Executive Function Predicts Response to Antiaggression Treatment in Schizophrenia: A Randomized Controlled Trial

Menahem I. Krakowski, MD, PhD, and Pal Czobor, PhD

ABSTRACT

Objective: Despite extensive experience with antipsychotic medications, we have limited capacity to predict which patients will benefit from which medications and for what symptoms. Such prediction is of particular importance for the proper treatment of violence. Our goal was to determine whether executive function predicts outcome of treatment for aggressive behavior and whether such prediction varies across medication groups.

Method: Ninety-nine physically aggressive inpatients (aged 18–60 years) with schizophrenia or schizoaffective disorder (diagnosed according to *DSM-IV*) who completed tests of executive function were randomly assigned in a double-blind, parallel-group, 12-week trial to clozapine (n = 32), olanzapine (n = 32), or haloperidol (n = 35). The number and severity of aggressive events as measured by the Modified Overt Aggression Scale (MOAS) were the outcome measures. Psychopathology and medication side effects were also assessed. The study was conducted from 1999 to 2004.

Results: Poor executive function predicted higher levels of aggression, as measured by MOAS scores over the 12-week period, in all 3 medication groups ($F_{1,98} = 222.2$, $P < .0001$). There was, however, a significant interaction effect between medication grouping and executive function ($F_{1,98} = 15.32$, $P < .001$): clozapine exerted an antiaggression effect even in the presence of executive dysfunction.

Conclusions: Executive function was a strong predictor of response to antiaggression treatment in all medication groups, but clozapine still retained clinical efficacy in the presence of poor executive functioning. Olanzapine was particularly efficacious in the absence of executive dysfunction. These findings have important implications for a targeted approach to the treatment of aggression in patients with schizophrenia.

Trial Registration: clinicaltrials.gov Identifier: NCT01123408

J Clin Psychiatry 2012;73(1):74–80

Submitted: *June 30, 2011; accepted September 15, 2011.*
Online ahead of print: *November 29, 2011 (doi:10.4088/JCP.11m07238).*
Corresponding author: *Menahem I. Krakowski, MD, PhD, The Nathan S. Kline Institute for Psychiatric Research, 140 Old Orangeburg Rd, Orangeburg, NY 10962 (krakow@nki.rfmh.org).*

Proper management of violence in schizophrenia is of great importance, as this behavior causes harm to its victims and is disruptive to its perpetrators. Violence is a frequent reason for psychiatric admissions, prolongs hospital stays,[1] and constitutes a barrier to reintegration into the community.[2,3] It would be helpful to define predictors of treatment response in order to provide proper therapy. This would include identifying, on the basis of specific deficits, the medications that are best suited for aggression. For instance, clozapine has strong antiaggression properties,[4,5] but, given its potentially dangerous side effects and the burdensome monitoring required for its administration, there is a need to identify which patients will benefit from this medication and which patients will do as well or better on other medications.

Executive function is particularly promising as a predictor of response to antiaggression treatment. It is involved in inhibitory control[6,7] and in regulation of aggression.[8] Executive dysfunction interacts with situational factors, moods, or symptoms in such a way as to result in aggression. This dysfunction influences the way in which provocation is perceived and the reaction to it, ie, anger.[9] In studies on the effect of alcohol, subjects with lower executive function became aggressive with provocation when they drank alcohol; subjects with better executive function did not.[10] Good executive function has also been associated with better social and occupational outcomes in schizophrenia[11–13] and with better response to antipsychotic medication.[14,15]

METHOD

Study Participants

Written informed consent was obtained from each participant after procedures and possible side effects were fully explained according to a protocol approved by the Nathan S. Kline Institute Institutional Review Board and compliant with the Declaration of Helsinki (clinicaltrials.gov Identifier NCT01123408). Study subjects were 99 patients aged 18–60 years with schizophrenia or schizoaffective disorder (according to the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition). The study was conducted from 1999 to 2004.

Patients were required to have a confirmed episode of physical aggression during the present hospitalization, plus additional aggression—physical, verbal, or against property. Research staff monitored subjects and ward documentation daily; once an incident was found, records were reviewed to determine, retrospectively, aggressive incidents for the prior 4 weeks. Patients were excluded if they had been hospitalized for more than a year; had a history of nonresponse or intolerance to clozapine, olanzapine, or haloperidol; or had received a depot antipsychotic in the prior 30 days.

Study Procedures and Treatments

Patients who met inclusion/exclusion criteria and who signed informed consent were transferred to the research ward, so as to provide a uniform environment and to ensure close monitoring of medication administration and high treatment compliance. The ward included a multicamera audiovisual system that recorded activities in public areas and allowed for constant

observation of aggression. A detailed description of the ward and camera system is available.[16]

After baseline assessments were completed, patients were randomized to clozapine, olanzapine, or haloperidol. The study used a block randomization scheme with a block size of 3 and no baseline stratification. The 12-week trial consisted of a 6-week escalation/fixed-dose period and a 6-week variable-dose period. During the first 6 weeks, prestudy antipsychotics were gradually discontinued while doses of olanzapine, clozapine, and haloperidol were escalated to their target levels (20 mg/d, 500 mg/d, and 20 mg/d, respectively), where they remained fixed until the end of the first period. During the last 6 weeks, the dose was allowed to vary within these ranges: clozapine, 200–800 mg/d; olanzapine, 10–35 mg/d; haloperidol, 10–30 mg/d. Psychiatrists, blinded to treatment group assignment, could change doses by prescribing various "levels" of medication. At the end of the variable-dose period, mean doses (mg/d) were 565.5 for clozapine (standard deviation [SD] = 112.7 mg/d), 24.7 for olanzapine (SD = 6.1 mg/d), and 23.3 for haloperidol (SD = 7.1 mg/d).

Throughout the study, all patients received (double-blind) benztropine, benztropine placebo, or both. Benztropine (4 mg/d) was administered prophylactically to patients receiving haloperidol. Patients receiving mood stabilizers or antidepressants prior to study entry continued receiving these at the same dose.

All study procedures, including blood draws, were identical for all 3 groups to preserve the blind. Raters blinded to treatment group performed all study assessments.

Aggression Assessments

The Modified Overt Aggression Scale (MOAS)[17] was used to rate incidents of aggression. The MOAS includes physical aggression against other people, verbal aggression, and physical aggression against objects, with a severity score for each type of aggression. A total MOAS score was obtained by assigning a different weight for each type of aggression, using a psychometrically validated method.[17] The total MOAS score and the MOAS physical aggression score were the 2 outcome variables. They were calculated for each subject by summing weekly scores over the 12 weeks.

There were multiple sources of information for the MOAS, including shift-to-shift reports, patient monitoring forms, and interviews with patients and staff. Nursing staff reported all behaviors contemporaneously on monitoring forms that allowed entries to be made for each patient at 30- to 60-minute intervals. Research personnel interviewed nursing staff to confirm incidents of aggression and obtain additional information. In addition, as indicated in the section above on study procedures, recordings from a multicamera system were also reviewed. The intraclass correlation coefficient for the MOAS, established prior to the study and intermittently throughout, was above 0.90.

Cognitive Battery

Executive function. Executive function, the predictor variable, was assessed through the Wisconsin Card Sorting Test (WCST),[18] which measures cognitive flexibility and problem-solving skills, and the Trail Making Test, Part B,[19] which requires the subjects to connect consecutively numbered and lettered circles by alternating between the 2 sequences.

For the WCST, we used the scores for categories completed, as well as the scores for the number of perseverative errors and nonperseverative errors. A total baseline executive function score was computed on the basis of the *z*-transformed values of these 4 constituting variables.

Other cognitive assessments. The other cognitive domains that were assessed consisted of simple motor function, verbal and visual memory, and visuospatial ability. Simple motor function was assessed through the Finger Tapping Test[20] (right and left hand) and the Purdue Pegboard Test[21] (right, left, and both hands). Verbal memory comprised the immediate and delayed recall measures of the Wechsler Memory Scale-Revised.[22] Visual memory consisted of the immediate and delayed recall measures of the Wechsler Memory Scale-Revised Figural Memory.[22] Visuospatial ability was assessed through the Wechsler Adult Intelligence Scale-Revised Block Design Test.[23]

These cognitive tests were administered before randomization and at the end of 12 weeks. To minimize sedation effects, assessments were postponed until 24 hours after the last dose of any sedative medication for aggression or agitation.

Assessments of Psychiatric Symptoms and Medication Side Effects

The Positive and Negative Syndrome Scale (PANSS)[24] was used by 2 independent raters to assess clinical symptoms at baseline, week 6, and week 12 (or end point). Interrater reliability of the PANSS, estimated by intraclass correlation coefficient, exceeded 0.90. Side effects were assessed with the Extrapyramidal Symptom Rating Scale (ESRS),[25] which also includes an evaluation of peripheral anticholinergic side effects, and the Nurses Observation Scale for Inpatient Evaluation (NOSIE)[26] sedation item.

Statistical Analyses

Analysis was based on the intent-to-treat principle: all randomized patients who met inclusion criteria and were administered baseline executive function tests were included

Clinical Points

- Executive function is an important predictor of response to antiaggression treatment in patients with schizophrenia.
- It is possible to customize treatment of aggression on the basis of the patient's level of executive functioning.
- Clozapine has a unique antiaggression profile, resulting in decreased violence even in patients with poor executive function prior to treatment.

© Copyright 2011 Physicians Postgraduate Press, Inc.

Table 1. Baseline Characteristics of Patients Assigned to Receive Clozapine, Olanzapine, or Haloperidol (N = 99)

Characteristic	Clozapine (n = 32)	Olanzapine (n = 32)	Haloperidol (n = 35)	χ^2	*P*
Categorical variables, n (%)					
Male sex	26 (81.3)	26 (81.3)	29 (82.9)	0.4	.98
Race/ethnicity					
White	6 (18.8)	4 (12.5)	7 (20.0)		
African American	18 (56.3)	24 (75.0)	21 (60.0)	4.6	.60
Hispanic	7 (21.9)	4 (12.5)	7 (20.0)		
Other	1 (3.1)	0 (0.0)	0 (0.0)		
Diagnosis					
Schizophrenia	22 (68.8)	19 (59.4)	20 (57.1)	1.1	.59
Schizoaffective disorder	10 (31.3)	13 (40.6)	15 (42.9)		
Continuous variables, mean (SD)				*F*	
Age at randomization, y	34.3 (11.4)	33.7 (8.3)	33.0 (10.6)	0.1	.88
Duration of illness, y	15.0 (8.3)	15.3 (11.0)	14.4 (11.2)	0.1	.94
Prior psychiatric hospitalizations, no.	12.3 (9.9)	11.2 (10.1)	8.9 (4.6)	1.2	.32
Length of hospitalization, d[a]	83.2 (85.1)	85.9 (73.0)	97.9 (126.8)	0.2	.81
Cognitive function scores[b]					
Executive function	0.01 (0.62)	0.01 (0.55)	−0.09 (0.67)	0.3	.73
Simple motor function	0.00 (0.68)	0.18 (0.64)	−0.03 (0.59)	1.0	.36
Verbal memory	−0.03 (1.10)	−0.17 (0.77)	0.26 (1.02)	1.7	.18
Visual memory	0.11 (1.04)	−0.21 (0.87)	0.12 (0.91)	1.3	.29
Visuospatial ability (Block Design Test)	6.4 (2.2)	6.6 (1.8)	6.7 (2.6)	0.1	.89
Positive and Negative Syndrome Scale scores					
Positive subscale	22.8 (4.7)	21.9 (5.3)	22.9 (6.4)	0.3	.74
Negative subscale	19.6 (3.6)	18.7 (3.5)	19.7 (4.8)	0.7	.52
General subscale	42.2 (5.9)	40.8 (7.0)	42.4 (6.5)	0.6	.55
Total	84.6 (11.3)	81.4 (13.3)	85.0 (13.3)	0.8	.45

[a]Length of hospitalization in days upon entry into the study.
[b]Baseline cognitive function scores are based on the *z*-transformed values of the constituting variables, except for visuospatial ability (Block Design Test), for which the scaled score is provided here.

in the analyses. The association between executive function and aggression during treatment was tested by generalized linear model analysis (GENMOD procedure) using SAS software, version 9.2 (SAS Institute Inc, Cary, North Carolina). The MOAS total and physical aggression scores were the dependent variables (in separate analyses). Baseline executive function score, based on *z*-transformed values of the constituting variables, and treatment assignment were the independent variables. We also included the interaction between executive function and treatment assignment. In case of significant interaction, post hoc analyses examined pairwise differences between medication groups. Baseline MOAS score, change in sedation (NOSIE sedation), age, gender, and length of participation in study were the covariates. Additional analyses were done with the PANSS total and subscale scores and the ESRS total and subscale scores as covariates. As increasingly higher MOAS scores occurred with decreasing frequency (inverted J-curve), GENMOD analyses were based on the Poisson distribution.

Executive function was seen as a stable characteristic that interacts with changes produced by treatment. We hypothesized that baseline executive function would predict treatment outcome for aggression and that there would be a differential association between executive function and aggression across medications, ie, a significant interaction between treatment assignment and baseline executive function in determining aggression.

The relationship between aggression and baseline executive function is expressed as a regression slope. The predictive power of executive function on aggression is characterized by the exponentiated estimate of the regression coefficient, which provides information as to the actual statistical effect size: it can be interpreted as a relative (percentage) increase or decrease in aggression associated with a unit of change in the predictor. For the purpose of effect size estimation, we used 2 SD units, since an increase or decrease of this magnitude compared to the mean encloses 95% of the original population and is used to establish "high" and "low" values for test results. In other words, we investigated the extent to which executive function variations over 2 SDs resulted in increased or decreased aggression, expressed as a percentage increase or decrease in aggression over a standard (mean) value.

In addition to the above analyses, we assessed the specificity of executive function as a predictor by investigating the relationship between each cognitive domain and aggression, while taking into consideration the effect of the other cognitive domains. The baseline score for each cognitive function and treatment assignment were the independent variables in GENMOD, as above. The other baseline cognitive functions, other than the one under consideration, were the covariates.

To avoid α inflation, in our investigation, we applied the Hochberg correction for multiple testing.

RESULTS

Demographic Characteristics and Clinical Descriptive Data

Of the 110 subjects who entered the study, 11 did not have baseline executive function assessments, and, therefore, 99 subjects were included: 32 each in the clozapine and

olanzapine groups and 35 in the haloperidol group. Patient demographic and clinical characteristics are presented in Table 1. There were no significant differences between groups in terms of demographic characteristics, illness parameters, duration of time in the study, scores in the various cognitive domains, psychopathology ratings, sedation ratings, or ESRS scores. There were no differences in the proportions of patients receiving other psychotropics as concomitant medications or in the proportions of patients receiving typical versus atypical agents prior to enrollment. With regard to specific prestudy antipsychotic medications, the most common were olanzapine (37%), risperidone (27%), and quetiapine (21%). There were no significant differences between the 3 study groups in the proportions of patients receiving these medications.

In addition, when we investigated the changes in clinical symptoms over the course of the study, there were no significant differences between the 3 groups in the change in PANSS total score ($P = .24$) or ESRS total score ($P = .25$). There was, however, a significant difference in the severity of peripheral anticholinergic side effects (as indicated by end point assessment) ($F_{2,81} = 4.98$, $P < .01$). These side effects were most severe in the clozapine group and least severe in the olanzapine group. There was a significant pairwise difference between clozapine and olanzapine ($P = .002$) and a marginal difference between haloperidol and olanzapine ($P = .09$).

Baseline Executive Function and Aggressive Incidents During the Baseline Period

We determined number and severity of aggressive incidents by summing the MOAS total and physical aggression scores over the 4-week baseline period through chart review in the 3 groups that were subsequently randomized. There were no differences among the groups in MOAS total score ($F_{2,98} = 2.2$, $P = .11$) or physical aggression score ($F_{2,98} = 1.7$, $P = .18$). There was no significant association between baseline executive function and baseline MOAS total ($F_{1,98} = 0.17$, $P = .68$) or physical aggression ($F_{1,98} = 0.04$, $P = .85$) scores.

Baseline Executive Function and Aggression Over the Study Period

Baseline executive function was a strong predictor of aggression over the 12-week period in the total group of subjects, as assessed by the MOAS total aggression score ($F_{1,98} = 222.2$, $P < .0001$). The slope estimate (representing the strength of the association) was 1.00 (standard error [SE] = 0.07; $t = 14.91$, $P < .0001$). An executive function score that was higher by 2 SDs compared to the mean was associated with a 63% decrease in total MOAS score, as indicated by the exponentiated estimate.

There was also a significant main effect for baseline executive function on physical aggression ($F_{1,98} = 135.5$, $P < .001$), with a slope estimate of 1.20 (SE = 0.10; $t = 11.64$, $P < .001$). There was a 70% decrease in physical aggression when the executive function score was higher by 2 SDs compared to the mean.

Baseline Executive Function and Aggression in the 3 Medication Groups

There were significant differences in MOAS total aggression ($F_{2,98} = 43.30$, $P < .0001$) and physical aggression ($F_{2,98} = 35.43$, $P < .001$) among the 3 medication groups over the 12 weeks. Post hoc paired comparisons showed that clozapine was superior to haloperidol ($P < .001$) and olanzapine ($P < .001$) and that olanzapine was superior to haloperidol ($P < .001$) for MOAS total and physical aggression scores. This finding is in line with the results of the previous investigation[27] that focused on aggression and psychopathology.

There was a significant interaction between medication grouping and baseline executive function in determining MOAS total aggression ($F_{1,98} = 15.32$, $P < .001$) and in determining MOAS physical aggression ($F_{1,98} = 5.23$, $P < .01$). Thus, while executive function predicted aggression in all subjects, it did not do so equally in all medication groups.

Table 2 presents the predictive power of executive function on aggression for each medication. The findings are represented as relative differences between levels of aggression over 2 SDs in baseline executive function. The estimates are significant for all 3 medications in determining aggression scores. The table shows that, for a baseline executive function that was higher by 2 SDs, there was a 79%, 45%, and 58% reduction in MOAS total aggression in the olanzapine, clozapine, and haloperidol groups, respectively. Pairwise comparisons are presented on the right side of the table. The predictive power of executive function was significantly stronger for olanzapine than for haloperidol and for olanzapine than for clozapine. The difference between clozapine and haloperidol approached statistical significance.

For a baseline executive function that was higher by 2 SDs, there was a 75%, 52%, and 78% reduction in physical aggression in the olanzapine, clozapine, and haloperidol groups, respectively. The predictive power of executive function was significantly stronger for olanzapine than for clozapine and for haloperidol than for clozapine, with no difference between haloperidol and olanzapine (Table 2).

We repeated the above analyses using baseline PANSS total and subscale scores, ESRS total and subscale scores, and change in these variables over the treatment period as covariates. We also examined the effect of prestudy medication by including olanzapine, risperidone, and quetiapine, the 3 most commonly used prestudy medications, as additional dichotomous (*yes* or *no*) covariates in the analyses. The previous results were essentially unchanged with the introduction of these additional covariates.

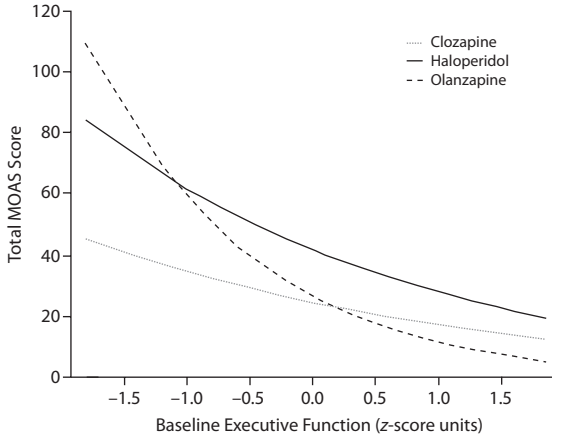
To investigate the relative superiority of clozapine over olanzapine, and olanzapine over clozapine, as a function of baseline executive function, we plotted the estimated mean total MOAS score over various executive function levels for each medication (Figure 1). As we proceed from average executive function levels to better functioning (ie, right of center), olanzapine becomes significantly better than clozapine when baseline executive function improves by 0.50 SD over average ($t_{97} = 2.2$, $P < .001$). Conversely, there is significantly less aggression with clozapine than with olanzapine

Table 2. Relationship Between Baseline Executive Function and Modified Overt Aggression Scale (MOAS) Scores During the Treatment Period for Aggressive Patients With Schizophrenia or Schizoaffective Disorder Randomly Assigned to Receive Olanzapine, Clozapine, or Haloperidol (N = 99)[a]

MOAS Score and Medication Group	Slope Estimates for the Relationship Between Executive Function and Aggression					Pairwise Comparisons of Slope Estimates Between Medication Groups										
						Olanzapine-Haloperidol				Clozapine-Haloperidol				Olanzapine-Clozapine			
	Estimate	SE	*t*	*P*	Exp, %[b]	Difference[c]	SE	*t*	*P*	Difference[c]	SE	*t*	*P*	Difference[c]	SE	*t*	*P*
MOAS total						0.68	0.16	4.14	<.001[d]	0.27	0.16	1.75	.08	0.95	0.18	5.39	<.001[e]
Clozapine	0.59	0.12	4.91	<.001	45												
Olanzapine	1.54	0.13	12.00	<.001	79												
Haloperidol	0.86	0.10	8.64	<.001	58												
Physical aggression						0.14	0.25	0.56	.58	0.78	0.25	3.17	.002[f]	0.64	0.28	2.32	.02[e]
Clozapine	0.73	0.20	3.72	<.001	52												
Olanzapine	1.37	0.19	7.08	<.001	75												
Haloperidol	1.50	0.15	10.14	<.001	78												

[a]Generalized linear model (GENMOD) analyses for the association between baseline executive function and MOAS scores during the 12-week double-blind treatment. Covariates included baseline MOAS score, sedation, age, gender, and length of participation in the study. The left side of the table indicates the predictive power of baseline executive function on subsequent aggression, as represented by the exponentiated estimate. The right side of the table provides pairwise comparisons. All results with nominal significance remained statistically significant after the Hochberg correction for multiple testing was applied.
[b]Indicates the relative percentage increase or decrease in MOAS score associated with a unit of increase or decrease in the predictor variable, baseline executive function.
[c]Difference in slope estimates between the medication pairs.
[d]Predictive power stronger for olanzapine than for haloperidol.
[e]Predictive power stronger for olanzapine than for clozapine.
[f]Predictive power stronger for haloperidol than for clozapine.
Abbreviation: Exp = exponentiated estimate.

Figure 1. MOAS Total Aggression Scores by Treatment Group During 12-Week Treatment Versus Executive Function at Baseline



Abbreviation: MOAS = Modified Overt Aggression Scale.

Table 3. Relationship Between Baseline Cognitive Functions and Modified Overt Aggression Scale (MOAS) Scores During the Treatment Period, With the Other Cognitive Functions as Covariates[a]

Cognitive Function and MOAS Score	Estimate	SE	*t*	*P*	Exponentiated Estimate, %[b]
Executive function					
MOAS total	0.80	0.08	10.6	<.001	55
Physical aggression	1.14	0.11	9.9	<.001	68
Simple motor function					
MOAS total	0.14	0.07	2.0	.05	13
Physical aggression	0.20	0.11	1.8	.07	−20
Verbal memory					
MOAS total	0.21	0.06	3.7	<.001	19
Physical aggression	0.48	0.09	5.4	<.001	38
Visual memory					
MOAS total	0.06	0.06	1.0	.31	6
Physical aggression	0.10	0.09	1.1	.27	−10
Visuospatial ability					
MOAS total	0.19	0.05	3.7	<.001	−21
Physical aggression	0.02	0.01	2.6	.01	2

[a]Generalized linear model (GENMOD) analyses for the association between each baseline cognitive function and MOAS scores during the 12-week double-blind treatment. All domain scores were *z*-transformed. Covariates included the other cognitive functions in addition to baseline MOAS score, sedation, age, gender, and length of participation in the study.
[b]Indicates the relative percentage increase or decrease in MOAS score associated with a unit of increase or decrease in the predictor variable, baseline executive function.

when executive function *decreases* by 0.10 SD below average ($t_{97} = 2.31$, $P = .02$).

Similar results were obtained for physical aggression. Olanzapine was better than clozapine at higher executive function levels, but the difference did not reach statistical significance. With decreases in executive function level, clozapine became significantly better than olanzapine when baseline executive function was slightly above average, ie, by 0.10 SD ($t_{97} = 2.12$, $P = .04$).

Aggression and Baseline Cognitive Functions

To determine the specificity of executive function, we examined the relationship between each baseline cognitive function and subsequent aggression (with the other cognitive functions as additional covariates) (Table 3). We repeated all the above analyses for executive function with the other cognitive domains as covariates. There was, again, a strong association between baseline executive function and MOAS total aggression ($F_{1,90} = 113.1$, $P < .001$) and physical aggression ($F_{1,90} = 97.0$, $P < .001$) scores. There were also significant interactions between medication and executive function in determining MOAS total aggression ($F_{1,90} = 16.1$, $P < .001$) and physical aggression ($F_{1,90} = 6.4$, $P < .01$) scores.

Percentage reductions in aggression in each of the 3 medication groups were similar to the results reported above.

As seen in Table 3, the results were not significant for visual memory, and simple motor function reached only the .05 level of significance. Verbal memory was related to both total MOAS ($F_{1,90} = 13.6$, $P < .001$) and physical aggression ($F_{1,90} = 28.8$, $P < .001$) scores, with significant interactions between medication and verbal memory in determining MOAS total aggression ($F_{1,90} = 61.2$, $P < .001$) and physical aggression ($F_{1,90} = 62.2$, $P < .001$) scores. These significant relationships were limited entirely to the olanzapine group: for a baseline verbal memory score higher by 2 SDs, total MOAS score was reduced by 62% and physical aggression by 83%. There was no relationship in the clozapine or haloperidol groups.

There was a significant association between visuospatial ability (Block Design Test) and MOAS total aggression ($F_{1,90} = 13.4$, $P < .001$) and physical aggression ($F_{1,90} = 6.6$, $P = .01$) scores. Yet, a unit increase in visuospatial ability resulted in only minimal improvement in physical aggression score and was associated with *worsening* of total MOAS score (Table 3).

DISCUSSION

Executive Function and Response to Treatment

Executive function predicted the number and severity of aggressive incidents during the study period. This finding is consistent with the importance of executive function for aggression. As hypothesized, there was specificity to this association, as better functioning in other cognitive domains was not associated with less aggression, with the exception of verbal memory, but this association was restricted to the olanzapine group.

The importance of executive function as a predictor of aggression cannot be explained on the basis of the antipsychotic effect or side effects of medications, as there were no changes in its predictive power when these measures were used as covariates. There was no significant relationship between executive function and aggression assessed during the baseline period. Thus, the strong relationship between executive function and subsequent aggression reflects primarily a lack of response to treatment. Executive function was a stable characteristic that did not change over the treatment period; it interacted with the changes produced by treatment in determining aggression during the study period.

Differences Between the Medications

In each medication group, baseline executive function predicted aggression, but this relationship was not as strong for clozapine, which is still moderately effective in reducing aggression in the presence of executive dysfunction. Clozapine was superior to both olanzapine and haloperidol in its antiaggression effect. Its superiority may be due to its greater efficacy when severe executive dysfunction is present.

Neurophysiologic mechanisms underlying executive function and antipsychotic drug action may provide an explanation for our findings. The prefrontal cortex is essential for executive function, and deficits in these functions are indicative of frontal abnormalities. These executive function deficits have an effect on behavioral inhibition, aggression, and self-correcting behavior,[28,29] but there are important interactions between frontal areas and the limbic system with regard to behavioral inhibition and aggression.[30] Clozapine has been shown to have greater limbic selectivity[31]; response to clozapine treatment may therefore depend less on the integrity of frontal areas and rely more on its limbic effect. This possibility may explain its greater antiaggression effect in the presence of executive dysfunction.

In addition, electrophysiologic data point to clozapine's preferential action on serotonergic receptors in the orbitofrontal cortex.[32] In animal models, clozapine's antiaggression effect has been linked to its serotonergic action.[33] Thus, its action on frontal serotonergic receptors may compensate for impediments caused by executive dysfunction.

Verbal memory predicted the number and severity of aggressive incidents in the olanzapine group only. This cognitive ability is influenced by both cholinergic and serotonergic transmission, and its baseline value may be indicative of the responsiveness of these neurotransmitter systems. In the olanzapine group, good verbal memory may represent greater serotonergic responsiveness, which, in turn, would be associated with better control of violent behavior.[34] For haloperidol and clozapine, however, the relationship between baseline verbal memory and subsequent aggression may be affected by the strong anticholinergic effect of these medications. Some of their antiaggression effect may be the result of this anticholinergic activity, as the latter has been associated with reduction in aggression.[35] The patients who already have compromised cholinergic function, as reflected in poor verbal memory at baseline, would be more likely to be affected by the anticholinergic effect of these medications, which would also include an antiaggression effect. Hence, the relationship between verbal memory and subsequent aggression would be reduced in the clozapine and haloperidol groups.

Limitations and Advantages of the Study

This study was unique in being specifically designed for the investigation of aggression in subjects who were selected on the basis of physical aggression. It was conducted entirely on an inpatient research ward. This setting allowed for a uniform environment, careful monitoring of aggressive incidents, and high treatment compliance. These strengths, however, also limit the generalizability of our results, especially for the prediction of community violence, for which factors such as poor treatment compliance, substance abuse, and adverse social environments increase the risk of violence.[36] There was an additional selection bias, in that only patients who could be tested for cognition were included.

Our study is the first to demonstrate a relationship between executive function and response to antiaggression treatment. Our findings would aid clinicians in identifying aggressive

© Copyright 2011 Physicians Postgraduate Press, Inc.

patients who are resistant to antipsychotics and need different medications or supplementary behavioral interventions. While a comprehensive neuropsychological assessment is not always administered in various clinical settings, some executive function tests, such as the Trail Making B test, are easy to administer. In addition, cognition has become a major outcome variable in treatment, and neuropsychological testing is increasingly more often part of the clinical evaluation of patients.

The study also suggests that clozapine may be the antipsychotic of choice in patients with greater executive dysfunction but that olanzapine should be given preference for patients with better executive function.

Drug names: benztropine (Cogentin and others), clozapine (Clozaril, FazaClo, and others), haloperidol (Haldol and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal and others).
Author affiliations: The Nathan S. Kline Institute for Psychiatric Research, Orangeburg, New York (Drs Krakowski and Czobor); Department of Psychiatry, New York University School of Medicine, New York (Dr Krakowski); and Departments of Psychiatry and Psychotherapy, Semmelweis University, Budapest, Hungary (Dr Czobor).
Potential conflicts of interest: None reported.
Funding/support: Supported by R01 grant MH74767 and additionally by grant MH85322 from the National Institute of Mental Health (NIMH), Bethesda, Maryland. Eli Lilly and Company, Indianapolis, Indiana, and Novartis Pharmaceuticals Corporation, East Hanover, New Jersey, provided medications for the study, and Eli Lilly contributed supplemental funding for the encapsulation of the medications.
Disclaimer: Overall experimental design, data acquisition, statistical analyses, and interpretation of the results were implemented with no input from NIMH or the pharmaceutical sponsors.

REFERENCES

1. Lelliott P, Wing J, Clifford P. A national audit of new long-stay psychiatric patients, 1: method and description of the cohort. *Br J Psychiatry*. 1994;165(2):160–169.
2. Bigelow DA, Cutler DL, Moore LJ, et al. Characteristics of state hospital patients who are hard to place. *Hosp Community Psychiatry*. 1988;39(2):181–185.
3. Greenfield TK, McNiel DE, Binder RL. Violent behavior and length of psychiatric hospitalization. *Hosp Community Psychiatry*. 1989;40(8):809–814.
4. Wilson WH, Claussen AM. 18-month outcome of clozapine treatment for 100 patients in a state psychiatric hospital. *Psychiatr Serv*. 1995;46(4):386–389.
5. Volavka J, Zito JM, Vitrai J, et al. Clozapine effects on hostility and aggression in schizophrenia. *J Clin Psychopharmacol*. 1993;13(4): 287–289.
6. Giancola PR. Neuropsychological functioning and antisocial behavior: Implications for etiology and prevention. In: Fishbein D, ed. *The Science, Treatment and Prevention of Antisocial Behavior*. Kingston, NJ: Civic Research Institute; 2000:111–116.
7. Morgan AB, Lilienfeld SO. A meta-analytic review of the relation between antisocial behavior and neuropsychological measures of executive function. *Clin Psychol Rev*. 2000;20(1):113–136.
8. Luria A. *Higher Cortical Functions in Man*. New York, NY: Basic Books; 1980.
9. Sprague J, Verona E, Kalkhoff W, et al. Moderators and mediators of the stress-aggression relationship: executive function and state anger. *Emotion*. 2011;11(1):61–73.
10. Lau MA, Pihl RO, Peterson JB. Provocation, acute alcohol intoxication, cognitive performance, and aggression. *J Abnorm Psychol*. 1995;104(1):150–155.
11. Lysaker PH, Bell MD, Bioty SM. Cognitive deficits in schizophrenia: Prediction of symptom change for participators in work rehabilitation. *J Nerv Ment Dis*. 1995;183(5):332–336.
12. Velligan DI, Bow-Thomas CC, Mahurin RK, et al. Do specific neurocognitive deficits predict specific domains of community function in schizophrenia? *J Nerv Ment Dis*. 2000;188(8):518–524.
13. Evans JD, Bond GR, Meyer PS, et al. Cognitive and clinical predictors of success in vocational rehabilitation in schizophrenia. *Schizophr Res*. 2004;70(2–3):331–342.
14. Smith RC, Largen J, Vroulis G, et al. Neuropsychological test scores and clinical response to neuroleptic drugs in schizophrenic patients. *Compr Psychiatry*. 1992;33(2):139–145.
15. Chen EY, Hui CL, Dunn EL, et al. A prospective 3-year longitudinal study of cognitive predictors of relapse in first-episode schizophrenic patients. *Schizophr Res*. 2005;77(1):99–104.
16. Nolan KA, Czobor P, Roy BB, et al. Characteristics of assaultive behavior among psychiatric inpatients. *Psychiatr Serv*. 2003;54(7):1012–1016.
17. Kay SR, Wolkenfeld F, Murrill LM. Profiles of aggression among psychiatric patients, 1: nature and prevalence. *J Nerv Ment Dis*. 1988;176(9):539–546.
18. Berg EA. A simple objective test for measuring flexibility in thinking. *J Gen Psychol*. 1948;39(1):15–22.
19. Radford LM, Chaney EF, O'Leary MR, et al. Screening for cognitive impairment among inpatients. *J Clin Psychiatry*. 1978;39(9):712–715.
20. Reitan RM, Wolfson D. *The Halstead-Reitan Neuropsychological Test Battery: Theory and Clinical Interpretation*. 2nd ed. Tucson, AZ: Neuropsychology Press; 1993.
21. Tiffin J, Asher EJ. The Purdue Pegboard; norms and studies of reliability and validity. *J Appl Psychol*. 1948;32(3):234–247.
22. Wechsler D. *The Wechsler Memory Scale*. 3rd ed. San Antonio, TX: Psychological Corporation (Harcourt); 1997.
23. Wechsler D. *The Wechsler Adult Intelligence Scale*. 3rd ed. San Antonio, TX: Psychological Corporation (Harcourt); 1997.
24. Kay SR, Fiszbein A, Opler LA. The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. *Schizophr Bull*. 1987;13(2):261–276.
25. Chouinard G, Ross-Chouinard A, Annable L, et al. Extrapyramidal Symptom Rrating Scale. *Can J Neurol Sci*. 1980;7:233–239.
26. Honigfeld G, Gillis RD, Klett CJ. NOSIE-30: a treatment-sensitive ward behavior scale. *Psychol Rep*. 1966;19(1):180–182.
27. Krakowski MI, Czobor P, Citrome L, et al. Atypical antipsychotic agents in the treatment of violent patients with schizophrenia and schizoaffective disorder. *Arch Gen Psychiatry*. 2006;63(6):622–629.
28. Wilder-Willis KE, Shear PK, Steffen JJ, et al. The relationship between cognitive dysfunction and coping abilities in schizophrenia. *Schizophr Res*. 2002;55(3):259–267.
29. Brower MC, Price BH. Neuropsychiatry of frontal lobe dysfunction in violent and criminal behaviour: a critical review. *J Neurol Neurosurg Psychiatry*. 2001;71(6):720–726.
30. Davidson RJ, Putnam KM, Larson CL. Dysfunction in the neural circuitry of emotion regulation: a possible prelude to violence. *Science*. 2000;289(5479):591–594.
31. Chiodo LA, Bunney BS. Possible mechanisms by which repeated clozapine administration differentially affects the activity of two subpopulations of midbrain dopamine neurons. *J Neurosci*. 1985;5(9):2539–2544.
32. Bergqvist PBF, Dong J, Blier P. Effect of atypical antipsychotic drugs on 5-HT2 receptors in the rat orbito-frontal cortex: an in vivo electrophysiological study. *Psychopharmacology (Berl)*. 1999;143(1):89–96.
33. Sánchez C, Arnt J, Hyttel J, et al. The role of serotonergic mechanisms in inhibition of isolation-induced aggression in male mice. *Psychopharmacology (Berl)*. 1993;110(1–2):53–59.
34. Coccaro EF, Siever LJ, Klar HM, et al. Serotonergic studies in patients with affective and personality disorders: correlates with suicidal and impulsive aggressive behavior. *Arch Gen Psychiatry*. 1989;46(7):587–599.
35. Smith DE, King MB, Hoebel BG. Lateral hypothalamic control of killing: evidence for a cholinoceptive mechanism. *Science*. 1970;167(3919):900–901.
36. Swartz MS, Swanson JW, Hiday VA, et al. Violence and severe mental illness: the effects of substance abuse and nonadherence to medication. *Am J Psychiatry*. 1998;155(2):226–231.