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COMMENTARY

Beyond Response: Aiming for Quality Remission in Depression

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ABSTRACT

To define treatment response in depression as at least a 50% reduction in total symptom severity is to accept that up to half of patients will continue to have residual symptoms, most commonly low mood/loss of interest, cognitive problems, lack of energy, and difficulty sleeping. In fact, patients' goals for treatment are to return to premorbid levels of functioning. This highlights the importance of assessing both functional outcomes and symptom improvement when evaluating the efficacy of antidepressant medication. Not all patients who achieve symptomatic response/remission will achieve a functional response/remission. In two studies (one with agomelatine and one with escitalopram), 54% of patients receiving agomelatine and 47% of those receiving escitalopram achieved a symptomatic response, and 53% of patients in each study achieved a functional response. However, 42% of patients receiving agomelatine and 35% of those receiving escitalopram had both a symptomatic and a functional response. The four symptoms of depression with the most marked effect on function are sad mood, impaired concentration, fatigue, and loss of interest. Low energy is particularly associated with poor occupational functioning, highlighting the importance of ongoing assessment of patients with depression, focusing particular attention on the symptoms that affect their ability to function, such as fatigue. Depending on the type of residual symptoms, some patients may benefit from combination therapy, such as adding dopamine modulator therapy. Antidepressant therapy is only effective if patients continue to take their medication, and high rates of early discontinuation have been reported. Therefore, when selecting treatment for depression, physicians can maximize the likelihood of adherence and persistence by taking into account both the antidepressant efficacy of treatment, its adverse effects and acceptability to patients.

Keywords: Depression; Treatment; Antidepressants; Residual symptoms; Functioning; Response; Adherence; Persistence

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Key Summary Points

Symptomatic improvement is an early sign of antidepressant treatment response but functional outcomes provide an indicator of meaningful change.

Symptomatic and functional outcomes do not always overlap, as patients may achieve a symptomatic response without achieving a functional response, and vice versa.

The symptoms with the greatest impact on function are sad mood, impaired concentration, fatigue, and loss of interest.

Patients should be monitored for residual symptoms, and treatment tailored towards improvement in both symptoms and function.

INTRODUCTION

For the last 30 years, the accepted outcome to confirm the efficacy of antidepressant therapy in clinical trials has been 'response', i.e., at least a 50% reduction in total symptom severity [1], although the merits of this dichotomy have been challenged [2]. Under this definition, many patients continue to have residual symptoms, and are therefore at high risk of developing recurrent or chronic depression, and suicidality [1]. While measurement-based care, particularly using self-reported measures, such as the Patient Health Questionnaire-9 (PHQ-9) [3] or Quick Inventory of Depressive Symptoms-Self Report (QIDS-SR) [4], is gaining acceptance in clinical practice, these instruments continue to measure only symptomatic outcomes, which do not necessarily correlate with functional outcomes. This emphasizes the importance of capturing both symptomatic and functional data when assessing antidepressant outcome.

The purpose of this commentary is to describe, with specific reference to agomelatine, the measurement of functional outcomes in depression, and to highlight the importance of functional outcome assessment as part of an integrated approach to defining recovery, utilizing data from two clinical studies assessing agomelatine [5] and escitalopram [6].

IMPORTANCE OF FUNCTIONAL OUTCOMES

A systematic review on the relationship between symptoms and function in patients with depression by McKnight and colleagues identified symptom change as an early sign of treatment response, while functional outcomes acted as indicators of a meaningful change [7]. The importance of functional outcome assessment in depression was highlighted by the Canadian Network for Mood and Anxiety Treatments consensus recommendations, published in 2015 (Table 1) [8]. These recommendations include the need for measurement-based care using valid and reliable tools to evaluate both symptoms and function. Examples of these tools include the Sheehan Disability Scale (SDS; Fig. 1) [9]. The SDS consists of a set of questions asking patients to grade the extent to which their symptoms have disrupted three aspects of their lives, work/school, social life, and family life/home responsibilities, on a scale from 0 (not at all) to 10 (extremely) [9]. The SDS is a simple tool that can be quickly used to assess the impact of depression in patient's functioning during routine clinical practice. Another potential tool is the Depression Inventory Development scale, which rates various symptoms including cognition, anhedonia, and fatigue (Fig. 1). In this scale, patients are asked to rate the frequency and intensity of the impact of depression on executive function, concentration, memory, social activities, sexual activity, hobbies and pastimes, drive/motivation, daytime sleepiness, emotional fatigue, and physical weakness [10].

Table 1 Consensus recommendations on functional outcomes in depression from the Canadian Network for Mood and Anxiety Treatments [8]

All stakeholders should recognize the clinical significance of functional outcomes in the management of major depressive disorder
Valid and reliable tools for measuring functional outcomes should be developed, evaluated, and disseminated
Clinical trials should be designed with functional outcomes as primary or co-primary outcomes
Stakeholders involved in funding, regulation, and knowledge transition of clinical trials should promote and ensure the inclusion of functional outcomes
Measurement-based care should incorporate functional outcome measures
Research about functional outcomes should be shared widely through integrated knowledge translation strategies

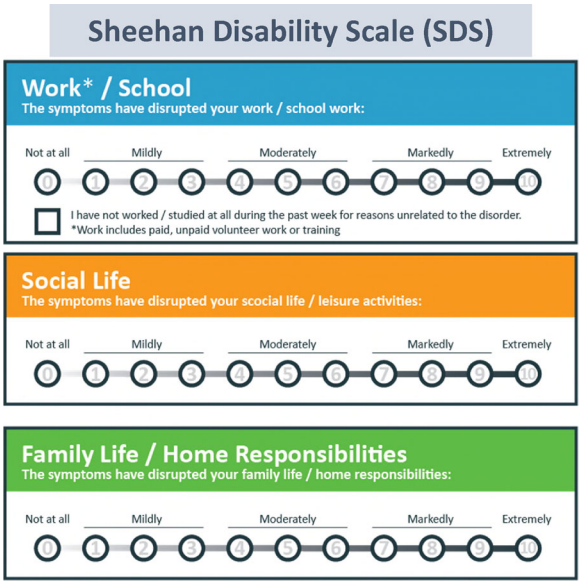

Fig. 1 The Sheehan Disability Score [9]. Reprinted with permission from Handbook of Psychiatric Measures (Copyright © 1983), American Psychiatric Association. All rights reserved

IMPACT OF TREATMENT ON FUNCTION

To illustrate the impact of treatment on patient functioning, agomelatine was selected because there are recent data on the effects of agomelatine on this outcome in patients with major depressive disorder (MDD), using SDS to rate function [5, 11]. Three doses of agomelatine (10 mg/day, 25 mg/day, or a starting dose 25 mg/day titrated to 50 mg/day) were compared with placebo over 6 months in patients with MDD. The primary endpoint was the change in Hamilton Depression Rating Scale [HDRS (or HAM-D)] total score, while the SDS was assessed at weeks 6 and 24 as a secondary endpoint, with functional remission defined as an SDS score ≤ 6 [11]. All agomelatine doses significantly reduced HDRS total score compared with placebo ($P < 0.0001$). In addition, at week 24, significantly more patients in the groups receiving agomelatine 25–50 mg/day (64.1%) or 25 mg/day group (52.5%) than in the placebo group (26.9%) had achieved functional remission ($P < 0.001$ vs. placebo for both dose groups; Fig. 2). This study also demonstrated that a dose of agomelatine of ≥ 25 mg/day is required for a patient to experience a meaningful functional remission [11].

It should be noted that not all patients who achieve a symptomatic response or remission will achieve a functional response or remission. Two studies—a pooled analysis of two randomized placebo-controlled trials of agomelatine (total $n = 633$) [5] and a single-arm, open-label, practice-based study of escitalopram ($n = 211$) [6]—investigated both functional and symptomatic response rates with antidepressant pharmacotherapy. In both studies, functional response was defined as an SDS total score ≤ 12, while symptomatic response was defined as $\geq 50\%$ reduction in HDRS total score in the agomelatine study, and as $\geq 50\%$ reduction in

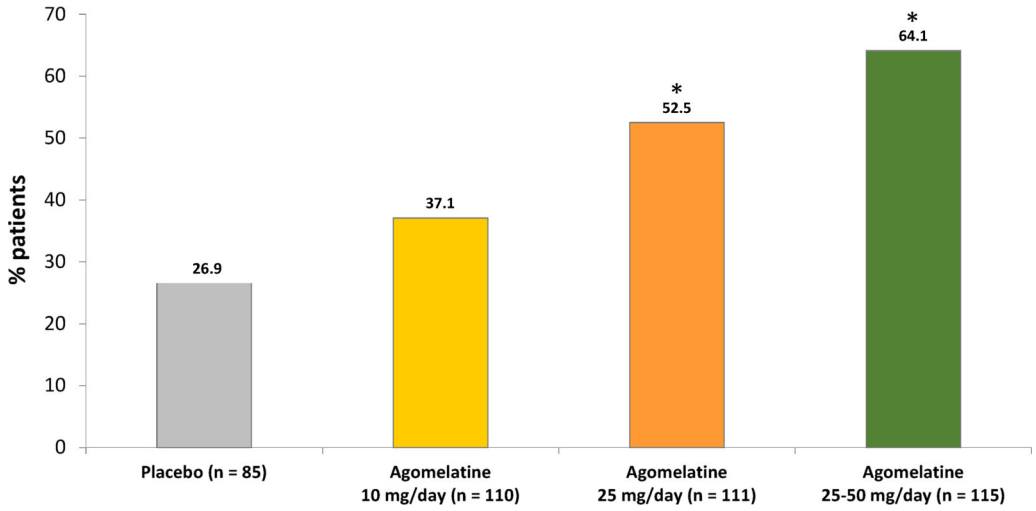

Fig. 2 Effect of agomelatine on the achievement of functional remission (total Sheehan Disability Score of ≤ 2) after 6 months of treatment in a randomized, placebo-controlled study [11]. *$P < 0.0001$ vs. placebo

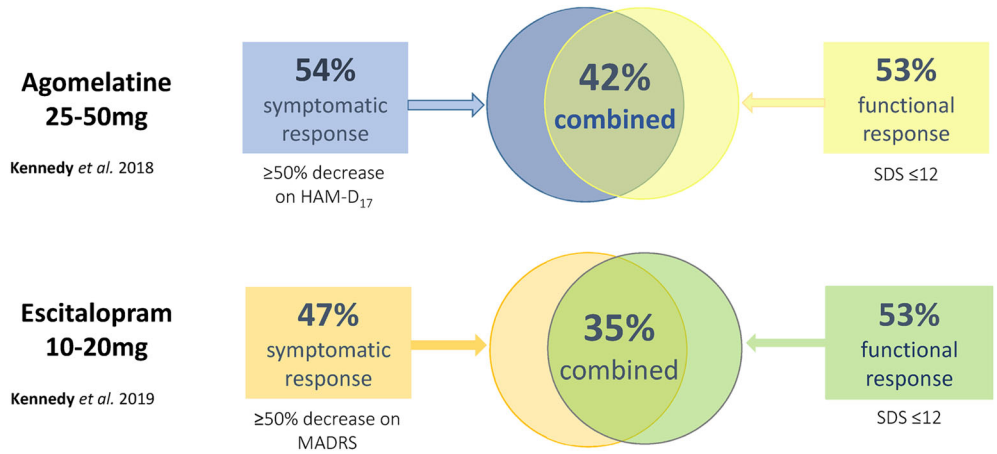

Fig. 3 Rates of symptomatic response, functional response and both, in studies with agomelatine or escitalopram [5, 6]. *HAM-D_{17}* Hamilton Depression Rating Scale, *MADRS* Montgomery–Åsberg Depression Rating Scale, *SDS* Sheehan Disability Score

Montgomery–Åsberg Depression Rating Scale (MADRS) in the escitalopram study [5, 6]. Approximately 54% of the patients receiving agomelatine and 47% of those receiving escitalopram achieved a symptomatic response, and 53% of patients in each study achieved a functional response. However, the proportion of patients who achieved both a symptomatic and functional response was lower: 42% in the study with agomelatine [5] and 35% in the study with escitalopram (Fig. 3) [6]. The escitalopram study also investigated the rate of symptomatic and functional remission, defined as a MADRS score $\leq 10\%$ and SDS score ≤ 6, at 8 and 16 weeks [6]. The rate of remission significantly increased between week 8 and week 16, from 31% (symptomatic remission) at week 8 to 80% at week 16, and from 24% (functional remission) at week 8 to 57% at week 16 ($P < 0.001$) [6]. However, the proportion of patients who

achieved both symptomatic and functional remission was lower at both time-points: 18% at week 8 and 52% at week 16 [6]. These data highlight the importance of assessing functional outcomes, because we cannot assume that patients who experience a symptomatic improvement are also achieving a functional improvement.

THE DISCONNECT BETWEEN SYMPTOMS AND FUNCTION

The differential effect of treatment on symptoms and function is because of the many potential combinations of symptoms that are possible among patients with depression. In an analysis of the Sequenced Treatment Alternatives to Relieve Depression study, four specific symptoms had the greatest impact on function [12]. Similarly, in an earlier naturalistic study in 573 patients receiving pharmacotherapy for depression, 91% of individuals reported low energy, and this was more strongly correlated with work and social function impairment than other depressive symptoms [13]. Moreover, increased energy was more predictive of an improvement in occupational functioning than was a decrease in the number of depressive symptoms [13]. Furthermore, a prospective study by Conradi and colleagues found that, after 3 years, patients who had achieved remission still experienced residual symptoms of depression, such as low mood/loss of interest, cognitive problems, lack of energy, and difficulty sleeping [14].

These data highlight the importance of ongoing assessment of depressed patients, paying particular attention to the symptoms that affect their ability to function, such as fatigue. They are also a pertinent reminder of the widely cited study by Zimmerman and colleagues in which patients ranked the absence of depressive symptoms sixth on their list of desired outcomes from treatment [15]. Therefore, physicians need to recognize the full range of outcomes that patients want from their treatment (positive mental outlook, emotional control, energy, normal functioning), and incorporate these into their treatment plan and goals in addition to aiming for a change in HDRS score. These data also highlight the importance of using validated patient-reported outcome (PRO) measures to assess response in clinical trials and clinical practice.

One such PRO measure is the Multidimensional Assessment of Thymic States (MAThyS), a 20-item instrument in which patients rate dimensions on a visual analogue scale from 0 to 10, where 0 represents the most inhibited/inactive end of the spectrum, 10 the most active/excited end, and 5 indicates an average level. An observational study in 1565 outpatients with MDD, who were prescribed agomelatine, found that motivation was the most impaired MAThyS domain at baseline [16]. In addition, the motivation domain (a proxy measure of anhedonia or reward function) was the most sensitive to change, showing the greatest improvement after 2 weeks of treatment, and an early improvement in motivation the best predictor of a symptomatic response at week 16 [16].

COMBINATION THERAPY

Patients who do not meet the criteria for response during treatment with a selective serotonin reuptake inhibitor (SSRI) may benefit from adjunctive therapy with a dopamine modulator. For example, in the first study of the Canadian Biomarker Integration Network in Depression (CAN-BIND-1), patients who did not meet the response criteria after 8 weeks of treatment with escitalopram (at least 50% decrease from baseline on the HDRS total score) received adjunctive aripiprazole from week 8 onwards; after 8 weeks of combination therapy, 61% of these patients achieved symptomatic response and 53% achieved functional response [6].

Another analysis from the CAN-BIND-1 study showed that patients with high baseline interest–activity scores may benefit from combination therapy with an SSRI and a dopamine agonist [17]. In that analysis, greater loss of interest and reduction in activity scores predicted a poor outcome on escitalopram monotherapy, whereas the same measure was

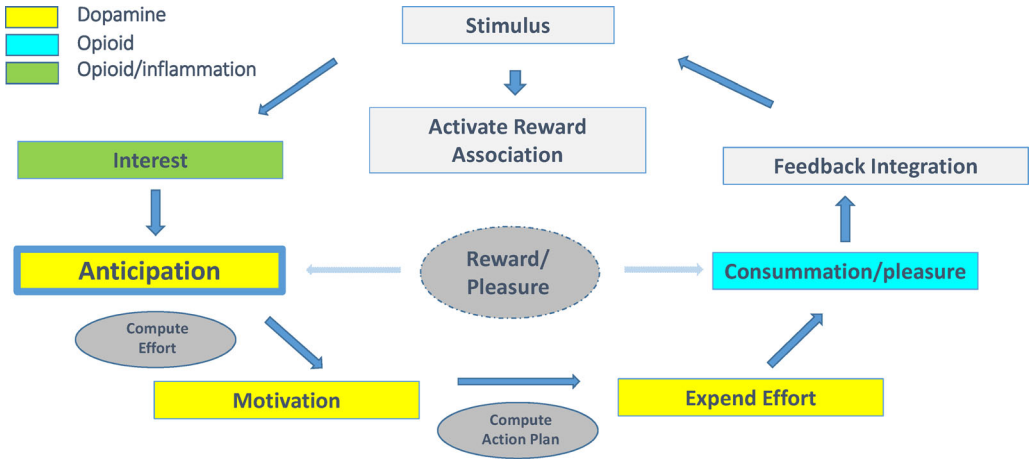

Fig. 4 Model of reward processing [21]. Modified from Rizvi et al. 2016 [21] and Kring and Barch 2014 [22]. Reprinted from Rizvi SJ, et al. Assessing anhedonia in depression: potentials and pitfalls. Neurosci Biobehav Rev. 2016;65:21–35; and Kring E and Barch DM. The motivation and pleasure dimension of negative symptoms: neural substrates and behavioral outputs. Eur Neuropsychopharmacol. 2014;24:725–736, with permission from Elsevier; permission conveyed through Copyright Clearance Center, Inc

predictive of response improvement when aripiprazole was added [17].

The interest–activity score is a single score derived from six parameters from depression rating scales [18], and reflects anhedonia. Specifically, in the CAN-BIND-1 study, these parameters were 'concentration', 'lassitude', and 'inability to feel' from the MADRS, and 'concentration', 'energy', and 'interest' from the QIDS-SR [17]. The relationship between interest–activity scores and poor response to SSRIs has been reported in other studies [18], suggesting that this parameter may help to predict which patients may benefit from combination therapy.

ANHEDONIA AND RESPONSE PREDICTION

The concept of 'anhedonia' has evolved since it was first coined by Ribot in 1897 to describe the inability to feel pleasure [19]. Today, anhedonia is understood to include the inability to pursue reward or experience rewarding activities [20]. Several different neurotransmitters are implicated in the stimulus–reward cycle, controlling interest, anticipation, motivation, and action (Fig. 4) [21, 22]. This implies that aspects of anhedonia, such as reward anticipation, may influence the response to antidepressants.

In the CAN-BIND-1 study, participants were asked to complete a Monetary Incentive Delay task, which measures anticipatory and consummatory responses to reward during functional magnetic resonance imaging (fMRI), at baseline and after 2 weeks of treatment with escitalopram [23]. Greater anhedonia severity at baseline was associated with a poor response to escitalopram. Moreover, an early increase in functional connectivity between the ventral striatum and rostral anterior cingulate nucleus on fMRI between baseline and week 2 correlated with the reduction in MADRS score at week 8 [23]. These data suggest that we may soon be able to apply precision psychiatry by identifying patients who are likely to have a remission during antidepressant therapy, by tailoring treatment more effectively.

TREATMENT PERSISTENCE

Antidepressant therapy is only effective if patients continue to take their medication. Real-world data from the United States have shown that about 50% of patients discontinued their antidepressant therapy after 3–4 months

of treatment, and that more than 75% discontinued treatment within a year [24]. Treatment-related adverse effects, particularly those that may interfere with daily function, can have a major impact on patient adherence. The adverse effects of medication perceived by patients to have the greatest effect on their ability to function at work were daytime sleepiness, difficulty sleeping at night, headache, and anxiety/agitation [25]. Therefore, when selecting treatment for depression, physicians need to consider both antidepressant efficacy and acceptability to patients including their ability to work with minimum interference from side effects. In a large-scale meta-analysis of antidepressant treatments conducted by Cipriani and colleagues, agomelatine, escitalopram, and vortioxetine offered the best balance of efficacy and acceptability [26]. Given the relatively high rates of non-response and non-remission with antidepressant monotherapy, augmentation with atypical dopamine agonist antipsychotic agents is a common strategy to achieve better outcomes [27, 28]. However, given the potential for dopamine-associated akathisia and tardive dyskinesia, it is important to carefully monitor the use of these drugs [29, 30].

COST–BENEFIT OF EFFECTIVE TREATMENT FOR DEPRESSION

Because depression has a marked impact on patients' productivity and work performance, effective treatment of depression has the potential to make a significant contribution not only to individual patients' well-being but also to global economic well-being. According to one estimate, each dollar invested in effective treatment of depression and anxiety yields between US$3 and $6 in total economic gains, with improved occupational productivity contributing about half of these benefits [31].

CONCLUSION

Functional remission is an important treatment goal because it is better than symptomatic remission as an indicator of overall recovery. The best outcomes of depression are achieved when the treatment provides an optimal balance between efficacy and tolerability. In the future, it is likely that physicians are to individualize the treatment of depression based on clinical symptoms and bio-signatures [32].

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