Remission in schizophrenia: Results from a 1-year follow-up observational study

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Abstract

Objectives: This study used the Remission in Schizophrenia Working Group operational-severity criteria to, a) provide descriptive data on prevalence and stability of symptomatic remission, b) attempt a criterion (concurrent) validation of this measure of remission, and c) explore correlates of remission stability.

Methods: From an unselected sample of 1010 stable outpatients with schizophrenia (DSM-IV-TR), a subgroup of 452 (44.8%) in symptomatic remission was followed for 1 year. Of these, 376 were re-evaluated in a research diagnostic assessment. In addition to relevant sociodemographic and clinical data, measures included symptoms, depression, functioning, social cognition, attitudes towards medication, and quality of life. Estimates of point prevalence are provided. Correlates of remission were identified by logistic regression.

Results: Symptomatic remission at baseline correlated with better premorbid adjustment, better social cognition, good treatment compliance, younger age, the absence of comorbid substance abuse, current or past participation in psychotherapy, and a lack of past participation in rehabilitation. After 1 year, 338 out of the 376 (89.9%) patients re-evaluated were found again in remission. In this assessment, better premorbid adjustment, good treatment compliance, and improvement of depressive symptoms and social cognition during follow-up again correlated with remission.

Conclusions: The results of this study suggest that symptomatic remission (as defined above) has considerable criterion validity and is a realistic goal in the treatment of schizophrenia. Attaining and sustaining remission may warrant better clinical and functional outcomes for patients.

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1. Introduction

Modern psychiatry is faced with the challenging task of measuring complex subjective concepts. Particular difficulties arise in the field of schizophrenia because of both its multifaceted nature and its heterogeneous course. The proposal by the Remission in Schizophrenia Working Group (Andreasen et al., 2005) of a set of operational criteria for symptomatic remission is the first formal standardized goal for treatment of schizophrenia and may represent a significant advance, as far as it constitutes a reliable and valid representation of a useful construct for research and clinical practice. The Group developed the criteria on the basis of a dimensional approach to psychopathology; they recognized three dimensions that...
had been identified by prior factor analysis and validation (Lindenmayer et al., 1995) and correspond to the DSM-IV diagnostic criteria. The Group required a patient to have a symptom severity score of mild or less in all dimensions for at least six months to qualify for symptomatic remission (Andreasen et al., 2005).

Soon after the formulation of the criteria, a retrospective analysis of a series of symptomatically stable patients followed for one year revealed that remission is a more rigorous measure of treatment success than clinical stability and is well correlated with measures of psychopathology (Docherty et al., 2007; Lasser et al., 2005). This was corroborated in patients suffering their first psychotic episode (Malla et al., 2006; Wunderink et al., 2007). More formal construct validation in prospective investigations related remission with relevant improvements in functioning (De Hert et al., 2007; Helldin et al., 2007; van Os et al., 2006b) and cognitive abilities (Helldin et al., 2006), and this measure of remission has good predictive validity related to psychopathology (Opler et al., 2007).

In this observational research we applied the severity component of the remission criteria to a large cohort of outpatients with chronic schizophrenia considered to be in a stable state. Those found in remission at the first evaluation were reassessed after 1 year. Authors worked with the hypothesis that remission is associated with superior outcomes, like in the aforementioned studies, and aimed to increase our insight on the meaning and consequences of remission. Particular objectives were: a) to investigate the prevalence and stability of symptomatic remission in a nonselected cohort of stable patients regularly attending mental health care facilities, b) to perform a concurrent clinical validation of this measurement of remission, and c) to explore the factors associated with sustaining remission after 1 year.

2. Experimental/materials and methods

2.1. Design and patients

This cross-sectional, nationwide, epidemiological research was followed by a prospective 1-year follow-up cohort study of the subgroup of patients in symptomatic remission (severity criteria) at the cross-sectional evaluation. To ensure sample representativity, 125 public or private facilities attending schizophrenia outpatients located across all 17 regions within Spain were involved at the cross-sectional phase. The number of sites from each Community was proportional to the regional overall census in January 2004. These included public outpatient specialized practices of tertiary care institutions (both psychiatric and general) and community mental health centers, as well as private practice offices. Included subjects were stable outpatients with a diagnosis of schizophrenia according to the revised criteria of the Diagnostic and Statistical Manual of Mental Disorders, text revision of the fourth edition (DSM-IV-TR) (American Psychiatric Association, 2000), attending the routine follow-up visits to their psychiatrists, and capable of completing the instruments used. A predefined schedule based on the appointment logs was employed to screen candidates and minimize selection bias.

Data collection occurred throughout the fourth quarter of 2005 (cross-sectional evaluation) and 2006 (prospective follow-up) by the same psychiatrist from each center. The assessments included the administration of questionnaires and scales described below, review and collection of relevant data from medical files, and a short interview with both the patient and closest relative. This work was always done during routine visits. All participants provided written informed consent to have their data collected and analyzed. The study fulfilled all the applicable regulatory requisites for this type of investigation in Spain.

2.2. Assessment

Symptomatic remission was defined according to the severity component of the operational criteria by the Remission in Schizophrenia Working Group (Andreasen et al., 2005), using the Scales for the Assessment of Positive (SAPS) and Negative (SANS) Symptoms and scored according to the authors’ proposal (Andreasen, 1982; Andreasen and Olsen, 1982). Complete sociodemographic and clinical data were collected, including age, gender, marital, familiar and vocational status, type of schizophrenia, duration of untreated psychosis (<3, 3–12, >12 months obtained by direct questioning of the patient or relative), age of first psychotic episode, time since the diagnosis, number of prior psychotic episodes, current pharmacotherapy, current and past participation in psychotherapy and/or rehabilitation, history of substance/alcohol abuse, and other psychiatric comorbidities. Premorbid functioning was assessed with the Premorbid Assessment Scale (PAS) (Cannon-Spoor et al., 1982) and scored as originally proposed (van Mastrip and Addington, 2002). Psychosocial functioning was evaluated with the Global Assessment of Functioning (GAF) scale as included in the DSM-IV-TR. A total minimum score of 81 points was considered an indicator of optimal psychosocial functioning (Luborsky, 1962). The Strauss-Carpenter Outcomes Scale (SCOS) (Strauss and Carpenter, 1974) was used to provide a single continuous measure of global functioning and outcome. Depressive symptoms were evaluated with the Montgomery-Asberg Depression Rating Scale (MADRS) (Zimmerman et al., 2004), considering a score ≤9 as indicative of clinical remission of depression (Zimmerman et al., 2004). Social cognition was addressed with both versions (patient- and caregiver-rated) of the scale of social cognition for psychosis by the Spanish Group for the Optimization and Treatment of Schizophrenia (Grupo Español para la Optimización del Tratamiento de la Esquizofrenia, GEOPTE) (Sanjuan et al., 2003), which provides a measurement of cognitive operations performed on social stimuli (social cognition) rather than of neuropsychological functions. It is a Likert-type sum scale containing 15 items that inquire about the perceived difficulty to manage specific tasks or situations, scored each from 1 (none) to 5 (much) to provide a global score between 15 and 75. Patients’ attitudes toward medication were evaluated with the 10-item version of the self-reported Drug Attitude Inventory (DAI-10) (Hogan and Awad, 1992). Finally, quality of life was assessed with the Medical Outcomes Study 12-item Short Form health survey (SF-12) (Ware et al., 1996).
2.3. Data analysis

Data were analyzed for patients who met and did not meet the remission criteria at both assessment points. Comparisons between the groups were performed by either t or chi-square tests. Baseline characteristics were also analyzed separately in the subgroup of patients that participated in the prospective evaluation according to their remission status after 1 year. Changes from baseline of the SAPS, SANS, MADRS, GAF, and SCOS total scores and of the Mental and Physical Component Summary scores of the SF-12 (MCS-12 and PCS-12) were compared between the latter groups by means of analysis of covariance adjusting by their corresponding baseline values.

Logistic regression analyses were used to explore the contributions of various factors to remission as well as to its stability after 1 year. One binary model included remission status at baseline as the dependent variable and patients’ characteristics and the baseline scores of the PAS, GEOPT and DAI-10 as independent variables (the baseline SAPS and SANS scores were not included as covariates because they were used in the remission definition). Another binary model investigated the correlates of remission after 1 year, and only included patients who participated in the prospective evaluation. The changes from baseline of the assessment instruments (with the exception of SAPS and SANS) functioned as independent variables in addition to those included in the baseline model. In both cases, single regression was used to select the initial set of independent variables showing significant bivariate associations. The models were then reduced by selecting the set of independent variables that minimized the Akaike’s Information Criterion.

3. Results

3.1. Patient characteristics, prevalence and stability of remission

3.1.1. Status at baseline

A total of 1010 patients were included in the cross-sectional study. They were primarily male (n=670, 66.3%) with a mean age of 38.8 (standard deviation, SD=10.8) years, and a mean disease duration of 14.9 (SD=9.8) years. Only one third (n=309, 34.7%) had an untreated psychosis shorter than 3 months. Of the total study population, 452 patients (44.8%; 95% confidence interval, CI: 41.7% to 47.9%) met the severity component of the remission criteria. The remission status of 3 patients was unknown because of missing data. Of the remaining 555 patients, 286 showed remission of only positive symptoms, and 59 of negative symptoms (Fig. 1).

3.1.2. Status at follow-up

After 1 year, 76 of the 452 patients in symptomatic remission at the initial assessment were lost to follow-up, though their baseline characteristics were similar to those of the remaining 376 (data not included for brevity). The reasons for these drops were not documented. Thirty seven patients lost remission since baseline, and the remission status could not be determined in one additional patient; thus 338 patients (89.9%) were determined to be in remission at follow-up (Fig. 1).

3.2. Concurrent validity of remission

3.2.1. Sociodemographic and clinical characteristics

Patients’ characteristics differed according to remission status at baseline (Table 1). Patients in remission were younger, had a more recent diagnosis, had more frequently durations of
untreated psychosis shorter than 3 months, and experienced four or less prior psychotic episodes. They were less frequently single or receiving any social disability benefit, and more likely to engage in paid employment. Furthermore, compared to unremitted patients, those in remission had less severe depressive symptoms, better scores of social cognition, better global functioning, and better scores in the mental component of the SF-12 survey.

Monotherapy with second-generation antipsychotics was the most common pharmacotherapy, (694 patients; 68.7%). This proportion was significantly higher in remitted (335 out of 452, 74.1%) than in unremitted patients (357 out of 555, 64.3%). Only 342 out of 1010 (33.9%) were participating or had participated in any psychotherapeutic activity, and this proportion was slightly, but not significantly, greater among those in remission.

3.2.2. Correlates of remission at baseline

Because of missing data, adjusted analyses were performed for 873 patients; of those patients, 473 (54.2%) met and 400 (45.8%) did not meet the remission criteria. Logistic regression analysis (Fig. 2) indicated that younger age, better social cognition, better premorbid adjustment, current or past participation in psychotherapy, good treatment compliance, and the absence of substance abuse were independently associated with a greater likelihood of remission at baseline. Duration of untreated psychosis was almost significant, but was finally excluded from the final model. Past participation in any rehabilitation program was conversely associated with a reduced chance of remission.

3.3. Factors associated with sustained remission

The group of 338 patients that were still in remission after 1 year differed significantly at baseline from those who no longer in remission during follow-up; they had less severe psychopathology as reflected by lower scores in both SAPS and SANS, better psychosocial functioning, less severe symptoms of depression, and better scores in the MCS-12 (Table 2). The changes from baseline of the patients’ scores on these instruments also differed between these two groups. With the exception of the PCS-12 score, which did not change, the evolution was significantly better in all measures of outcome among patients in remission at follow-up. Conversely, the GAF and SCOS scores worsened in patients losing remission; they also showed a marked aggravation of depressive symptoms (Table 2). Modifications of antipsychotic pharmacotherapy were significantly less frequent (chi-square p-value = 0.001) among patients remaining on remission at endpoint (73 out of 338, 21.6%) than in those who lost remission during follow-up (15 out of 37, 40.5%).

The logistic model that analyzed the correlates of symptomatic remission at 1 year (Fig. 3) showed that better premorbid adjustment, better compliance with pharmacotherapy, and improvements of depressive symptoms (MADRS) and of social cognition (GEOPTE scale) scores during follow-up were associated with a greater chance of sustaining remission.

4. Discussion

4.1. Key findings

The results of this research offer support for several facets of schizophrenia treatment. First, the consensus remission criteria (severity component) define a status that is feasible and attainable by a large proportion of stable outpatients with schizophrenia who regularly attend mental health care.
Fig. 2. Adjusted odds ratios and 95% confidence intervals of the likelihood of meeting the remission criteria (severity component) at baseline obtained in the final logistic regression model after backward stepwise selection of independent variables (n valid: 473). SGM = second-generation antipsychotic monotherapy; SGC = combined therapy with two or more second-generation antipsychotics; FGM = first-generation antipsychotic monotherapy; FGC = combined therapy with two or more first-generation antipsychotics; CM = combined mixed therapy with first- and second-generation antipsychotics; OR = odds ratio; CI = confidence interval.
facilities and are at different stages of the illness. The observational nature of this investigation reinforces the robustness of the remission concept and the criteria for measuring it, particularly for everyday clinical use by diverse raters under non-optimal conditions where reliability cannot be tested formally. Such applicability may have important implications for the assessment of needs and resource planning of mental health care systems.

Second, as already noted (Lasser et al., 2005; van Os et al., 2006a), this operationalization of symptomatic remission appears to be a clinically valid construct that is more useful than prior subjective and heterogeneous evaluations of clinical stability. In this study, like in others that evaluated non-acute, responsive patients with a steady condition not requiring immediate adjustments of antipsychotic treatment (De Hert et al., 2007; Helldin et al., 2007; van Os et al., 2006b), about 45% of patients initially evaluated were in remission; the criteria accurately separated those with fewer factors associated with poor prognosis, less psychotic and affective symptoms, better social cognition and abilities, better psychosocial functioning and performance (were less frequently unemployed, receiving disability benefits, or single), and to a lesser extent, better results on the SF-12 survey. Furthermore, many of these features were less evident at baseline among patients that would eventually lose remission, while some improved further in patients who were still in remission after 1 year. These findings constitute solid evidence of good concurrent validity, in terms of clinical significance of this measurement of remission; and reinforce the notion that remission is a common prerequisite for functional improvement that is in the foundation of the consensus criteria (Andreasen et al., 2005).

Third, our data suggest that remission status has considerable stability. We found that just 10% of patients lost remission after 1 year. This proportion is slightly lower than the 15% reported in a prior study in which patients were also followed for 1 year (Lasser et al., 2005), albeit such divergence is easily explainable by the fact that these authors included interim visits and considered the time component of the criteria, while we did not. For longer time periods, the proportions increased further: 22% after approximately 2 years without considering the time component (De Hert et al., 2007) and 35% after approximately 3 years considering the time component (van Os et al., 2006b). In combination, these data suggest that remission may be lost at an approximate rate of 10% per year.

Fourth, negative and affective symptoms and treatment compliance appear critical to the durability of remission. The importance of continued antipsychotic treatment to the outcome of schizophrenia is widely accepted (Lieberman et al., 2005), but the impact of depressive symptoms is only recently being recognized (Perkins et al., 2008). The careful evaluation of comorbid depression and optimization of therapy may be an effective means of achieving and ensuring remission in a larger proportion of patients.

4.2. Other findings

It is somewhat counter-intuitive that patients involved in rehabilitation had a lower likelihood of remission at baseline. Because access to rehabilitation services within the public mental health care system in Spain is limited, this result is possibly the consequence of a negative selection bias (only the most severe cases have access to it) and is not indicative of an actual negative association. Of note is also the paradox between the high mean GAF score and the low proportion of active workers for the remitted patients. This is also a regional feature of this sample because of the high proportion of schizophrenia patients receiving social disability benefits in Spain who are actually able and working outside the competitive market (Ciudad et al., 2004; Torres and Olivares, 2005).

The low proportion of patients with combined antipsychotic treatment in this sample is an encouraging finding,

Table 2
Baseline status and evolution of patients’ clinical aspects by remission status after 1 year

<table>
<thead>
<tr>
<th>Aspect</th>
<th>Baseline status a</th>
<th>Change to 1 year b</th>
<th>95% CI of change</th>
<th>Baseline status a</th>
<th>Change to 1 year b</th>
<th>95% CI of change</th>
<th>p-value a</th>
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</thead>
<tbody>
<tr>
<td><strong>Psychopathology</strong></td>
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<tr>
<td>SAPS global score f</td>
<td>1.9 (2.0)</td>
<td>−0.6 (0.1)</td>
<td>−0.8 to −0.4</td>
<td>2.9 (2.1)</td>
<td>0.8 (0.3)</td>
<td>0.1 to 1.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SANS global score f</td>
<td>4.5 (2.9)</td>
<td>−1.0 (0.1)</td>
<td>−1.3 to −0.8</td>
<td>6.2 (2.3)</td>
<td>3.1 (0.5)</td>
<td>2.0 to 4.1</td>
<td>&lt;0.001</td>
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<td><strong>Psychosocial functioning</strong></td>
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<tr>
<td>GAF total score c</td>
<td>69.9 (12.7)</td>
<td>3.5 (0.5)</td>
<td>2.5 to 4.4</td>
<td>58.5 (9.0)</td>
<td>−3.7 (2.2)</td>
<td>−8.2 to 0.8</td>
<td>&lt;0.001</td>
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<tr>
<td>Global function and outcome</td>
<td></td>
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<tr>
<td>SCOS total score c, f</td>
<td>11.7 (3.0)</td>
<td>0.5 (0.1)</td>
<td>0.3 to 0.7</td>
<td>10.0 (2.6)</td>
<td>−0.8 (0.4)</td>
<td>−1.6 to 0.0</td>
<td>&lt;0.001</td>
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<tr>
<td><strong>Depressive symptoms</strong></td>
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<td>MADRS global score d, f</td>
<td>10.2 (6.5)</td>
<td>−2.1 (0.3)</td>
<td>−2.7 to −1.5</td>
<td>13.7 (8.1)</td>
<td>1.6 (1.2)</td>
<td>−1.0 to 4.0</td>
<td>&lt;0.001</td>
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<td>Quality of life</td>
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<tr>
<td>PCS-12 score c, f</td>
<td>50.4 (8.3)</td>
<td>0.6 (0.4)</td>
<td>−0.3 to 1.4</td>
<td>48.6 (9.0)</td>
<td>−0.8 (1.7)</td>
<td>−4.2 to 2.6</td>
<td>0.310</td>
</tr>
<tr>
<td>MCS-12 score c, f</td>
<td>43.4 (11.1)</td>
<td>3.7 (0.6)</td>
<td>2.5 to 4.8</td>
<td>37.2 (13.0)</td>
<td>1.6 (2.1)</td>
<td>−2.7 to 5.8</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

CI = confidence interval; SAPS = Scale for the Assessment of Positive Symptoms; SANS = Scale for the Assessment of Negative Symptoms; GAF = Global Assessment of Functioning scale; SCOS = Strauss-Carpenter Outcomes Scale; MADRS = Montgomery-Asberg Depression Rating Scale; PCS-12 = Physical Component Score of the Medical Outcomes Study 12-item Short Form health survey; MCS-12 = Mental Component Score of the Medical Outcomes Study 12-item Short Form health survey.

a Values are expressed as means (standard deviation).
b Values are expressed as means (standard error of the mean).
c The scores for one patient in remission were missing at follow-up.
d The scores from two patients in remission were missing at follow-up.
e The p-value is derived from the ANCOVA factor informing of the remission status at follow-up.
f The scores at baseline differed significantly between both groups defined by the remission status at follow-up.
Fig. 3. Adjusted odds ratios and 95% confidence intervals of the likelihood of meeting the remission criteria (severity component) after 1 year (n=375; 338 on remission) obtained in the final logistic regression model after backward stepwise selection of independent variables (n valid: 375). FGA = first-generation antipsychotics; SGA = second-generation antipsychotics; OR = odds ratio; CI = confidence interval.
suggesting that combined antipsychotic treatment is not an important issue in actual clinical practice. It is also in agreement with the current evidence base that supports monotherapy over antipsychotic combinations (Barbui et al., in press; Correll et al., in press).

The proportion of patients excluded because of unavailable data was lower than in a prior similar work (De Hert et al., 2007). This is probably a consequence of the personalized and dedicated care delivered by psychiatrists in Spain, who typically follow the same patients for prolonged periods.

4.3. Conceptual implications

Despite the heterogeneity of prior definitions of favorable outcome in schizophrenia, some predictors had been consistently included, such as good premorbid adjustment (Schmael et al., 2007), female gender (Häfner, 2003), and duration of untreated psychosis (Haas et al., 1998). The use of standardized criteria in this study has corroborated the importance of premorbid adjustment. Fewer clear associations were found between duration of untreated psychosis and gender. The fact that the data on duration of untreated psychosis were aggregated into an ordinal variable and unreliably obtained by direct questioning of patients/relatives and the low proportion of females in our sample may have accounted for the lack of more clear associations. Our findings, however, are consistent with recent reports, which suggest that these factors are actually confounded with premorbid adjustment (Norman et al., 2007; Schmael et al., 2007). In this vein, premorbid adjustment may be a consequence of the insidiousness of the prodromal phase, with longer periods of untreated psychosis reflecting greater difficulties in diagnosis (Norman et al., 2007).

We have found a relevant association between depressive symptoms and the likelihood of remission. However, van Os et al. (2006b) have demonstrated that the inclusion of depression and suicidality items in the definition of remission did not increase its responsibility to differences in functional outcomes. Therefore, it seems feasible that a direct effect of depressive symptomatology on functioning is less important than the mediation of symptomatic remission. Furthermore, the extent to which treatment side effects manifest as negative or depressive symptoms and their influence on losing remission status remains undetermined. Further causal directional research with appropriate experimental designs to gain insight into these relationships is advisable, in that it may contribute to the development of the conceptual framework of recovery from schizophrenia.

4.4. Limitations

First, an evident limitation is that unremitting patients at baseline were not followed. This precluded any analysis of predictive validity of remission criteria. In a study by Lasser et al. (2005) 18% of patients gained remission after 1 year; this is probably an overestimation for our sample because these authors recruited patients when they were experiencing acute problems. Second, because the time criterion of remission was not considered in this study, it is not possible to separately analyze which factors are associated with the severity component (which has been recently regarded as “resolution” (Peuskens et al., 2007)) regardless of the time component. In the observational study reported by De Hert et al. (2007), patients meeting the full remission criteria at endpoint did better than those only meeting the severity component. Third, the results of our follow-up are conditional upon the evolution of the 76 patients who could not be reassessed. In the worst case (that all of these patients had relapsed at endpoint), we had found 25% of patients losing remission. However, this appears to be an over-conservative assumption given that the sensitivity analyses did not reveal substantial differences between these and the patients that remained in the study and that our results compare with prior series in terms of stability of the remission status, as discussed above. Fourth, patients who choose not to attend mental health services were neglected by this study. Last, given the large sample size, statistical significance does not imply clinical relevance, especially concerning the bivariate comparisons of baseline characteristics between remitted and unremitting patients.

5. Conclusion

The results of this 1-year observational follow-up study clearly support the incorporation of the concept of remission in the management of patients with schizophrenia in routine practice. The application of the remission criteria requires little time to accomplish in the routine practice and may serve to establish whether a patient achieves a meaningful therapeutic goal.

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Contributors

Antonio Ciudad and Inmaculada Gilaberte participated in the design of the study, writing of protocol, interpretation of results, and writing/review of the manuscript for intellectual content. Pepa Polavieja participated in the design of the study, supervised the statistical analyses and has reviewed the manuscript for intellectual content. Julio Bobes, Enric Alvarez and Luis San participated in the design of the study, writing of protocol, coordination of clinical investigators, interpretation of results, and writing/review of the manuscript for intellectual content.

Conflict of interest

Antonio Ciudad, Pepa Polavieja and Inmaculada Gilaberte are full-time employees of Lilly, S.A., an affiliate of Eli Lilly and Company. Julio Bobes has received consulting fees and honoraria within the last three years from AstraZeneca, Bristol-Myers-Otsuka, GlaxoSmithKline, Janssen-Cilag, Eli Lilly, Pfizer, Sanofi-Aventis and Schering-Plough. Enric Alvarez has received consulting fees and honoraria within the last three years from Eli Lilly, Bristol-Myers-Otsuka, Lundbeck, Pfizer, Sanofi-Aventis, Almirall and GlaxoSmithKline. Luis San has received grant/research support, received honoraria and participated in speakers/advisory boards from AstraZeneca, Bristol-Myers-Squibb, Eli Lilly, Pfizer, Janssen and Wyeth.

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