Assessing the Effects of Atypical Antipsychotics on Negative Symptoms

Collaborative Working Group on Clinical Trial Evaluations

Attempts to clarify the domains of schizophrenia gained importance when the atypical antipsychotics joined the armamentarium of schizophrenia treatments because of evidence that these agents are superior to conventional antipsychotics for the treatment of negative symptoms. Negative symptoms can be divided into 3 components: (1) deficit or primary enduring negative symptoms that may or may not respond to treatment, (2) primary nonenduring negative symptoms, and (3) secondary negative symptoms that are associated with positive symptoms, extrapyramidal symptoms, depression, and environmental deprivation. The atypical antipsychotics have generally been found to be more effective than conventional antipsychotics against the totality of negative symptoms, but their effects on specific components are still under study. Sophisticated statistical tools such as path analysis have been used in investigations of the direct and indirect effects of atypical antipsychotics on negative symptoms, but these tools have limitations. Future study is needed to identify specific components of negative symptoms that may respond preferentially to one or another of the atypical antipsychotics.
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Negative symptoms comprise an integral element in the psychopathology of schizophrenia. Strauss et al.,[1] in 1974, proposed 3 independent processes that underlie the symptoms of schizophrenia and can be used to evaluate prognosis and outcome: negative symptoms, such as blunted affect and emotional withdrawal; positive symptoms, such as delusions and hallucinations; and disordered relationships. Crow,[2] in 1980, formulated the 2-syndrome hypothesis of schizophrenia. He argued that the positive subtype (type I) is characterized by acute onset, prominent positive symptoms, normal brain structure and function, a biochemical disorder involving dopaminergic transmission, response to neuroleptic treatment, and better outcome than the negative subtype (type II), which is characterized by underlying irreversible structural abnormalities in the brain. While the Strauss et al. formulation described the processes of schizophrenia, the Crow hypothesis helped to root the thinking about positive and negative symptoms into relationships between brain function and behavior. Andreasen and Olsen[3] suggested that positive and negative symptoms were dichotomously distributed in schizophrenic patients and proposed that the presence of positive or negative symptoms defined 2 distinct types of patients with schizophrenia (i.e., positive symptom patients and negative symptom patients). In a subsequent study[4] it was found that the largest majority of patients with schizophrenia were classified as mixed, rendering the categorizing of patients as having either positive or negative schizophrenia to be of limited utility.

Carpenter et al.[5] stressed that negative symptoms in schizophrenia do not constitute a homogenous entity and emphasized the need to differentiate between primary and secondary negative symptoms. "Primary" negative symptoms were defined as those intrinsic to schizophrenia, while "secondary" negative symptoms were defined as those occurring in association with (and presumed to be secondary to) positive psychotic symptoms, depression, extrapyramidal side effects of antipsychotic medications, lack of stimulation in the environment, etc. Carpenter et al.[6] subsequently refined this concept and proposed that schizophrenia be subclassified into deficit and nondeficit schizophrenia on the basis of the presence or absence of primary enduring negative symptoms, respectively.

Attempts to clarify the domains of schizophrenia gained importance when the atypical antipsychotics joined the armamentarium of schizophrenia treatments. While clear evidence exists that the atypical agents clozapine,[7,8] risperidone,[9] olanzapine,[10] quetiapine,[11] and ziprasidone[12] are superior to the conventional antipsychotics for the treatment of negative symptoms, further research is needed to establish and document the usefulness of atypical antipsychotics for enduring negative symptoms and to

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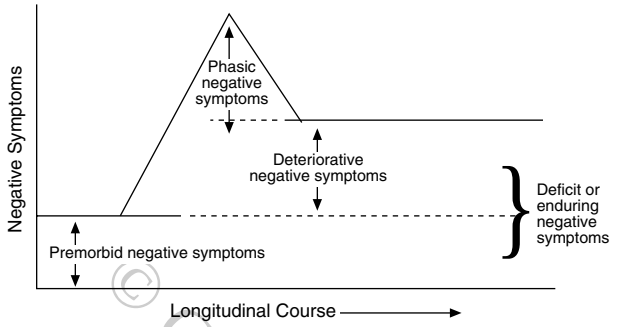
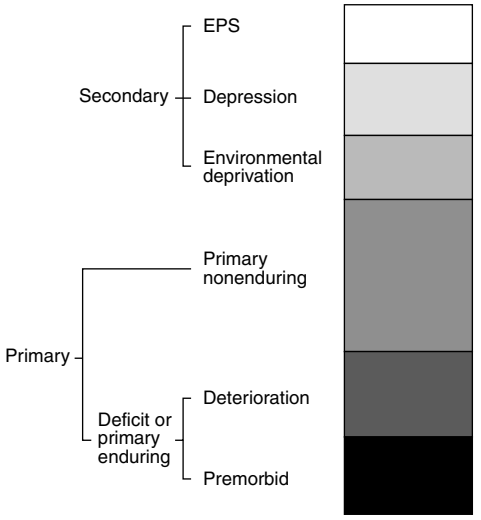
Figure 1. Longitudinal Course of Negative Symptoms*



*Data from reference 20.

Figure 2. Components of Negative Symptoms*



*Data from reference 20.

separate the direct versus the indirect effects of specific agents on the negative symptoms of schizophrenia.

DEFINITION OF NEGATIVE SYMPTOMS

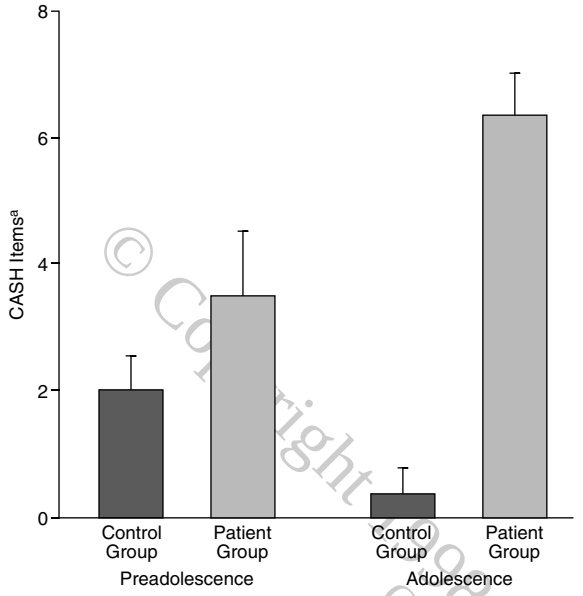
One basic component of schizophrenia research is the rating scale. Several tools—e.g., the Scale for the Assessment of Negative Symptoms (SANS)[13] and the Scale for the Assessment of Positive Symptoms (SAPS),[14] which were developed by Andreasen et al. in 1982, and the Positive and Negative Syndrome Scale (PANSS), which was created by Kay et al.[15] in 1987—have been used extensively to refine the definition of the dimensions of schizophrenia. These scales assess performance in such relevant areas as perception, inference, language, behavioral monitoring and activity, emotional expression, conceptual and verbal fluency, pleasure drives, volition, and attention. The original SAPS and SANS identified symptoms that correspond to the negative and positive domains only. The PANSS added the domain of general psychopathology to rate symptoms that are not clearly linked to either the positive or negative construct but are characteristic of patients with schizophrenia. Andreasen et al.[16] later divided the positive symptoms into 2 dimensions: the psychosis dimension consists mainly of delusions and hallucinations, and the disorganization dimension is composed of disorganized speech and behavior and inappropriate affect. The SANS subscales rate affective flattening, alogia, avolition/apathy, anhedonia/asociality, and impaired attention. The PANSS assesses blunted affect, emotional withdrawal, poor rapport, passive/apathetic social withdrawal, difficulty in abstract thinking, lack of spontaneity and flow of conversation, and stereotyped thinking (including poverty of speech).

Carpenter et al.[6] distinguished between what he termed deficit symptoms and transient negative symptoms that are secondary to other factors such as depression, environmental deprivation, and extrapyramidal symptoms (EPS). In a longitudinal study (mean duration of participation = 29 months), the authors determined that a subgroup (N = 15) of 103 patients had deficit symptoms. The authors proposed diagnostic criteria for what they labeled the deficit syndrome of schizophrenia. These criteria included restricted affect, diminished emotional range, poverty of speech with curbing of interest and decrease in curiosity, diminished sense of purpose, and diminished social drive; at least 2 of these symptoms must always have been present, even during periods of clinical stability, for the previous 12 months.

The deficit-nondeficit dichotomy idea has been very influential over the past decade. However, the ability to make primary-secondary negative symptom distinctions reliably is questionable.[17] Furthermore, deficit is probably more appropriately described in terms of degree or severity rather than as being present or absent; a dimensional rather than dichotomous view of deficit may be more valid.[18,19] A longitudinal perspective of negative symptoms is necessary (Figure 1).[20] Components of negative symptoms (Figure 2)[20] thus include (1) deficit or primary enduring negative symptoms, which appear in patients with premorbid illness and are also associated with deterioration from the disease process; (2) primary nonenduring negative symptoms that wax and wane; and (3) secondary negative symptoms that are linked with positive symptoms, EPS, depression, and environmental deprivation.

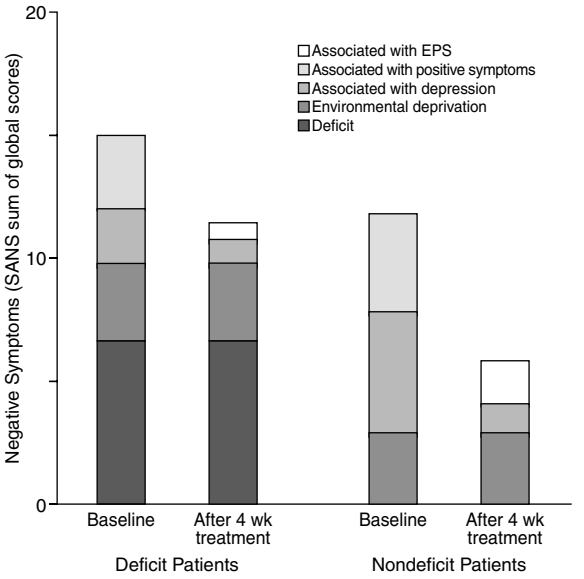
Treatment often can improve one component of schizophrenia and worsen another. For example, the net benefit of a conventional neuroleptic is dependent on the improvement in those primary negative symptoms that are associated with positive symptoms versus the worsening in those symptoms associated with EPS. The atypical antipsychotics have generally been found to be more effective than conventional neuroleptics against the total negative

Figure 3. Increase in Negative Symptoms From Preadolescence to Adolescence*



*From DL Garver, TR Nair, JD Christensen, et al, unpublished data, 1997. Abbreviation: CASH = Comprehensive Assessment of Symptoms and History. The modified Phillips scale from the CASH, indicating social withdrawal and impairment of interests and peer relationships, was used.
[a]$p < .05$ between patient groups in preadolescence and adolescence.

Figure 4. Changes in SANS Scores Associated With Components of Negative Symptoms in Deficit and Nondeficit Patients*



*Data from reference 22.

symptomatology, but their effects on each specific component are still under study. For example, what percentage of the effect of the atypical antipsychotics on negative symptoms can be attributed to a decrease in primary negative symptoms and what percentage to improvements in depression- or EPS-associated negative symptoms? Do deficit symptoms respond to atypical antipsychotics?

In many patients, the presence of negative symptoms can be traced back to before the development of frank psychotic symptoms. Using a Phillips Scale as modified in the Comprehensive Assessment of Symptoms and History (CASH),[21] Garver et al. (D.L. Garver, T.R. Nair, J.D. Christensen, et al., unpublished data, 1997) found that scores representing social withdrawal and impairment of peer relationships increased significantly ($p < .05$) between preadolescence and adolescence in a subgroup of patients who later developed florid schizophrenic psychosis (Figure 3). Following 8 weeks of treatment of the overt psychosis, this subgroup of patients with schizophrenia continued to demonstrate marked negative symptoms. It appeared that in these patients a "trait-like" pattern that emerged during adolescence also persisted throughout adult life despite treatment.

Although Carpenter et al.[6] suggested that the deficit syndrome was unlikely to respond to antipsychotic treatment, there is some evidence that primary enduring symptoms improve after treatment with atypical antipsychotics. Miller et al.[7] found that core negative symptoms measured on the SANS responded to 6 weeks of clozapine treatment in a group of treatment-refractory schizophrenic patients ($N = 29$). The improvement was correlated with improvement in disorganization but not in psychotic symptoms or changes in EPS or depression, which indicated that a portion of the effect of clozapine on enduring negative symptoms may be mediated through a direct effect on the underlying pathophysiology of schizophrenia that is associated with negative symptoms. On the other hand, Breier et al.[8] reported that negative symptoms responded to clozapine treatment in patients without, but not with, deficit schizophrenia. The authors suggested that the effects of clozapine are more marked on secondary than on primary negative symptoms.

While the deficit syndrome, which develops in approximately 5% to 25% of patients with schizophrenia, may be difficult to treat, primary and secondary negative symptoms—e.g., anhedonia, flat affect, anergia, lack of spontaneity—often respond to antipsychotics. Tandon et al.[22] investigated SANS scores in a group of patients with deficit and nondeficit symptoms at baseline and after 4 weeks of treatment. Although the mean global SANS score declined in both groups, the decrease was larger in the patients with nondeficit symptoms. The improvement in negative symptoms was associated with a decrease in positive symptoms (Figure 4).[22] Clinicians often find that negative symptoms improve whether the patient is classified as having deficit or nondeficit schizophrenia, particularly since patients with enduring symptoms are also likely

to have primary and secondary negative symptoms. Atypical antipsychotics are effective against negative symptoms, but future studies are needed to ascertain whether the benefits are due to a reduction in deficit symptoms or to an effect on primary or secondary negative symptoms.

The short duration of a clinical trial may skew findings about negative symptoms, which are affected by the patients' interactions with their environment. Much of the improvement in negative symptoms found during phase 2 and 3 clinical trials, which generally last 6 to 8 weeks, may be secondary to a decrease in positive symptoms or EPS. Before changes in motivation can be detected, patients must be given an opportunity to do something interesting. Long-term studies that combine pharmacologic treatment with intensive rehabilitation or social skills training are needed to assess the direct effects of the atypical antipsychotics on enduring negative symptoms. In addition, the interaction taking place between the patient and the clinician is more integral to the reliable assessment of negative, as opposed to positive, symptoms; these interactions are particularly critical in determining the degree of apathy and anhedonia. Thus, it is important to consider the results on all the negative symptom rating scales used in a particular clinical trial when comparing the effects of the atypical antipsychotics on negative symptoms. For example, in a head-to-head comparison of olanzapine and risperidone,[23] scores on only 1 (the SANS summary score) of 4 negative symptoms assessments that were used showed a significant ($p = .02$) benefit for olanzapine. The geographic region by therapy interactions were also significant ($p = .04$) for the SANS summary score, which raises questions about interrater reliability for negative symptom scores and improvement in SANS summary scores between sites in that study.

Distinguishing between core enduring and nonenduring primary negative symptoms is a diagnostic challenge. Certain schizophrenic patients, whose negative symptoms are enduring and unrelated to depression, EPS, or lack of environmental stimulation, may respond better to 1 atypical agent than another, but persuasive data are lacking. Assessing drug effects on negative symptoms is complicated by the fact that many of the reported trials included patients with both positive and negative symptoms during an acute episode of schizophrenia instead of limiting the sample to those with only deficit or primary enduring symptoms. The overlap of negative symptoms, EPS, and depression complicates the assessment of different pharmacologic treatments for negative symptoms. If 1 agent is found to be more effective than another in treating negative symptoms, this beneficial effect might be produced directly through greater efficacy on negative symptoms or indirectly because of improvements in positive symptoms, depression, EPS such as akinesia, or sedation. One population that may provide information consists of untreated patients with substantial enduring negative symptoms but minimal positive symptoms, depression, and EPS. However, such patients are difficult to identify, particularly since EPS often mimic negative symptoms.[17,18]

ATYPICAL ANTIPSYCHOTICS AND NEGATIVE SYMPTOMS

It should be emphasized that although negative symptoms were traditionally considered to be poorly responsive to neuroleptic treatment, they do partially respond to treatment with conventional antipsychotics.[24–27] Atypical antipsychotics appear to be more effective than conventional neuroleptics, however.[22,28] Clinical trials of the atypical antipsychotics have provided clear evidence that they are effective for the treatment of negative symptoms.[11,29–38] In addition, several investigations have been directed specifically at the effects of these agents on negative symptoms. Tandon and colleagues[19] observed a significant reduction in the severity of negative symptoms during clozapine treatment in a sample of 40 neuroleptic-refractory schizophrenic patients; improvement in negative symptoms occurred concomitantly with improvement in positive symptoms. The authors concluded that clozapine's greater efficacy on negative symptoms may be related to its lower propensity for causing EPS. Breier et al.[8] found that clozapine was superior to haloperidol for treating negative symptoms in outpatients with nondeficit chronic schizophrenia. This study was notable because most samples in clozapine studies have been composed of severely ill inpatients. A multiple regression analysis was used in a study of the effects of clozapine on negative symptoms in treatment-refractory schizophrenic patients.[7] The authors reported that improvement in negative symptoms was correlated with improvement in disorganization but not psychotic symptoms, depression, or EPS and suggested that at least a portion of the effect of clozapine on core negative symptoms is mediated through a direct effect on the underlying pathology of schizophrenia associated with negative symptoms. Relatively high doses of olanzapine (15–25 mg/day) were found to be useful for negative symptoms in treatment-refractory schizophrenics ($N = 25$).[39] The patients showed statistically significant ($p < .05$) improvement from baseline to 6 weeks.

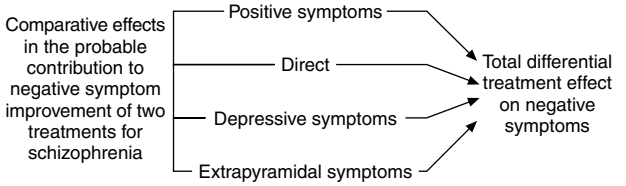
Several investigations of the usefulness of risperidone for negative symptoms have been published. In a meta-analysis of the pooled results from 6 double-blind trials involving 675 patients, Carman et al.[40] found that patients receiving risperidone, at doses ranging from 4 to 8 mg/day, had a significantly ($p < .004$) higher negative symptom response rate, defined as the percentage of patients with a 20% or more reduction in scores on the PANSS negative subscale, than patients receiving the active controls haloperidol, perphenazine, or zuclopenthixol. Most patients in these studies had been ill for at least 2 years, had been hospitalized several times, and had responded poorly to

conventional neuroleptics. The results suggest that more risperidone-treated patients than neuroleptic-treated patients will show improvement in negative symptoms. Schooler[41] evaluated the data base of the North American risperidone trials (N = 513) and reported that risperidone doses of 6, 10, and 16 mg/day—unlike 20 mg/day of haloperidol—were effective against negative symptoms. Schooler concluded that 6 mg/day of risperidone is probably the most effective dose. Marder et al.,[9] however, in a factor analysis of the same data base, reported that, even at the lowest dose of 2 mg/day, risperidone was significantly ($p \leq .05$) superior to haloperidol in reducing negative symptoms. On the other hand, Smith et al.[42] failed to find substantial reduction in negative symptom scores in a group (N = 25) of hospitalized, chronically ill schizophrenics who had not responded to conventional neuroleptics. They found that higher negative symptom scores at baseline correlated with poorer response to 6 to 16 mg/day of risperidone. However, the authors noted that a number of patients in the study may have fit the deficit syndrome criteria of Carpenter et al.[6] Rossi et al.[43] evaluated the effects of risperidone on both negative symptoms and cognitive deficit in 25 patients with schizophrenia. Baseline scores on the PANSS, the Wisconsin Card Sort Test (WCST), and 2 Wechsler Adult Intelligence Scale subtests were compared with scores at the end of 4 weeks of risperidone treatment. Negative symptoms ($p < .001$) and scores on the WCST ($p < .05$) improved significantly from baseline to week 4.

PATH ANALYSIS

A European working group, composed of clinicians and researchers from university hospitals and the pharmaceutical industry, has established methodological guidelines for the evaluation of drug effects in negative symptoms.[44] They proposed the use of statistical analyses that investigated the interaction of negative symptoms with positive symptoms, depression, and EPS. Möller et al.[45] followed their suggestion and used a path-analytical approach to differentiate between direct and indirect drug effects on negative symptoms in a reevaluation of the North American risperidone study. Similarly, Tollefson et al.[10] used path analysis to reevaluate a portion of the olanzapine data base. Path analysis is a statistical tool—a multivariate approach—that has been used by social scientists for more than 30 years to investigate causal relationships by testing a covariance structural model, using confirmatory factor analysis. The covariance structural model consists of 2 steps. The first step is development of a confirmatory factor model, which needs to be specified in terms of (1) the number of common factors; (2) the number of observed variables; (3) the variances and covariances observed among the common factors; (4) the relationships among observed variances and latent factors; (5) the relationships among the unique factors and observed variables; (6) the variances and covariances among the unique factors. This represents the measurement component of the covariance structure model, which is used to relate observed variables to factors. The second step is developing a structural equation model by placing these factors in the form of a structural regression equation. This involves specifying a set of structural relations among these factors, followed by estimation of structural coefficients and parameters.

Figure 5. A Model of Path Analysis for Negative Symptoms*



*Reprinted from reference 10, with permission.

For negative symptoms, the variables include the drug's direct effects on negative symptoms as well as effects related to improvement in positive symptoms, depressive symptoms, and EPS (Figure 5).[10] Changes on rating scale scores during treatment that can be linked to improvements in positive symptoms, depression, and EPS are subtracted, and the remainder is viewed as a direct effect on primary enduring negative symptoms. While the term *direct effect* is generally used, essentially the numerical remainder represents a residual, unexplained variance with regard to changes in scores on negative symptom rating scales that cannot be attributed to improvement in other factors, which is a major limitation of the technique. The variance may be due to measurement problems or to experimental errors. Additional models are needed before the unexplained variance can be correctly defined as a direct effect on primary, enduring negative symptoms.

The assumptions of path analysis are that no relevant variables are omitted in the model, that measures of variables are clearly independent and unconfounded, that there are no interactions between the predictors of shift in negative symptoms, and that all relationships between the predictors of shift and change in negative symptoms are linear. A limitation of applying path analysis to negative symptoms is that some of these assumptions may be questionable. Factors besides the effects of an agent on positive symptoms, depression, and EPS may be relevant to the study of effects on negative symptoms.

Path analysis has been applied to explore the effects of 6 mg/day of risperidone versus 20 mg/day of haloperidol. Möller et al.[45] used the data from 523 patients with chronic schizophrenia who participated in the North American risperidone trials.[31,32] Regression analyses in the total sample and within treatment groups confirmed a strong relationship between improvement in negative symptoms and 2

other variables studied, positive and extrapyramidal symptoms. Depressive symptoms did not contribute statistically to the results. Path analysis showed that the greater mean change ($p < .05$) in negative symptoms during risperidone—compared with haloperidol—treatment could not be explained simply by its greater effect on secondary negative symptoms associated with positive or extrapyramidal symptoms. The authors later expanded their model[46] and concluded that an estimate of direct and indirect treatment effects can be obtained with this approach. However, what was termed a direct effect could be argued to be an unexplained variance in the scores.

Tollefson et al.[10] also used a path analytical approach to evaluate data from a comparison of 3 dose ranges of olanzapine versus 10 to 20 mg/day of haloperidol in 335 inpatients with schizophrenia who participated in the olanzapine clinical trials.[47] The mean ± SD low dose of olanzapine was 5 ± 2.5 mg/day, the medium dose was 10 ± 2.5 mg/day, and the high dose was 15 ± 2.5 mg/day. First, improvement in negative symptoms was correlated with improvement in positive, depressive, and extrapyramidal symptoms. Then, path analysis of last-observation-carried-forward endpoint change in SANS summary scores indicated that treatment with high-dose olanzapine was associated with a response superior to the response for placebo after adjustment for change in positive, depressive, and extrapyramidal symptoms. The indirect benefit of improved positive symptom control was a major contributor to negative symptom improvement; the indirect benefits of lower levels of depression and EPS contributed minimally. The superior effect on SANS summary scores of high-dose olanzapine was attributed primarily to a direct effect of treatment on presumably primary negative symptoms. The authors concluded that the path analytic method revealed both direct and indirect improvements in negative symptoms during olanzapine treatment. However, it can be argued that what was termed a direct effect was, in fact, an unexplained variance in the scores.

In general, path analysis is a useful technique for interpreting changes in core negative symptoms, but there are limitations in applying this approach to existing data on the atypical antipsychotics because all the assumptions that are required for path analysis may not be completely satisfied. However, distinguishing specific effects of atypical agents on various components of negative symptoms is more a research than a clinical problem, and evidence is growing that these newer antipsychotics are more effective than conventional agents for treating the total negative symptomatology and reducing the disability and impaired social function that usually accompany schizophrenia.

CONCLUSION

Negative symptoms are a dimension of schizophrenia that have historically been difficult to treat, particularly in the subgroup of patients with primary enduring or deficit symptoms. Many of these patients are chronically ill and hospitalized. There is preliminary evidence that core negative symptoms in some patients may respond to treatment with an atypical antipsychotic.[7] In most patients, however, negative symptoms are associated with positive symptoms or are secondary to EPS or depression. One of the advantages of the atypical agents is their clear benefit for negative symptoms in general. Future studies should attempt to identify which components of negative symptoms may respond preferentially to one or another of the atypical antipsychotics.

Drug names: clozapine (Clozaril), haloperidol (Haldol and generic brands), olanzapine (Zyprexa), perphenazine (Trilafon), quetiapine (Seroquel), risperidone (Risperdal).

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DISCLOSURE OF OFF-LABEL USAGE

The authors of this article have determined that, to the best of their clinical estimations, no investigational or off-label information about pharmaceutical agents has been presented that is outside Food and Drug Administration–approved labeling.