Effects of Low-Dose Risperidone and Low-Dose Zuclopenthixol on Cognitive Functions in First-Episode Drug-Naïve Schizophrenic Patients

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FOCUS POINTS

- Most cognitive deficits are stable, regardless of clinical state and are present before, during, and after psychotic episodes.
- The best predictors of social and occupational function for schizophrenic patients are cognitive deficits, negative symptoms, and formal thought disorder.
- Equivalent antipsychotic doses, adjunctive anticholinergic medication, and retest effects are all crucial issues to consider when examining effects of antipsychotics on cognition in a longitudinal design.

ABSTRACT

Background: *Studies on the effects of antipsychotics on cognitive deficits in schizophrenia mostly suggest a superior effect of atypical over typical compounds, although findings are inconsistent and effect sizes small. Several methodological issues, such as heterogenous patient samples, incomparable drug doses, effects of prior medication, construct validity, and retest effects on neuropsychological tasks, confound most results and the comparability between studies. Consequently, the conclusion concerning effects of antipsychotics on cognition is still equivocal.*

Objective: *The present randomized clinical trial examined the effects on cognition of comparatively low doses of a typical antipsychotic (zuclopenthixol) and an atypical antipsychotic (risperidone) in a homogenous group of drug-naïve first-episode schizophrenic patients in a longitudinal setting.*

Methods: *First-episode schizophrenic patients who had never previously been exposed to antipsychotic treatment (N=25) were randomly allocated to treatment with flexible doses of zuclopenthixol or risperidone in an open-label design. Cognitive functions were examined both when patients were drug-naïve, and after 13 weeks of treatment. A comprehensive neuropsychological battery was used in order to optimize construct validity, and principal components of cognitive functions were extrapolated in order to reduce type I errors. A healthy control group was tested at baseline and after 13 weeks, in order to examine retest effects. The cognitive domains studied were executive functions, selective attention, and reaction time.*

Results: *The patients showed considerable cognitive deficits when drug-naïve. There were few differential effects of risperidone and zuclopenthixol on cognitive deficits, except for a differential significance, respectively, tendency towards improved reaction and movement times in the risperidone group, and a lack of such in the zuclopenthixol group. These differences were no longer significant after covarying for extrapyramidal side effects and anticholinergic medication that were more prevalent in the zuclopenthixol group and the increases after medication were comparable with retest effects in controls.*

Conclusion: *The study underscores the importance of examining impact of factors, such as clinical improvement,*

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extrapyramidal side effects, anticholinergic medication and retest effects in longitudinal efficacy studies. This study does not support efficacy of either risperidone or zuclopenthixol on cognitive functions in drug-naïve schizophrenia patients after 3 months of medication, because neither could be distinguished from retest effects of the healthy control group.

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INTRODUCTION

The focus on cognitive deficits as targets for pharmacologic intervention in the treatment of schizophrenia has increased in recent years. This is due to overwhelming evidence from numerous studies that place cognitive deficits as core deficits of the illness, independent of clinical symptoms.[1-3] Furthermore, the impact of cognitive deficits on the functional outcome of patients is striking.[1,2,4-6] The prognosis of patients concerning social and occupational function is poor in spite of treatments effectively controlling clinical symptoms. While difficult to quantify in general terms, several researchers suggest that even small improvements in cognitive deficits (ie, increases of 1/2 a standard deviation point) are clinically relevant,[7,8] and that differences of this magnitude could have significant impact on relevant outcome measures.[9] Therefore, the incentive for finding effective treatments that can improve cognitive deficits in schizophrenia is considerable.

Studies[10-12] comparing typical and atypical antipsychotics have shown similar effectiveness on positive symptoms, differential effects favoring atypical over typical compounds regarding negative symptoms, and fewer extrapyramidal side effects (EPS) with atypical medications. Most studies and meta-analyses[7,13-20] also favor atypical over typical compounds regarding effects on cognitive deficits. However, the conclusions that can be drawn from these studies are confounded by several methodological issues, the most important of which concerns incomparable doses of medications. A recent meta-analysis[11] concluded that differential effects on cognition were only present when low-dose atypicals were compared with high dose typicals, and that this superior effect of atypicals disappeared when compared to low-dose typical compounds. In support of this, a recent study[21] using comparatively low doses of typical and atypical compounds have failed to show differential effects on cognitive deficits, and several authors stress the importance of using similar, low doses in comparative studies.[13,22]

Besides dosage, several other methodological issues limit the conclusions that can be drawn concerning the effects of different antipsychotic compounds on cognition, such as heterogeneous patient samples, effects of prior medication, lack of control for retest-effects on cognitive measures, inadequate correlations of cognitive changes to clinical symptoms, EPS, and adjunctive anticholinergic medication. Therefore, the interpretation of findings from studies showing changes in cognitive deficits over time is at issue presently, and it is unclear whether changes reflect direct drug-related improvements, clinical improvement, or effects due to repeated testing.[23,24] Similarly, a lack of change over time (eg, in patient groups treated with high doses of typical compounds) could reflect stability of cognitive deficits, or actual detrimental effects of the medication resulting in lack of a normal retest effect. This detrimental effect could be directly related to the drug or indirectly through more EPS and, consequently, more adjunctive anticholinergic medication, which is known to have deleterious effects on some cognitive functions.[25,26] The conclusion concerning effects of antipsychotics (typical and atypical) on cognition is still equivocal.[13,22]

The present randomized clinical trial examined the effects of comparable, low doses of a typical compound (zuclopenthixol) or an atypical compound (risperidone) on executive functions, selective attention and reaction time in a homogenous group of drug-naïve, first-episode schizophrenic patients in a 13-week longitudinal setting. Retest effects on cognitive measures were examined in a gender- and age-matched healthy control group.

METHODS

Patients

Patients were included from the psychiatric wards of five participating hospitals in the Copenhagen catchment area (background population of ~500,000 inhabitants). All patients fulfilled the *International Classification of Diseases, Tenth Edition* (*ICD-10*) F.20 criteria for schizophrenia.[27] Diagnoses were made by referring psychiatrists and confirmed by the same experienced psychiatrist (Staff Specialist TM) who was trained in using the Schedules for Clinical Assessment in Neuropsychiatry Version 2.1 (SCAN-2.1 [World Health Organization]).[28] Psychopathology ratings were likewise carried out by TM at baseline and at follow-up after 13 weeks of treatment, using the Positive and Negative Syndrome Scale (PANSS). Only antipsychotic-naïve patients admitted for treatment for the first time were included. Patients with known retardation were excluded, as were patients who were deemed in acute need of medication, or were compulsorily hospitalized. EPS were rated using the Extrapyramidal Symptom Rating Scale (ESRS).

A total of 31 patients were included. Of these, 25 completed the study. The reasons for drop-out of

patients were: change to another antipsychotic compound (n=1); compulsory hospitalization (n=1); acute medication at baseline (n=1), patient withdrawal (n=1), and inability to participate in neuropsychological testing at baseline due to psychotic symptoms (n=2). The average age of patients was 27.3 (±5.9), ranging from 19–37 years. The duration of untreated psychosis ranged from 4–78 months (median=14 months). The duration of untreated psychosis was very short in some instances; however, *ICD-10* schizophrenia diagnoses can be made after 1 month (compared with 6 months, according to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (*DSM-IV*),[29] with similar diagnostic validity[30]), and diagnoses were all validated at the follow-up examination after 3 months.

Patients were randomly allocated to treatment with comparable low flexible doses of either risperidone 2–7 mg (median=3 mg) or zuclopenthixol 6–26 mg (median=8 mg) in an open-label design. Zuclopenthixol is an intermediate-potency conventional antipsychotropic compound with preferential affinity for dopamine D2 receptors, and a modest affinity for dopamine D1 receptors. In Europe, it is commonly used for management of acute and chronic psychotic states.

Treatment responsibility remained localized to clinicians outside the project, who determined and adjusted drug doses according to clinical response. The average dose in the risperidone group was 3.6±1.6 mg, and the average dose in the zuclopenthixol group was 9.6±5.9 mg, which is equivalent to ~3–4 mg haloperidol.[31] After random allocation to treatment groups, 15 patients received risperidone and 10 patients zuclopenthixol. (The fewer patients in the zuclopenthixol group was coincidental and not due to increased drop-out from this group after medication.) Benzodiazepines were allowed throughout the study, except on examination days. In the risperidone group, 60 % of patients received benzodiazepines at baseline and 33.3% after 13 weeks of medication, which was not significantly different from 70% at baseline and 40% after 13 weeks in the zuclopenthixol group. Anticholinergics were allowed (except on examination days), but were kept to a minimum by lowering the dose of antipsychotics when EPS occurred. Eighty percent of patients in the zuclopenthixol group and 26.7 % of patients in the risperidone group received anticholinergics, a difference that was highly significant (Pearson's χ^2=6.8; *df*=1; *P*=.009). There were no differences between medication groups before allocation to treatment in terms of demographic measures (age, gender, socioeconomic status), duration of untreated psychosis, psychopathology, or cognitive deficits.

Healthy Controls

Healthy controls (n=25) were recruited among hospital staff and university students, and were matched to the patients 1:1 according to gender, age, and parental education/occupation. (Education and occupation was recorded from the parent with the highest rating, either according to education or occupation.) Exclusion criteria for controls were the presence of a psychiatric diagnosis (assessed by TM using SCAN 2.0), somatic illness, psychiatric diagnoses in first-degree relatives, history of drug or alcohol abuse, presence of mental retardation or any known learning disabilities. Healthy controls participated in all the same examinations as patients at baseline. In order to examine retest effects, 12 of the healthy controls were retested on the cognitive measures after 13 weeks.

The present study encompassed an extensive examination program of psychopathology and EPS ratings, cognitive tests, sensory gating (using prepulse inhibition), as well as functional magnetic resonance imaging and single photon emission computed tomography (^{123}I-epidepride) scans. The effects of risperidone and zuclopethixol on prepulse inhibition have been presented,[32] and the remaining data will be presented elsewhere.

Written informed consent was obtained from all subjects prior to inclusion into the study. The study was approved by the scientific ethics committee for Copenhagen and Frederiksberg.

Cognitive Functions

Executive functions and selective attention were examined using tests from the computerized Cambridge Neuropsychological Test Automated Battery (CANTAB),[33,34] Wisconsin Card Sorting Test (WCST)[35] as well as verbal fluency, figural fluency, and Trail Making Tests A and B.[36] Tests of reaction and movement time were assessed using CANTAB. Premorbid intelligence was estimated using the Danish Adult Reading Test (DART); the Danish version of the New Adult Reading Test.[37] Cognitive functions were tested by the same examiner (BF) at baseline and retest. The comprehensive neuropsychological battery was used in order to optimize construct validity,[38] and principal components of cognitive functions were extrapolated in order to minimize Type I errors.

Cognitive Tests

The original 128-card version of the WCST was used.[35] The WCST assesses the ability to make and maintain hypotheses by sorting cards according to the categories color, shape, or number, and assesses

attentional set shifting ability by requiring subjects to use feedback to shift hypotheses when relevant (ie, when the correct sorting category changes). Outcome measures are number of categories achieved (maximum score: 6); total number of errors; perseverative errors; unique errors; other errors; total number of cards used.

The CANTAB Intra-Extra Dimensional set shifting task (IED) consists of nine different stages of increasing difficulty that test the ability to utilize feedback to discriminate between figures, as well as to make, maintain, and shift hypotheses within and between categories. The IED assesses attentional set shifting similarly to the WCST. The outcome measures were the number of stages completed; total errors (adjusted for stages not completed); errors made at the extradimensional set shifting stage; number of trials (adjusted for stages not completed). The CANTAB Stockings of Cambridge (SOC) presents two arrays of colored balls, where subjects are required to move the balls at the bottom of the screen to match the array presented at the top of the screen. The SOC assesses planning ability, strategy formation, and execution similar to the Tower of London. Outcome measures are: number of problems solved with minimum number of moves (ie, most efficiently); mean number of moves used to solve problems (averaged from 2, 3, 4, and 5 move-problems); initial thinking times (ie, planning time, from the problem is presented on the screen until the subject touches the screen); subsequent thinking times (ie, time from first touching the screen until the problem is solved; controlled for motor times).

The Trail Making Test A assesses visuospatial scanning and psychomotor speed by subjects combining circles with ascending numbers. In addition to these functions, the Trail Making Test B also assesses attentional set shifting ability by subjects combining circles, continuously alternating between ascending numbers and letters in alphabetical order. Outcome measures are: time to complete Trail Making A; Trail Making B and Trail Making B minus Trail Making A.

Verbal phonological fluency was assessed by subjects generating as many words as possible in 60 seconds beginning with the letter "S". Verbal semantic fluency was assessed by subjects generating words from the category "animals" in 60 seconds. Figural fluency was assessed using Regard's Figural Fluency Task,[39] in which subjects draw as many figures as possible in 3 minutes, by combining two or more of five dots in different combinations. Outcome measures are number of words with the letter S; number of animals; and number of figures.

The CANTAB Rapid Visual Information Processing Test (RVP) is a continuous performance test, in which different numbers are continuously presented in random order on a computer screen, for 7 minutes. The target consists of three numbers (3, 5, 7) that subjects have to continuously attend and respond to within a series of other numbers. The RVP assesses selective attention and vigilance with a small working memory component. The outcome measures are signal detection; number of hits; and number of misses.

The CANTAB Reaction and Movement Time Test presents yellow dots on a touchscreen, to which subjects respond by releasing a press pad and touching the dot on the screen as fast as possible. The reaction time is the time taken to release the press pad in response to the stimulus, while the movement time is the time taken to touch the stimulus on the screen after the press pad has been released. Simple reaction time and simple movement time is when there is only one location on the screen, in which the stimulus can appear, while choice reaction time and choice movement time is when the stimulus can appear in any of five locations.

Statistical Analysis

Data were analysed using Statistical Package for the Social Sciences (SPSS), version 11.0. All analyses used two-tailed levels of significance. Missing data was extrapolated (using substitution of group mean) for one patient on DART. Results from the reaction time and movement time tasks did not fit a normal distribution and data were log transformed to reduce skew. Parametric statistics were used for all analyses. Results were standardized to *z*-scores, using the healthy control group as reference point with an average of 0 and a standard deviation of 1.

The numerous neuropsychological measures were reduced using principal component analysis as extraction method into 1 or 2 factors per test. (Principal component analysis was carried out on all subjects participating in a larger study which, in addition to these 25 adult schizophrenic patients and 25 healthy controls, included 40 schizophrenic and/or psychotic adolescents and 40 age-matched controls (N=130). Nominal data were analyzed using Pearson's χ^2. Effects of medication were examined using a repeated-measures analysis of covariance, with the subtracted difference between the baseline score and retest score as the dependent measure. The between-subject variable was medicine group (risperidone, zuclopenthixol, none [healthy controls]). Baseline scores were included as covariates, in order to control for group differences at baseline. In secondary post hoc analyses, changes in psychopathology (PANSS ratings), side effects (ESRS

ratings), and anticholinergic medication were separately assessed as covariates.

RESULTS

Socioeconomic Status

Socioeconomic status (SES) was calculated based on a combination of parental education/occupation (6 groups) and household income (3 groups) according to criteria from the Danish Institute of Clinical Epidemiology, and resulted in 3 socioeconomic groups. Parental SES is considered a reliable indicator of potential SES of offspring and was used instead of patient SES, which would underestimate the potential SES since the illness has profound impact on education, vocation and income because of the common timing of illness onset during early adulthood. There were no significant differences between the parental education/occupation of patients and controls, but there was a significantly lower level of income in the patient group (χ^2= 8.30; *df*=2; *P*=.02), and, consequently a lower combined SES (χ^2= 7.1; *df*=2; *P*=.03). The sociodemographic data (parental education/occupation, income, and SES) of patients and controls are shown in Table 1.

Psychopathology

There were no differences between medication groups before or after medication. Both medication groups improved significantly on PANSS Positive, Negative, General, and Total scores after 13 weeks, with no differential improvements between the effects of risperidone and zuclopenthixol (Table 2).

Cognitive Deficits

Cognitive Deficits at Baseline

There were no differences between the medication groups at baseline before allocation to treatment. Table 3 shows the cognitive deficits of all drug-naive patients at baseline. Compared with the healthy control group, patients were significantly impaired on premorbid intelligence: DART (*P*=.04; *z*=–0.69), and on most principal component cognitive measures; WCST (*P*=.009; *z*=–1.36), SOC Planning efficiency (*P*=.02; *z*=–0.62), Fluency (*P*<.0001; *z*=–1.57), Trail Making (*P*=.006; *z*=–1.86), RVP selective attention (*P*=.01; *z*=–1.64), movement time (*P*<.0001; *z*=–1.91), and reaction time (*P*<.009; *z*=–2.28). There was an impairment tendency on the IED set shifting test (*P*=0.09; *z*=–0. 72). SOC subsequent thinking times were significantly impaired (*P*=.001; *z*=–0.77), while SOC initial thinking times were not (all *df*=48).

TABLE 1. DEMOGRAPHICAL DATA: PARENTAL EDUCATION/OCCUPATION, INCOME, AND SOCIOECONOMIC STATUS

	N				
Parental Education/ Occupation	*Patients*	*Controls*	*Pearson's* χ^2	*df*	P *(2-sided)*
Academic	6	9	3.16	5	.676
Bachelor	10	8			
Expert	2	4			
Skilled	4	2			
Non-skilled	2	2			
Non-skilled, unemployed	1	–			
Parental Income					
	N				
Parental Income	*Patients*	*Controls*	*Pearson's* χ^2	*df*	P *(2-sided)*
High	3	10	8.30	2	.016
Middle	15	14			
Low	7	1			
	N				
Socioeconomic status	*Patients*	*Controls*	*Pearson's* χ^2	*df*	P *(2-sided)*
A (High)	3	9	7.12	2	.028
B (Middle)	18	16			
C (Low)	4	–			

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Between-Group Differences

Treatment effects were examined in two steps; initially comparing only risperidone and zuclopenthixol, and subsequently comparing both medication groups to the healthy control group. This was done in order to first examine differential changes in the medication groups and secondly examine whether these changes could be ascribed to improvements due to medication or were parallel to retest effects in the healthy control group. Using baseline scores as covariates, with differences between baseline and retest scores as the dependent measure, there were only few differential changes between the risperidone and zuclopenthixol groups on the cognitive measures (Table 4). There was a significant ($F_{(1.22)}$=4.96; *P*=.04) differential change between the risperidone group and the zuclopenthixol group on movement time, and a tendency towards a differential change between the two groups on reaction time ($F_{(1.22)}$=3.30; *P*=.08). There were no differential changes between risperidone and zuclopenthixol on any other cognitive measures (of executive functions and selective attention).

The difference between risperidone and zuclopenthixol on movement time changes remained when improvements in psychopathology were included as covariates in the repeated measures analysis. However, when EPS (as measured by ESRS) and anticholinergic medication were entered as covariates in separate analyses, the difference between risperidone and zuclopenthixol was no longer significant. The tendency towards differential changes in reaction times between the medication groups remained when covaried for improvements in psychopathology scores regarding negative, general, and total PANSS scores, but disappeared when covaried for improvements in positive PANSS scores (Table 4). In separate analyses, ESRS ratings and anticholinergic medication each covaried out the tendency towards differential changes between risperidone and zuclopenthixol on reaction times.

Within-Group Differences

The risperidone group showed significant within-group changes on reaction times (*P*=.04), Fluency (*P*=.01), RVP selective attention (*P*=.03), and SOC subsequent thinking latencies (*p*=001), and tendencies to changes on WCST (*P*=.09), and movement times (*P*=.07) (all *df*=14). The zuclopenthixol group showed significant within-group changes on one measure only: SOC subsequent thinking latencies (*P*=.006), and a tendency toward improvement on initial thinking times (*P*=.09) and Trail Making (*P*=.09) (all *df*=9).

Retest Effects

The healthy control group showed significant retest-effects on several measures. Significant within-group changes were seen on Trail Making (*P*=.04), RVP selective attention (*P*=.004), movement times (*P*=.003), SOC planning efficiency (*P*=.01), and SOC subsequent thinking latencies (*P*=.01), and tendencies towards improvements on reaction times (*P*=.06) and IED set shifting (*P*=.07) (all *df*=11).

In most cases the changes in both medication groups were parallel to the retest effects in the healthy control. However, the healthy control group showed a significant (*P*=.004) improvement on movement times that was significantly different from the changes

TABLE 2. **PSYCHOPATHOLOGY CHANGES FROM BASELINE (DRUG-NAIVE) TO 13 WEEKS**

	Risperidone						*Zuclopenthixol*					
	Baseline (drug-naïve)		*After 13 weeks medication*				*Baseline (drug-naïve)*		*After 13 weeks medication*			
	Mean	*SD*	*Mean*	*SD*	*df*	*Percent Change*	*Mean*	*SD*	*Mean*	*SD*	*df*	*Percent Change*
PANSS Positive	20.9	4.3	10.8	2.4	14	48.2 %*	19.1	3.0	9.8	1.9	9	48.7%*
PANSS Negative	20.7	5.5	17.0	3.7	14	18.0 %†	18.2	5.0	15.5	2.8	9	14.8%‡
PANSS General	31.0	6.0	20.8	2.9	14	32.9 %*	29.0	7.6	20.5	3.1	9	29.3%†
PANSS Total	72.6	12.4	49.0	6.7	14	32.5 %*	66.3	13.0	45.8	4.8	9	30.9%*

* *P*<.003
† *P*<.01
‡ *P*<.05

PANSS=PANSS=Postive and Negative Syndrome Scale.

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TABLE 3. **COGNITIVE DEFICITS AT BASELINE***

Principal components and component measures	*Patients at baseline (N=25)* *Variance explained (%) and correlations*	*Mean*	*SD*	*Healthy controls (N=25)* *Mean*	*SD*	*Significance levels (z-scores)*	*Effect size*
DART		24.32	9.18	29.44	7.44	0.04	–0.69
Executive Functions							
WCST	70.3	0.63	1.51	–0.29	0.67	0.009	–1.36
Categories achieved (max 6)	r=.822	5.12	1.83	5.92	0.40		
Total number of errors	r=.989	23.76	20.98	11.12	10.17		
Perseverative errors	r=.730	10.60	7.33	6.44	3.19		
Unique errors	r=.724	4.32	10.76	1.36	5.98		
Other errors	r=.831	8.84	9.27	3.32	1.99		
Number of cards used	r=.903	91.20	23.10	76.80	12.05		
IED set shifting	87.5	0.20	1.26	–0.30	0.70	0.087	–0.72
Stages completed	r=.955	8.40	1.16	8.80	0.58		
Total errors (adjusted)	r=.985	28.32	30.05	15.24	14.54		
Errors at the EDS stage	r=.818	7.96	10.61	4.60	6.86		
Number trials (adjusted)	r=.973	100.6	52.56	78.28	24.18		
SOC planning efficiency	95.2	–0.44	0.90	0.34	1.26	0.02	–0.62
Number problems/min moves	r=.976	8.32	1.73	9.88	2.15		
Mean number of moves	r=.976	4.33	0.41	4.00	0.65		
Trail Making	98.2	0.51	1.37	–0.35	0.46	0.006	–1.86
Trail-Making A (sec)	r=.727	33.12	11.72	24.57	8.66		
Trail-Making B (sec)	r=.990	89.77	47.45	58.07	16.60		
Trail-Making B-A (sec)	r=.919	56.64	39.92	33.49	13.83		
Fluency	63.4	-0.61	0.77	0.77	0.88	<0.001	–1.57
Phonological verbal fluency	r=.844	11.84	3.44	17.24	5.09		
Semantic verbal fluency	r=.820	19.04	4.70	26.00	5.47		
Figural fluency	r=.740	30.64	10.41	42.20	12.00		
Attention							
RVP selective attention:	99.5	–0.42	1.36	0.34	0.46	0.01	–1.64
Signal detection	r=.998	0.97	0.03	0.99	0.01		
Number of hits	r=.995	49.64	6.04	53.24	2.07		
Number of misses	r=.999	6.04	6.16	2.76	2.07		
Reaction Times							
Reaction time	83.8	0.68	1.83	–0.39	0.47	0.009	–2.28
Simple reaction time (log)	r=.915						
Choice reaction time (log)	r=.915						
Movement time:	96.9	0.91	0.95	–0.24	0.60	<0.001	–1.91
Simple movement time (log)	r=.985	638.49		181.14	469.05	76.09	
Choice movement time (log)	r=.985	648.02		192.29	468.93	76.60	
SOC initial thinking time (log)		8.49	0.64	8.72	0.53	NS	
SOC subsequent time (log)		6.54	0.92	4.92	2.15	0.03	–0.77

* Through factor extraction, the principal components were standardized to a mean of 0 and a standard deviation of 1. The principal component means may have negative signs (depending on direction of scores), but patients did not perform better than controls on any measure. Means and standard deviations are given for all measures, but significance levels and effect sizes only for principal components.

DART=Danish Adult Reading Test; WCST=Wisconsin Card Sorting Test; max=maximum score; IED=Intra-Extra Dimensional set shifting taks; EDS=Extra-Dimensional Shift; SOC=Stockings of Cambridge; min=minimum; sec=seconds; RVP=Rapid Visual Imformation Processing Test; NS=not significant.

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in both the risperidone group (*P*=.005) and the zuclopenthixol group (*P*=.006). While the risperidone group showed a tendency towards improvement on movement times, the change was not as large as the retest effect in the healthy control group. The zuclopenthixol group showed a lack of retest effect on the movement times. In addition, the significant retest effect of the healthy control group on SOC planning efficiency was significantly different ($F_{(1.19)}$=6.42; *P*=.02) from the lack of change in the zuclopenthixol group, which can be interpreted as a lack of retest effect in the zuclopenthixol group.

TABLE 4. EFFECTS OF MEDICATION AND RETEST: DIFFERENCE SCORES FROM BASELINE TO 13 WEEKS

Principal Components	*Within-group differences*			*Between-group differences*				
				Covaried for baseline scores			*Covaried PANSS*	*Covaried ESRS and antichol medication*
	RIS	*ZUC*	*COn*	*RIS vs ZUC*	*RIS vs CON*	*ZUC vs CON*	*RIS vs ZUC*	*RIS vs ZUC*
	P	*P*	*P*	*P*	*P*	*P*	*P*	
WCST	.09							
IED set shifting			.07					
SOC planning efficiency			.01			.02		
Trail Making		.09	.04					
Fluency	.01							
RVP attention	.03		.004					
Reaction time	.04		.06	.08			.08†	NS
Movement time	.07		.003	.04	.005	.006	.04	NS
SOC initial planning time		.09						
SOC subsequent thinking time	.001	.006	.01					

* Through factor extraction, the principal components were standardized to a mean of 0 and a standard deviation of 1. Only results that are significant or tendencies are presented.

† Results were no longer different when covaried for positive PANSS scores only.

PANSS=Postive and Negative Syndrome Scale; ESRS=Extrapyramidal Symptom Rating Scale; antichol=anticholinergic; RIS=risperidone; ZUC=zuclopenthixol; vs=versus; CON=healthy controls; WCST=Wisconsin Card Sorting Test; IED=Intra-Extra Dimensional set shifting task; SOC=Stockings of Cambridge; RVP=Rapid Visual Imformation Processing Test; NS=not significant.

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DISCUSSION

Effects of Medication

The risperidone- and zuclopenthixol-treated patients showed few differential changes after medication, with no differences on changes in psychopathology or most cognitive measures. The exceptions were movement times and reaction times, on which the zuclopenthixol group showed a lack of change over time on both measures. This was significantly different from the tendency of the risperidone group to improve over time on movement time, and was different at trend level from the significant within group improvement of the risperidone group on reaction time.

The differential improvement tendency in reaction times in the risperidone group disappeared when covaried for improvements in positive PANSS scores which suggests that the improved reaction times in this group may be related to clinical improvement of positive symptoms. Covarying for improvements in psychopathology did not affect the differential change of risperidone on movement times. However, when EPS were entered as covariate in separate analyses, the differential change of risperidone over zuclopenthixol on both reaction times and movement times disappeared. This indicates that the lack of improvement in reaction times and movement times in the zuclopenthixol group may be related to the significantly (P=.02) more prevalent EPS in this group. These secondary post hoc analyses should be interpreted with caution, because the risk of type 2 errors is high due to the small sample size.

Retest Effects

The changes in both medication groups were parallel to the changes in the healthy control group on most measures. Both the risperidone group and zuclopenthixol group showed significantly less retest effects than the healthy control group on movement times. While the risperidone group had a tendency towards improvement that was significantly different from the lack of change in the zuclopenthixol group, this change did not reach the retest effect of the healthy control group. In other words, the healthy control group showed larger improvements in movement time than either of the medication groups, but the risperidone group showed an improvement in movement time which was different from the lack of change in the zuclopenthixol group. The healthy control group showed only a tendency towards improvements on reaction times, while the risperidone group improved significantly on reaction times. However, after covarying for the large differences in baseline scores, there were no differential changes between any of the groups. The zuclopenthixol group showed a lack of retest effect on SOC planning efficiency compared with the improvement in the healthy control group.

The zuclopenthixol group showed within-group changes on only few measures. While the risperidone group showed significant or tendencies towards within-group changes on several measures, these changes were not significantly different from the changes in the zuclopenthixol group or the changes in the healthy control group. This raises the question whether within-group changes in medication groups should be interpreted as effects of medication or mere retest effects. Whether retest effects in schizophrenia patients are similar to that of healthy controls is unclear. While few studies have found less retest effects in patients than controls,[40] most have found similar retest effects over both short and long time intervals.[38,41,42] In a longitudinal design, Heaton and colleagues[38] found similar retest effects in schizophrenic patients as healthy controls, interestingly regardless of level of psychopathological symptoms and clinical state. Covert, procedural learning seems to be one of the few neuropsychological domains in which schizophrenic patients are not particularly impaired.[43] Conversely, the interpretation of a lack of effect over time as stability of deficits or detrimental effects reflected in a lack of normal retest effect is dependent on the examination of retest effects. Whether changes in patient groups (eg, on an executive task) represent practice effects (intact learning), or improved executive functions (and impaired learning) cannot be distinguished in lieu of a placebo-controlled patient group. The inclusion of unmedicated patient groups in longitudinal studies of medication effects on cognition would be theoretically preferable, but ethically problematic. Therefore, examining retest effects in a matched, healthy control group as a minimum is necessary as standard of reference in studies using repeated cognitive testing. However, in the present study, both medication groups showed less retest effects than controls on certain measures. This indicated that schizophrenic patients may show less retest effects than healthy controls, or that antipsychotic medication (perhaps typical compounds in particular) may interfere with learning and retest effects.

Theoretical Implications

The conclusions concerning the efficacy of antipsychotics on cognitive deficits are still at issue.[23,24] That low doses of atypicals are superior to high doses of typicals has been well established in several studies and reviews.[7,13-16,18-20,44] Recent studies[21] have found similar effects of typicals and atypicals, when comparably low doses are used. Because of different receptor profiles and methods of action of various atypical compounds, it is possible that different compounds have differential

effects on cognitive measures. Few comparative studies have been done, and they yield conflicting results. Some studies[17,19] support differential effects of different atypicals while another[7] tentatively supports slight differential effects. However, for the time being, there is insufficient evidence to substantiate different profiles of effect. Findings from a recent large-scale study including almost 400 patients did not support differential effects of low doses of risperidone and olanzapine on cognitive functions.[8] The impact of retest effects on these changes over time has not been addressed in most studies. The inconclusive data on the efficacy of antipsychotics on cognitive deficits appears to encompass at least some areas of early information processing as well. The superior efficacy of atypicals over typicals on deficits of prepulse inhibition of the gating response has recently been challenged by negative findings in longitudinal studies from Duncan[45] and our own group.[32] Whether these deficits should be considered as stable vulnerability indicators is unclear, since other treatment strategies may impact on these functions.

Clinical Implications

In terms of the clinical relevance of the present results, the zuclopenthixol group showed a lack of change over time on most measures, and had more EPS and needed more adjunctive anticholinergic medication than the risperidone group.

Strengths of the Study

The inclusion of only first-episode drug-naïve patients in the study makes it possible to delineate the profile of cognitive deficits early in the disease process, and assess the impact of medication, where the possibly confounding factor of previous medication is not present. Only few previous studies have examined effects of medication in drug-naïve patients.[46] The study was a randomized clinical trial, where medication effects were tested in a longitudinal setting that was naturalistic. After allocation to treatment groups, any treatment changes were decided by psychiatrists outside of the project, based on clinical response. The doses used were comparable, low doses in both medication groups. Retest effects were examined in an age- and gender-matched, healthy control group.

Limitations of the Study

The 25 patients included in this study constitute a small sample size, which increases the risk of both Type 1 and Type 2 errors. Especially the inability to reject the null-hypothesis in this sample may be compounded by the small sample size and, therefore, the low power. Subsequent studies with more patients will help strengthen the results. Furthermore, 13 weeks may not be sufficient time to observe differential improvements between the compounds that may potentially occur later. In a 2-year longitudinal design, Green and colleagues[21] found that the effects of haloperidol were observed more quickly than the effects of risperidone, but that the beneficial effects of risperidone gained momentum and surpassed haloperidol after 12 months. The present study was open-label because a double-blind design was not a practically viable option, and investigators were not blind to subject assignment. The examination of retest effects using a healthy control group is necessary to establish the expected level of retest effects in patients; however, the conclusions that can be drawn are limited in lieu of an unmedicated schizophrenic control group. A final note on the results is that there may be a selection bias in the patients included in this study. The examination program was very comprehensive, and besides participating in psychopathology ratings and neuropsychological tests, patients were tested with prepulse inhibition and scanned with single photon emission computed tomography and functional magnetic resonance imaging both before and after medication. Therefore, the patients included were relatively motivated and could manage to participate in all parts of the study, and were neither deemed in need of acute medication nor compulsorily hospitalized. However, the patients included fulfilled the study criteria for *ICD-10* F.20 schizophrenia diagnosis and had considerable cognitive deficits, and, as such, were not necessarily a biased representation of drug-naïve, first-episode patients.

CONCLUSION

The results from the present study do not support the effectiveness of antipsychotics (neither typical nor atypical) on cognitive deficits, but suggest that while the risperidone group shows mainly normal retest effects, the zuclopenthixol group may show a lack of retest effects on certain measures, perhaps due to more prevalent EPS, effects of adjunctive anticholinergic medication, or deficits in learning. The results indicate that retest effects on cognitive tests is an important issue to consider in studies examining the effects of medication on cognition in a longitudinal setting. Distinguishing cognitive changes (improvements, no change, or deleterious effects) from retest effects is not a trivial issue, but a methodological necessity in clinical trials using repeated testing. The results support careful consideration of whether changes over time are due to direct effects of the antipsychotic compounds or indirect effects of, for example, clinical improvements, EPS, or anticholinergic medication. However, the conclusions that can be drawn are limited by the small sample size and the time interval of 3 months, which may be too short to detect potential differential effects of different antipsychotic compounds. CNS

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