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ORIGINAL PAPER

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Qualitative changes in symptomatology as an effect of treatment with escitalopram in generalized anxiety disorder and major depressive disorder

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Abstract The purpose of this article is to examine the similarities and differences between patients with Major Depressive Disorder (MDD) versus Generalized Anxiety Disorder (GAD) versus MDD with anxiety symptoms. Data were analysed from all randomized double-blind clinical studies with escitalopram that measured symptoms using either Hamilton Anxiety Scale (HAMA) or Montgomery–Åsberg Depression Rating Scale (MADRS). The contribution of each item of a scale to the total score was calculated before and after treatment, in remitters. Most single items of the HAMA contribute nearly equally in patients with GAD. In patients with MDD, four symptoms (i.e. *anxious mood*, *tension*, *insomnia* and *concentration*) contribute to most to the HAMA total score. In patients with GAD, three symptoms (*tension*, *sleep* and *concentration*) contribute two-thirds of the MADRS total score. In contrast, most MADRS items contribute equally to the total score in patients with MDD. After treatment to remission, the profile of residual symptoms MDD or GAD was similar to the symptom profile before treatment. Anxiety symptoms are very common in patients with MDD or GAD, and the symptomatic pattern is similar. In both disorders, the symptomatic pattern of residual symptoms is similar to the pattern of symptoms before treatment.

Key words dimensional approach · Hamilton anxiety rating scale · Montgomery–Åsberg depression rating scale · residual symptoms · major depressive disorder · generalized anxiety disorder

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Introduction

The relationship between anxiety and depressive disorders has long been a matter of controversy. In individuals with no depressive or anxiety disorder, these two emotions fluctuate as an adaptive response to both external and internal events. This adaptability is lost with the onset of a pathological state and a set of symptoms persists over long periods relatively independent of external events. Two different theories have been proposed for the classification of pathologically anxious or depressive patients.

On one hand, the different syndromes of mood and anxiety disorders are considered to be distinct categories that are likely to differ in their aetiological basis [36]. It has been argued that anxious and depressive symptoms have a bimodal distribution and are stable over time, and that the response to treatment and the long-term outcome (4 years) were different for depressed versus anxious patients [24]. The third edition of the Diagnostic and Statistical Manual of Mental Disorders [4] embodied such a taxonomic model.

On the other hand, some authors consider a single nosological entity with predominantly depressive symptoms at one extreme of a continuum and predominantly anxiety disorders at the other extremity [39]. Based on meta-analysis of treatment outcome in four types of neuroses, Andrews et al. [5] found that antidepressant drugs or cognitive behavioural therapy produced equivalent improvement in all conditions and interpreted these data as a support for the existence of a "general neurotic syndrome". When assessing the variations in symptoms of anxiety and depression, Duncan-Jones [14] was among the first to show that constitutional

and personality factors explained 70% of the variance. This was also consistent with the existence of a "general neurotic syndrome".

Based on the DSM approach, the likelihood of both a depressive and an anxiety disorder in the same individual at the same time or during two separate periods is extremely high [25], which clearly suggests the existence of significant common risk factors. The anxiety disorder usually develops first and depression later [35]. Approximately 85% of patients with pure depression will also have a significant number of anxiety symptoms [18]. Similarly, up to 80% of patients initially diagnosed with GAD will develop comorbid depression over their lifetime [41].

The clinical databases of pharmaceutical companies used to assess the therapeutic properties of their products, can be analysed for the relationships between anxious and depressive disorders, and may contribute substantially to this debate for a number of reasons. First, since several trials are conducted with a single drug, the number of patients is large, often several thousands. Indeed, in this article, data from 7,354 patients in the escitalopram clinical database for major depression (MDD) and generalized anxiety disorder (GAD) were analysed. Second, the majority of patients are followed for the entire duration of the trial, both before initiating pharmacotherapy, and after completing the assessment period. Third, patients are diagnosed using structured diagnostic interviews to ascertain the presence or absence of diagnostic criteria. For example, the Mini International Neuropsychiatric Interview (MINI) [26] was used for all patients treated with escitalopram in this analysis, providing a categorical diagnosis. Fourth, symptom severity is assessed using

Table 1 Summary of escitalopram clinical trials included in the ITT analysis

Studies	Design	Inclusion criteria	Duration (weeks)	Patients (*n*) (% completed)	Efficacy measures
GAD (DSM-IV)					
[3]	Open-label (+ randomized double-blind − relapse prevention)	HAMA ≥20 HAMA item 1 and 2 ≥2 MADRS ≤16	12	491 (86.4)	HAMA MADRS HAD
[7]	Randomized, double-blind, placebo-controlled	HAMA ≥20 HAMA item 1 and 2 ≥2 MADRS ≤16	12	674 (86.4)	HAMA MADRS HAD
[17, 38]	Randomized, double-blind, placebo-controlled	HAMA ≥18 HAMA item 1 and 2 ≥2 HAM-D ≤16	8	252 (76.9)	HAMA HAD
[17, 38]	Randomized, double-blind, placebo-controlled	HAMA ≥18 HAMA item 1 and 2 ≥2 HAM-D ≤16	8	281 (82.4)	HAMA HAD
[13]	Randomized, double-blind, placebo-controlled	HAMA ≥18 HAMA item 1 and 2 ≥2 HAM-D ≤16	8	307 (78.8)	HAMA HAD
[10]	Randomized, double-blind comparative study	HAMA ≥18 HAM-D ≤17	24	121 (59.5)	HAMA HAD
MDD (DSM-IV)					
[40]	Randomized, double-blind, placebo-controlled	MADRS ≥22	8	377 (85.9)	MADRS
[27]	Randomized, double-blind, placebo-controlled	MADRS ≥22	8	468 (93.4)	MADRS
[12]	Randomized, double-blind, comparative study	MADRS ≥22	24	339 (83.2)	MADRS HAMA
[22]	Randomized, double-blind, placebo-controlled	MADRS ≥22 Age ≥65 years	8	514 (82.8)	MADRS
[29]	Randomized, double-blind, comparative study	MADRS ≥18	8	288 (86.5)	MADRS
[9]	Randomized, double-blind, comparative study	HAMD ≥20	8	195 (70.7)	MADRS
[6]	Randomized, double-blind, comparative study	MADRS ≥22	8	321 (73.0)	MADRS HAD
[11]	Randomized, double-blind, placebo-controlled	MADRS ≥22	8	485 (76.9)	MADRS
Described in [34]	Randomized, double-blind, placebo-controlled	MADRS ≥22	8	368 (81.5)	MADRS
Data available on website [16]	Randomized, double-blind, comparative study	MADRS ≥22	8	194 (73.7)	MADRS HAMA
[2]	Randomized, double-blind, comparative study	MADRS ≥22	8	211 (85.8)	MADRS HAMA
[23]	Randomized, double-blind, placebo-controlled	HAM-D24 ≥25	8	294 84.0)	MADRS HAMA
[1]	Randomized, double-blind, comparative study	MADRS ≥22	8	398 (81.9)	MADRS HAMA
[32]	Open-label	MDD ± anxiety	12	774 (83.9)	MADRS HAMA

HAD: Hospital Anxiety and Depression Scale, HAMA: Hamilton Anxiety Scale, HAMD: Hamilton Depression Rating Scale, GAD: generalized anxiety disorder, ITT: modified intent-to-treat, MADRS; Montgomery–Åsberg Depression Rating Scale, MDD: major depressive disorder

rating scales, and thus affords a measure of objectivity and allows quantitative analysis. Finally, residual symptoms are carefully assessed after treatment.

Some authors argue that residual symptomatology is part of achieving remission [21, 33], others consider residual symptoms to be sequelae due to depression [37], or symptoms related to underlying personality traits. They are a major factor in predicting relapse of MDD [15, 20, 33]. Little is known about residual symptoms in GAD.

Analysis of the escitalopram clinical database may help to shed light on some of the following points: Do qualitative differences exist between MDD and GAD patients before treatment? Does treatment actually modify the qualitative nature of the symptomatology? Does the residual symptomatology reflect the initial symptomatology or does it reveal other pathological features, such as personality traits, masked by severity of the initial symptomatology?

Methods

The present analysis included all randomized studies with escitalopram in MDD or GAD patients in which the Hamilton Anxiety Scale (HAMA) [19], and/or the Montgomery–Åsberg Depression Rating Scale (MADRS) [28] were used.

There were 6 double-blind studies in GAD (n = 2,126), 13 in MDD (n = 4,452) and one open-label study in MDD that included patients with comorbid anxiety disorders (n = 774) (Table 1). Within each indication, the trials had similar inclusion and exclusion criteria for patient selection, in addition to common rating scales. For GAD, 3 trials lasted 8 weeks, 2 trials lasted 12 weeks and 1 trial lasted 24 weeks. In MDD, 12 were 8-week trials, and 1 lasted for 24 weeks. The mean completion rate was 82.0% in the GAD studies and 82.1% in the MDD studies.

Study population

Each study involved primary care and/or psychiatric care patients with MDD or GAD, and with similar inclusion/exclusion criteria. Eligible patients were outpatients, aged 18 or over. For participation in the GAD studies, patients had to present DSM-IV-TR criteria for GAD and a score of 18 or more on the HAMA at baseline; patients with comorbid psychiatric disorders, including MDD, were excluded using the MINI, and only mild depressive symptoms were allowed (MADRS≤16). To be eligible for participation in the MDD studies, patients had to fulfil DSM-IV-TR criteria for MDD and a score of 22 or more on the MADRS at baseline. In most MDD studies, patients with current comorbid anxiety disorders were excluded using the MINI, as were patients with a MADRS item 10 ≥5 (suicidal thoughts). Patients included in the open-label study suffered from MDD with (61%) or without a secondary comorbid anxiety disorder (39%).

Clinical rating scales

The HAMA is an anxiety rating scale consisting of 14 items exploring anxious mood, tension, fears, insomnia, intellectual (cognitive) symptoms, depressed mood, behaviour at interview, somatic (sensory), cardiovascular, respiratory, gastrointestinal, genitourinary, autonomic and somatic (muscular) symptoms. Each symptom is rated from 0 (absent) to 4 (maximum severity). In the original version, only the content of each item was described, whereas in the modified version by Bech et al. [8], which was used in the escitalopram studies, specific anchor points for each score were provided.

The MADRS is a 10-item depression rating scale assessing: apparent sadness, reported sadness, inner tension, reduced sleep, reduced appetite, concentration difficulties, lassitude, inability to feel, pessimistic thoughts and suicidal thoughts. The rating of severity ranges from 0 (symptom absent) to 6 (extreme severity) for each item.

Analysis

In order to explore the pattern of symptoms of patients with GAD or MDD, the relative contribution of each item to the total score was calculated using the following formula:

$$\text{Contribution} = \frac{\text{Score of the item}}{\text{Total score}} \times 100$$

This has the advantage of describing the pattern of symptoms independently from severity, which was needed to compare the symptomatic profile after treatment versus the profile before treatment.

The symptom patterns on the HAMA and the MADRS were examined both at baseline and after treatment with escitalopram. In order to explore residual symptoms after treatment, we believed that the most relevant population was the one who had achieved remission. The post-treatment symptomatic contribution of each item to the total score was therefore calculated in escitalopram remitters. Remission was defined as a HAMA score of 7 or less and as a MADRS score of 12 or less in GAD and MDD patients, respectively. The symptom pattern of patients with MDD ± comorbid anxiety disorders was analysed before, but not after, treatment because of the open nature of this study. Patients randomized to placebo or comparators were not included in the post-treatment analysis.

All analyses were based on a modified intent-to-treat (ITT) dataset (i.e. patients with at least one dose of study drug and one post-baseline efficacy assessment). All analyses were performed with the *last-observation-carried-forward* method (LOCF), except for single item analyses on remitters, which used the *observed-cases* method (OC).

Results

Individual item scores prior to treatment

HAMA

At baseline, the scores for the somatic items of the HAMA, as well as the items *fears* and *depressed mood*, were relatively low in patients with GAD (n = 2,126) (Fig. 1a). The items with the highest scores were *anxious mood*, *tension*, *insomnia* and *difficulties in concentration*.

In patients with MDD (n = 4,452), the level of symptom severity was lower, except for *depressed mood*, which was higher.

Depressed patients with comorbid anxiety and GAD patients show more symptomatic severity than pure MDD patients. This is true for all item with the exception of mood. However this is due to the lower severity of pure MDD and we will see below (Fig. 2a) that when looking at the participation of each item to the total score then psychic item are rather similar between pure MDD and comorbid MDD.

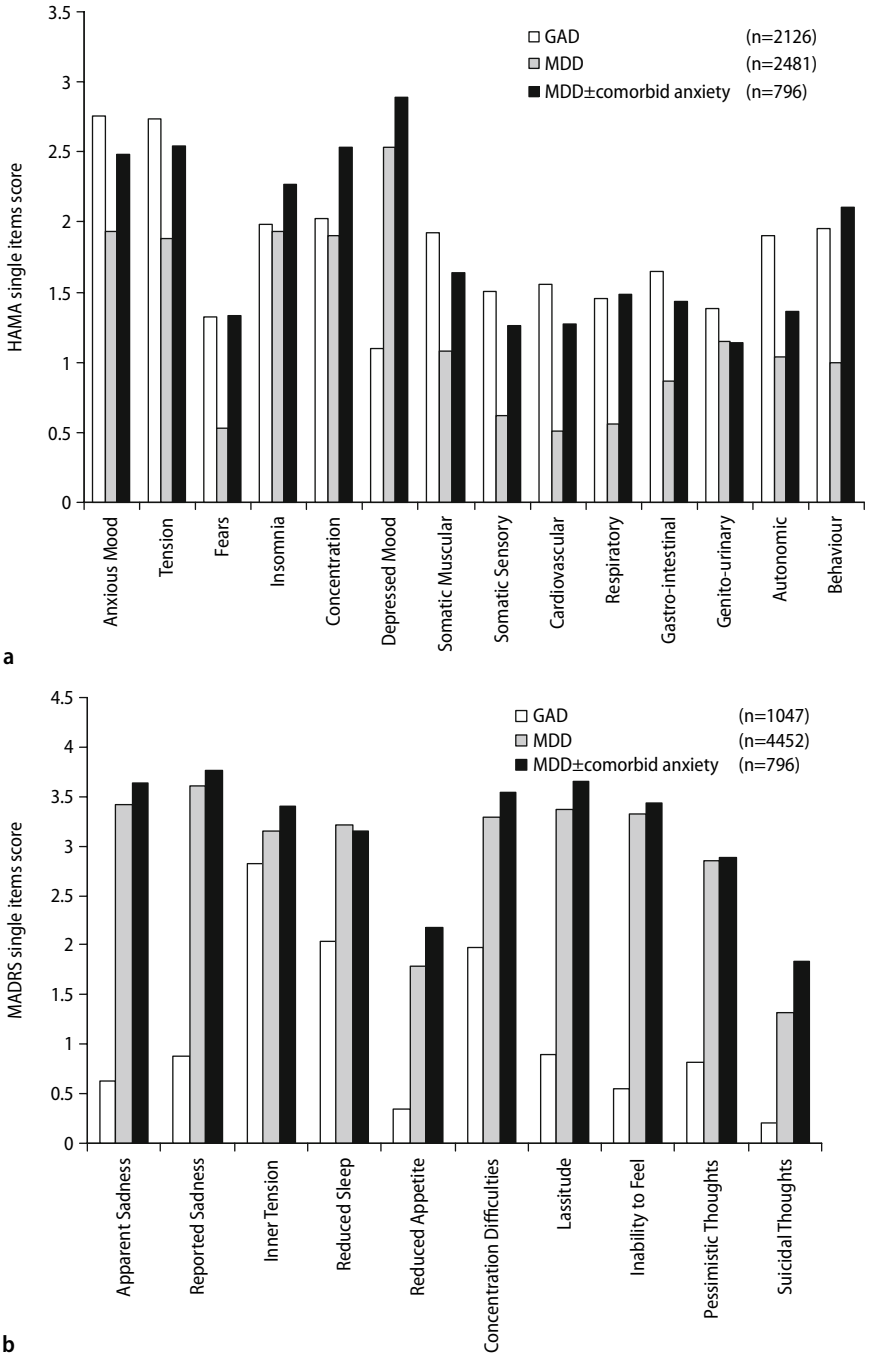

Fig. 1 Mean score of individual items before treatment (**a**) HAMA, (**b**) MADRS. The total number of patients (all treatment groups) is shown in parentheses. For the HAMA, there were 1,375 patients treated with escitalopram and for the MADRS, there were 1,925 patients treated with escitalopram

MADRS

On the MADRS, the items *apparent sadness*, *reported sadness* and *inability to feel* had a low score in patients with GAD (Fig. 1b).

In patients with MDD, all items contributed almost equally to the total score with the exception of *reduced appetite* and *suicidal thoughts*. For this last item, the results simply reflect the exclusion criterion.

The individual scores for depressed patients with comorbid anxiety disorders were almost identical to those of patients with MDD.

Symptom profile prior to treatment

HAMA

The contribution (%) of each item of the HAMA to the total score at baseline in patients with GAD, MDD or MDD ± comorbid anxiety disorders is shown in Fig. 2a.

In patients with GAD, each symptom contributed almost equally to the total baseline score, except *fears* and *depressed mood*, which was not entirely surprising as it was an exclusion criterion to have

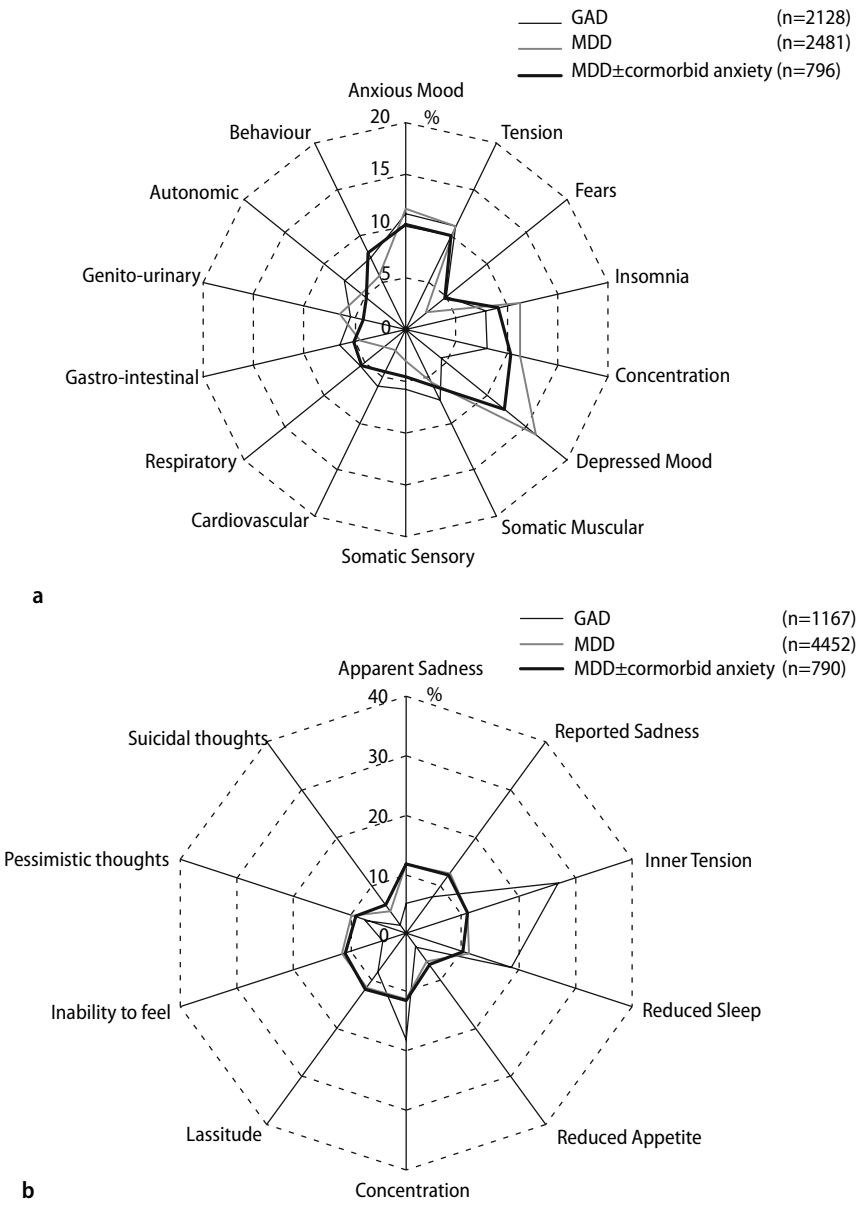

Fig. 2 Relative contribution of each item to the total score in patients with GAD, MDD or MDD with comorbid anxiety disorders. (**a**) HAMA profile prior to treatment. (**b**) MADRS profile prior to treatment. The total number of patients (all treatment groups) is shown in parentheses. For the HAMA, there were 1,375 patients treated with escitalopram and for the MADRS, there were 1,925 patients treated with escitalopram

an additional diagnosis on Axis I in the trials included in this analysis. The contribution of those items corresponding to the DSM-IV diagnostic criteria for GAD was slightly higher, especially *anxious mood* and *tension*.

In patients with MDD, *depressed mood* contributed substantially to the total baseline score, as did the psychic component of anxiety, that is, *anxious mood*, *tension*, *insomnia* and *concentration*.

When comparing the three diagnostic groups, the somatic items of *respiratory, cardiovascular* and *somatic sensory* on the HAMA scale differentiate between patients with GAD and those with MDD. Depressed patients with comorbid anxiety resemble patients with MDD alone, with higher scores on the *depressed mood* item, and resemble patients with GAD on the somatic items.

MADRS

The contribution (%) of each item of the MADRS to the total score at baseline in patients with GAD, MDD or MDD ± comorbid anxiety disorders is presented in Fig. 2b. In patients with GAD, three symptoms contributed to two-thirds of the total score: *inner tension, reduced sleep* and *concentration difficulties*. The other symptoms of the MADRS had a minimal contribution to the total score.

In patients with MDD, each item of the MADRS contributed almost equally (about 10% each) to the total baseline score, with the exception of *reduced appetite* and *suicidal thoughts*. The low contribution of the latter item reflects the exclusion criteria.

In depressed patients with comorbid anxiety, the pattern of symptoms was nearly identical to that observed in patients with "pure" MDD.

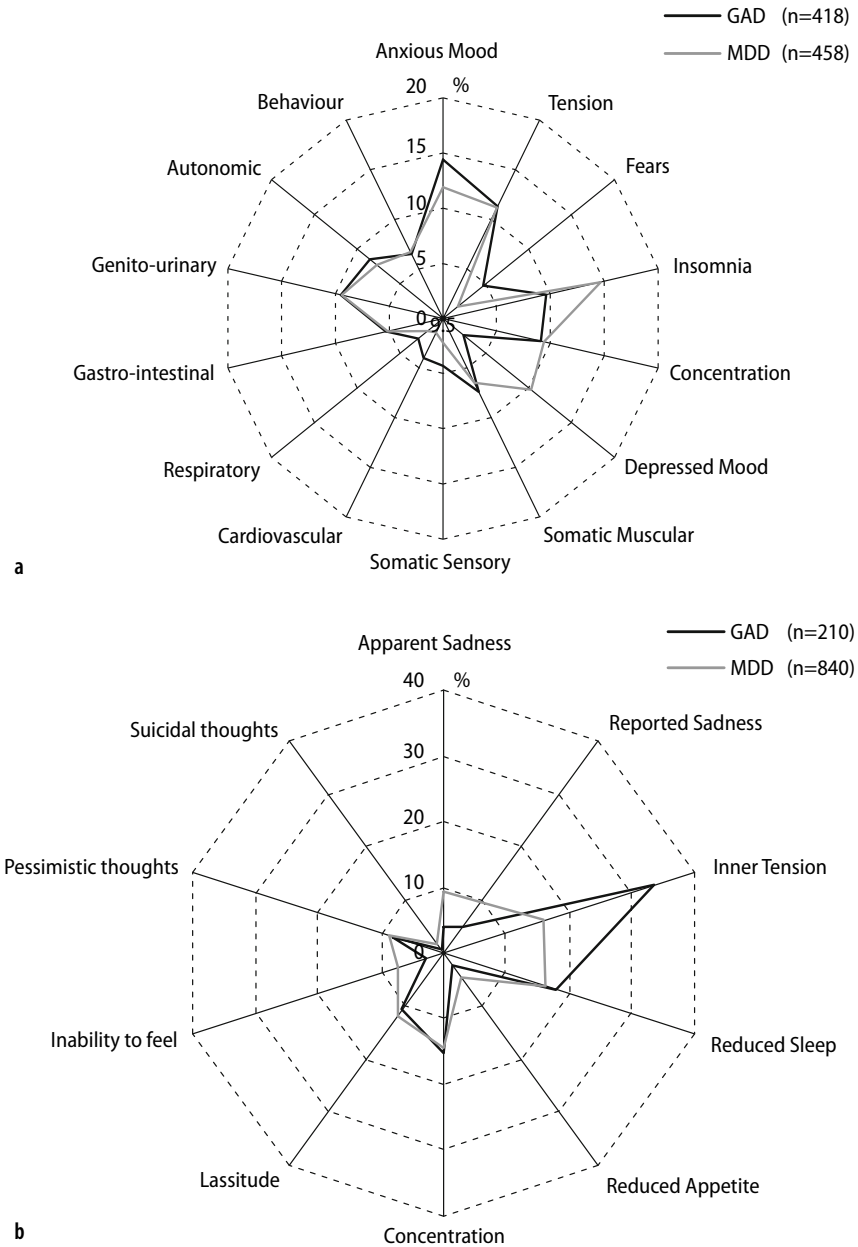

Fig. 3 Relative contribution of each item to the total score in patients with GAD and MDD in remission. (**a**) HAMA profile after treatment with escitalopram. (**b**) MADRS profile after treatment with escitalopram. A total of 465 patients with GAD treated with escitalopram achieved remission (HAMA ≤7), but the 12 remitted patients who withdrew before 8 weeks and the 35 with a HAMA score of 0 were not included in this analysis.A total of 971 patients with MDD treated with escitalopram achieved remission (MADRS ≤12), but the 61 remitted patients who withdrew before 8 weeks and the 70 with a MADRS score of 0 were not included in this analysis

Symptom profile after treatment

HAMA

The contribution (%) of each item of the HAMA to the total score after treatment in remitted patients with GAD or MDD is shown in Fig. 3a. In patients with GAD, the pattern of symptoms was very similar to that observed at baseline: items corresponding to the diagnostic criteria for GAD contributed somewhat more to the total score, especially *Anxious mood, tension, insomnia* and *concentration*.

In patients with MDD, the pattern of symptoms was very similar to the initial pattern with strong similarities between MDD and GAD patients, with the exception of the mood item.

MADRS

The contribution (%) of each item of the MADRS to the total score after treatment in remitted patients with GAD or MDD is presented in Fig. 3b. In patients with GAD, the pattern of symptoms was very similar to that observed at baseline. Three symptoms contribute to two-thirds of the total score: *inner tension, reduced sleep* and *concentration difficulties*.

In patients with MDD, each symptom contributed almost equally to the total baseline score, with the

exception of *reduced appetite* and *suicidal thoughts*. Again, the pattern of symptoms was similar to that observed at baseline.

Discussion

The symptomatic pattern of patients with MDD, GAD or MDD with comorbid anxiety disorders was determined before treatment initiation for all three groups and after treatment with escitalopram for patients with MDD or GAD alone.

The symptomatology is assessed in two ways—quantitatively and qualitatively. First, the actual scores on each item are compared across the three diagnoses. This allows for a quantitative look at the rating scales, and can show for example, that depressed patients with anxiety symptoms are quantitatively nearly identical with "pure" MDD patients on the single item scores of the MADRS. Thus, it is possible to quite readily distinguish patients with GAD versus those with MDD using the MADRS, but this scale would not distinguish between patients with MDD and those with MDD and anxiety symptoms. The picture is somewhat more complicated with the HAMA: the somatic items cannot differentiate patients with GAD from depressed patients with comorbid anxiety symptoms. The psychic components show mixed results with *depressed mood*, the only item that distinguishes patients with GAD from depressed patients with or without anxiety. Three items, *anxious mood, tension* and *fears* show the most robust differentiation between GAD and MDD and comorbid anxiety versus MDD alone. Second, the relative contribution (%) of each item to the total score of the MADRS and of the HAMA was calculated for each diagnostic entity. This was done in order to assess the "weight" of each individual item in the total score.

At baseline, prior to treatment initiation, the contribution of the somatic items of the HAMA as well as the items *fears* and *depressed mood* was rather low in GAD patients. The items with a major contribution were *anxious mood*, *tension*, *insomnia* and *difficulties in concentration*. In patients with MDD the pattern of symptoms was very similar with an additional contribution of the item *depressive mood*. The profile of the comorbid patients was similar to the profile of patients with MDD. On the MADRS, patients with GAD had a high contribution of the items *inner tension*, *reduced sleep* and *concentration*, which is very consistent with the results on the HAMA. The items *apparent sadness*, *reported sadness* and *inability to feel* had a low score in GAD patients. In patients with MDD, all items contributed almost equally to the total score with the exception of *reduced appetite* and *suicidal thoughts*. For this last item the results simply reflect the exclusion criteria. The pattern of MDD patients with comorbidity was almost identical to that of patients with MDD. The contribution of the anxiety symptoms in GAD patients was higher because of the low contribution of depressive items such as a*pparent sadness* and *reported sadness* and *inability to feel*. This is not to say that the scores were higher. In this way, the contribution of *inner tension* to the pattern of GAD patients is much higher than that of MDD patients, although the mean score on this item is similar. Overall, using either the MADRS or the HAMA, the profile of the three groups is rather similar.

After treatment to remission, the pattern of the residual symptoms in patients with MDD is similar to that of symptoms observed at baseline. This is consistent with the data of Nierenberg et al. [30] for the residual symptomatology in responders with an initial diagnosis of depression. The result is even more striking when observed in remitters.

In GAD patients, the remitters also had the same pattern after treatment with escitalopram. This strongly suggests that residual symptoms, even in patients reaching remission criteria, reflect the nature of the underlying GAD and MDD process. The contribution of each item of the HAMA and the MADRS to the total score before and after treatment also suggests that, when using the current DSM-IV criteria, GAD and MDD are qualitatively very similar, with the depressive mood item present in MDD patients by definition, and absent by definition in GAD patients

In conclusion, the symptomatic profile of GAD patients is very similar to that of MDD with the addition of *depressed mood*. Treatment does not modify this profile, based on these analyses of the escitalopram database. Even in remitters the residual symptomatology shows a pattern very similar to the pre-treatment pattern.

The results from this analysis of the database of patients with anxiety and depressive disorders treated with escitalopram support the hypothesis of a common underlying pathological process. The similarity in disease profiles with only one or two symptoms differentiate MDD and GAD intervention, supporting the claim that, while a categorical approach might still be needed for clinical decision-making, a dimensional model for the diagnosis of anxiety and affective disorders is warranted [31].

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