What does the MADRS mean?

Leucht, Stefan; Fennema, Hein; Engel, Rolf; Kaspers, Marion; Lepping, Peter; Szegedi, Armin

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What does the MADRS mean? Equipercentile linking with the CGI

Running Title: Linking the MADRS and CGI scales

Authors: Prof Stefan Leucht, Dr Hein Fennema, Prof Rolf Engel, Dr Marion Kaspers, Prof Peter Lepping, Dr Armin Szegedi

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Key words: Montgomery Asberg Depression Rating Scale (MADRS), Clinical Global Impression (CGI), clinical relevance, major depression, remission, response, equipercentile linking

Abstract

Little is known about the clinical relevance of the Montgomery Asberg Depression Rating Scale (MADRS) total scores. It is unclear how total scores translate into clinical severity, or how commonly used measures for response (reduction from baseline of ≥50% in the total score) translate into clinical relevance. Moreover, MADRS based definitions of remission vary. We therefore compared: a/ the percentage and absolute change in the MADRS total scores with Clinical Global Impression – Improvement (CGI-I); b/ the absolute and percentage change in the MADRS total scores with Clinical Global Impression – Severity (CGI-S) absolute change. The method used was equipercentile linking of MADRS and CGI ratings from 22 drug trials in patients with Major Depressive Disorder (MDD) (n=3,288). Our results confirm the validity of the commonly used measures for response in MDD trials: a CGI-I score of 2 ('much improved') corresponded to a percentage MADRS reduction from baseline of 48% to 57%, and a CGI-I score of 1 ('very much improved') to a reduction of 80% to 84%. If a state of almost complete absence of symptoms were required for a definition of remission, a MADRS total score would be < 8, because such scores corresponded to a CGI-S score of 2 ('borderline mentally ill').

Key words: Montgomery Asberg Depression Rating Scale, Clinical Global Impression, equipercentile linking

Introduction

The Montgomery Asberg Depression Rating Scale [1] is a 10-item clinician rated instrument developed to quantify the severity of depression in subjects already diagnosed with this disorder. It is one of the most widely used outcome measure in depression, utilized in many trials of new antidepressants submitted to the Food and Drug Administration (FDA) and the European Medicines Agency (EMA). Another frequently used clinician rated instrument in depression research, the Clinical Global Impressions Scale (CGI) [2], describes a patient's overall clinical state as a global impression. It separates between the patient's illness severity (CGI-S) on a scale from 1 to 7, and change from baseline on an improvement scale (CGI-I, formerly CGI-Change; details see below). It thus provides information about the clinical relevance of changes observed during treatment. It has been shown that CGI appears to be intuitively understood by clinicians, achieving good inter-rater reliability[3]. It has been demonstrated that a substantial correlation exists between the MADRS and other frequently used clinician rated scales used in depression, such as the Hamilton Rating Scale for Depression (HAM-D) [4,5], the Global Assessment Scale (GAS) [6] or the Beck Depression Inventory [7]. While response is usually defined as at least 50% reduction of the MADRS total score from baseline, little consensus exists about the definition of remission, where cut-offs points of ≤4 [8], ≤ 9 [8], ≤ 10 [9,10], ≤ 12 [11], of the MADRS have all been used. However, few studies have examined the validity of such cut-off points. They remain expert opinion–based definitions, so that an ACNP task force asked for validation studies [12]. Furthermore, little is known about the clinical relevance of MADRS total scores in terms of their correspondence with clinically judged illness severity. In other words, how globally ill does a clinician judge someone to be who has a MADRS score of, for example, 20 or

30? How much does a clinician really notice a MADRS reduction of, say 50% of the patient's baseline total score? The CGI was designed to give answers to these questions so that we decided to use it in an equipercentile linking analysis (see method section[13]). There is a lot of clinical utility in the ability to link such scales, as it allows the nominal translation of vast amounts of data into other scales, adding significantly to the available clinical data for various treatments without the need for new trials. This has already been shown to be possible and useful in the evaluation of clinical relevance of antipsychotics in schizophrenia and Transmagnetic Stimulation in major depression.

The purpose of this study was to find corresponding points for simultaneous MADRS and CGI ratings within a large sample of patients with Major Depressive Disorder (MDD) who were participating in drug trials following the methods of a previous analysis on the relationship between the HAMD [4] and the CGI [14].

Materials and methods

The clinical trial data used for this study come from studies conducted with full sponsorship from Organon. Mirtazapine was used as a treatment in placebo controlled, comparator controlled or open-label trials in patients with Major Depressive Disorder (MDD). We examined absolute as well as percentage reductions from baseline in MADRS total scores and correlated them with CGI-Severity of Illness (CGI-S) and CGI-Improvement (CGI-I) scores, using the equipercentile linking method [13]. This method allows a nominal translation from MADRS scores into CGI scores linking the relative values of the two scales. In other words, it gives any

particular MADRS total score or percentage change an equivalent value on the CGI-S or CGI-I scale.

Rating scales

The ratings on the MADRS [1] are determined with a semi-structured clinical interview, yielding a maximum score of 60. The 10 items are rated on a 0-6 point scale with anchors at 2 points intervals. The CGI-S and CGI–I (formerly CGI-C) scales are clinician rated scales [2]. For the severity scale (CGI-S), clinicians rate patients relative to their past experience with other patients with the same diagnosis, with or without collateral information. For the CGI-S, the time span considered is the week before the rating, and the following scores can be given: 1=normal, not at all ill, 2=borderline mentally ill, 3=mildly ill, 4=moderately ill, 5=markedly ill, 6=severely ill, and 7=among the most extremely ill patients. The CGI-I scale assesses the patient's improvement or worsening since the start of the study using the following scores: CGI-I: 1=very much improved, 2=much improved, 3=minimally improved, 4=no change, 5=minimally worse, 6=much worse, 7=very much worse.

The database

We used individual patient data from all studies assessing the antidepressant mirtazapine (tablets and intravenous formulation) in MDD and used MADRS as well as CGI. All those studies were sponsored by Organon, now part of Merck (MSD). We only analyzed studies in which MADRS and CGI-S and CGI-I assessments were performed at baseline, and days 7, 14 and 28. (for an overview of included studies see Table 1). Table 1 about here

Statistical analysis

'Linking' pertains to the search for corresponding points on different, but correlated, psychometric instruments [13], and is considered as a manner of anchoring that helps in understanding the clinical meaning of a given scale score [15,16]. It has been previously noted that a regression analysis, although frequently used, would not be an appropriate statistical approach [15,16], because linear regression treats one scale as the independent variable measured without error and the other as the dependent variable measured with error. Thus, this approach could be considered conceptually wrong because both variables are actually measured with random error. For this study we therefore used equipercentile linking, a technique that identifies those scores on both measures that have the same percentile rank. This approach was previously used in a number of studies linking the HAM-D [14], and outcome measures in schizophrenia and anxiety with the CGI [15-22]. The SAS program EQUIPERCENTILE [23] was used. In the first step, percentile rank functions are calculated for both variables linking is performed for. Using the percentile rank function of one variable and the inverse percentile rank function of the other, for every score of one variable a score on the other variable that has the same percentile rank is identified applying the algorithms described by Kolen and Brennan (2004)[24]. For each linking task, all patients with values which were valid on both measures were included in the analysis. The duration of the studies included in our database ranged from 28 to 156 days (4 to 21 weeks), but not all studies provided data for the same time points. To avoid trial effects that could have biased the results, our analysis only included data from baseline and Days 7, 14 and 28. The following analyses were performed:

a. Linking the MADRS total scores with CGI-S
b. Linking the absolute and percentage change in the MADRS total scores with CGI-S absolute change
c. Linking the percentage and absolute change in the MADRS total scores with CGI-I

Results

We identified 22 studies (one dose finding study, three placebo controlled studies, four placebo and active compound controlled studies, nine direct comparisons between mirtazapine and another antidepressant, one double blind oral versus intravenous, and four open-label studies). The study data was received courtesy of Organon for the independent use in our group. Our database includes all available studies from Organon on mirtazapine. Included patients had a diagnosis of a MDD according to Diagnostic and Statistical Manual of Mental Disorders (DSM) III, DSM III-R or DSM IV criteria (APA, 1980, 1987, 1994). A total of 3,288 patients participated in the examined studies (1,230/37.4% males; 2,057/62.6% females; mean age (standard deviation [SD]): 44.9 (13.5) years; mean weight (SD): 70.8 (16.5) kg; mean height (SD): 167.9 (9.5) cm). The mean total MADRS score (SD) at baseline was 31.1 (6.5), the mean CGI-S Score (SD) was 4.6 (1.0); indicative of moderately severe depression and moderate to marked illness severity, respectively.

a. The correlations between the MADRS total scores and CGI

The correlations between the MADRS and CGI are presented in Table 2. The observed correlations were statistically significant at all time points (p-value <0.0001) and across all

variables analyzed (Spearman correlation between 0.47 and 0.87, Table 2), thus allowing linking analysis.

Table 2 about here

b. *Linking of the MADRS total scores with CGI-S*

Figure 1 presents the results of the linking between MADRS total scores and CGI-S scores. They suggest that a CGI-S score of 1 ('normal, not at all ill') corresponds to a MADRS scores of 2 at weeks 1, 2, and 4, and of 17 at baseline. CGI-S scores of 2 ('borderline mentally ill') corresponded to MADRS scores of between 6 and 19; CGI-S scores of 3 ('mildly ill') to a MADRS scores between 14 and 22; the score 4 ('moderately ill') to the scores between 22 and 27, the score 5 ('markedly ill') to those between 31 to 34, the score 6 ('severely ill') to those between 39 and 40, and the score 7 ('extremly ill') to 47-49 and higher. It should be noted that the outlier values of the MADRS at baseline (CGI-S scores of not ill, borderline mentally ill and mildly ill corresponding to MADRS scores of 17, 19 and 21, respectively) may not be valid. They are most likely due to the fact that patients who are currently only mildly depressed are usually excluded from such trials. This means that few such patients were available due to minimum severity thresholds.

Figure 1 about here

c. Linking of the percentage change from baseline in the MADRS total scores with the CGI-I score

The results were rather consistent across time points analyzed. A CGI-I score of 3 ('minimally improved') corresponded to a percentage reduction from baseline in the total MADRS score of between 21 and 28 %; a CGI-I score of 2 ('much improved') corresponded to a reduction of between 48 and 57 %; and a CGI-I score of 1 ('very much improved') to a reduction of between 80 and 84 % (Figure 2).

Figure 2 about here

d. Linking of the absolute change in the MADRS total scores with CGI-I scores

The results were consistent for all assessment points examined. A CGI-I score of 4 ('no change') corresponds with a slight reduction on the MADRS of 1 point. A CGI-I score of 5 ('minimally worse') corresponded to a minimal increase in the MADRS total score of 4. CGI-I scores of 3 ('minimally improved') corresponded to a reduction of the MADRS of 7-9 points; CGI-scores of 2 ('much improved') corresponded to a reduction on the MADRS by 16-17 points, and a CGI-I score of 1 ('very much improved') corresponded to a reduction by 27-28 points on the MADRS (Figure 3).

Figure 3 about here

e. Linking of the absolute change in the MADRS scores with absolute change in the CGI-S scores

Results were consistent across all time points analyzed. A reduction by one severity step on the CGI-S corresponded to a reduction of about 8-9 points on the MADRS.

Figure 4 about here

Discussion

Our analysis based on over 3,288 individual patients supports the MADRS criterion for response (reduction of at least 50% from baseline on the total MADRS), as a CGI-I score of 2 ('much improved') corresponded to a reduction from baseline in the total MADRS score of between 48 and 57%. Moreover, we suggest that in future trials response could be presented in tables of 25% steps indicating how many patients were unimproved or worse (≤0% MADRS reduction), how many had 1- 24% MADRS reduction, 25 to 49% reduction, 50 to 75% reduction and 75-100% reduction [17]. Such tables would show the *distribution of response* in addition to the primary cut-off (≥50%). They fit well to the anchors found by our analysis (CGI-I score of 'minimally improved' (3) = 21 to 28 % MADRS reduction, CGI-I 'much improved' (2) = 48 to 57 % MADRS reduction; and CGI-I 'very much improved' (1) = 80 and 84 % reduction). It also corresponds to definitions that describe ≥25% reduction as partial response and ≥50% as response [3].

If remission is defined as an (almost) complete absence of illness, a cut-off of ≤ 7 could be used because 6-7 points on the MADRS corresponded to a CGI-S score of 2 ('borderline mentally ill'), and a MADRS score of 2 corresponded to a CGI-S score of 1 ('normal, not at all ill'). These results are in line with the findings of Hawley et al. [25] who suggested a cut-off of ≤8/≤9, and Zimmerman [8] (≤9), although they who used different methods. Bandelow et al.[26] compared the MADRS with the CGI in a database of citalopram trials and found that a MADRS score of 11 corresponded to 'borderline mentally ill' on the CGI. As their linking method is not clearly

described (it appears that corresponding scores were derived manually rather than with a special software), it is difficult to understand the difference, but it is striking that in figures showing correlations there is no CGI-S score higher than 5 (see their Figure 4a). The authors state that linking results for CGI-S values higher than 4 (moderately ill) could not be provided, because too few patients were more than moderately ill. A reason for this might have been the exclusion of baseline values, a point in time when many patients are still severely ill. They used data of up to 8 weeks, while we restricted our dataset to 4 week results, but they did not find a time effect. As their MADRS scores seem to consistently correspond to approximately one CGI point higher than ours (e.g. CGI-S of 2 = 11 in their analysis compared to 7 in ours, CGI-S of 3 = 19 compared to 14 in our analysis), we wonder whether a different coding of CGI scores might have occurred. It should be noted that in our analysis - in particular among patients with a CGI score of "mildly ill" or even less - the MADRS versus CGI-severity linking analysis at baseline deviated from the other weeks. A likely reason for this phenomenon is that due to the studies' inclusion criteria which usually require at least moderately ill patients, few such patients were available at baseline. Therefore, the baseline results may not be representative for this comparison.

In terms of linking the MADRS absolute change with the CGI-improvement score, on average a 7 to 9 MADRS points reduction was necessary to be "minimally better", and an 8 to 9 MADRS points change reflected a CGI-severity score reduction of 1 point. These results could be used as a proxy for the *minimal clinically important change*. However, as the results are as a measure of reduction from baseline rather than from a difference between mirtazapine and comparators,

we would be hesitant to use it as a measure of a minimum clinically important *difference between treatments.*[27]

Strengths and limitations

The main strengths of our analysis include that it was based on individual data from a large number of patients (>3,000), participating in clinical studies of a single antidepressant (mirtazapine), all of whom had the same diagnosis (MDD), while belonging to different patient categories (e.g. inpatients, outpatients, patients with melancholia, elderly patients, severely ill patients). Thus, the results can be perceived as robust and with solid generalizability. However, subjects with dysthymia, non-responsive depression or chronic depression were not included in the studies, and the results of a linking analysis including those subjects could have been somewhat different.

A potential weakness was the inclusion of open-label and dose-finding studies along with double blind comparisons into the study sample. Spielmans (2006)[28] showed that the difference between the HAM-D and CGI-S ratings appeared moderated by the degree of trial blindness. However, as patients participating in open-label and dose-finding studies of mirtazapine represented only 23% of our total sample, it is unlikely that their data could have substantially impacted on the overall results. The time effect (different results according to time endpoints examined), previously described in a linking analyses of subjects with schizophrenia [15,16] was not seen in our analysis except for the baseline deviance of the MADRS total and CGI-S results. It is conceivable that clinicians' expectations of treatment differ in

patients with schizophrenia and depression, with clinicians expecting earlier responses from antidepressants compared to antipsychotics. No data were available for inter-rater reliability across the included studies, all of which could have impacted on the ratings included in the analysis. Furthermore, typically at each assessment point the MADRS is the first among the assessment scales included in an individual clinical trial report form, thus allowing for the possibility that physicians rating the CGI based their judgement on the symptoms that were already measured on the MADRS.

In conclusion, despite the methodological limitations, we believe our results will contribute to a better understanding and improved interpretation of clinical trial results in MDD.

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Tables

Table 1. Summary of mirtazapine MDD studies included in the analysis (possible online supplement)

Internal study number/ Reference if published	Antidepressive drug used	Sample size	Duration (days)	Title	Mean MADRS score at baseline
003−001	Mirtazapine	12	28	Org 3770 dose−finding study in moderately depressed patients.	32,42
003−002	Mirtazapine / Placebo	90	42	A placebo controlled study of Org 3770 in moderately depressed outpatients.	28,89
003−003	Mirtazapine / Placebo	90	42	A placebo−controlled study of Org 3770 in moderately depressed outpatients.	28,66
003−008	Mirtazapine / Placebo	150	42	A controlled dose range study of Org 3770 in outpatients with major depression.	27,64
003−020	Mirtazapine / Amitriptyline / Placebo	130	42	A controlled study of Org 3770 in out−patients with major depression.	27,38
003−021	Mirtazapine / Amitriptyline / Placebo	150	42	A controlled study of Org 3770 in out−patients with major depression.	29,81
003−022	Mirtazapine / Amitriptyline / Placebo	150	42	A controlled study of Org 3770 in out−patients with major depression.	37,1
003−023	Mirtazapine / Trazodone	150	42	A controlled study of Org 3770 in elderly outpatients with major depression.	25,14
003−024	Mirtazapine / Amitriptyline / Placebo	150	42	A controlled study of Org 3770 in outpatients with major depression.	28,07
22506	Mirtazapine / Clomipramine	29	42	An assessor−blind, randomized, multicentre, group−comparative Clinical Trial of intravenously administered Org 3770 and Clomipramine in depressed patients with a treatment period of 10 days followed by a double−blind oral treatment period of 32 days.	34,1
22519	Mirtazapine / Fluoxetine	131	42+126	A Multicenter, Open, Randomized, Fluoxetine−controlled Study To	33,69

				Evaluate Efficacy and Safety of Six Weeks Treatment with Oral Administration of 30 mg Org 3770 (Mirtazapine) Once Daily to Subjects with Major Depressive Disorder	
88013	Mirtazapine / Amitriptyline	115	42	A multicentre, double−blind, randomized, group comparative study to evaluate the effects of six weeks treatment with Org 3770 and amitriptyline administered to elderly patients with major depressive disorder.	31,37
E−1562	Mirtazapine / Citalopram	272	56	A Multicenter, Double−blind, Randomized, Citalopram Controlled Efficacy and Safety Study with Org 3770 in Depressed Subjects.	29,39
E−1620	Mirtazapine / Fluoxetine	299	57	A multicenter, double blind, randomized, fluoxetine−controlled efficacy	35,29
E−1621	Mirtazapine / Venlafaxine	178	57	A multicenter, double blind, randomized, venlafaxine controlled efficacy, safety and tolerability study (phase IIIb/phase IV) with mirtazapine (Org 3770) in severely depressed patients with melancholic features.	34,4
E−1639	Mirtazapine / Paroxetine	62	42	A single−center, randomized, double blind, group comparative study on the therapeutic effects of six weeks treatment with mirtazapine, paroxetine and their combination in 60 patients with major depression.	32,87
E−1690	Mirtazapine / Sertraline	354	56	A multicenter, double−blind randomized sertraline−controlled efficacy and safety trial with mirtazapine in subjects with a major depressive episode (according to DSM−IV criteria).	30,77
E−1699	Mirtazapine	182	56	Multicenter randomized double−blind comparative groups trial in 168 patients with severe depression, intended to compare the efficacy, safety and acceptability of intravenous mirtazapine in comparison with	34,69

				treatment with oral mirtazapine, followed, by 46 days of oral treatment	
E−1711	Mirtazapine	103	42	An open, multicenter trial with mirtazapine in moderate to severe major depressive episode, assessing ist therapeutic efficacy, safety and tolerability and exploring clinical predictors of therapeutic outcome.	31,98
E−1715	Mirtazapine	192	156	A multi−centre, open−labelled, randomised, prospective, clinical naturalistic pharmakokinetic and pharmacodynamic postmarketing surveillance study bsaed on Therapeutic Drug monitoring (TDM) with mirtazapine in depressed patients.	28,15
E−1734	Mirtazapine	136	42	An open−label, multicentre study of Mirtazapine in the treatment of major depressive episodes.	29,2
E−1745	Mirtazapine	163	42	Efficacy and safety profile of Mirtazapine in patients with moderate to severe major depressive disorder.	32,83

Table 2. Correlations between the MADRS and CGI scores

Linking	Assessment	Number of Observations	Spearman correlation coefficient	P−value
MADRS−10 total score vs CGI−severity	Baseline	3219	0.55	<.0001
	Week 1	2773	0.70	<.0001
	Week 2	2702	0.80	<.0001
	Week 4	2867	0.87	<.0001
MADRS−10 absolute change vs CGI−Severity change	Week 1	2758	0.47	<.0001
	Week 2	2688	0.61	<.0001
	Week 4	2853	0.71	<.0001
MADRS−10 percent change vs CGI−Severity change	Week 1	2758	0.47	<.0001
	Week 2	2688	0.61	<.0001
	Week 4	2853	0.72	<.0001
MADRS−10 absolute change vs CGI−Improvement	Week 1	2578	0.70	<.0001
	Week 2	2524	0.75	<.0001
	Week 4	2692	0.78	<.0001
MADRS−10 percent change vs CGI−Improvement	Week 1	2578	0.73	<.0001
	Week 2	2524	0.79	<.0001
	Week 4	2692	0.84	<.0001

Figure legends

Figure 1. Linking of the MADRS total scores and the CGI-S scores

Figure 2. Linking the percentage change in the MADRS total scores with the CGI-I scores

Figure 3. Linking the absolute change in the MADRS score with the CGI-I score

Figure 4. Linking of the absolute changes from baseline in the MADRS and CGI-S scores

Figure 1

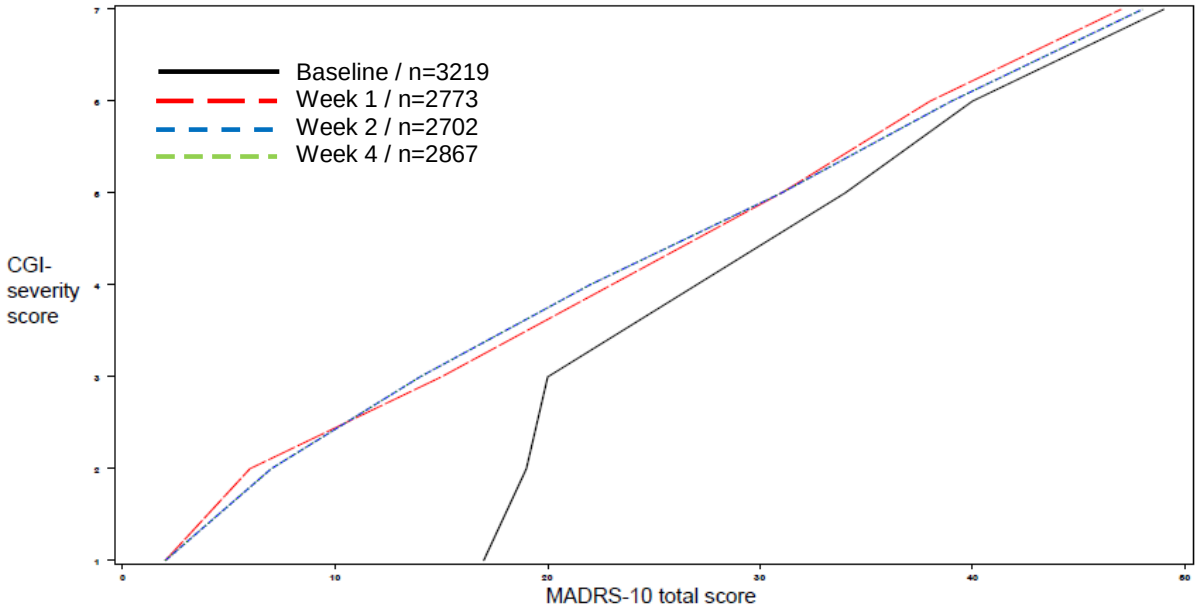

Figure 2

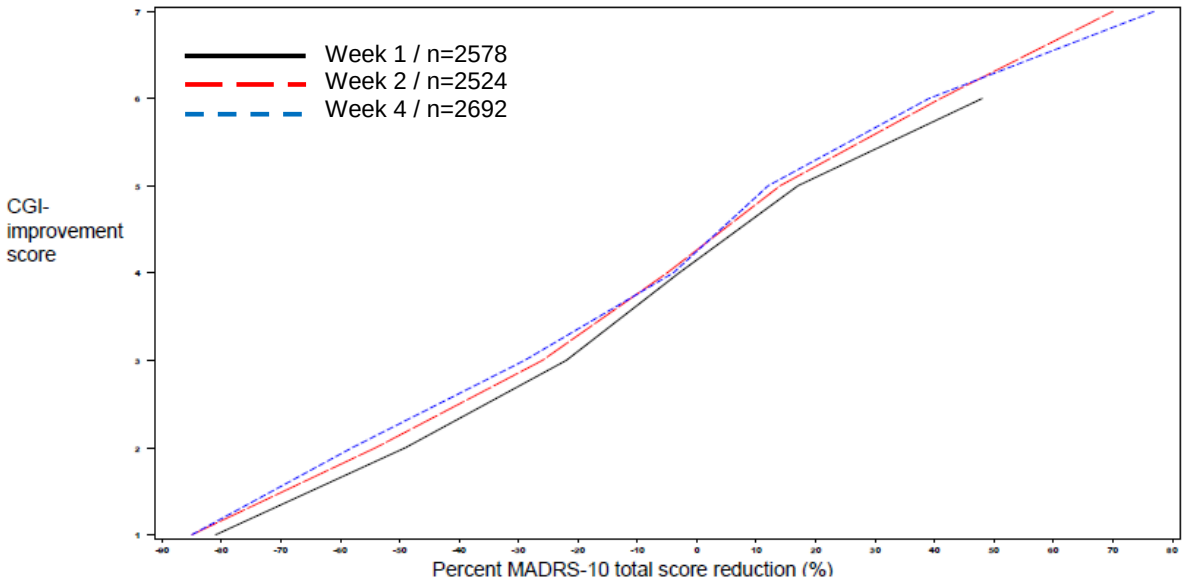

Figure 3

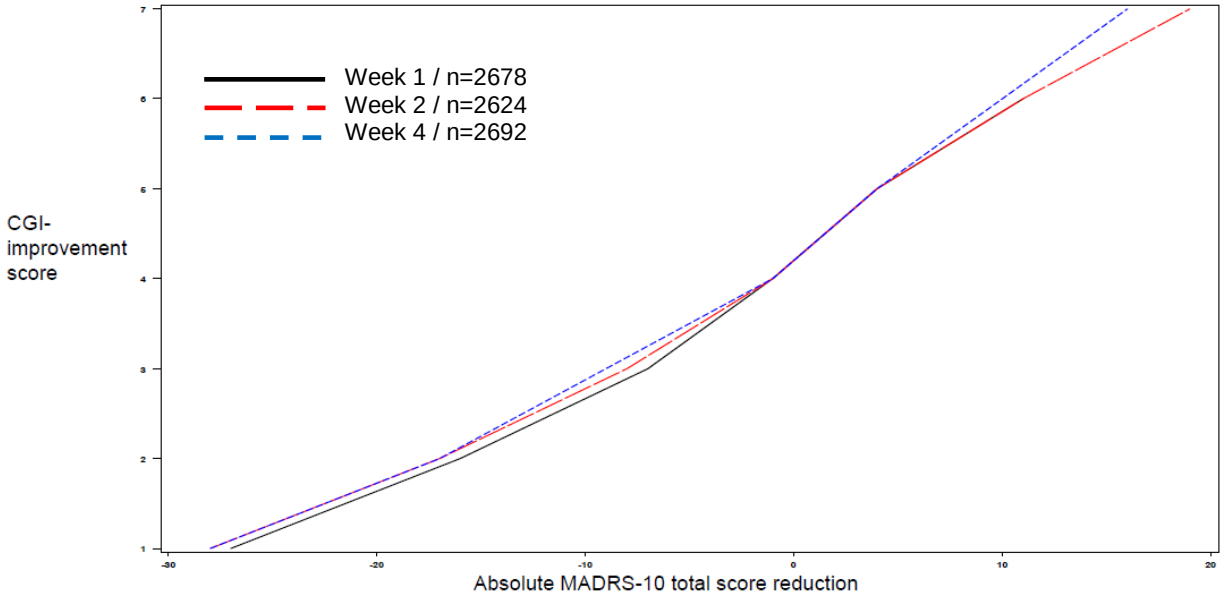

Figure 4