Notice of correction 6/9/2011: *The key to Figure 1 on page 283 has been corrected—the gray square represents "No negative symptom" and the black square represents "At least one negative symptom."*

Prevalence of Negative Symptoms in Outpatients With Schizophrenia Spectrum Disorders Treated With Antipsychotics in Routine Clinical Practice: Findings From the CLAMORS Study

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Objective: To analyze the prevalence of negative symptoms in antipsychotic-treated outpatients with schizophrenia spectrum disorders.

Method: A cross-sectional, retrospective multicenter study was carried out between May 2004 and April 2005 in 1,704 adult psychiatric outpatients meeting *DSM-IV* criteria for schizophrenia, schizophreniform, or schizoaffective disorder. We used 5 items of the Positive and Negative Syndrome Scale (PANSS) negative symptoms subscale to individually determine the presence of a negative symptom when the score on the item was > 3. Primary negative symptoms were considered present when patients fulfilled all of the following: > 3 score on the corresponding item; < 3 score on any positive item; no extrapyramidal symptoms; ≤ 3 score on anxiety and depression items; dose of haloperidol, when applicable, ≤ 15 mg/d; and no antiparkinsonian treatment.

Results: A total of 1,452 evaluable patients (863 men, 60.9%), 40.7 ± 12.2 (mean ± SD) years of age, were included. One or more negative symptoms were present in 57.6% of patients, with primary negative symptoms in 12.9% of subjects. The most frequent negative symptom items were social withdrawal (45.8%), emotional withdrawal (39.1%), poor rapport (35.8%), and blunted affect (33.1%). Negative symptoms (1-blunted affect, 2-emotional withdrawal, 3-poor rapport, 4-social withdrawal, 5-verbal fluency) were most associated with maleness (symptom 4); age > 40/45 years (men/women; symptoms 1,2,4); single/unmarried status (symptoms 2–4); unemployment (symptoms 3,4); higher score on the Clinical Global Impressions (CGI) scale and PANSS total score (symptoms 1–5); lower score on the PANSS positive symptoms subscale (symptoms 1,3); more than 52 weeks of treatment (symptoms 1–3,5); and high antipsychotic dose (symptom 2).

Conclusions: The prevalence of negative symptoms in patients with schizophrenia spectrum disorders treated with antipsychotics in routine clinical practice not only is still considerably high but also seems to be related to poorer functioning, unemployment, greater severity, and less positive symptomatology and higher antipsychotic dose.

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For a long time, research efforts in schizophrenia were generally directed toward improvement of positive symptoms, those that are more directly related to the safety of the patient and those around him or her. However, negative symptoms are undoubtedly critical to a patient's quality of life and particularly crucial to his or her social life. The psychiatric scientific community is now focusing efforts on improving knowledge and appropriate management of these types of symptoms. Negative symptoms are intrinsic to the pathology of schizophrenia and are associated with significant deficits in motivation, verbal and nonverbal communication, affect, and cognitive and social functioning,[1] which, in turn, contribute to poor outcome and functioning in schizophrenia.[2,3] The underlying mechanisms of negative symptoms are not well understood, which complicates the search for a therapeutic arsenal with a known mechanism of action. Investigation of the different entities characterized by negative symptoms, such as persistent primary negative symptoms, in addition to enhancing our understanding of the pathophysiology of this core dimension of the disease, may help to unravel the psychopathologic and biologic heterogeneity of schizophrenia.[4]

Persistence of negative symptoms has received recent attention in terms of developing clinical trials to assess different mechanisms of action to treat a dimension of the disease.[5,6] One of the major problems when assessing drug efficacy in negative symptoms is the lack of distinction between primary and secondary negative symptoms.[5,7] On the basis of some studies, the scientific literature has been claiming that second generation antipsychotics (SGAs) are more effective than conventional antipsychotics in the treatment of negative symptoms.[8] However, the initial optimism that SGAs would prove to be powerful agents to improve negative symptoms has given way to relative pessimism.[4,9–11] Although SGAs seem to be effective for secondary negative symptoms, they

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have shown no efficacy for primary negative symptoms, and new mechanisms of drug action appear to be required to address this aspect of the disease syndrome.[12] Therefore, we expect a high prevalence of negative symptoms, even in patients treated with SGAs.

This article examines the prevalence of negative symptoms within the framework of a large cross-sectional study assessing cardiovascular, lipid, and metabolic outcomes in patients with schizophrenia, schizophreniform, or schizoaffective disorders treated with the antipsychotics most commonly used in daily practice, most of them SGAs (Cardiovascular, Lipid, and Metabolic Outcomes Research in Schizophrenia [CLAMORS] Study[13]).

METHOD

Investigators, Patients, and Design

The methods of the CLAMORS study have been published in detail elsewhere.[13] Briefly, this was a cross-sectional, retrospective, multicenter study enrolling consecutive adult outpatients of both sexes, ages 18–74 years, with a diagnosis of schizophrenia, schizophreniform, or schizoaffective disorder according to the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (*DSM-IV*) classification, and who received oral antipsychotic treatment for at least 12 weeks with any 1 of the following antipsychotic drugs: risperidone, olanzapine, quetiapine, ziprasidone, amisulpride, or haloperidol. Patients receiving treatment with 2 or more antipsychotics at the time of evaluation and/or those admitted to the hospital were excluded. An accredited Clinical Research Ethics Committee from 1 of the participating centers approved the study protocol. Written informed consent was obtained from all patients prior to enrollment.

According to the study protocol, each participating center was to recruit at least the first 12 consecutive patients meeting the selection criteria. The first 2 patients receiving treatment with each of the most commonly used antipsychotic drugs in our health care setting (risperidone, olanzapine, quetiapine, ziprasidone, amisulpride, and haloperidol) were consecutively invited to participate in the study.

Variables and Measurement Instruments

Prevalence of negative symptoms. Clinical severity and, particularly, the prevalence of negative symptoms were determined using the schizophrenia Positive and Negative Syndrome Scale (PANSS).[14,15] Negative symptoms were assessed using 5 items of the PANSS negative symptoms subscale[16]: 1—blunted affect; 2—emotional withdrawal; 3—poor rapport; 4—social withdrawal; and 5—verbal fluency. Presence of a *negative symptom* was defined as severity score > 3 (on a response scale ranging from 1—absence of symptom to 7—extremely severe symptom). In addition to a severity score > 3, a *primary negative symptom* was considered present when patients fulfilled all of the following criteria: absence of positive symptoms (defined as a score < 3 for any positive symptom); absence of extrapyramidal symptoms (EPS) as assessed by psychiatrist interview; items 2 (anxiety) and 6 (depression) on the General Psychopathology PANSS subscale ≤ 3; dose of haloperidol not higher than 15 mg/d; and no antiparkinsonian treatment. In addition to the presence of negative symptoms, an overall negative symptoms PANSS subscore was calculated by the sum of the scores of these 5 items. The decision to use 5 items of the PANSS negative symptoms subscale was taken because 2 of the symptoms on the original 7-item subscale—difficulty in abstract thinking and stereotyped thinking—are consistently found not to be part of a negative symptoms factor.[16]

In order to ensure the accuracy of the data, psychiatrists were trained in the use of the PANSS scale. Accordingly, the study patient recruitment process began with clear instructions on the diagnostic criteria for the different schizophrenia spectrum disorders. This was done for all participating psychiatrists. These instructions dealt mainly with the standard psychiatric interview of the *DSM-IV* diagnostic criteria (anamnesis and exploration of mental condition), the PANSS scale, and the different study inclusion/exclusion criteria, along with other aspects of the study. Also, recruitment and diagnosis was carried out only by experienced psychiatrists belonging to the Spanish National Health System, in which all patients were followed. In Spain, National Health System positions require passing a high-level standard examination, which ensures that personnel have uniform expertise. In addition, all the physician participants in the CLAMORS study fulfilled the following criteria: certified psychiatrist working in out-patient mental health center facility for 3–4 years with previous experience in trials in the field of schizophrenia disorders.

Other measurements. Sociodemographic and clinical data were recorded including marital status, occupational status, body mass index (BMI), disease duration, and number of previous hospital admissions. These data were collected by the psychiatrists from the medical record (BMI, disease duration, and number of previous hospital admissions) or by patient interview (marital status, occupational status). Clinical severity was also determined using the Clinical Global Impressions-Severity scale (CGI-S).[17]

Statistical Analysis

A safety-only sample of evaluable patients was used for the analyses, including all patients receiving 1 of the 6 aforementioned antipsychotic drugs. Frequencies and percentages were used for qualitative variables and to estimate the prevalence of overall and primary negative symptoms. The mean, standard deviation (SD), and range were calculated for quantitative variables.

Sociodemographic and clinical characteristics of patients were compared by sex using the χ^2 test and the Mann-Whitney *U* test. Prevalence of negative symptoms was compared by diagnosis of psychotic disorder, employment

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Table 1. Sociodemographic and Clinical Characteristics of Patients by Sex and Overall[a]

	Male (n = 863)	Female (n = 555)	Total (n = 1,452)	*P* Value
Sex[b]	—	—	1,418 (100.00)	—
Male	—	—	863 (60.9)	—
Female	—	—	555 (39.1)	—
Age, mean (SD), y[b]	39.3 (11.6)	42.5 (12.6)	40.7 (12.2)	< .001[d]
Marital status[b]	856 (100.0)	550 (100.0)	1,431 (100.0)	< .001[e]
Single	653 (76.3)	288 (52.4)	958 (66.9)	
Married	145 (16.9)	172 (31.3)	324 (22.6)	
Divorced/separated	49 (5.7)	61 (11.1)	111 (7.8)	
Widowed	9 (1.1)	29 (5.3)	38 (2.7)	
Occupational status[b]	845 (100.0)	534 (100.0)	1,403 (100.0)	< .001[e]
Active	176 (20.8)	99 (18.5)	278 (19.8)	
Unemployed	155 (18.3)	79 (14.8)	238 (17.0)	
Sick leave	62 (7.3)	23 (4.3)	86 (6.1)	
Disability pension	411 (48.6)	243 (45.5)	666 (47.5)	
Others	41 (4.9)	90 (16.9)	135 (9.6)	
Body mass index[b]	855 (100.0)	551 (100.0)	1,432 (100.0)	.001[e]
Normal (< 25)	221 (25.8)	176 (31.9)	402 (28.1)	
Overweight (≥ 25–< 30)	385 (45.0)	195 (35.4)	589 (41.1)	
Obese (≥ 30)	249 (29.1)	180 (32.7)	441 (30.8)	
Disease duration, mean (SD), y[b]	14.7 (10.4)	16.6 (11.3)	15.5 (10.8)	.002[d]
No. of hospital admissions[c]	2.6 (2.9)	2.8 (3.1)	2.6 (3.0)	.335[d]

[a]Values are n (%) unless otherwise indicated.
[b]Some patients failed to provide information.
[c]Due to the psychotic disorder.
[d]Mann-Whitney *U* test.
[e]χ^2 test.

status, dose, and antipsychotic treatment using the χ^2 test. Mean negative symptoms scores were compared by diagnosis of psychotic disorder using an analysis of variance (ANOVA). Bonferroni corrections were used for all multiple comparisons of negative symptoms. Logistic regression analyses were used to determine those factors associated with the presence of negative symptoms, including sex, age, marital status, work status, BMI, treatment time, type and dose of antipsychotic treatment, CGI severity, and total and positive PANSS scores, as potential factors associated with the presence of negative symptoms.

The *P* values correspond to the statistical significance of 2-tailed tests. A *P* value ≤ .05 was considered statistically significant. The statistical package SPSS version 13.0.1 (SPSS Inc, Chicago, Illinois) was used throughout.

RESULTS

Patients and Distribution by Groups

A total of 1,704 patients were recruited by 117 psychiatrists at 91 different outpatient centers. Of these, 252 (14.8%) who failed to meet the study selection criteria were excluded. The main reason for exclusion (202 patients, 11.9%) was current treatment with any antipsychotic for less than 12 weeks. Thus, 1,452 patients were considered evaluable.

Sociodemographic, Clinical, and Lifestyle Characteristics

Table 1 shows the main sociodemographic and general clinical characteristics of the patients. The diagnosis was schizophrenia in 1,108 patients (77.1%), schizophreniform disorder in 61 patients (4.2%), and schizoaffective disorder in 268 patients (18.6%) of the 1,437 patients with these data available. The mean duration (SD) of the psychotic disorder was 15.5 years (10.8 years), with a mean of 2.6 (3.0) hospital admissions attributable to the psychotic disorder since onset of the disease. The current treatment had been initiated due to a change in the previous antipsychotic therapy in 727 patients (51.7%), due to an exacerbation of symptoms in 508 (36.1%), and to manage a first episode in 171 patients (12.2%) of the 1,406 patients with these data available. The type of antipsychotic drug was distributed as follows: amisulpride (n = 213, 14.7%), haloperidol (n = 202, 13.9%), olanzapine (n = 306, 21.1%), quetiapine (n = 218, 15.0%), risperidone (n = 268, 18.5%), and ziprasidone (n = 240, 16.5%). The mean duration of antipsychotic treatment was 136.4 weeks (210.1 weeks). Most of the patients enrolled in the study did not have healthy lifestyle habits: few patients were on a diet of some kind (16.5%), controlling calorie or salt intake (21.2% and 14.3%), avoiding saturated fats/cholesterol (23.8%), or eating a high fiber diet (26.2%).

Prevalence of Negative Symptoms

At least 1 negative symptom was present in 57.6% of patients, and all negative symptoms were present in 17.8% of subjects only. As shown in Table 2, the most frequent negative symptoms were social withdrawal (45.8% of cases) and emotional withdrawal (39.1%). The mean (SD) scores on social (3.2 [1.4]) and emotional (3.1 [1.2]) withdrawal items were significantly higher ($P < .05$) than the corresponding values for the rest of the negative items evaluated: 2.9 (1.2), 2.9 (1.3), and 2.8 (1.3) for blunted affect, poor rapport, and verbal fluency, respectively. One or more primary negative symptoms were present in 12.9% of subjects, with social withdrawal (9.4%), poor rapport (7.2%), and emotional

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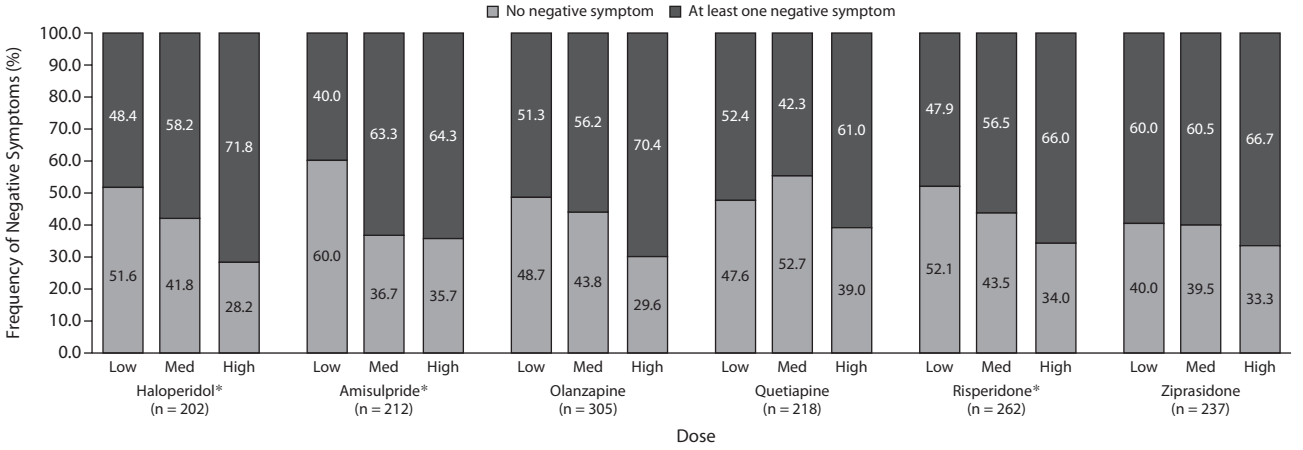
Table 2. Presence of Negative Symptoms (PANSS-N), Symptom-by-Symptom and Overall, for the Total Sample and by Subtype of Psychotic Disorder

Negative Symptoms (PANSS-N)	Total n (%[a])	Schizophrenia n (%[a])	Schizophreniform Disorder n (%[a])	Schizoaffective Disorder n (%[a])	*P* Value[b]
Total no. of patients	1,452 (100.0)	1,108 (100.0)	61 (100.0)	268 (100.0)	—
1. Blunted affect	480 (33.1)	401 (36.2)	14 (23.0)	59 (22.0)	< .05
2. Emotional withdrawal	566 (39.1)	469 (42.3)	17 (27.9)	72 (26.9)	< .05
3. Poor rapport	518 (35.8)	430 (38.8)	15 (24.6)	65 (24.3)	< .05
4. Social withdrawal	663 (45.8)	535 (48.3)	24 (39.3)	95 (35.4)	< .05
5. Verbal fluency	457 (31.5)	374 (33.8)	14 (23.0)	63 (23.5)	< .05
At least 1 negative symptom	836 (57.6)	670 (60.5)	31 (50.8)	125 (46.6)	< .0001
All negative symptoms	258 (17.8)	217 (19.3)	8 (13.1)	28 (10.4)	< .0001

[a]Percentages calculated with respect to the total evaluable patients with data available for each subtype of diagnosis.
[b]Degree of statistically significant differences were found by subtype of schizophrenia for each symptom and all negative symptoms (χ^2 test: $P < .05$).
Abbreviation: PANSS-N = Positive and Negative Syndrome Scale-negative symptoms subscale.

Figure 1. Presence of Negative Symptoms (PANSS-N) by Dose and Antipsychotic Treatment[a]



[a]Dose groups of patients were defined as following: ≤ 5 (low), > 5 and ≤ 10 (medium), > 10 (high) mg/d for haloperidol; ≤ 200 (low), > 200 and ≤ 600 (medium), > 600 (high) mg/d for amisulpride; ≤ 10 (low), > 10 and ≤ 20 (medium), > 20 (high) mg/d for olanzapine; ≤ 300 (low), > 300 and ≤ 500 (medium), > 500 (high) mg/d for quetiapine; ≤ 3 (low), > 3 and ≤ 6 (medium), > 6 (high) mg/d for risperidone; ≤ 80 (low), > 80 and ≤ 160 (medium), > 160 (high) mg/d for ziprasidone.
*Statistically significant differences between patients with low, medium, and high antipsychotic dose and percentage of presence of negative symptoms (χ^2 test: $P < .05$).
Abbreviation: PANSS-N = Positive and Negative Syndrome Scale-negative symptoms subscale.

withdrawal (6.9%) being the most frequent primary negative symptoms, followed by blunted affect in 6.0% and verbal fluency in 5.9% of subjects.

Mean scores for each negative symptom and the overall PANSS negative symptoms subscore were compared by diagnosis of psychotic disorder. This analysis found higher average scores for schizophrenia (mean = 20.9 [SD = 8.0]) than for schizophreniform (mean = 17.9 [SD = 7.1]) and schizoaffective (mean = 17.8 [SD = 7.6]) disorders (ANOVA, $P < .05$). The presence of each negative symptom and all negative symptoms was also compared by diagnosis of psychotic disorder, and we found more patients with negative symptoms for schizophrenia than for schizophreniform and schizoaffective disorders (χ^2 test, $P < .05$, Table 2).

Negative symptoms, overall and also symptom-by-symptom, were significantly more prevalent among unemployed/inactive patients than among working patients (χ^2 test, $P < .001$, in all cases). For all negative symptom comparisons, there was a significant association with employment status; that is, a higher level of negative symptoms was related to being unemployed. Among those working, 37.8% had at least 1 negative symptom compared with 62.3% of those patients who were not working, while the largest difference was seen for social withdrawal; 23.7% of employed patients had this symptom, compared with 51.2% of those who were not working ($P < .001$). Presence of at least 1 negative symptom was statistically nondifferent between antipsychotic treatments. However, presence of at least 1 negative symptom was associated with drug doses for haloperidol, amisulpride, and risperidone, which showed significant direct linear association; the lower the dose, the lowest the prevalence (χ^2 test, $P < .05$, Figure 1).

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Table 3. Factors Associated With the Presence of Negative Symptoms, Symptom-by-Symptom and Overall[a]

	1. Blunted Affect	2. Emotional Withdrawal	3. Poor Rapport	4. Social Withdrawal	5. Verbal Fluency	At Least 1 Negative Symptom	All Negative Symptoms
Sex							
Female (protective factor)				0.697 (0.523–0.931)		0.726 (0.537–0.982)	
Age, y							
≥ 40 (men)/ ≥ 45 years (women)	1.574 (1.172–2.115)	1.659 (1.215–2.267)		1.656 (1.237–2.219)		1.732 (1.288–2.330)	
Marital status							
Not married		1.756 (1.211–2.546)	1.547 (1.091–2.194)	1.756 (1.211–2.546)			
Work status							
Unemployed/inactive			1.889 (1.214–2.940)	1.526 (1.040–2.237)			3.815 (1.862–7.816)
CGI severity							
3–4	4.848 (2.050–11.460)	2.819 (1.462–5.433)	6.490 (2.553–16.499)	4.144 (2.287–7.510)	5.251 (2.228–12.376)	5.431 (3.237–9.111)	
5–7	20.896 (8.151–53.571)	8.905 (4.161–19.056)	26.051 (9.418–72.058)	14.626 (7.061–30.295)	10.160 (4.074–25.340)	29.759 (12.492–70.893)	
PANSS total							
> median (68)	7.884 (5.601–11.099)	10.210 (7.347–14.188)	8.275 (5.923–11.561)	6.644 (4.980–8.863)	8.252 (5.873–11.595)	12.773 (9.285–17.572)	22.428 (12.533–40.132)
PANSS positive							
≥ 26 (protective factor)	0.441 (0.232–0.838)		0.373 (0.196–0.709)				
Treatment time, wk							
> 52 weeks	1.501 (1.111–2.028)	1.409 (1.039–1.910)	1.551 (1.151–2.090)		1.512 (1.136–2.014)		2.040 (1.448–2.875)

[a]All factors are measured as OR (95% CI).
Abbreviations: CGI = Clinical Global Impressions scale, OR = odds ratio, PANSS = Positive and Negative Syndrome Scale.

Factors Associated With the Presence of Negative Symptoms

Table 3 displays all the factors that were associated with the presence of negative symptoms and the corresponding odds ratio (with its 95% confidence interval) of the association for each of these factors. Presence of negative symptoms varied diversely according to sex, age, marital status, working status, overall clinical severity, general and positive symptomatology, and duration of antipsychotic treatment. Clinical severity, as assessed by CGI and PANSS total (above median value) scores, showed a significant higher association with the presence of all negative symptoms individually, and with the presence of at least 1 negative symptom. This association was more robust with increased severity of disease as perceived by the clinician on the CGI scale. More than 1-year duration of antipsychotic treatment was also significantly associated with the presence of all negative symptoms individually (except for social withdrawal) and with the presence of at least 1 negative symptom.

Social withdrawal was the only negative symptom associated with being female (protective factor). Poor rapport, social withdrawal, and presence of all negative symptoms were significantly associated with work status (unemployed/inactive). Hence, for example, presence of poor rapport increases the risk for unemployed/inactive status by a mean of 88.9%, or presence of all negative symptoms increases the risk for this same working situation to a mean of 281.5%.

DISCUSSION

In this cross-sectional study, we estimated the frequency of negative symptoms in a large cohort of subjects with schizophrenia spectrum disorders treated with the antipsychotics most frequently used in daily practice, 5 different SGAs and 1 classic antipsychotic. Even though no studies similar to this have been found in the literature review,[18] our results confirm that the prevalence of negative symptoms in patients receiving antipsychotic treatment in routine clinical practice for at least 12 weeks is considerably high, with a presence of 1 or more symptoms in 57.6% and a presence of all symptoms in 12.9% of patients. The most frequently present negative symptoms were those related to the integration of emotion and cognition: social withdrawal (45.8%), emotional withdrawal (39.1%), poor rapport (35.8%), and blunted affect (33.1%). These results are consistent with those obtained in previous studies,[11] emphasizing these abnormalities as the hallmark characteristics of schizophrenia.

Furthermore, the results of this study confirm a strong association between the presence of negative symptoms and psychosocial outcomes, such as employment status or severity of illness, which may be reflected in the day-to-day life of patients, although raters were not instructed to ignore negative symptoms when using the CGI scale and this must be considered a potential confounding factor. Our results agree with those of a previous study[19] in which negative symptoms

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and internal locus of control together accounted for 47% of the variance in occupational engagement. The results of this study also suggest that subjects with the highest positive symptoms scores (> 26) were less likely to have negative symptoms. This result may be controversial. However, in most studies, the positive correlation between positive and negative symptoms is during acute episodes. In this study, we were dealing with a stable outpatient population in which the positive correlation found in most studies with acute population may not be in place as we may be dealing with 2 types of stable patients: those with positive and those with negative residual symptoms. In that regard, some authors have supported the idea of a distinct schizophrenia subtype based on negative symptoms, as there are neurobiologic correlates of the negative symptom typology. However, these hypotheses have yielded mixed results.[2,9,20] Further research should be undertaken on the potential usefulness of clinical dimensions such as negative symptoms, which may be more informative for the clinician than the use of classic subtypes.

Our study shows that schizophrenia seems to be more associated with the presence of any negative symptom than with a diagnosis of schizophreniform or schizoaffective disorder, as has been pointed out in previous studies.[4,21,22]

Negative symptoms of schizophrenia are still considered controversial because of the difficulty defining and measuring them, and because of the higher failure rate of available therapies. It seems necessary to conduct more research on the evaluation and treatment of negative symptoms, particularly with studies of longitudinal and prospective design, which should produce additional knowledge on managing and treating patients with these types of symptoms. However, this additional research would probably benefit from additional refinement and innovation in the methodology to be used, so that better treatments may be realized.[2] In this regard, the use of mixed tools has been the subject of recent criticism, as in the case of the negative symptoms PANSS score used in the present study—it being argued that social, cognitive, and emotional measures do not interact properly.[23]

Current rating scales "capture" key domains of negative symptoms, in spite of considerable overlap between these domains. It has also been pointed out that negative symptoms can be difficult to evaluate objectively, particularly if researchers wish to balance rigorousness and brevity of assessment and ease of use.[9] Additionally, although all psychiatrists were trained in the use of the PANSS scale, due to the observational nature of the study, no interrater reliability analysis could be carried out. This lack is another limitation of this study (as it is for most studies in this field). Therefore, the proposal of new methods for measuring these symptoms more accurately but feasibly, such as the "proxy" case identification tool using standardized symptom ratings instead of the Schedule for the Deficit Syndrome,[24] which requires an independent clinical assessment, suggested by Kirkpatrick et al,[25–27] may be powerful for future research in this field.

Prevalence of negative symptoms with haloperidol, amisulpride, and risperidone was sensitive to antipsychotic dose, presenting significant dose-dependent associations (the lower the dose, the lower the prevalence of negative symptoms). This result is controversial when compared with previous studies.[28] However, the findings in the study relative to patients treated with haloperidol, amisulpride, or risperidone for at least 12 weeks might indicate that higher doses of selective D_2 antagonists may worsen or induce negative symptoms, which would be in agreement with the hypodopaminergic pathophysiology postulated as being responsible for negative symptoms and with negative symptoms caused by D_2 antagonists in healthy volunteers.[4,29] Recent results with lower doses of olanzapine on negative symptoms may support this postulate.[30] In our study, although a linear numerical trend was also observed between dose classification and presence of negative symptoms in subjects treated with olanzapine, dosage was statistically unrelated to frequency of negative symptoms. The cross-sectional nature of the study confirms that there was an association between higher doses of haloperidol, amisulpride, and risperidone and higher prevalence of negative symptoms. However, no conclusion can be reached as to whether higher doses of these antipsychotics actually induce negative symptoms. Nor can we establish whether this high prevalence of negative symptoms is due to the fact that clinicians use higher doses in patients with negative symptoms or due to the fact that the time of evolution of illness may be longer in these patients.

In conclusion, these findings from the CLAMORS study have shown that the prevalence of negative symptoms in patients treated with antipsychotics in daily clinical practice is considerably high. We consider this to be a source of concern for public health. The results of this study have shown the presence of negative symptoms to be associated with poor employment status and severity of disease. Increasing our understanding of the variables associated with negative symptoms in this vulnerable population may help to establish preventive and therapeutic programs for higher risk groups. Improving our methods for measuring these devastating symptoms, coupled with the ongoing development of novel antipsychotic agents, may fuel renewed interest in the evaluation of negative symptoms and optimism that better treatments for negative symptoms can be found.

Drug names: haloperidol (Haldol and others), olanzapine (Symbyax, Zyprexa, and others), quetiapine (Seroquel), risperidone (Risperdal and others), ziprasidone (Geodon).

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