The symptom-specific efficacy of antidepressant medication vs. cognitive behavioral therapy in the treatment of depression: results from an individual patient data meta-analysis

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A recent individual patient data meta-analysis showed that antidepressant medication is slightly more efficacious than cognitive behavioral therapy (CBT) in reducing overall depression severity in patients with a DSM-defined depressive disorder. We used an update of that dataset, based on seventeen randomized clinical trials, to examine the comparative efficacy of antidepressant medication vs. CBT in more detail by focusing on individual depressive symptoms as assessed with the 17-item Hamilton Rating Scale for Depression. Five symptoms (i.e., "depressed mood", "feelings of guilt", "suicidal thoughts", "psychic anxiety" and "general somatic symptoms") showed larger improvements in the medication compared to the CBT condition (effect sizes ranging from .13 to .16), whereas no differences were found for the twelve other symptoms. In addition, network estimation techniques revealed that all effects, except that on "depressed mood", were direct and could not be explained by any of the other direct or indirect treatment effects. Exploratory analyses showed that information about the symptom-specific efficacy could help in identifying those patients who, based on their pre-treatment symptomatology, are likely to benefit more from antidepressant medication than from CBT (effect size of .30) versus those for whom both treatments are likely to be equally efficacious. Overall, our symptom-oriented approach results in a more thorough evaluation of the efficacy of antidepressant medication over CBT and shows potential in "precision psychiatry".

Key words: Depression, antidepressant medication, cognitive behavioral therapy, depressive symptoms, depressed mood, feelings of guilt, suicidal thoughts, psychic anxiety, general somatic symptoms, precision psychiatry

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Previous studies have consistently shown that both antidepressant medication and cognitive behavioral therapy (CBT) are effective acute phase treatments for depression[1-3]. Conventional meta-analyses indicated that their efficacy is comparable[4], while a recent individual patient data meta-analysis (IPDMA) showed that antidepressant medication is slightly more efficacious than CBT[5].

IPDMA is a relatively new technique in the field of mental health, that has the advantage to use raw data rather than pooling outcomes as in conventional meta-analyses[6]. This results in higher statistical power and provides the opportunity to not only detect relatively small treatment effects but also to assess treatment efficacy in more detail.

Randomized clinical trials (RCTs) on the comparative efficacy of antidepressant medication vs. CBT have primarily focused on changes in overall depression severity, and related outcomes such as response and remission rates. Scales for assessing depression severity are often multifactorial[7-10], and some RCTs have shown that these subscales differ in their response to antidepressant medication vs. CBT[7-9].

Fried et al[10] reported, however, that the multifactorial structure of several commonly used depression scales is not stable over time and, consequently, scale or subscale scores may be inappropriate as outcome measures. It would therefore be valuable to use data of an IPDMA, with its substantial statistical power, to assess the comparative efficacy of antidepressant medication vs. CBT in more detail; namely, by focusing on individual symptoms[11-13].

An additional advantage of a focus on individual symptoms is that it could help in generating hypotheses regarding the differential working mechanisms of treatment. Our group was the first to apply network estimation techniques in research on treatment efficacy, reporting that adjunctive antidepressant medication, relative to psychotherapy alone, was directly related to larger improvements in five specific symptoms (i.e., direct treatment effects), which were subsequently related to larger improvements in two other symptoms (i.e., indirect treatment effects)[13]. Adjunctive medication had no effects, neither directly nor indirectly, on nine other symptoms. As network estimation techniques can identify the complex patterns

in which symptom improvements are related, they have great potential in shedding light on the processes taking place during treatment.

A detailed assessment of the symptom-specific comparative efficacy of antidepressant medication vs. CBT would be important, as it could inform clinicians more precisely about the preferred treatment option for depressed patients in general. This is especially valuable as symptoms differ in their clinical relevance; for example, an effect on "suicidal thoughts" would be more relevant than an effect on "loss of weight".

The findings might also help in identifying patients who, based on their pre-treatment symptomatology, would benefit the most from one treatment relative to the other. That is, patients primarily suffering from symptoms that are affected by one treatment would probably benefit more from that treatment than patients primarily suffering from other symptoms. A focus on individual symptoms may therefore also be an important step in "precision psychiatry".

To our knowledge, this is the first IPDMA that focused on individual symptoms in a more detailed assessment of the comparative efficacy of antidepressant medication vs. CBT in the treatment of depression. In a second step, we used network estimation techniques to test whether the identified effects were direct or indirect. Thirdly, we wanted to explore whether information about the symptom-specific effects of antidepressant medication vs. CBT could help in identifying patients who, based on their pre-treatment symptomatology, are likely to benefit more from one treatment relative to the other.

METHODS

Sample

Our starting point was a recent IPDMA including data of individual patients who participated in RCTs directly comparing antidepressant medication vs. CBT[5]. Only studies including outpatients with a primary diagnosis of a DSM-II, DSM-III or DSM-IV depressive disorder (major depressive disorder or dysthymia), as established by a standardized diagnostic interview, were included. In addition, CBT was required to be manualized and use cognitive restructuring as the main treatment component. Studies focusing on remitted patients or including patients younger than 18 years were excluded. Studies enrolling patients with comorbid general medical disorders were not excluded, and no language restrictions were applied.

Twenty-four studies were identified for the IPDMA. Authors were invited via email to provide original data from their trial. If the authors did not respond to the request after one month, a reminder email was sent and efforts to contact co-authors were made. Authors of four studies were unreachable and authors of another four studies no longer had access to the data. Of the remaining sixteen studies, fourteen[14-27] used the Hamilton Depression Rating Scale (HAM-D) to assess depressive symptoms and were included in the current analyses (responsible for 1,472 patients). Three studies[28-30] were added (responsible for 384 patients) as an update of the dataset.

Of the 1,856 included patients, 843 (45.4%) were randomly assigned to CBT and 1,013 (54.6%) to antidepressant medication (i.e., several studies had double-sized medication conditions). In total, 1,513 (81.5%) had complete pre-treatment data on all individual depressive symptoms, with no difference between antidepressant medication and CBT (82.0% versus 80.9%, p=0.53). Of the patients with complete pre-treatment data, 1,070 (70.7%) had complete post-treatment data on all individual items and comprised the sample for our analyses. Slightly more patients had incomplete post-treatment data in the medication relative to the CBT condition (31.4% versus 26.7%, p=0.04).

Assessment of depressive symptomatology

Individual depressive symptoms were assessed by separate items of the 17-item HAM-D[31], both before and after treatment (i.e., 8-20 weeks after the pre-treatment assessment). The HAM-D includes seventeen items, which are scored from 0 to 4 (items 1-3, 7-11,15-16) or 0 to 2 (items 4-6, 12-14, 17). We chose the HAM-D for the assessment of individual depressive symptoms, as this was the most often used instrument in studies on the comparative efficacy of antidepressants vs. CBT. Overall depression severity was calculated by the sum of all HAM-D items.

Statistical analyses

All non-network analyses were performed using SPSS (version 24). First, baseline characteristics were compared between patients in the medication vs. CBT condition using X^2 statistics for categorical variables (i.e., gender and recruitment setting) and independent samples t-tests for continuous variables (i.e., age, timing of post-treatment assessment, overall depression severity and individual depressive symptom scores). Then, paired t-tests were performed to compare post-treatment to pre-treatment symptom scores for medication and CBT separately. Independent samples t-tests were performed to determine whether change scores of individual symptoms differed between the two treatment conditions.

As a sensitivity analysis, we repeated the above tests in a dataset (N=1,513) in which change scores of patients with missing post-treatment symptom scores were imputed using multiple imputation with baseline symptom scores and sociodemographics as predictor variables.

In a next step, statistical software R (version 3.3.3) was used to estimate a network including treatment condition (medication vs. CBT) and changes in individual depressive symptoms. As this combines a dichotomous variable (treatment condition) with continuous variables (change scores), the network was estimated with package mgm[32] using a mixed graphical model. This package uses the glmnet package[33] to fit penal-

ized generalized linear models to perform neighborhood selection[34]. Package qgraph[35] was used to visualize the network.

In this network, a direct connection between treatment condition and a change in a particular symptom indicates a direct symptom-specific effect, which is independent of the symptom-specific effects on other symptoms. If treatment condition is connected to a particular symptom via one or more changes in other symptoms, it may be interpreted as an indirect symptom-specific effect.

As a sensitivity analysis, we estimated networks including changes in individual symptoms for antidepressant medication and CBT separately. The package network comparison test[36] was used to test whether the networks differed.

Lastly, we explored whether it was possible to identify those patients who are likely to benefit more from one treatment relative to the other. We expected that patients primarily suffering from symptoms that were affected by one treatment would benefit more from that treatment than patients primarily suffering from other symptoms. To test this, two specific severity measures were calculated, based on the simple sum of scores on those pre-treatment symptoms that: a) were significantly impacted by one treatment relative to the other; and b) were the least impacted by one treatment condition relative to the other. We expected that the effect of treatment condition on overall depression severity would be larger in patients with higher scores on the first specific severity measure, but not in patients with higher scores on the second specific severity measure.

RESULTS

Baseline characteristics

Of the 1,070 included patients, 500 received CBT and 570 received antidepressant medication. Patients in the two conditions did not differ in any of the socio-demographic and study characteristics, except for recruitment setting. In addition, no significant differences were found with respect to baseline overall depression severity or any of the individual depressive symptoms (see Table 1).

Symptom-specific comparative efficacy of antidepressant medication vs. CBT

Although overall depression severity improved significantly in both treatment conditions (both $p<0.001$), this improvement was slightly but significantly larger for antidepressant medication than for CBT (Cohen's d=.15) (see Table 2). All individual symptoms also showed significant improvements in both conditions (all p values ≤0.01 for CBT and ≤0.04 for antidepressant medication), but significant differences between the two conditions were found only for the symptoms "depressed mood", "feelings of guilt", "suicidal thoughts", "psychic anxiety" and "general somatic symptoms". These symptoms showed larger improvements for medication than for CBT, although effect sizes were small (Cohen's d ranging from .13 to .16). No significant effects of treatment condition were found for the other twelve symptoms.

The results of the sensitivity analysis based on the imputed dataset were similar; p values differed somewhat, but improvements between conditions remained comparable.

Direct and indirect symptom-specific effects of antidepressant medication vs. CBT

To provide more information about the direct and indirect symptom-specific effects of antidepressant medication vs. CBT, a network was estimated including treatment condition and changes in individual symptoms (Figure 1). The previously identified symptom-specific effects on "feelings of guilt", "suicidal thoughts", "psychic anxiety" and "general somatic symptoms" were, at least partly, direct, indicating that the larger improvements for antidepressants relative to CBT could not be fully explained by any of the other direct or indirect symptom-specific effects.

The previously identified symptom-specific effect on "depressed mood" was fully indirect, suggesting that improvements in the four symptoms that were directly affected by medication relative to CBT resulted, both directly and indirectly, in a larger improvement in "depressed mood".

Sensitivity analyses showed that the two networks including changes in all seventeen individual symptoms did not differ for antidepressant medication vs. CBT ($p=0.77$ for global connectivity, and Holm-Bonferroni corrected p values all ≥0.95 for individual connections).

Identifying patients who benefit more from antidepressant medication relative to CBT

Lastly, we explored whether it was possible to identify patients, based on their pre-treatment symptomatology, who would benefit more from antidepressant medication than from CBT. A specific pre-treatment severity measure was calculated based on the five symptoms that were significantly affected by medication over CBT. As expected, only those patients with the highest scores on this measure improved significantly more from antidepressants than from CBT (Cohen's d=.30, see Figure 2).

As a comparison, another specific severity measure was calculated based on the five symptoms that responded the least to antidepressant medication relative to CBT (i.e., "agitation", "somatic anxiety", "genital symptoms", "loss of weight", and "insight"; all non-significant effects), which was only weakly correlated with the first severity measure (r=.23). As expected, patients with the highest scores on this measure did not show significantly larger improvements for antidepressant medication relative to CBT, but, interestingly, patients with the lowest scores did (Cohen's d=.33, see Figure 3).

Table 1 Sample characteristics

	ADM condition (N=570)	CBT condition (N=500)	p
Gender (% female)	67.0	68.8	0.53
Age at baseline (years, mean±SD)	39.8±12.7	40.0±12.6	0.85
Recruitment setting (%)			<0.001
Community	29.1	18.6	
Clinical	51.2	59.2	
Both	19.6	22.2	
Timing of post-treatment assessment (weeks, mean±SD)	13.2±3.1	13.3±3.1	0.44
Overall depression severity (HAM-D total score, mean±SD)	18.6±4.8	18.3±4.5	0.30
HAM-D scores for individual symptoms (mean±SD)			
Depressed mood	2.2±0.8	2.2±0.8	0.64
Feelings of guilt	1.6±0.9	1.6±0.9	0.25
Suicidal thoughts	0.8±1.0	0.7±0.9	0.14
Early night insomnia	1.0±0.9	1.0±0.9	0.36
Middle night insomnia	1.1±0.8	1.1±0.8	0.57
Early morning insomnia	0.8±0.8	0.7±0.8	0.34
Work and activities	2.4±0.9	2.3±0.9	0.15
Retardation	0.5±0.7	0.6±0.7	0.38
Agitation	0.7±0.9	0.7±1.0	0.22
Psychic anxiety	1.7±0.9	1.7±0.9	0.65
Somatic anxiety	1.6±0.9	1.6±0.9	0.73
Gastrointestinal symptoms	0.6±0.7	0.5±0.7	0.18
General somatic symptoms	1.4±0.6	1.5±0.6	0.38
Genital symptoms	1.2±0.8	1.1±0.8	0.31
Hypochondriasis	0.6±0.8	0.7±0.8	0.16
Loss of weight	0.3±0.6	0.3±0.6	0.26
Insight	0.1±0.4	0.1±0.3	0.33

ADM – antidepressant medication, CBT – cognitive behavioral therapy, HAM-D – Hamilton Depression Rating Scale

DISCUSSION

Principal findings

To our knowledge, this study is the first IPDMA that considered individual depressive symptoms in the comparison of the efficacy of antidepressant medication vs. CBT. Five symptoms (i.e., "depressed mood", "feelings of guilt", "suicidal thoughts", "psychic anxiety" and "general somatic symptoms") showed larger improvements in the medication relative to CBT condition, whereas no differences were found for the twelve other symptoms. Network estimation techniques revealed that all effects were direct, except for the indirect effect on "depressed mood". Our findings further suggest that information about the symptom-specific efficacy could help in identifying those patients, based on their pretreatment symptomatology, who are likely to benefit more from antidepressant medication than from CBT.

Symptom-specific efficacy of antidepressant medication vs. CBT

Weitz et al[5] recently demonstrated that antidepressant medication was slightly more efficacious in improving overall depression severity than CBT. This conclusion was not only confirmed by our updated IPDMA, but also extended by providing detailed information about the symptom-specific efficacy. As the effect on overall depression severity was small (effect size of .15), it is not surprising that the five identified symptom-specific effects were also small (effect sizes ranging from .13 to .16).

Small effects are, however, not uncommon in studies on the comparative efficacy of treatments. Given the robustness of the findings as well as the clinical relevance of the identified symptom-specific effects (especially the effect on "suicidal thoughts"), we believe that it would be unwise to ignore the beneficial effects of antidepressant medication over CBT.

Table 2 Improvements in depressive symptomatology in the ADM versus CBT condition

	ADM condition (N=570)	CBT condition (N=500)	p	Cohen's d
Overall depression severity (HAM-D total score, mean±SD)	10.49±6.84	9.43±6.87	0.01	.15
HAM-D scores for individual symptoms (mean±SD)				
Depressed mood	1.43±1.11	1.28±1.19	0.03	.13
Feelings of guilt	0.99±1.14	0.82±1.05	0.02	.16
Suicidal thoughts	0.60±1.04	0.44±0.97	0.007	.16
Early night insomnia	0.52±0.95	0.49±1.00	0.56	.03
Middle night insomnia	0.50±1.02	0.45±0.95	0.39	.05
Early morning insomnia	0.38±0.98	0.29±0.96	0.13	.09
Work and activities	1.53±1.29	1.39±1.33	0.08	.11
Retardation	0.40±0.67	0.36±0.76	0.32	.06
Agitation	0.35±0.97	0.37±0.97	0.68	–.02
Psychic anxiety	1.00±1.09	0.85±1.17	0.03	.13
Somatic anxiety	0.68±1.10	0.69±1.16	0.88	–.01
Gastrointestinal symptoms	0.32±0.78	0.29±0.71	0.47	.04
General somatic symptoms	0.75±0.92	0.64±0.83	0.05	.13
Genital symptoms	0.55±0.94	0.57±0.98	0.77	–.02
Hypochondriasis	0.29±0.84	0.32±0.94	0.67	–.03
Loss of weight	0.15±0.69	0.15±0.66	0.91	–.00
Insight	0.04±0.40	0.04±0.40	0.78	–.00

ADM – antidepressant medication, CBT – cognitive behavioral therapy, HAM-D – Hamilton Depression Rating Scale

To our knowledge, no previous RCTs have examined a broad spectrum of individual depressive symptoms in comparing the efficacy of antidepressant medication vs. CBT, but some have considered subscales based on combinations of symptoms[7-9]. None of these studies have found differences in the efficacy on cognitive and affective symptoms[7-9], although two identified short-term effects that disappeared at a later stage[7-8].

An explanation for the identified symptom-specific effects in our study could lie in the use of IPDMA, which, with its substantial statistical power, makes it possible to detect relatively small effects. In addition, the strategy of combining symptoms into subscale scores may have obscured differential responses at the level of individual symptoms. Fournier et al[9] found, for example, no differences between cognitive therapy and antidepressants on the "mood" subscale, which incorporates both symptoms that did (i.e., "depressed mood") and did not (i.e., "work and activities" and "retardation") differ between treatment conditions in our study. This combination of findings underlines the importance of sufficient statistical power as well as a focus on individual symptoms in research on treatment efficacy.

Although Fournier et al did not find any differences in subscales of cognitive and affective symptoms, they did find that cognitive therapy was more efficacious than medication in improving atypical-vegetative symptoms[9]. Additional analyses showed that this effect was only present for hypersomnia, but not increased appetite. It is important to note that these two atypical-vegetative symptoms are not included in the 17-item HAM-D and, thus, are not considered as outcomes in our study.

We believe that it would be important for future studies to also consider atypical-vegetative symptoms as well as other clinically relevant symptomatology (e.g., anxiety symptoms or alcohol problems). In addition, it would be interesting to consider other outcomes that are clinically relevant, such as various aspects of quality of life or daily functioning, in order to provide a more thorough evaluation of treatment options.

Direct and indirect symptom-specific effects of antidepressant medication vs. CBT

Our study used network estimation techniques to shed light on the mechanisms of change during treatment. These analyses revealed that four of the five symptom-specific effects were direct (i.e., "feelings of guilt", "suicidal thoughts", "psychic anxiety" and "general somatic symptoms") and, thus, were independent of any of the other direct or indirect symptom-specific effects of antidepressant medication over CBT. The effect on "depressed mood" was indirect, indicating that the larger improvement was only present in patients who also experienced larger improvements in other symptoms in the medication relative to CBT condition. It is, however, important to note that

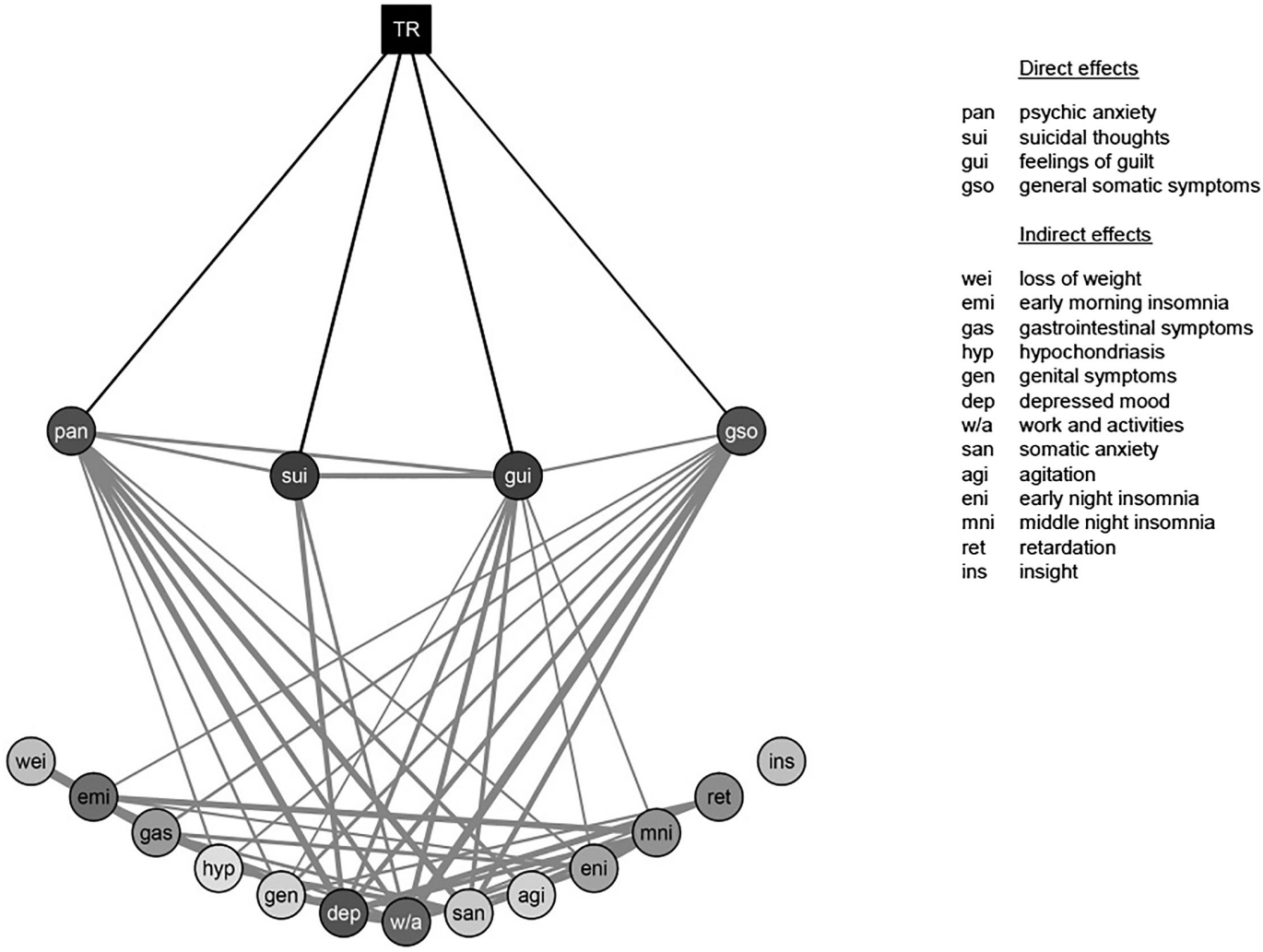

Figure 1 Direct and indirect symptom-specific effects of antidepressant medication (ADM) vs. cognitive behavioral therapy (CBT). Treatment type is represented by the square (TR), and individual symptoms as circles. Black lines indicate direct connections between treatment condition and improvements in individual symptoms (i.e., direct treatment effects), whereas grey lines indicate connections between improvements in individual symptoms (i.e., potential indirect treatment effects). Thicker lines represent stronger connections. Darker circles represent stronger effects of ADM over CBT. The network is presented at γ=0.25.

network estimations employ regularization techniques which set weak connections to zero and, thus, conservatively identify the most relevant connections. This implies that, in reality, antidepressant medication may have a weak direct effect on "depressed mood" and, thus, this effect would not be fully indirect. The same might be true for other connections in the network. Network estimations are, therefore, not intended to formally test for mediation, but do provide insights into the patterns in which symptom improvements are related and can be used in generating hypotheses.

The network further revealed that improvements in symptoms were related in very complex patterns, with connections that were often intuitively plausible. It is, for example, easy to imagine that patients reporting less depressed mood after treatment often also reported fewer problems with work and activities, whereas patients reporting fewer gastrointestinal symptoms often reported less loss of weight. Interestingly, the networks were similar for the two treatment conditions, indicating that, regardless of the treatment, patients tend to report the same simultaneous symptom improvements. The only difference between the treatment conditions, thus, lies in the magnitude of improvement of the five symptoms that were specifically affected by antidepressant medication over CBT.

Although our findings demonstrate potential in generating hypotheses regarding the mechanisms of change during treatment, it is important to remark that changes in symptoms were assessed simultaneously and, consequently, the temporal relationships between them remain unknown. To examine the actual dynamics of symptoms over time, it would be more appropriate to use experience sampling method data, including multiple assessments with short time intervals[37]. For such research, it would be valuable to also consider other clinically

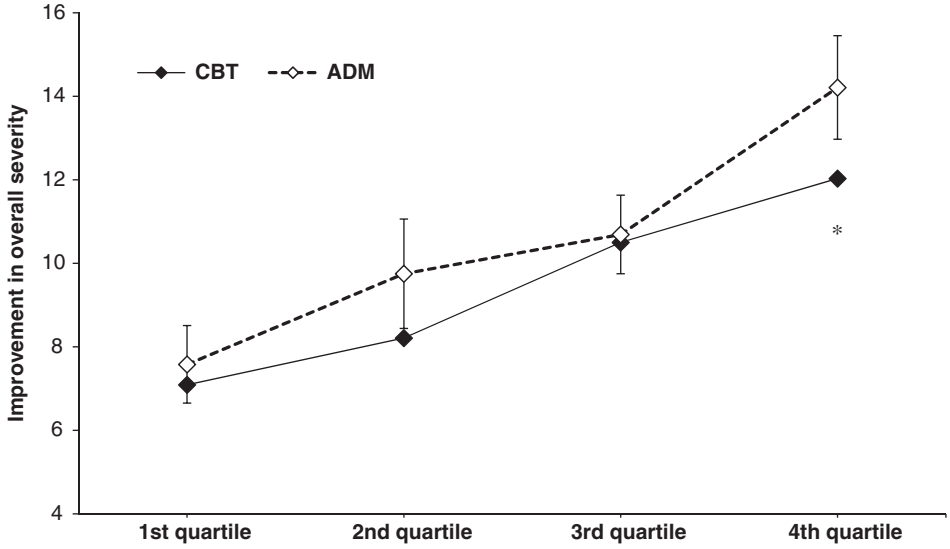

Figure 2 Stratification based on increasing scores on a specific pre-treatment severity indicator calculated by summing the five symptoms that responded the most to antidepressant medication (ADM) relative to cognitive behavioral therapy (CBT). * Cohen's d=.30.

relevant outcomes, as well as factors that are hypothesized to play a role in the working mechanisms of treatment, such as therapeutic alliance or social support.

Identifying patients who benefit more from antidepressant medication relative to CBT

Our findings showed that, in general, antidepressant medication was more efficacious than CBT in improving "depressed mood", "feelings of guilt", "suicidal thoughts", "psychic anxiety", and "general somatic symptoms" (effect sizes ranging from .13 to .16). This suggests that patients primarily suffering from these five symptoms would benefit more from antidepressant medication than from CBT, which was supported by our exploratory analyses. Only patients with the highest scores on these five symptoms showed significantly and substantially larger improvements in overall depression severity after medication relative to CBT (effect size of .30). In contrast, antidepressants and CBT were equally efficacious for patients with lower scores on these symptoms. Our findings, thus, may be an important step in "precision psychiatry", as they can inform clinicians more precisely about the preferred treatment option based on the pre-treatment symptomatology of a patient.

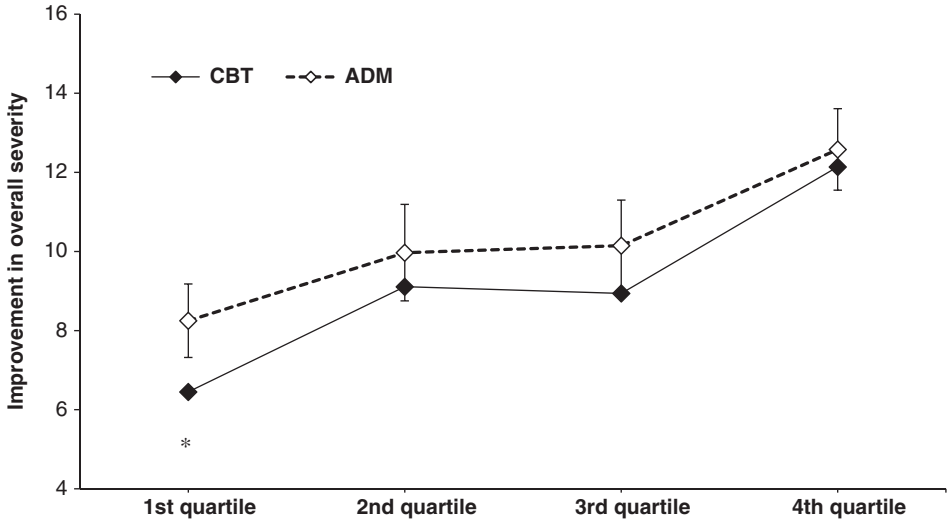

Figure 3 Stratification based on increasing scores on a specific pre-treatment severity indicator calculated by summing the five symptoms that responded the least to antidepressant medication (ADM) relative to cognitive behavioral therapy (CBT). * Cohen's d=.33.

Strengths and limitations

Strengths of the current study were that we used data from an updated IPDMA, which enabled us to assess treatment efficacy in more detail by focusing on individual symptoms. Although several studies have used network analysis techniques to examine the relations between depressive symptoms at a single time point[38-41], we were the first to use these techniques on changes in symptoms over time in order to distinguish direct and indirect treatment effects[13].

However, a focus on symptoms also brings challenges. For example, some studies have shown that the inter-rater reliability of several HAM-D items was poor[42], whereas others were more positive[43]. Therefore, more research is needed on the reliability and validity of assessing individual symptoms, especially as a measure of treatment efficacy. In addition, the number of response categories on the HAM-D differs across symptoms. Sensitivity to detect changes in symptom severity may be higher for symptoms with more response categories and this could explain the fact that, in general, the largest symptom-specific effects in our study, as well as in the study of Hieronymus et al[12], were observed for symptoms with more response categories.

The HAM-D items comprise a relatively narrow scope of possible outcomes and, therefore, it would be valuable to also consider other outcomes that are clinically relevant. It would also be interesting to consider other treatment options and to differentiate between antidepressant medication types, which are known to have different side effects[44].

CONCLUSIONS

Our study showed that antidepressant medication was more efficacious than CBT in improving five, but not twelve other, depressive symptoms. Although the five symptom-specific effects were small (effect sizes of .13 to .16), the specific symptoms, such as "suicidal thoughts", were all clinically relevant and, therefore, it would be unwise to ignore them. In addition, exploratory analyses suggested that this information could be helpful in "precision psychiatry": based on the pre-treatment symptomatology of patients, it was possible to identify those who were likely to benefit more from antidepressant medication than from CBT (effect size of .30) and those for whom both treatments were equally efficacious.

We think that such a symptom-oriented approach will be a step forward in research on treatment efficacy and we strongly encourage other researchers to adopt this approach in studies on other treatment options and/or to consider other outcomes.

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