

Irene Romera<sup>1,2</sup>  
Víctor Pérez<sup>3</sup>  
Inmaculada Gilaberte<sup>1</sup>

# Remission and functioning in major depressive disorder

<sup>1</sup>Clinical Research Department  
Lilly S.A.  
Madrid, Spain

<sup>2</sup>Universidad Autónoma de Barcelona, España

<sup>3</sup>Department of Psychiatry  
Hospital de Sant Pau i de la Santa Creu. Barcelona  
Universidad Autónoma de Barcelona, CIBERSAM, España

Evidence from numerous clinical studies has shown that the optimal goal for the treatment of depression is remission. Remission implies that the signs and symptoms of the disease are absent or virtually absent, which is typically associated with a return to the patient's previous daily functioning. Functioning in depression is a broad concept that covers different domains. There are many validated instruments for its assessment, these being reviewed in this article. Furthermore, recovering the pre-morbid level of functioning level is increasingly being identified as a significant target in addition to symptomatic remission. In this sense, functional recovery has been associated with better prognosis of depression and is also a clinical goal expressed by the patient. Several factors, like complete remission of symptoms, with no residual symptoms, maintenance of remission, quality of remission, early remission, have been identified as contributors to functional recovery. In order to facilitate the clinical outcomes, evaluation of and search for symptomatic remission as well as functional recovery need to be integrated into the clinical practice.

**Key words:** Remission, Functioning, Depression

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## Remisión y funcionalidad en el trastorno depresivo mayor

La evidencia procedente de numerosos estudios clínicos ha demostrado que el objetivo óptimo en el tratamiento de la depresión es la remisión. La remisión implicaría que los signos y síntomas de la enfermedad estén ausentes o prácticamente ausentes, lo cual se asocia típicamente con una vuelta a la funcionalidad diaria previa del paciente. La funcionalidad en depresión es un concepto amplio, que cubre diferentes dominios, existiendo numerosos instrumentos validados para su valoración que se revisan en este artículo. Asimismo, cada vez más se identifica que la recuperación de la funcionalidad al nivel pre-mórbido es un objetivo significativo adicional a la remisión sintomática. En este sentido, la recuperación de la funcionalidad se ha relacionado con un mejor pronóstico de la depresión, siendo también un objetivo clínico expresado por el paciente. Entre los factores contribuyentes a la recuperación funcional se encuentra la remisión completa de los síntomas, sin síntomas residuales, el mantenimiento de la remisión, calidad de la misma, así como que esta se produzca de una manera temprana. Con el fin de favorecer los resultados clínicos se hace necesaria la integración en la práctica clínica de la evaluación y búsqueda de no sólo la remisión sintomática sino también de la recuperación funcional.

**Palabras clave:** Remisión, Funcionalidad, depresión

**Correspondence:**

Pérez V, Hospital de Sant Pau i de la Santa Creu. C/Sant Antoni Maria Claret, 167.  
E-08025, Barcelona, Spain.  
Phone: +34.93.291.90.00  
E-mail: vperez@hsp.santpau.es  
Gilaberte I, Clinical Research Department, Lilly, SA. Avenida de la Industria, 30. E-28108, Alcobendas-Madrid, Spain.  
Phone: +34.91.663.50.00  
Fax: +34.91.663.52.31.  
E-mail: gilaberte\_inmaculada@lilly.com

In recent years, evidence from many clinical studies has demonstrated that remission is the best goal in the treatment of depression.<sup>1</sup> According to the American College of Neuropsychopharmacology (ACNP) work group recommendations on remission published in 2006, the concept of remission would imply that the signs and symptoms of the disease are absent or practically absent. This is typically associated with a return to the previous daily functioning of the patient.<sup>2</sup> The term remission also has been equated to the presence of "health."<sup>1</sup> As in other chronic diseases, health level in depression should be evaluated, taking

into consideration the combination of three key domains: symptoms, functional status and physiopathological changes.<sup>1</sup> Given the current limitations on the evaluation of the physiopathological changes, it is proposed that the best approach to the definition of remission would be a system that primarily takes into account the patient's psychosocial functioning. That is, the best result of the treatment would be remission with absence of symptoms and absence of functional alteration or re-establishment of complete and healthy functioning.<sup>1</sup> However, what do we understand by functioning? This is a wide concept that covers different domains. Areas that are commonly included in the concept of functioning are work functioning (ability to carry out tasks and activities associated with work), personal care, social (personal relations), familial and cognitive functioning. An accepted definition of the term functioning is "the ability to perform activities or tasks as expected or required."<sup>3</sup> In this way, social functioning has been defined as "the ability of the individual to perform and carry out a normal social role"<sup>4</sup> or "the interaction of the individual with his/her setting and ability to carry out his/her role within him/herself."<sup>5</sup>

It can be stated that the term functioning is sometimes confused with others as satisfaction or quality of life. Functioning and satisfaction are considered a component of the quality of life. However, functioning and satisfaction can vary independently. For example, functioning may be altered in a patient in different domains but the patient may be satisfied with his/her situation in life. Even more, satisfaction is subjective and therefore evaluated by the patient and functioning may be measured in a more objective way.<sup>3</sup>

### Measurement of functioning: evaluation instruments

Many validated instruments are commonly used in clinical studies to evaluate functioning in patients with depression (Table 1).

One of the scales used most, both in studies on depression and on anxiety, is the Sheehan Disability Scale (SDS). It covers three functional areas: work-studies, social and familial. The patients score how their symptoms have interfered in each one of these domains on a scale of zero to ten.<sup>6</sup> Normal functioning levels are considered to be total score less than or equal to 6<sup>7</sup>, 30 being the worst possible level of functioning.<sup>6</sup> The SDS is a well-established instrument whose advantage is that it is short, easy to use and that it has also been shown to be sensitive to change.<sup>3</sup>

Another commonly used scale is the SOFAS (Social and Occupational Functioning Scale), also known as EEASL in Spanish (escala de evaluación de la actividad social y laboral). This scale is derived from the DSM-IV-TR (Diagnostic and Statistical Manual of mental disorders, fourth edition revised).

The clinician or investigator indicates the individual's level of functioning on a continuum of 1 to 100 (100 is optimum functioning). This scale only measures functional alterations without considering the symptoms.<sup>8</sup> The highest intervals of the SOFAS, 81-90 and 91-100, describe individuals who do not have significant psychopathology and who have many traits of positive mental health, a wide range of interests, social effectiveness, etc. Thus, a score of  $\geq 80$  on the SOFAS is considered a normal level of functioning.<sup>9</sup> The advantage of the SOFAS is that it is a widely used instrument, it is easy and fast to use, and it evaluates functioning globally. At the same time, it has the disadvantage that it does not include specific aspects on evaluation of functioning.

Although there are many scales for the evaluation of functioning, it should be mentioned that these are fundamentally used in research, their use in the common clinical practice being scarce. This contrasts with that defended by the DSM-IV, which suggests that the symptoms of major depression should be evaluated in terms of their functional impact on the social, occupational area or on another type of relevant area and recommends the use of a global evaluation of functioning.<sup>8</sup> Even more, it seems that functional aspects are going to have more importance in the DSM-V and in the ICD-11 and efforts are being made to facilitate their evaluation (WHO, Department of Mental Health). It is possible that the low use of specific functioning assessment scales is a reflection of the greater weight that symptomatic aspects have traditionally had on the functions in the field of research on depression. The existence of new scales of recent appearance and the RDQ (Remission from Depression Questionnaire), that are easy to apply, accepted by the patient, may be strategies to consider in order to improve the patient evaluation procedure.<sup>10</sup> In this sense, the advantage of the RDQ is that it includes conditions that the patient considers important for recovery. Thus, symptomatic, functional, positive emotions, coping ability and experiences of well-being and satisfaction are included.<sup>10</sup>

Finally, one of the fundamental aspects to consider is the evaluation of pre-morbid functioning. In this, the use of the scales is limited and the clinical interview is the tool having the greatest weight. Evaluation of pre-morbid functioning takes on a relevant role to establish specific therapeutic objectives adapted to each patient.

### Symptomatic remission and functional recovery as therapeutic objective

Currently, symptomatic remission is the principal objective when treating the depression episode. However, functional recovery on the premorbid level is increasingly identified as an additional significant objective to symptomatic remission.<sup>11</sup>

Table 1      Functioning measurement instruments		
Instrument	Number of items	Domains included
SOFAS (Social and Occupational Functioning Scale)	Single	Social Occupational
Sheehan Disability Scale; SDS)	3	Social and leisure activities Occupational (paid- student-housework) Relations with family, role within family
Social Adjustment Scale (SAS)	48	Work (paid, home, student) Leisure and social activities Marital role Parent role Role as a member in the family
Global Assessment of Functioning scale (GAF)	Single	Severity of symptoms and functional alteration
WHODAS (World Health Organization Disability Assessment Schedule)	36	Cognition Mobility Self-care Interpersonal interactions Activities Participation in society
Endicott work productivity scale	25	Work efficiency and productivity
Longitudinal Interval Follow-up Evaluation-Range of Impaired Functioning Tool	9	Work Interpersonal relations General satisfaction with functioning Recreation
Life Functioning Questionnaire	14	Tasks at work/school Tasks in the home Leisure time with family Leisure time with friends
Health of the Nation Outcomes Scales	12	Behavior Dysfunction Symptoms Social functioning
Adapted from Endicott J et al. 2009		

Functional recovery has been related with a better prognosis of depression. Observational follow-up studies have found a significant association between functional alteration and greater episode duration.<sup>12</sup> It has also been seen that the presence of functional alteration, after recovery of the episode, is related with more depressive recurrences.<sup>13</sup> More recently, this same author studied the relationship between psychosocial functioning and recovery in a large sample of patients with major depression by means of a 20 year follow-up observational study. Recovery was defined as at least 8 consecutive weeks without symptoms or only one or two symptoms of mild intensity. Functional alteration was significantly associated with less likelihood of recovery of the major depression episode.<sup>14</sup>

Functional recovery is also a clinical objective expressed by the patient with depression. Zimmerman<sup>15</sup> studied which factors defined remission of the episode from the patient's point of view. To do so, he asked 535 patients with depression about

the importance of 16 factors to determine if depression was in remission. Social and work functioning, expressed as return to normal functioning level, was a factor identified as "very important" by 74% of the patients. This was even above absence of depressive symptoms, where 70% of the patients considered it as a "very important" factor. However, besides functional recovery, presence of positive mental health (optimism and self-confidence) and feeling as before, as oneself, were identified as "very important" by the patient.<sup>15</sup> In other words, from the patient's point of view, within the patient's recovery expectations, functional recovery is considered to be highly relevant.

### Factors that are associated with functional recovery

However, what factors are associated with functional improvement or restoration in patients with major depres-

sion? The factors that have been identified as contributing to this include, among others, functional pathway of the patient over life, treatment effectiveness, time to remission, duration of remission and quality of remission<sup>11</sup> (Table 2).

Premorbid functioning is a determining factor of the level of functioning after the episode. Ormel et al.,<sup>16</sup> in a prospective population study carried out in Holland, studied the psychosocial functional before, during and after the first episode of depression. They observed that after remission, functioning returned to premorbid levels. Psychosocial functional alteration greatly reflected the continuation of the premorbid functional alteration.

In relation to the effectiveness of the treatment, a complete and maintained resolution of the depressive symptoms is necessary to reach functional restoration. Thus, effective therapeutic approaches that lead to maintenance of the state of symptomatic remission would increase the patient's options of functional recovery.<sup>11</sup> The study of Miller et al.<sup>17</sup> showed this relation. Those patients who achieved remission (HAMD-17  $\leq 7$ ) after 12 weeks of acute treatment had better functioning than those who only responded (reduction in the total score of the HAMD-17 greater than or equal to 50%). Furthermore, they had similar levels of functioning as a control group without depression. In a more recent study, Papakostas evaluated the functioning in a group of patients with depression who received treatment with fluoxetine for 8 weeks. As in the Miller study, the functional improvement was greater in those patients who achieved remission (HAMD-17  $\leq 7$ ) vs. those who only responded.<sup>18</sup>

An observational study carried out in Spain regarding the complete resolution of the depressive symptoms and restoration of functioning should be mentioned.<sup>19</sup> Romera et al. studied the impact of the presence of residual symptoms after the acute treatment, partial remission, in the functional prognosis of the patient with depression. To do so, they prospectively followed up two paired cohorts of patients for six months: patients with complete remission (n=146) and patients with partial remission (n=146). It was seen that the presence of residual symptoms after acute treatment was associated with a significant alteration of functioning that persisted even after six months of continuation treatment. Thus, after 6 months, only 47% of the patients in partial remission achieved normal functioning vs. 77% of the patients with complete remission (Figure 1). After the follow-up period, the mean functioning levels for patients with partial remission were significantly below normality (76.2 [12.3]-partial remission vs. 84.6 [9.4] complete remission;  $p<0.0001$ ). During the 6 months of follow-up, the patients with partial remission had more sick leave time than patients with complete remission (63 vs. 20 days, respectively;  $p<0.001$ ), this being associated with greater cost.

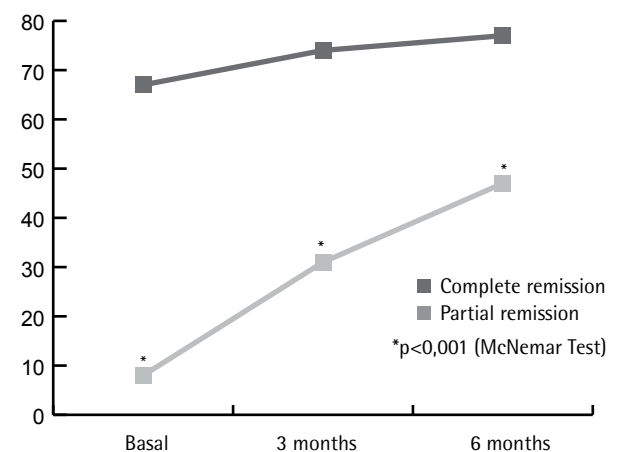
Regarding time to remission, earlier response and early remission were associated significantly to greater func-

Table 2

### Factors associated with the functional recovery

Functional pathway of patient over life time  
Medical and psychiatric comorbidity  
Effectiveness of the treatment  
Complete remission of the depressive symptoms  
Time to remission  
Duration or maintenance of the remission  
Quality or degree of remission

Adapted from Papakostas GI. 2009



SOFAS: Social and Occupational Functioning Assessment Scale.  
\*p<0,001 (Mc Nemar Test)

Figure 1

Percentage of patients who reached normal functioning (SOFAS  $\geq 80$ ) at baseline, at 3 and 6 months

nal improvement.<sup>18,20</sup> The Ciudad et al. study, recently carried out in Spain on a large sample of patients with major depression episode followed-up for 1 year, merits mention. This study showed that early response was the factor most frequently associated with functional improvement. Similarly, early remission, within the first 6 weeks of treatment, was a factor strongly associated with functional improvement. In the patients with early remission, normal ranges of functioning were globally observed as early as at 6 weeks. In those who did not achieve early remission, one year was needed to reach normal functioning levels.

Duration and maintenance of remission are factors that also contribute to functional restoration. Furukawa et al.<sup>21</sup> found that functioning improved with symptom improvement, but normal levels of functioning were not achieved until some months after symptomatic remission. That is,

these results seem to indicate that functional recovery "lags behind" in regards to symptom recovery. On the other hand, maintenance of remission, avoiding loss of this asymptomatic status, also becomes essential. Loss of remission not only contributes to functional deterioration but also to an increase of risk of relapse and recurrence and therefore loss of functional recovery.<sup>11</sup>

Finally, the quality or grade of remission is also associated with functional recovery. Significant differences have even been found in patients with remission in regards to degree of functioning.<sup>22-24</sup> An analysis carried out in 292 patients in Spain with major depressive disorder to find the optimum cutoff on the HAMD-17 scale that would best predict normal levels of social and occupational functioning showed that a score of  $\leq 5$  maximized sensitivity and specificity compared to other scores.<sup>23</sup> The mean score on the SOFAS for patients with a score of 0-5 on the HAMD-17 was 85.2 (CI 95%: 83.9-86.6), within the levels considered as normal. However, patients who had a score of 6-7, the mean score on SOFAS was 79.5 (CI 95%: 76.7-82.3), this being below the range considered as normal. Pimmerman et al. observed that patients who scored equal to or less than 2 on the HAMD-17 reported less psychosocial dysfunction than those who had a score between 3 and 7.<sup>22</sup> The same authors, in a recent study carried out with 274 patients with depression and remission (HAMD-17  $\leq 7$ ) found similar results.<sup>24</sup> The patients who scored 0-2 on the HAMD-17 had significantly better levels of psychosocial functioning, quality of life and better satisfaction with their mental health compared to patients who scored 3-7.<sup>24</sup> Similar results have been found using other instruments such as the Montgomery-Asberg Scale.<sup>25</sup> Therefore, when symptoms as well as recovery of social and work function are taken into account, the traditional cutoff on the HAMD-17 could be considered to be too high, that is, a score of HAMD-17  $\leq 7$  does not necessarily imply normal levels of functioning.<sup>23</sup>

Thus, remission of the symptoms is a key factor within the factors associated with functional recovery. However, it is not only important to achieve symptomatic remission. In order to maximize the options of functional recovery, this remission must occur in a short period of time, as soon as possible. Furthermore, "quality" or grade of remission is a factor to consider since even in remission, lower scores on symptomatic scales are associated with better functioning. Finally, this symptomatic remission must be maintained over time to consolidate functional recovery and decrease the risk of relapse and therefore the risk of functional loss.

## Limitations

Because the current article is not a systematic review, it does not include all of the possible works published on remission and functioning in depression. However, the purpose

of this work is to carry out a general review and a review of utility for the clinical practice.

## CONCLUSIONS

Symptomatic remission is the main objective of treatment of depression episode. However, functional recovery on the premorbid level is increasingly identified as a key objective in addition to symptomatic remission. Among the factors contributing to functional recovery are complete remission of the symptoms, without residual symptoms, and that this complete remission also occurs early. In order to favor the clinical results, it is necessary to not only integrate evaluation and search into the clinical practice but also functional recovery as well.

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