Journal of Affective Disorders 185 (2015) 97–103

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research report

An increase in joy after two weeks is more specific of later antidepressant response than a decrease in sadness

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ARTICLE INFO

Article history:
Received 31 December 2014
Received in revised form
14 June 2015
Accepted 15 June 2015
Available online 27 June 2015

Keywords:
Prediction
Joy
Emotion
Sadness
Treatment response
Major depressive disorder
Agomelatine

ABSTRACT

Background: Early improvement in positive emotions—more than decreases in negative emotions—was highly predictive of treatment response in an ecologically valid prospective manner. This result needs replication with simpler assessments to determine whether it can be translated into clinical practice.
Methods: 2049 adult depressed outpatients receiving agomelatine were assessed at inclusion, week 2, and week 6 using the clinician-rated Quick Inventory of Depressive Symptomatology, Sheehan Disability Scale, Clinical Global Impression scale, and Multidimensional Assessment of Thymic States (MATHYS), an auto-questionnaire rating the frequency of emotions, including sadness and joy, over the previous week.
Results: Joy and sadness had a relatively low correlation coefficient at baseline ($r=-0.277$), joy ($r=-0.160$) being less correlated with clinical severity than sadness ($r=0.317$). An increase in joy at week 2 had higher specificity (85.04%) and positive predictive value (70.55%) for treatment response than decreased sadness (57.92% and 66.04%, respectively), and the global capacity of the former to predict *remission*, either clinical (Yule Q coefficient, 39.96%) or functional (44.35%), was even better compared to the prediction of clinical *response* (37.38%).
Limitations: MATHYS retrospectively assesses emotions, with five possible ratings only, relying on self-rated frequencies. With only a 6-week follow-up, conclusions are limited to short-term aspects of clinical and functional remission.
Conclusions: Early improvement in joy during the first 2 weeks of treatment is strongly specific for treatment response and remission. The frequency of joy captures the predictivity and may deserve further study regarding inclusion in depressive rating scales.

1. Introduction

Although treatments for major depressive episode (MDE) have been available for many decades and are widely prescribed, treatment response is often suboptimal (Bech et al., 2000; Papakostas and Fava, 2009; Walsh et al., 2002). The limited availability of biological markers to help clinicians identify which patients will ultimately respond to treatment (Leuchter et al., 1999; Tadić et al., 2011) and the high cost of these treatments has limited their use. Until now, clinicians have had to rely on initial treatment response before choosing a new treatment strategy when incomplete treatment response is observed. Nevertheless, many guidelines propose a delay of 4 to 8 weeks before a prescribed antidepressant treatment is modified (Anderson et al., 2008; APA, 2010; Bauer et al., 2002; Lam et al., 2009; NICE, 2009).

As adapting the dosage, switching, or combining are clearly relevant treatment options in the case of suboptimal response (Marangell, 2001), deciding if and when to carry out such modifications has become an important clinical issue. Furthermore,

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http://dx.doi.org/10.1016/j.jad.2015.06.019
0165-0327/

shortening the duration of depression could reduce the "toxic effect" of depression (Gorwood et al., 2008), and potentially improve the long-term outcome.

A meta-analysis of all relevant studies showed that a lack of early improvement (usually defined as a 20% decrease in depression severity at week 2 predicts the absence of subsequent treatment response, which could potentially save weeks of inadequate treatment (Gorwood et al., 2013). Indeed, 60% of the improvement that occurs on active antidepressant and placebo may take place during the first 2 weeks of treatment (Posternak and Zimmerman, 2005). However, the usual method of assessing whether there has been a reduction in the severity of depressive symptoms involves a single aspect of treatment improvement (usually a decrease of the total score of a clinical instrument), and a decrease in severity might be more powerfully captured with additional approaches. For example, emotional processing in depression may be altered not only within the dimension of negative affect but also positive affect (Leppanen, 2006). In support of these results, studies have shown that antidepressant use affects the processing of both positive and negative emotions (e.g. Harmer et al., 2009; Rawlings et al., 2010), and recent studies suggest that changes in positive rather than negative emotions may be important in predicting recovery from depression (Cohn et al., 2009; Wichers et al., 2009, 2010). For example, recovery from depression was associated with an increase in the ability to experience reward in daily life (Wichers et al., 2009). A high ability to experience positive emotions in daily life was also associated with increased resilience against the development of affective symptoms (Wichers et al., 2010), with positive, but not negative, emotions predicting psychological resilience (Cohn et al., 2009). A recent study in 49 depressed patients analyzed the predictivity of an early decrease in negative emotions versus an early increase in positive emotions regarding antidepressant efficacy (Geschwind et al., 2011a, 2011b). Early improvement in positive affect during the first week of treatment predicted response (odds ratio [OR]=4) and remission (OR=9) at week 6, while the effect of an early change in negative emotions was only half as large and disappeared when evaluated simultaneously with early change in positive emotions (Geschwind et al., 2011).

Provided that these data are replicable and replicated, such a large effect size would mean that assessing the improvement in positive emotions would be of great clinical value in predicting treatment response. Indeed, the aforementioned study used an'-experience sampling method' whereby participants assess their affect in an ecologically valid prospective study in their daily living environment using a programmed wristwatch emitting a signal at an unpredictable moment in each of 10 90-min time blocks, 17 h a day. Although this method probably holds considerable research interest, it is difficult to use for systematic assessments, retrospective self-assessment probably being the easiest way. Furthermore, with 49 patients included in the final assessment (from an original sample of 83), replication in a larger sample is needed.

We therefore assessed a large sample of depressed outpatients treated with agomelatine and rated the changes in the frequency of their emotions (including sadness and joy) at baseline versus week 2 to compare their capacity to predict treatment response at week 6.

2. Methods

A total of 2351 adult outpatients with major depressive disorder enrolled in psychiatric care sites and receiving agomelatine were assessed at inclusion, week 2, and week 6 using the Quick Inventory of Depressive Symptomatology-Clinician-rated (QIDS-C) and the Clinical Global Impression (CGI) scale, as described elsewhere (Gorwood et al., 2013).

The study was performed according to international and French regulatory guidelines and current codes of Good Clinical Practice. Each patient was informed about the aims and procedures of the study and provided written, informed consent. The study protocol was submitted to and approved by the local Ethics Committee. With respect to confidentiality of patient records, data handling for the study was authorized by the *Commission Nationale d'Informatique et de Libertés* (CNIL), the French agency which ensures that all medical information is kept confidential and anonymous.

Clinical response was defined as a decrease in QIDS-C scores of $\geq$ 50% from baseline, and clinical remission as being when the last assessment at week 6 showed a QIDS-C score of $\leq$ 5 (Rush et al., 2003).

The study included adult outpatients fulfilling DSM-IV (*Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*) diagnostic criteria for an MDE and who required treatment. The severity of the MDE had to be moderate to severe, defined as a score on the CGI severity scale (CGI-S) (NIMH, 1976) of $\geq$ 4 and a score of $\geq$ 16 on the 16-item QIDS-C (Rush et al., 2003). Patients with (i) psychotic or (ii) catatonic features were excluded, as were those with (iii) current alcohol or (iv) substance use disorders, (v) a history of non-response with agomelatine or (vi) a contra-indication to agomelatine, (vii) patients with any condition that could interfere with the implementation or interpretation of the study, and (viii) pregnant or (ix) breastfeeding women. Concomitant psychoactive medication was not allowed, with the exception of benzodiazepines already prescribed at the inclusion visit.

All patients received agomelatine (25–50 mg) once daily at bedtime. Patients were evaluated at an inclusion visit (week 0) and returned for two follow-up visits at week 2 and week 6. Starting at 25 mg, the dose of agomelatine could be increased at week 2 up to 50 mg at the discretion of the investigator, with no specific recommendations in order to reflect the usual practice.

The Multidimensional Assessment of Thymic States (MATHYS) was used at baseline, week 2, and week 6. MATHYS is an auto-questionnaire that includes the frequency rating of seven emotions (sadness, joy, irritability, panic, anxiety, anger, and exaltation) occurring during the previous week. Rating is based on a Likert scale, with five frequencies: never (0), occasionally (1), frequently (2), very frequently (3), and constantly (4) (Henry et al., 2007).

The Sheehan Disability Scale (SDS) is a patient-rated, discretized analog measure of functional disability in work, social, and family life, the cut-off for functional remission being a global score of $\leq$ 6 (Sheehan et al., 2011).

2.1. Statistics

The MATHYS rates seven emotions that could be considered as either positive (joy and exaltation) or negative (sadness, irritability, panic, anxiety and anger). To test how these emotions are organized, we made a principal component analysis and used the generated composite scores for each detected principal components (with eigenvalue above 1). We focused on baseline values (to detect the organization of its initial structure), and the change of scores between baseline and week 2) to test their capacity to predict treatment response. The predictivity of the sum of'joy' and'exaltation' was also analyzed, after standardizing their scores, as these two items did not have the same average and variance.

Sensitivity (proportion of true positives), specificity (proportion of false negatives), positive predictive value (PPV; probability that treatment outcome is obtained when the frequency of the studied emotion changes appropriately), and negative predictive value (NPV; probability that treatment outcome is not present when the