

Clozapine, Negative Symptoms, and Extrapyramidal Side Effects

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The importance of persistent negative symptoms in schizophrenia as a limiting factor in psychosocial and vocational rehabilitation has been increasingly emphasized. As a result, treatment trials and new drug development programs are focusing more attention on negative symptoms. Unfortunately, there is enormous phenomenological overlap between negative symptoms and neuroleptic-induced parkinsonism. We report data from a cohort of 56 clozapine-treated patients demonstrating significant correlations between measures of akinesia and anergia. Despite an average drug washout of over 2 weeks, the persistence of drug-induced parkinsonism can confound the assessment of therapeutic drug effects on negative symptoms.

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Over the past decade, there has been renewed research interest in negative symptoms of schizophrenia.^{1,2} Efforts have focused on conceptual definition, assessment techniques, pathophysiologic hypothesis, and treatment research. Though some progress has been made, clinicians and researchers continue to struggle with all of these issues.

One critical challenge in the cross-sectional or short-term assessment of negative symptoms is their potential overlap with drug-induced parkinsonism (and depression). Although longitudinal studies involving drug dosage reduction or discontinuation, and/or use of antiparkinsonian agents can help, to some extent, to differentiate true negative symptoms from the apathy, amotivation, blunted affect, and psychomotor retardation associated with drug-induced parkinsonism, these strategies have rarely been employed in selecting patients for treatment trials.

It is also quite possible that those patients with pre-existing negative symptoms may be more vulnerable to

developing drug-induced parkinsonism (or a more severe degree of the latter). If dopaminergic hypoactivity and/or muscarinic hyperactivity contribute to the production of negative symptoms,³ then the potential complexity of these phenomena and their interaction with pharmacologic agents is further heightened.

Given the importance of negative symptoms in contributing to the psychosocial and vocational disability associated with schizophrenia and the clinical impression that negative symptoms are less responsive than positive symptoms to traditional antipsychotic drug treatment,^{1,2} increasing attention has been focused on developing better pharmacologic treatments.

Though inadequate response to antipsychotic medication has frequently been associated with the presence of negative symptoms,^{1,2} many studies have reported significant improvement in negative symptoms in the context of acute treatment.⁴⁻⁷ The extent to which improvement in negative symptoms with drug treatment is secondary to or covaries with improvement in positive symptoms continues to be a subject of considerable debate. In addition, these findings of improvement in negative symptoms may be undermined by inadequate conceptual and methodological approaches to studying this problem.^{8,9}

With this background, there has been considerable interest in determining whether new or atypical antipsychotic drugs have any advantage over traditional medications in the treatment of negative symptoms. Clozapine has been shown to be superior to standard antipsychotic agents in the treatment of neuroleptic-non-responsive schizophrenic patients in reducing both positive and negative symptoms.¹⁰ Some investigators have

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gested that negative symptoms improved independently from reductions in positive symptoms with clozapine treatment,^{7,11} while others have found negative symptoms to covary with positive symptoms in clozapine-treated patients.¹² Still other reports have not found improvement in negative symptoms with clozapine treatment.¹³ Given the reduced propensity of clozapine to produce extrapyramidal side effects,¹⁴ the potential role of this attribute in improving apparent "negative" symptoms in patients previously treated with traditional medications also requires examination.

The present report is an attempt to examine the relationship between ratings of drug-induced parkinsonism and negative symptoms, cross-sectionally and over time, in a cohort of clozapine-treated patients.

METHOD

The sample consisted of patients treated with clozapine based on the operational criteria for treatment refractoriness that we have previously employed.¹⁰ In addition, patients were required to meet the following criteria: (1) be aged between 18 and 40 years; (2) have a primary diagnosis of schizophrenia or schizoaffective disorder (DSM-III-R) uncomplicated by current substance abuse; and (3) have no current or past history of serious medical illness, particularly idiopathic or drug-induced blood dyscrasia. Both patients and families were required to give informed consent.

All patients were admitted to the inpatient service at Hillside Hospital and were withdrawn from all medication (except amobarbital and/or chloral hydrate, if needed for behavioral control) for up to 28 days, depending upon their tolerance of the drug-free period prior to clozapine initiation.

Before the first dose of clozapine, baseline evaluations were performed utilizing the Brief Psychiatric Rating Scale (BPRS),¹⁵ the Clinical Global Impressions (CGI) scale,¹⁶ the Simpson-Angus scale for extrapyramidal side effects,¹⁷ and a modified Simpson dyskinesia scale.¹⁸ The Scale for the Assessment of Negative Symptoms (SANS)¹⁹ was added partway through the study (and is, therefore, available only on a subset of patients).

After baseline evaluation, clozapine 25 mg/day was administered; the dose was gradually titrated by a standard schedule as tolerated to a maximum of 500 mg/day by treatment Day 14 and then held fixed for at least 1 week. After Day 21, the dose could be adjusted as clinically indicated (up to a maximum of 900 mg/day). The mean dose \pm SD at Week 6 was 599 ± 201 mg/day. Patients were evaluated at Weeks 3, 6, 12, 26, 39, and 52. Patients could be discharged from the hospital after 6 weeks of treatment. The decision to continue treatment with clozapine was based upon clinical judgment and

Table 1. Demographics of 56 Treatment-Refractory Schizophrenics*

Variable	N	%
Sex		
Male	37	66
Female	19	34
Race		
White	47	84
Black	8	14
Other	1	2
Diagnosis (DSM-III-R)		
Schizophrenia/paranoid type	33	58
Schizophrenia/undifferentiated type	16	29
Schizophrenia/disorganized type	5	9
Schizoaffective disorder	2	4
Duration of washout before starting clozapine		
< 7 days	8	14
\geq 7 days	48	86
	Mean	SD
Age (y)	27.6	5.9
Duration of illness (y)	8.4	5.6
Age at onset (y)	19.2	4.5
Daily dose at Week 6 (mg)	599	201
Daily dose after Week 6 (mg) (range, 100-900)	599	212
Baseline ratings		
BPRS sum	50.1	13.1
BPRS anergia factor	9.1	4.8
CGI	5.3	1.0
Simpson-Angus akinesia ^a	.4	.8
SANS	2.7	.8

*Abbreviations: BPRS = Brief Psychiatric Rating Scale; CGI = Clinical Global Impressions; Simpson-Angus = Simpson-Angus scale for extrapyramidal side effects; SANS = Scale for the Assessment of Negative Symptoms.

^a0 = absent; 1 = mild; 2 = moderate; 3 = marked; 4 = extreme.

made in conjunction with patients and families. The mean clozapine dose during maintenance treatment was 599 ± 212 mg/day.

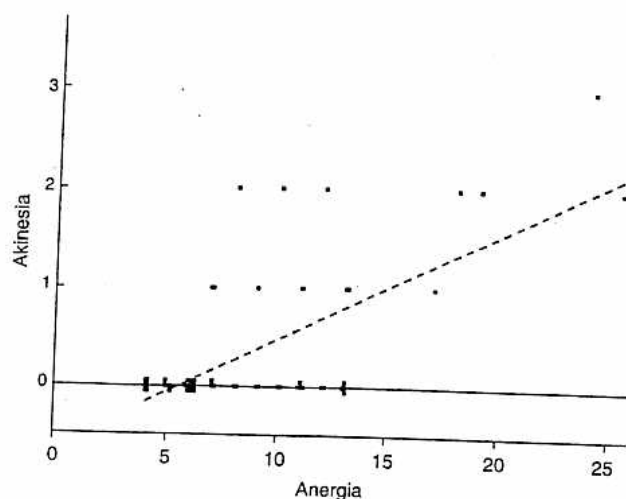
Statistical methods mainly involved linear bivariate correlational analyses. The effect of extreme data points (outliers) was examined by recalculating the correlates with outliers deleted. A plot of bivariate relation between pairs of variables was examined to verify that the assumption of linearity was realistic. The nonparametric Spearman rank-order correlation coefficient was calculated as well. In addition, the partial correlation coefficient was calculated to control statistically for days of washout and degree of psychopathology at baseline. Multiple linear regression was used to quantify the cumulative impact of multiple measures (e.g., the 10 items on the Simpson-Angus scale) on a single variable such as the anergia factor on the BPRS.

RESULTS

The demographic characteristics of the 56 patients included in these analyses are presented in Table 1.

Two measures of presumptive negative symptoms were available. The anergia factor of the BPRS includes the items emotional withdrawal, blunted affect, motor re-

Figure 1. Linear Association Between Brief Psychiatric Rating Scale Anergia Factor and Akinesia at Baseline*

* $r = .68$, $N = 56$, $p < .001$.

tardation, and disorientation. Thirty-four of the 56 patients included in this analysis also had SANS assessments at baseline, Week 6, and Week 26. The results reported for the anergia factor were equally true for the SANS as well. We chose to report the BPRS anergia factor since it was available for all patients and at more frequent intervals. We have focused specifically on the akinesia item on the Simpson-Angus scale because it represents that aspect of drug-induced parkinsonism most likely to be confused with negative symptoms.^{20,21}

The mean \pm SD length of drug washout from prior neuroleptics before beginning clozapine treatment was 16.6 ± 11.4 days. Only 8 (14%) patients had a washout of less than 7 days. The length of prior neuroleptic washout did not correlate with mean Simpson-Angus scale total score, but significant negative correlations were found with 8 of 10 of the individual items ($p < .05$; one-tailed sign test). This would suggest that the longer the washout, the fewer extrapyramidal side effects will be observed.

Statistically significant correlations were found at baseline and Weeks 3, 6, 12, 26, and 39 between akinesia and the anergia factor (see Figure 1 for a scatterplot of the baseline data). When those patients with less than 2 weeks' washout were eliminated, the correlations at baseline, Week 3, and Week 6 remained significant. The correlations are summarized in Table 2. The pattern of high positive correlation is not changed if extreme values are eliminated or if a Spearman rank-order correlation is used. Controlling for possible confounding variables, CGI, and days of washout did not alter the results. Finally, none of the other nine Simpson-Angus scale items consistently correlated with the BPRS anergia factor, either individually or when added to akinesia in a multiple linear regression model.

Table 2. Correlation of Simpson-Angus Akinesia Item With BPRS Anergia Factor

Item	Baseline	Week			
		3	6	12	26
r	.68	.59	.43	.48	.40
N	56	49	47	28	28
p Value*	.00	.00	.00	.01	.03

*Two-tailed significance.

It is not surprising that these measures would be highly correlated as they are measures that involve, to a large extent, the same objective phenomena. Compare the previously defined BPRS anergia factor with the anchored description of a "moderate" rating on the Simpson-Angus item akinesia: "poverty of movement, little or no gestures, little or no spontaneous speech." A similar detailed analysis of the 34 patients for whom SANS ratings are available reveals that akinesia correlates significantly (and explains at least 25% of the variance) only with the global ratings for affective flattening and alogia. Likewise, affective flattening and alogia were the only SANS global ratings that correlated highly with all three of the BPRS items that were related to akinesia (emotional withdrawal, motor retardation, and blunted affect).

Prosser et al.²¹ also reported a significant correlation between negative symptoms and parkinsonian features associated with akinesia; however, they also found a significant correlation between tremor and the BPRS anergia factor (after controlling for age, plasma neuroleptic levels, and anticholinergic activity levels). Since tremor is a manifestation of drug-induced parkinsonism that is readily distinguishable from negative symptoms, this correlation may add weight to the argument that parkinsonism and negative symptoms share some common pathophysiologic aspects and/or that patients with negative symptoms are more prone to develop drug-induced parkinsonism. In our analysis, however, we did not find correlations between tremor and anergia. In fact, when length of washout was controlled for, the correlations between all nonakinesia parkinsonism items and anergia disappeared.

In examining the overlap between akinesia and anergia, of special interest were those 16 patients who were rated as not having akinesia at baseline yet were given ratings of 8 or higher on the anergia scale. In all cases, patients falling into this category had abnormal ratings (moderate or higher) on the emotional withdrawal and/or blunted affect items, but not on motor retardation. (The disorientation item was not correlated with akinesia in any subset of patients and contributed nothing but noise to the data.)

In comparison, those 12 patients rated as having both akinesia and anergia had a substantially higher (2 point) mean motor retardation level; 95% confidence interval

of the difference between means, 1.0 to 2.1. By way of contrast, the mean emotional withdrawal and blunted affect ratings among those with anergia were not significantly different from those with versus those without akinesia, which would suggest that raters were utilizing the degree of motor retardation as a way of differentiating akinesia and anergia. Clearly, the validity and reliability of this distinction has not been established.

One might argue that longer drug washouts could help to eliminate confounding residual drug effects; however, at the same time, increasing length of neuroleptic withdrawal may lead to an exacerbation of negative symptoms (as well as positive symptoms), further complicating assessments. In addition, the response of putative akinesia to pharmacologic manipulation may not be as discriminating as one would hope if true negative symptoms also respond somewhat to anticholinergic medication.³

These results would suggest that an apparent improvement in negative symptoms, however defined, could be at least partially due to improvement in extrapyramidal side effects, and perhaps more importantly that a 2- to 3-week neuroleptic washout may not be adequate to eliminate extrapyramidal side effects resulting from prior neuroleptic treatment.

Interestingly, two reports^{22,23} examining predictors of clozapine response suggested that higher baseline levels of extrapyramidal side effects were associated with better treatment response. If one included treatment-intolerant patients in such an analysis, those results might be expected; however, the analysis we are reporting here specifically excluded patients who had received clozapine because of treatment intolerance. In fact, our data suggest that it is akinesia that is the main determinant of the relationship between baseline extrapyramidal side effects and better clozapine response.

CONCLUSION

It remains unclear to what extent the apparent superiority of clozapine for negative symptoms represents a further consequence of its superior efficacy for positive symptoms, its reduced propensity to produce extrapyramidal side effects, and/or some third factor.

At the same time, given the enormous phenomenological overlap and possible pathophysiologic overlap, the important clinical value of drugs that produce less akinesia and/or improve anergia should not be diminished because of our conceptual, methodological, or pathophysiologic uncertainties. The value of such treatments to patients is enormous regardless of the theoretical underpinnings. At the same time, further advances in our understanding of this issue may also shed important light on the disease itself as well as mechanisms of drug action.

Drug names: amobarbital (Amytal), chloral hydrate (Noctec), clozapine (Clozaril).

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