Research report

What is important in being cured from: Does discordance between physicians and patients matter? (2)

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ABSTRACT

Aims: The influence of discordance in what is important in being cured from depression on clinical outcome at 6 months, assessed with a divergence index.
Methods: 304 outpatients treated for depression by general practitioners or by psychiatrists and completing a 6-month treatment period: a divergence index (divergence between physician and patient view on what is important in being cured from depression) was calculated for each physician–patient pair. The relation between this index and outcome at 6 months was analyzed (including depressive, anxious and somatic symptom severity, positive effect, functional impairment and quality of life (psychological and social relations).
Results: Response rates (50% improvement) were 65.9% for depressive symptomatology and 46.2% for anxious symptomatology. The subgroup with a poor physician–patient agreement (highest quartile) on expectations had a worse clinical outcome than the subgroup with an excellent physician–patient agreement (lowest quartile): differences in response rate between these groups ranged from 9% to 27%; this difference reached statistical significance for 3 outcome variables (anxiety, positive effect and social relationships).
Conclusions: The study shows that outcomes with standard antidepressant drugs are still suboptimal and that discordance between what patients' and physicians' consider important in the definition of cure from depression significantly influences clinical outcomes at 6 months.

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1. Introduction

A meta-regression analysis showed that response rates are 53.8% for a typical antidepressant and 37.3% for placebo suggesting that about two thirds of antidepressant efficacy is due to a non-specific placebo effect (Papakostas and Fava, 2009). But again, important differences were found between observer-rated and self-rated outcomes. Using non-disease specific scales, it has indeed been reported that the percentage of patients with a 'global improvement' during antidepressant treatment was 10% higher in the physician's assessment than in the patient's assessment (Demyttenaere et al., 2009a, 2009b). Moreover, in a group of patients being in (observer-rated) remission (i.e. a HDRS – Hamilton Depression Rating Scale – ≤ 7), only 55111% considered themselves in remission (not defined, but

based on personal conceptualization of remission) (Hamilton, 1960; Zimmerman et al., 2012). Interestingly, patients in observer-rated remission who also considered themselves in remission had higher scores on positive mental health and had significantly less functional impairment than patients with only observer-rated remission (Zimmerman et al., 2012).

The reasons for these clinically important discrepancies have been insufficiently investigated and they could theoretically be influenced by clinical variables, trial or design features, patient attitudes and behaviors, and doctor–patient relationship. For example, it has been shown that a higher baseline discrepancy between scores derived from an observer-scale and a self-rating scale leads to a poorer outcome, is generally observed in patients with a comorbid personality disorder and positively correlates with anxiety levels (Rane et al., 2010). Factors related to patient expectations from antidepressant have also been shown to influence outcome. Response rates in patients treated with an antidepressant were found to be 65.4% in drug–drug studies, 57.7% in

drug–drug–placebo studies and 51.7% in drug–placebo studies while in patients treated with placebo, response rates were 44.6% in drug–drug–placebo trials and 34.3% in drug–placebo trials (Sinyor et al., 2010). This is further illustrated by a study showing higher HDRS scores immediately postrandomization (moving to placebo or staying on fluoxetine): this increase in HDRS scores was found as well in patients staying on fluoxetine as in patients moving to placebo (Rutherford et al., 2014). This suggests that treatment changes influence paitents' expectations of improvement, which, in turn, affect their depression symptom severity. These data suggest that the chance of being on active treatment (through physician and patient expectations) is an important predictor of outcome. Another study investigating the influence of baseline attitude to taking (antidepressant) medication showed that patients with a baseline positive/neutral/negative attitude towards antidepressants presented a placebo response rate of 46%, 37% and 30% and an antidepressant response rate of 67%, 60% and 56%, respectively, again suggesting that baseline expectations and attitudes predict outcome (Demyttenaere et al., 2011). The NIMH-funded study on the efficacy of hypericum perforatum did not find any significant difference in response rates between the hypericum arm, the sertraline arm and the placebo arm but a reanalysis taking into account patient's guess of which treatment they got showed important differences in outcome: patients guessing they were on sertraline had a 56% response rate, patients guessing they were on hypericum had a 68% response rate while patients guessing they were on placebo had a 24% response rate (Hypericum Depression Trial Study Group, 2002; Chen et al., 2011). Further, the attitude and behavior of the prescribing psychiatrists are also important: the psychiatrist is not only a provider of treatment but also acts as a mean of treatment. Indeed, the proportion of variability in outcomes was shown to be due less to the antidepressant treatment received (imipramine or placebo) than to the psychiatrist administering the treatment (McKay et al., 2006). Interestingly, the psychiatrist effects were not as dramatic for the observer-rated measure than for the self-report measure (6.7% and 9.1% of the variance, respectively).

We previously showed that what physicians and patients consider to be important in being cured from depression is different, and the present paper investigates whether these differences influence outcome in depressed patients treated with antidepressants.

2. Methods

Ethics statement, patient recruitment and data collection were described in the previous paper (Demyttenaere et al., submitted).

2.1. Treatment and clinical outcome

The protocol stipulated that the treatment was entirely left to the discretion of the physician: one antidepressant was prescribed to 92.5% of the patients and two antidepressants were prescribed to 7.1% of the patients (no antidepressant was prescribed to 0.2% of the patients and 43 different antidepressants were prescribed to 0.2% of the patients). In 45.2% of the patients, at least one modification in the antidepressant treatment was observed during the 6-month study period.

The clinical status of the patient was assessed with the following mentioned self-rating scales: the Patient Health Questionnaire-Depression (PHQ-depression; depressive symptoms), Hospital Anxiety and Depression Scale-anxiety (HADS-anxiety; anxious symptoms), Patient Health Questionnaire-Somatic Symptoms severity (PHQ-somatic; somatic symptoms), the Positive And Negative Affect Schedule-Positive effect subscale (PANAS-positive effect), the

Sheehan Disability Scale (SDS; functional impairment), and the Abbreviated World Health Organization QoL (WHOQOL-BREF; quality of life-psychological and social relationships), at baseline and after 6 months of treatment (Kroenke et al., 2001, 2002; Zigmond and Snaith, 1983; Watson et al., 1988; Sheehan et al., 1996; WHO-QOL group, 1998).

2.2. Statistical analysis

Discordance index based on the top 10 DEsCRIBE™ items of the patient.

The discordance between what patients and physicians consider important in defining cure from depression was based on their respective baseline scores on the DEsCRIBE™questionnaire, where a ranking (importance for being cured from disorder) was given to depressive, anxious and somatic symptoms, positive effect, disability and quality of life items (Demyttenaere et al., submitted). A discordance index (DI) was constructed to evaluate the baseline agreement between physician and patient on the definition of being cured from depression. The discordance index was calculated for each possible pair (physician–patient) by using the differences between the item scores given by the physician and his/her patient. The items considered in the construction of the discordance index were the 10 DEsCRIBE™ items classified in first position of importance by the patients in the definition of being cure from depression. To correct for the fact that patients always gave higher scores than physicians, individual patient's scores were standardized by subtracting the corresponding mean of each item. The same correction was applied to the individual physician's scores. The absolute difference between the standardized score of the patient and the standardized score of the physician was calculated for each of the 10 selected items. The discordance index was then defined as the average of the 10 absolute differences. DI scores range between 0 and 5, where high values indicate strong divergence and low values strong agreement between physician and patient about the definition of being cured from depression

$$DI = \sum_{i=1}^{10} \frac{|(\text{score item } i - \text{mean item } i) \, \text{phys} - (\text{score item } i - \text{mean item } i) \, \text{pat}|}{10}$$

The mean DI was 1.1 ± 0.57 and the median 0.99. Based on their DI value, patients were classified into 4 groups (according to the quartiles): excellent agreement with physician (DI < 0.71), rather good agreement ($0.71 \leq$ DI < 0.99), rather poor agreement ($0.99 \leq$ DI < 1.47), and poor agreement (DI ≥ 1.47).

Results were summarized as mean and standard deviation (SD) for quantitative variables and scores; counts and proportions (%) were used for categorical variables. The correlation coefficient was computed to measure the association between two quantitative variables. Mean values were compared by one-way analysis of variance (ANOVA). Proportions were compared by the chi-squared test for contingency tables. The comparison of the clinical score at 6 months according to DI-categories was made by ordinal logistic regression. A Cochran–Armitage test for trend was used to compare the 6-month response rates between the DI groups. Results were considered significant at the 5% critical level ($P < 0.05$). Calculations were always done on the maximum number of data available. All statistical calculations were performed by using SAS (version 9.3 for Windows) and S-PLUS (version 8.1) packages.

3. Results

Of the 426 patients analyzed in the study, 304 (71.3%) completed the 6-month follow-up. Clinical status (responses and

50%-improvement rates) for the different clinical scales used to assess the outcome are given in Table 1. The PHQ-depression scores at 6 months showed that 11% of the patients were still suffering from major depression, 65.9% were responders (50% improvement) and only 49% were in remission (PHQ depression ≤ 4). The HADS-anxiety scores at 6 months showed that 24.4% of the patients were still probable cases for an anxiety disorder and that 46.2% were responders (50% improvement). Treatment changes between baseline and 6 months follow-up were found in 45.2% of the patients, and increasing the dose was the most frequently found strategy (21.5%) followed by switching (9.2%). The largest improvement, i.e. response rates, was found for depressive symptoms, functional impairment and psychological aspects of quality of life (65.9%, 54.9% and 52.7%, respectively) and the smallest improvement was found for social relationships in quality of life, somatic symptoms and anxiety symptoms (35.7%, 46.2% and 46.2%, respectively).

The discordance index based on the top 10 DEsCRIBE™ items of the patient, reflecting how far the physician reported important items in defining cure from depression were from the patient reported ones, was negatively correlated with the age of the patient ($r=-0.10$; $P=0.03$). The discordance index was also significantly higher in drop-outs than in completers (1.20 ± 0.55 versus 1.10 ± 0.58; $P=0.03$), especially in the subgroup of drop-outs due to patient's refusal to continue the medication (1.38 ± 0.54). Finally, the discordance index was significantly correlated with the length of the current depressive episode (weeks) ($r=0.13$; $P=0.006$) but not with the number of previous episodes.

The relation between the baseline discordance index and clinical outcome was tested in two ways: excellent, rather good/good, rather poor/weak and poor/poor baseline agreement versus 6-month mean score and versus 6-month response rates (50% improvement, i.e. a decrease of minimum 50% from baseline for the scales assessing depression, anxiety, somatic symptoms, functional impairment) or an increase of minimum 50% from baseline for the scores on positive effect-quality of life) for the different scales. When looking at the mean scores at 6 months, a greater discordance between physician and patient resulted in a numerically worse score on all scales but this reached statistical significance only for somatic symptoms (and with a trend for depressive symptomatology, anxious symptomatology and positive effect) (Table 2 and Fig. 1a). Response rates on the depression questionnaire for excellent, rather good, rather poor and poor agreement were 72%, 62%, 66% and 63%, respectively ($P=0.68$) and remission rates on the same questionnaire (PHQ-depressive ≤ 4) were 56%, 48%, 44% and 46%, respectively ($P=0.49$). When looking at response rates at 6 months, a poorer agreement resulted in a numerically lower response rate on all scales but this reached statistical significance only for anxiety symptoms, positive effect and social relationships in quality of life (Table 3 and Fig. 1b).

4. Discussion

The current study again underscores the suboptimal treatment in patients with a major depressive episode. After 6 months, response (50% improvement) in depressive symptomatology is achieved in only 65.9% of the patients, and remission only in 49% of the patients. The outcome is even worse when looking at the accompanying anxiety symptoms where response is achieved in only 46.2% of the patients. These figures are in the same range as those found in other large studies. The FINDER study showed a 6-month remission rate of 50% for depression and also a lower remission rate (40%) for anxiety disorders; STAR∗D found a 14-week and a 1-year (with up to 4 treatment steps) remission rate of 37% and in 67% of patients, respectively (Demyttenaere et al., 2009a, 2009b; Rush et al., 2006). It is worrying that after 6 months

Table 1
Clinical status at baseline and at 6 months.

Scale	Baseline	6 months	6-month response rate (%)
PHQ9-depression	16.5 ± 5.8	6.40 ± 5.6	65.9
HADS-anxiety	12.9 ± 3.9	7.11 ± 4.5	46.2
PHQ-somatic	9.69 ± 4.8	5.86 ± 4.4	37.6
PANAS-positive	21.1 ± 7.1	31.4 ± 9.3	47.1
SDS-total	19.2 ± 6.8	10.0 ± 9.0	52.8
WHOQOL-BREF psychological	35.6 ± 16.3	58.6 ± 20.6	52.7
WHOQOL-BREF social relationships	44.6 ± 21.2	60.0 ± 22.2	35.7

of treatment, 11% of the patients still fulfill criteria for major depression and 24% are yet probable cases for an anxiety disorder. In the FINDER study, these figures were 25% and 33%, respectively (Demyttenaere et al., 2009a,2009b). Since remission is the goal of antidepressant treatment, compliance with guidelines (on the physician side) is quite poor; although remission (for depression) was reached in only 49%, changes in the treatment regimen were noticed in merely 45% of patients. However, these figures are higher than what was found in a very large naturalistic database where therapy change rates during treatment with third-, second- and first-generation antidepressants was 19%, 21% and 43%, respectively (Sheehan et al., 2008).

A discordance index was calculated to assess how much the physician reported important items in defining cure from depression were from the patient reported ones at baseline. A lower discordance was found in older patients and a higher one in patients with a longer duration of the current episode. The baseline discordance was also higher in drop-outs than in completers and especially in the subgroup of drop-outs due to the patient's refusal to continue the medication, possibly suggesting that a high concordance of expectations is related to a better adherence to treatment.

The relation between the baseline discordance and clinical improvement during 6 months of treatment was also investigated. Interestingly there was a consistent trend for all outcome variables (at 6 months) that a weak discordance between physicians and patients resulted in a better outcome, although often only numerically. For example, the difference in response rates between the highest and lowest quartiles of the index (i.e. excellent versus poor agreement) amounted 9% for depression, 22% for anxiety, 6% for somatic symptoms, 27% for positive affect, 15% for functional impairment, 13% for the psychological aspects of quality of life, and 15% for the social relationships aspects of quality of life; these differences reach statistical significance for anxiety, positive affect and the social relationships aspects of quality of life. To put these figures into perspective, it is important to notice that in randomized clinical trials, the difference in response rates between antidepressants and placebo is 15.5%. Further, the difference in response rates between patients with a positive attitude towards taking an antidepressant and patients with a negative attitude towards taking an antidepressant reached 16% in patients on placebo and 11% in patients on an antidepressant (Demyttenaere et al., 2011). Anyhow, these differences taking into account expectations and attitudes are much larger than differences between different classes of antidepressant drugs: e.g. it was shown that the difference in response rates between venlafaxine and SSRIs was 4.3% in 8-week randomized clinical trials and that the difference in remission rates in a 6-month open-label trial between venlafaxine and SSRIs was only 3.5% (Papakostas et al., 2007; Thase et al., 2011).

To the best of our knowledge, this is the first paper investigating whether the discordance between what physician or patients

Table 2
Baseline discordance index and clinical status at 6 months (scores on different psychometric tests).

Scale	Baseline agreement between physician and patient				P-value*
	Excellent	**Rather good**	**Rather poor**	**Poor**	
PHQ9-depression	5.7 ± 5.3	6.2 ± 5.3	6.8 ± 5.9	7.1 ± 6.1	0.09
HADS-anxiety	6.0 ± 4.1	7.7 ± 4.0	7.2 ± 4.9	7.6 ± 4.9	0.07
PHQ-somatic	5.2 ± 3.9	5.7 ± 3.9	6.1 ± 5.3	6.8 ± 4.5	0.04
PANAS-positive	32.8 ± 9.5	31.0 ± 8.7	31.7 ± 9.4	29.7 ± 9.5	0.09
SDS-total	8.9 ± 8.9	10.1 ± 8.5	9.4 ± 8.8	11.8 ± 10.0	0.11
WHOQOL-BREF psychological	59.5 ± 21.1	57.8 ± 19.4	59.3 ± 21.3	56.9 ± 21.2	0.58
WHOQOL-BREF social relations	62.3 ± 21.4	58.4 ± 21.3	60.5 ± 23.9	57.6 ± 22.3	0.31

* Ordinal logistic regression (excellent versus poor agreement).
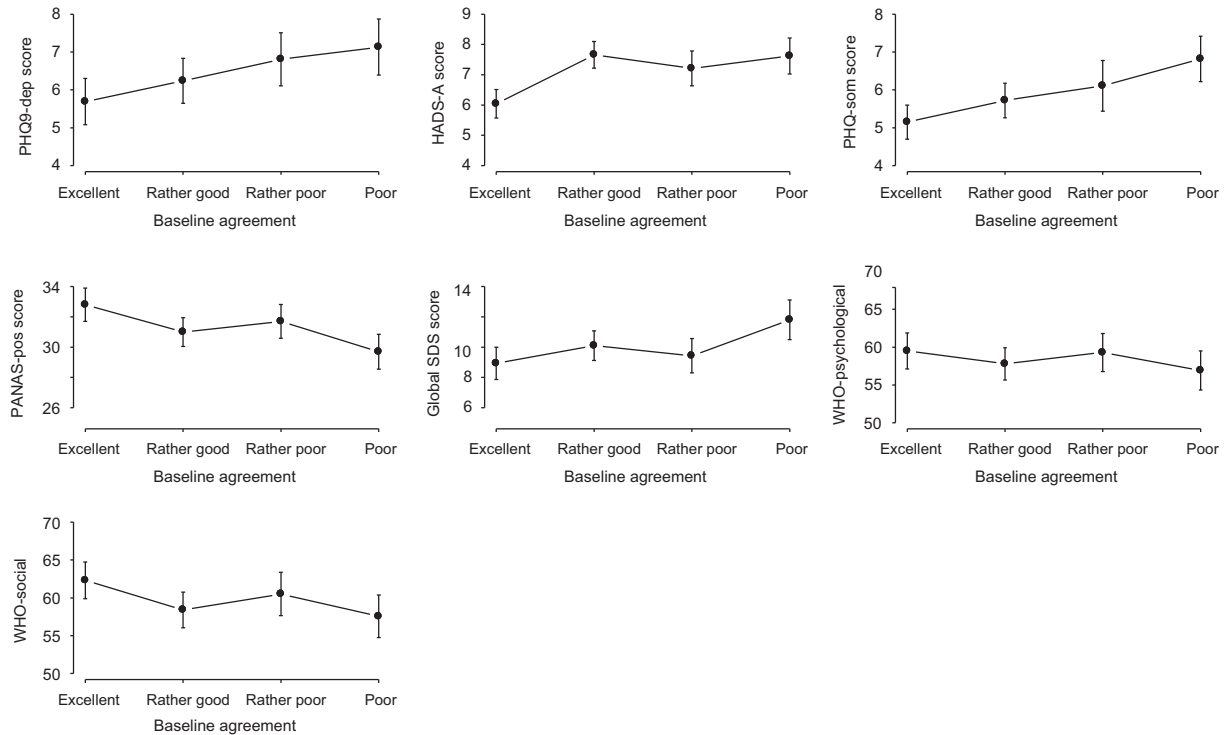
Fig. 1. Baseline agreement between physician and patient and clinical outcome: (a) clinical status at 6 months, (b) evolution from baseline to 6 months.

Table 3
Baseline discordance index and clinical status at 6 months (response rates – 50% improvement—for different psychometric tests).

Scale	Baseline agreement between physician and patient				P-value*
	Excellent (%)	**Rather good (%)**	**Rather poor (%)**	**Poor (%)**	
PHQ9-depression	72	62	66	63	0.68
HADS-anxiety	62	41	44	40	0.02
PHQ-somatic	42	34	38	36	0.61
PANAS-positive	66	38	47	39	0.01
SDS-total	63	52	56	48	0.38
WHOQOL-BREF psychological	65	48	46	52	0.13
WHOQOL-BREF social relations	51	32	22	36	0.02

* Trend test.

report as important items in defining cure from depression influences outcome in depression. We can only speculate why this discordance significantly influences outcome (anxiety, positive affect, and social relationships in quality of life). The literature reports several studies investigating either patient or physician expectations or therapeutic alliance but not the combination of these factors. For example, a study used path analysis to show that patients' treatment expectancies significantly influenced clinical improvement but only indirectly through the patient alliance; and that therapists' global expectancies also influence clinical improvement partly directly and partly through the patient alliance (valid conclusions for the 4 different treatment arms: cognitive-behavior therapy, interpersonal therapy, imipramine+clinical management, placebo+clinical management) (Meyer et al., 2002). Another interesting paper suggested that a good communication and a good alliance are even more important for some subgroups of patients; it was for example shown that a good communication and a good alliance were important for outcome (in diabetic control) mainly in patients with a dismissing attachment style (Ciechanowski et al., 2001).

Our research protocol did not include a scale assessing doctor–patient alliance but it could well be hypothesized that more common expectations are related to a better alliance. Anyhow, a lower discordance index illustrating more common expectations from antidepressant treatment and so probably a better therapeutic alliance between a patient and a physician could augment the efficacy of the prescribed drug, have a direct effect on clinical
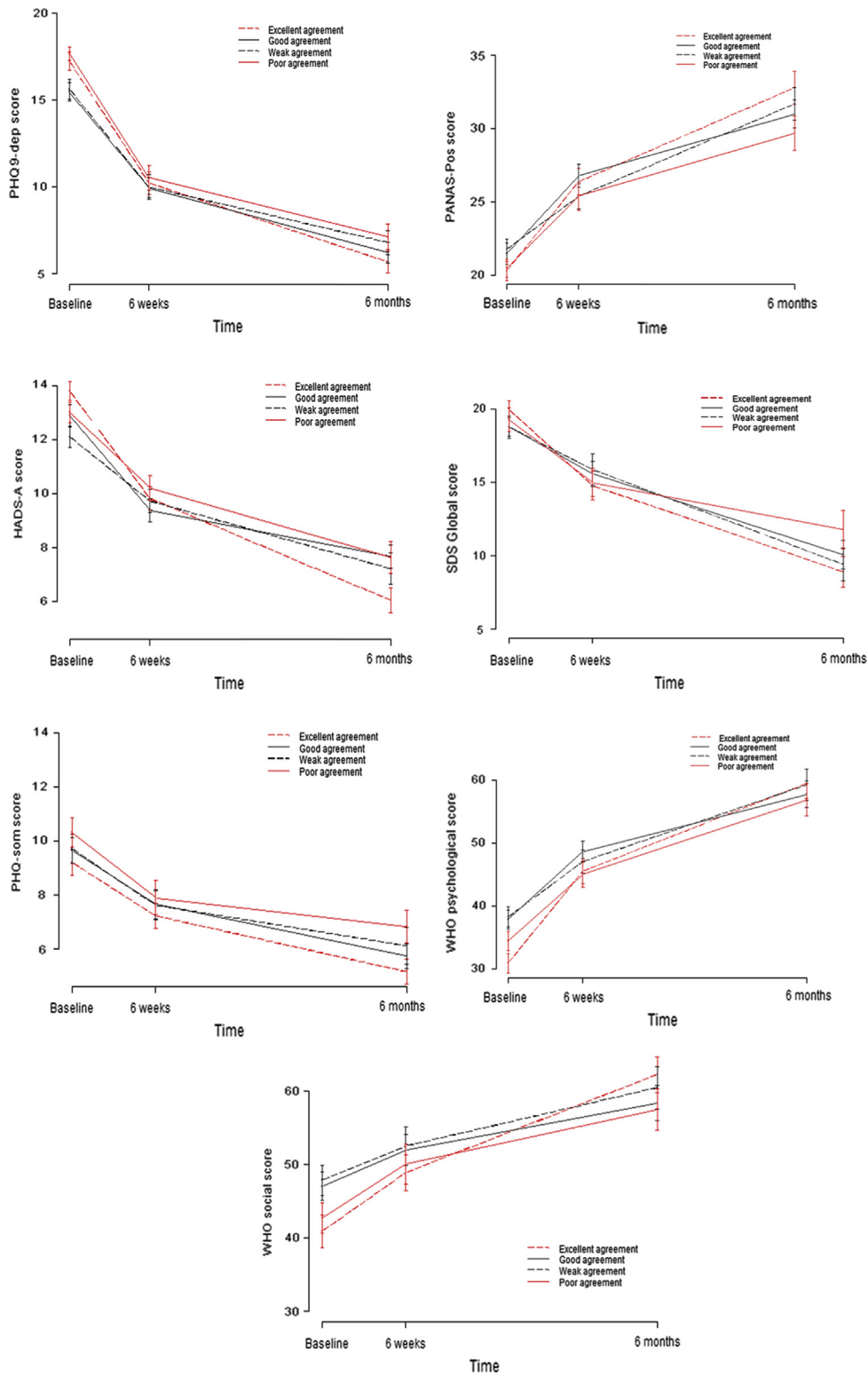
Fig. 1. (*continued*)

outcome or on outcome in the presence of the prescribed drug (Zuroff and Blatt, 2006). It cannot be forgotten that about two thirds of the antidepressant effect is 'placebo' but the latter refers to the common features of care: therapeutic alliance, hope, expectation, remoralization, receipt of an explanatory system, convincing rationale, therapeutic relationship, rituals, healing context including the patient's and the physician's beliefs and representations.

In conclusion, the present study illustrates that outcomes with standard antidepressant drugs are still suboptimal and that baseline discordance between physician and patient reported important items in defining cure from depression significantly influence clinical outcomes at 6 months, mainly for anxiety, positive affect and social relationships in quality of life.

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