted that cognitive improvement is a direct effect of antipsychotic drugs; however, any longitudinal cognitive change (either improvement or worsening) in schizophrenia might come from at least three sources: patient-related factors, neuropsychological assessment and treatment effects.

Patient-related factors

The pattern of cognitive impairment in patients with schizophrenia is likely to be a function of the heterogeneity within the disorder itself.[37] To homogenise the population as much as possible for differences in illness-phase,[38] we only included drug-naive patients with a first episode. Moreover, based on the current lack of definitive validation for any psychosis subtype,[39] we chose a broad approach by including schizophrenia-spectrum disorders. Nevertheless, the analysis from the statistical procedures performed only on patients with schizophrenia demonstrated that there were no great differences compared with the entire sample.

One of the most important determinants of neuropsychological performance is premorbid scholastic performance. Premorbid intra-individual intellectual performance variability has been associated with the risk of developing schizophrenia,[40] and low premorbid intellectual achievement may also be an early manifestation of the illness.[41] New to this study was that lower premorbid IQ predicted cognitive improvement over 6 months. This implies that patients with greater 'cognitive reserve', who are already experiencing cognitive changes related to schizophrenia, perform within normal limits until acute impairment is severe. Likewise, patients with lower cognitive reserve are less able to compensate for cognitive deficits; consequently, they are prone to develop greater cognitive dysfunction related to the acute episode and show a wider range of intra-individual variability on standard clinical cognitive testing.

Neuropsychological issues in the assessment of cognitive improvement

Accurate interpretations of the neuropsychological test findings are based on the premise that each test is reasonably free of measurement error, practice effects and that tests are not prone to floor and ceiling effects. In our study, the reliable change index method (both simple and practice) was used as a statistical technique to account for the reliability of intra-individual score changes. As was reported for patients with stable schizophrenia,[42] we found larger-than-expected percentages of patients with schizophrenia-spectrum disorders classified as cognitively changed on 6-month retest assessments. In this regard, although reliable change index methods allowed us to delineate cut-off points for cognitive improvement in neuropsychological tests, cognitive decline and cognitively stable patterns are better interpreted as 'lower performance than predicted'. Moreover, after inspection of the baseline and 6-month plots of our 14 neuropsychological measures, we determined that our results were not subject to floor or ceiling effects.

Antipsychotic drug effects on cognitive performance

There were no significant differences in cognitive effectiveness among the four treatment groups over the 6 months of treatment. These results added support to studies reporting that atypical antipsychotic drugs produced significant improvement in neurocognition,[16,43,44] although with a smaller effect than previously reported.[7,17]

To account for practice effects[19] we did not include a healthy control group but we employed differences in neuropsychological tests between the 1-month assessment, when patients were clinically stable, and the 6-month assessment to derive our RCI–p. The latter is in agreement with the findings of Heaton *et al*,[42] who found large standard errors in patients with schizophrenia, suggesting that results from normative populations might not be appropriate for them. The RCI–p and RCI–s results were similar, and nearly a half of our patients with schizophrenia-spectrum disorders (47.29 and 45.83%, RCI–s and RCI–p respectively) showed an improvement in GCS, irrespective of treatment allocation.

Moreover, since cognitive improvement was not only seen on tests more prone to practice effect – such as those involving a large speed component, requiring an infrequently practised response or those involving learning[45] – it seemed feasible in all 14 neuropsychological measures that cognitive improvement was not only due to practice, but was also a direct drug effect. There could also be an effect of the 'acute episode', but linear estimations by means of multiple regressions showed that variations in psychopathological syndrome scores only accounted for a small amount of the explained variance and not in all neuropsychological measures (Table 3). It seems unlikely that a placebo effect would only show an improvement between baseline and the 1-month assessment; however, it showed an effect that lasted for 6 months, even for the no-antipsychotic group and in a naturalistic setting.

An unexpected finding of our study was the lack of great differences in cognitive improvement between patients receiving atypical antipsychotic drugs and patients without antipsychotic drugs after the first 3 months of follow-up. This finding suggests that cognitive enhancement related to antipsychotic drugs in patients with first-episode schizophrenia-spectrum disorder might be apparent in the first weeks of treatment and might last for at least 6 months, irrespective of subsequent treatment.

Relevance of cognitive impairment at baseline for cognitive improvement

Individual improvement for each neuropsychological measure on the basis of RCI methods revealed that the higher the cognitive impairment at baseline assessment, the greater the rate of improvement with treatment. However, when individual profiles were compared between patients who showed improvement and worsening on the RCI, we discovered a limitation to this method:

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those who began with high scores could not demonstrate improvement because of a ceiling effect related to the capacity of being able to improve on neuropsychological tests beyond normal limits. These patients performing well at the beginning continued doing well during follow-up, and as a consequence, their cognitive change was clearly inferior to those starting at very low levels of performance.

The insight gleaned from our results will help guide future studies, which should be focused at the individual level in order to differentiate any potential factors contributing to the cognitive heterogeneity of our patients. Moreover, an added effort should be made to provide tools for clinicians to interpret and manage changes in cognitive functioning at the individual level such as RCI methods.

Limitations

Some caution is warranted owing to the small sample in the no-antipsychotic group, which might have led to our study being underpowered to detect real differences on cognitive performance in relation to other treatment groups. However, ANCOVA has been repeatedly demonstrated to be one of the most powerful methods of analysis for randomised comparative trials[46] and statistical power usually increases with repeated measures designs in situations where large individual differences are expected.[47]

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EXTRA CONTENT ONLINE

Psychiatrists in 19th-century fiction

Armadale (1866), Wilkie Collins

Fiona Subotsky

Lunatic asylums appear in other novels of Wilkie Collins, notably *The Woman in White* and *Jezebel's Daughter*, but their medical attendants are not significant for the stories. The villainous Dr Le Doux of *Armadale* makes up for this. He is represented as not only foreign (suspicious in itself) but unqualified; he has previously practised under another name as an abortionist. Collins can thus distance himself from medical criticism.

Wilkie Collins (1824–1889) largely wrote 'sensation' novels, with a strong element of suspense, rather than the clearly supernatural; however, 'gothic' motifs are readily recognisable. For instance, the approach to Dr Le Doux's Sanatorium in Hampstead is described thus:

> 'The day was overcast, and the place looked very dreary . . . at one corner of this scene of desolation stood a great overgrown dismal house, plastered with drab-coloured stucco, and surrounded by a naked, unfinished garden, without a shrub or flower in it – frightful to behold . . . The pallid withered old manservant in black, who answered the door, looked as if he had stepped up out of his grave to perform that service . . . I shivered as I crossed the threshold.'

Dr Le Doux has set up his new asylum as a money-making venture and has sent an invitation for a tour to the local population. Inside, by way of advertisement, he has a 'collection of photographic portraits of men and women' illustrating separately 'the effects of nervous suffering' and 'the ravages of insanity . . . while the space between was occupied by an elegantly illuminated scroll, bearing inscribed on it the time-honoured motto, ''Prevention is better than Cure.'' ' He also has exhibits serving to underline his (false) scientific credentials and to repel and fascinate the visitors and the readers:

> 'Horrible objects in brass and leather and glass, twisted and turned as if they were sentient things writhing in agonies of pain . . . shapeless dead creatures of a dull white colour floated in yellow liquid'.

The doctor is also a master of technology, with the very latest in provision and gadgetry for the comfort and treatment of his patients, notably the ventilation method, which he is later persuaded to put to deadly use:

> 'The asthmatic nervous patient gasps with terror at the idea of a chemical explosion in his room. I noiselessly fumigate one of them; I noiselessly oxygenize the other, by means of a simple apparatus fixed outside in the corner here. It is protected by this wooden casing; it is locked with my own key; and it communicates by means of a tube with the interior of the room. Look at it!'

In league with the evil Miss Gwilt, Dr Le Doux's plan is to trick the hero Armadale into staying, and then kill him. Subsequently, he intends to declare Armadale to have been deluded and 'certify his brain to have been affected by one of those mysterious disorders, eminently curable, eminently fatal'. The doctor is extremely well informed about the regulations of his day. 'This is not a mad-house; this is not a licensed establishment; no doctors' certificates are necessary here!' Later, however, he anxiously reflects that:

> 'A note may be smuggled out of the house, and may reach the Commissioners in Lunacy. Even in the case of an unlicensed establishment like mine, those gentlemen – no! those chartered despots in a land of liberty – have only to apply to the Lord Chancellor for an order, and to enter (by heavens, to enter My Sanatorium!) and search the house from top to bottom at a moment's notice!'

Suffice it to say that the plan does not work out as expected, and Miss Gwilt is found dead, possibly from an apoplexy. The epilogue comprises a letter from the family solicitor, who suspects Dr Le Doux of a great deal, but nothing can be proved. Indeed, his friends and admirers are about to present him with a Testimonial expressing sympathy. The solicitor concludes ruefully that: 'In this enlightened nineteenth century, I look upon the doctor as one of our rising men'.

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