

## ORIGINAL ARTICLE

# Preferences of psychiatric practitioners for core symptoms of major depressive disorder: a hidden conjoint analysis

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**Abstract**

According to ICD-10 and DSM-V, symptoms of depressive disorder are considered to be equally important for severity judgment. It was the goal to investigate the weight of selected symptom complexes for severity judgment. In workaday life severity judgment results from an overall impression rather than from calculating severity in different symptom complexes, separately. In fact, the drivers for overall judgment may not be known explicitly to the psychiatrist himself. A method of choice to resolve this is conjoint analysis. Based on the Montgomery–Asberg Depression Scale (MADRS) and the Sheehan Disability Scale (SDS) case vignettes were constructed. Different symptom severity in the domains mood, vegetative symptoms, cognition/inhibition, suicidality, and everyday functioning were worked into the vignettes. Different symptom complexes influence the severity judgment by clinical psychiatrists to a rather different extent. Mood has a greater impact on severity judgment than suicidality, cognition/inhibition, vegetative symptoms, and everyday functioning. We conclude that core complexes of major depressive disorder are valued with different clinical relevance by psychiatrists. Thus, diagnosis and appraisal of therapeutic efficacy are subject to individual preferences of clinical psychiatrists and prevalence and therapeutic efficacy may be over- or under-estimated unless these differences in preferences are taken into account.

**KEYWORDS**

clinical relevance, clinical symptoms, disease severity, everyday function, symptom preferences

## 1 | INTRODUCTION

In clinical practice as well as for clinical trials and research, the diagnosis of major depressive disorder rests on checklists compiled for the International Classification of Diseases (ICD) and the Diagnostic and Statistical Manual (DSM). In ICD-10, two of the following three symptoms are mandated for diagnosis of depressive disorder: depressed mood, loss of interest and enjoyment, reduced energy leading to increased fatigability and diminished activity. Moreover, at least two additional symptoms should also be present: reduced concentration and attention, reduced self-esteem and self-confidence, ideas of guilt and unworthiness, bleak and pessimistic views of the future, ideas or acts of self-harm or suicide, disturbed sleep, diminished appetite. In ICD-10, these symptoms are considered to be of equal relevance for the diagnosis and severity judgment is based on the number of

symptoms present. According to DSM-IV and DSM-V, diagnosis of major depressive disorder requires the presence of either depressed mood or pervasive loss of interest or pleasure and in addition symptoms such as either significant weight loss or weight gain, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue or loss of energy, feelings of worthlessness or excessive or inappropriate guilt, diminished ability to think or concentrate or indecisiveness, recurrent thoughts of death or recurrent suicidal ideation or suicide attempt or specific plan, to a total of at least five symptoms. Assignment of severity of depression is based on both, the number of symptoms present and the distress and functional impairment imposed by these symptoms. The symptoms making up the syndrome of major depressive disorder do not represent an orthogonal set of symptoms but are correlated with one another (Chelminski, McGlinchey, Young, & Zimmerman, 2006). Thus, even assignment of severity of disease is somewhat ambiguous considering the different extent of overlap between symptoms. Hence, while securing a standard of diagnosis, it remains unclear whether major depressive disorder as described by

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ICD and DSM represents a consistent and identical entity with severity determined by the number of symptoms or whether this diagnosis represents a heterogeneous pool of disturbances of brain function depending on the specific set of symptoms with severity determined by severity within the symptoms. In order to tackle these issues in the future, however, it needs to be clarified whether symptoms associated with major depressive disorder are of equal relevance for clinical psychiatrists when judging on the severity of depressive disorder.

The methodology used in the present study is motivated by the following line of thought: In workaday life the final diagnosis on the severity of depression is rather the result of an overall impression than the outcome of explicitly evaluating and weighting the severity of different symptoms. Even more, the drivers for the overall judgment may not be known explicitly to the psychiatrist himself.

Two of the methods to determine hierarchies of relevance and individual decision preferences in situations with a manifold of variables are conjoint analysis (CA) (Luce & Tukey, 1964) and analytic hierarchy process (AHP) (Saaty, 1980). Individual preferences for assessing the severity of major depressive episodes have been determined by means of AHP, previously (Danner et al., 2011). With this method, a set of alternative choices is presented and participants give their judgment on the relative importance of either alternative. One of the underlying axioms is that decisions are made on the basis of an existing hierarchical order. It is assumed that the judgment on the relevance of the feature characteristic of one variable is independent of the relevance of the feature characteristic of all other variables. While AHP is suitable to determine a prioritization of preferences of different stakeholders, labeling and pre-selection of alternatives have been shown to influence the result of the AHP in medical contexts (Bridges, Ijzerman, & van Til, 2012). More importantly, this procedure may not be applied when the individual factors are hidden in the context of real life situations (Page, 2012).

CA is based on the assumption that the overall evaluation of, say an illness, is not the result of a hierarchical process considering the relative importance of alternative choices of symptom severity but in contrast a simultaneous consideration of a full set of information on all symptoms making up the illness. With this method, a preference for a set of items is appraised and CA allows to determine the relevance of individual symptoms represented in the set by means of calculating multiple regressions. In other words, upon performing overall judgment on a number of cases (e.g. judgment on overall disease severity), CA allows to find out to what extent this overall judgment was driven by the hidden factors constituting the cases (e.g. different symptom complexes such as mood, cognition/inhibition, vegetative symptoms, or suicidality for depressive disorders). In particular this means that an overall judgment is made without the necessity to judge the explaining factors or their interactions, individually. CA then reveals which of the factors contributed the most to the severity judgment.

In a recent study on preferences concerning neurological disorders, patients preferred the approach of choosing sets of symptoms followed by CA over judging on symptoms by means of alternative choices followed by analysis according to AHP (Ijzerman, Snoek, & van Til, 2008). With somewhat arbitrarily predefined choices and factor levels a choice-based CA has been performed previously to determine the preferences of patients with depressive disorder

(Zimmermann et al., 2013). A more realistic approach resembling the daily work of practicing physicians is taken in the present study. Symptoms and severity thereof was embedded in case vignettes without explicitly labeling symptoms or severity.

Several clinical scales are used to screen for and assess the severity of depressive disorders, e.g. the Montgomery–Asberg Depression Scale (MADRS) (Asberg & Montgomery, 1979) or the Hamilton Depression Rating Scale (Hamilton, 1960). The MADRS has been shown to be reliable in judging the severity of symptoms in patients with major depressive disorder, elderly patients and when judging therapeutic efficacy (Engedal et al., 2012; Barca, Engedal, & Knapskog, 2011; Carmody et al., 2006).

Some stakeholders of the health system worldwide demand the use of functional or disability measures for the appraisal of disease severity and treatment efficacy. One such scale is the Sheehan Disability Scale (SDS) (Sheehan, 1983). This scale has been used successfully as a sensitive tool for identifying primary care patients with mental health-related functional impairment (Farber, Leon, Olfson, Portera, & Sheehan, 1997).

The present study analyzes the relevance of symptom clusters and everyday function for the judgment on severity of major depressive disorder by clinical psychiatrists.

## 2 | METHODS

The study was performed according to institutional guidelines (ethics committee Ulm University) and the principles outlined in the Declaration of Helsinki.

### 2.1 | Preparations for “hidden” conjoint analysis (CA)

Numerous variations have been developed in the past to take into account the complexity the participants of a CA might be faced with (Anderson, Babin, Black, & Hair, 2010). The design of the present study was motivated by the goal to mimic the clinical situation and to make the task for the participants as familiar as possible. Case vignettes were designed (see later) and the participating psychiatrists had to perform an overall judgment whether the case described was to be diagnosed as representing subjects with no, mild, moderate, or severe major depressive disorder. Other than in traditional CAs, the feature characteristic in the different domains (mood, cognition/inhibition, suicidality, vegetative symptoms) was not communicated to the participants. Thus, the analytic strategy in the present study needed to consider this uncertainty of the participants and therefore can be described as “hidden” CA. The technique to calculate the overall weights for the symptoms is the same as for conventional CA. Together with the participants' overall judgment of severity of the cases described in any such vignette the severities for the individual symptoms define a high-dimensional data-point that can be used for linear regression. To be more precise, let  $y_i^p$  denote the severity that the  $p$ -th participant assigns to the  $i$ -th case, i.e. the case described in the  $i$ -th vignette. Furthermore let  $x_{i,j}$  denote the severity of the  $j$ -th symptom complex in the  $i$ -th case and  $w_j^p$  the unknown weight the  $p$ -th participant implicitly assigns to the  $j$ -th symptom complex. This is the target value that should be revealed by means of the CA. Ideally  $y_i^p = \hat{y}_i^p := \sum_j w_j^p x_{i,j}$ , for

all vignettes. Then, using linear regression the weights are determined by minimizing  $\sum_i (y_i^p - \hat{y}_i^p)^2$ .

In a first step a total of 17 different vignettes were designed that describe realistic cases. There are, of course, the conflicting goals of, on the one hand, using as many vignettes as possible to increase the statistical reliability and, on the other hand, using as few as possible to make the data acquisition practically feasible. We applied the following compromise: While the minimum number of vignettes to conduct the CA in our context is five we selected seven vignettes to gain stability in the results and two additional ones for the later evaluation of the predictive performance of the results of CA based on these seven vignettes. We felt that assessing nine short vignettes was not to expect too much from the psychiatrists. Of course, the choice of the seven vignettes was determined through D-optimality (Boyd, Vandenberghe, & Wu, 1998). Intuitively this criterion makes sure that the vignettes are as distinct from each other as possible.

### 2.1.1 | Case vignettes

Each vignette presented information on the medical history and clinical symptoms of a fictitious patient and had a length of about 400 to 500 words. Description of the symptoms was guided by the items of the MADRS (Asberg & Montgomery, 1979) and the SDS (Sheehan, 1983).

The MADRS is a 10-item scale. Judgment of severity of these items is to be made on a 7-step scale from 0 (no symptoms) to 6 (severe symptoms). For example, severe vegetative symptoms were described in the case vignette (see Supporting Information) as the patient sleeping less than two to three hours per night (item score 6) and having no appetite (item score 4). Likewise, severity of the other symptoms was stamped into the vignettes using the wording from MADRS and SDS. Of course, the scores were not mentioned in the vignettes and participants in the study did not have to rate the severity for each symptom complex. Rather participants had to make a judgment on overall severity of depressive disorder for the patients described in the vignettes. The investigators did not suggest any kind of judgment, rather description of symptoms (mood, cognition/inhibition, suicidality, vegetative symptoms, everyday functions) were worked into the case vignettes with different severity. In the MADRS, mood is represented with 24 of 60 points, and cognition/inhibition, vegetative symptoms, and suicidality with 12 points each. The SDS has a maximum score of 30. In order not to prejudge importance of symptoms on behalf of the investigators the five factors (mood, cognition/inhibition, suicidality, vegetative symptoms, everyday functions) were normalized while performing the CA. CA on severity judgment for all of the vignettes then allows to find out which of the symptoms contributed to what extent for each participant and thus informs about the clinical preferences of individual psychiatrists.

In practice, CA requires a rather limited number of variables. Thus it was needed to group several items of the MADRS into fewer variables. For reasons of practicality four groups were chosen. Several factor analyses of the MADRS have been published with different factor solutions. In subjects with depressive symptoms and mild cognitive deficits items 1, 2, 8, 9 comprised factor 1, items 3, 4, 5, and 10 factor 2, and items 6 and 7 factor 3 (Gabryelewicz et al., 2004). Another study found four factors comprised of items 1 and 2 (factor 1),

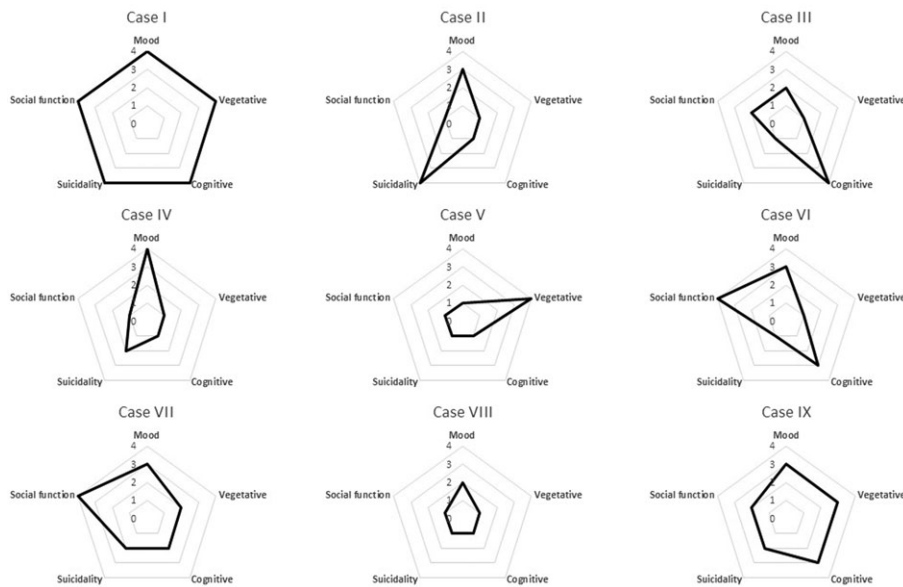
items 9 and 10 (factor 2), items 6, 7, and 8 (factor 3), and items 3, 4, and 5 (factor 4). In yet another study other combinations of items comprised each of three factors used to describe the MADRS factor structure (factor 1: items 1, 2, 3, 5, 7, 8; factor 2: items 9 and 10; factor 3 items 4 and 5) (Uher et al., 2008). Considering the setting- and cohort-dependence of factor solutions we grouped the items according to presumable clinical face validity. Meta-analysis of clinical symptoms show that pessimism and suicidal thoughts are associated (Jäger, Kliegel, & Phillips, 2007)—thus, items 9 and 10 were grouped into one symptom complex. From a clinical point of view vegetative symptoms comprise another group of symptoms—thus, items 4 and 5 were grouped. Yet another group of symptoms comprises symptoms relating to affect and anhedonia such as perceived or reported sadness, loss of interest and inner tension—thus, items 1, 2, 3, and 8 were grouped together. Eventually, impairment of concentration and lassitude, i.e. inhibition to start activities, are somewhat related and associated from a clinical point of view. Overall, we are aware, that grouping of symptoms sets the stage for CA and influences the outcome thereof, which certainly is a limitation of the current study. However, no gold standard is established to group clinical symptoms and picking one of the many reported factor setting- and cohort-dependent factor solutions would be arbitrary, also. Different severities of symptoms in the domains mood (items 1, 2, 3, and 8 of the MADRS), vegetative symptoms (items 4 and 5), cognition/inhibition (items 6 and 7), and suicidality (items 9 and 10) were worked into the vignettes. Likewise different impairments of everyday functioning as described in the SDS were also worked into the vignettes. The MADRS score in the case vignettes ranged from 13 to 57 out of 60 on the MADRS scale and from 4 to 27 on the SDS. The profile of severity in the domains mood, vegetative symptoms, cognition/inhibition, and social function is shown in Figure 1.

## 2.2 | Participants

From a database of all psychiatrists in Germany a countrywide random sample of 200 participants were contacted via regular mail and asked for participation. The participants received an invitation letter from a consulting firm (galor GmbH) with an accompanying letter from Lundbeck, Germany, asking for help in this academically driven project but offering participants financial reimbursement (100 €) for the time to read the nine case vignettes, perform their judgment and return their assessment. Fifty-seven (28.5%) of the psychiatrists consented to participation in the survey and responded with sending back a completed questionnaire.

## 2.3 | Data analysis

Fifty-seven out of 200 psychiatrists returned the questionnaire. For any vignette the average score and standard deviation were calculated from the individual ratings of the participants. Whenever the individual score deviated more than three times the standard deviation the participant was excluded from the analyses. Based on this 3-sigma rule 15 of these datasets were removed. The remaining 42 datasets together with the pre-specified matrix that encoded the degrees of severity of the first seven vignettes allowed for the subsequent CA.



**FIGURE 1** Fingerprints of disease severity constructed into the case vignettes according to the domains mood, vegetative symptoms, cognitive symptoms, suicidality, and social function. Severity in each domain was assigned on a 4-step scale within each domain

Histograms of severity judgment by the participants are shown in Figure 2.

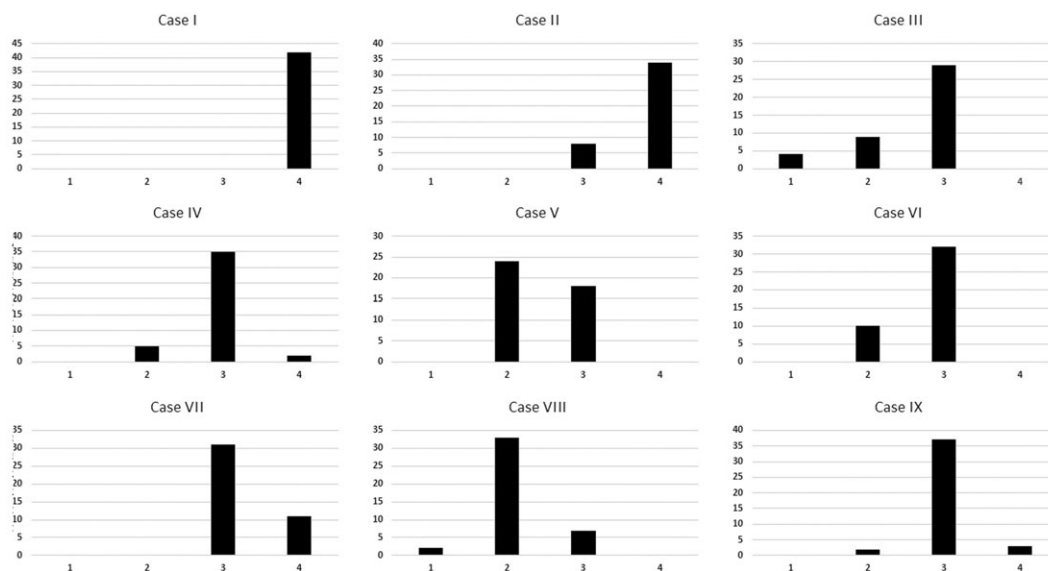
According to the usual way of quantifying the degree of depression as the sum of quantified severities of the different complexes of symptoms, a linear model  $\hat{y}_i^p = \sum_j w_j^p x_{i,j}$  without constant term was deployed and calculated with MATLAB for the seven vignettes. Ingredients of this model were for each vignette the predefined severities in the domains mood, cognition/inhibition, suicidality, vegetative symptoms (as mentioned before not known to the participants) and the assigned overall rating by each participants.

The quality of the obtained results was evaluated on the basis of the two remaining vignettes. Based on the individual weights of

the respondents the outcome for these vignettes was predicted and compared to the actual answer. Since the model allows for non-integral weights but the scale of the respondents does not, the predicted value was rounded to the next integral number.

The case vignettes had to be rated by the participants using a scale with “0” indicating that no depression was to be diagnosed, “1 to 3” that mild depression was present, “4 to 6” that depression was moderate, and “7 to 9” that severe depression was present.

Before starting the regression the following normalization step was performed. An answer “0” of the  $p$ -th participants was mapped to “ $y_i^p := 1$ ,” “1 to 3” to “ $y_i^p := 2$ ,” “4 to 6” to “ $y_i^p := 3$ ” and finally “7 to 9” yielded  $y_i^p := 4$ . Together with the range of values in the severity matrix that transformation allowed to interpret the resulting



**FIGURE 2** Histograms of overall severity of cases as rated by participants (0, case vignette indicating no depression; 1, case vignette indicating mild depression; 2, case vignette indicating moderate depression; 3, case vignette indicating severe depression)

weights  $w_j^p$  as percentage of importance of the  $j$ -th symptom complex for the overall judgment.

### 3 | RESULTS

The assignment of overall severity did not follow the most severe symptom but rather represented some averaging of the severity in the different domains (Figure 3; cases III, IV, V, VI, VII). For case II most of the participants rated the vignette as representing severe depression although the only severe symptom was suicidality and all other symptoms were mild to moderate. In contrast to all other domains, severe suicidality drives the overall assessment of severity.

Calculating the multiple regressions according to the procedures of the CA shows the order of relevance of the individual domains being mood (mean:  $36.9\% \pm 11.2\%$ , mean  $\pm$  standard deviation), suicidality ( $22.1\% \pm 9.2\%$ ), cognition/inhibition ( $15.5\% \pm 8.2\%$ ), vegetative symptoms ( $15.4\% \pm 8.1\%$ ), and social function ( $10.1\% \pm 6.5\%$ ).

If social function is excluded from the list and afterwards the sum of the weights of the four remaining complexes normalized to 100%, the weights are  $41.1\% \pm 12.5\%$  for the factor mood,  $17.1\% \pm 9.0\%$  for the factor vegetative symptoms,  $17.2\% \pm 9.1\%$  for the factor cognition/inhibition, and  $24.6\% \pm 10.2\%$  for the factor suicidality. Note that the greater variation of the weights is a simple consequence of the normalization step.

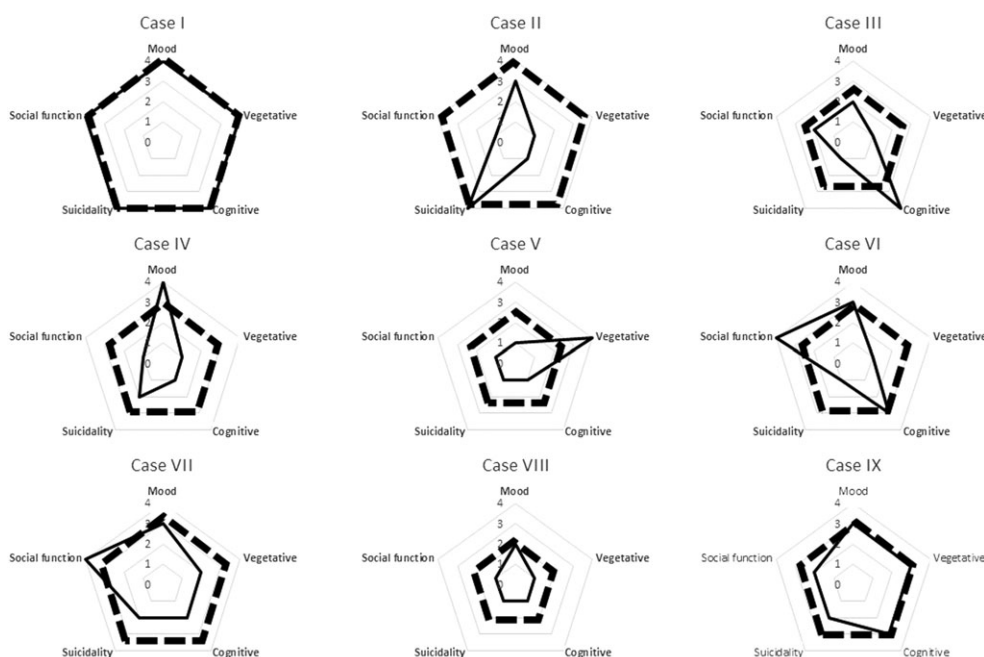
After having performed CA with seven out of the nine vignettes the prediction of the model was tested for the remaining two vignettes. For the first test vignette 32 answers out of 42 were predicted correctly and 100% of the answers deviated at most one from the predicted value. For the second test vignette 27 predictions are correct, 41 answers deviated at most one from the predicted value (Figure 4).

### 4 | DISCUSSION

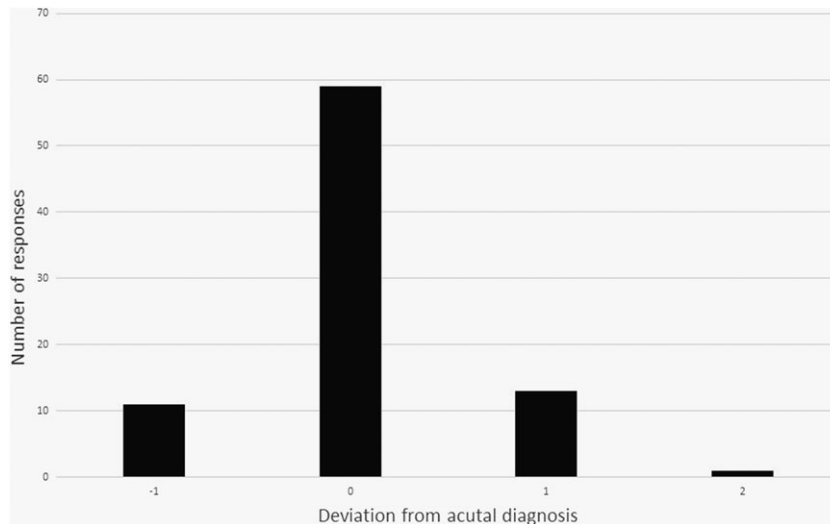
While ICD-10 mandates two out of three mandatory symptoms for diagnosis of depressive disorder and DSM-IV and DSM-V require two mandatory symptoms, both classification systems require the presence of additional symptoms that represent a diverse spectrum from suicidality to cognition. It is unclear, however, whether clinical psychiatrists value the different symptom complexes in an exchangeable manner as suggested by ICD-10 or DSM-IV or DSM-V.

While AHP is a straightforward method to analyze a hierarchy of symptoms it seems more realistic to analyze the overall severity of depressive symptomatology using case vignettes since this resembles the everyday work of clinicians. For reasons of methodological rigor description of severity of symptoms in the case vignettes for this study was based on an established scale for the severity assessment of depressive disorder (MADRS) and on an established scale for rating the impairment of everyday function (SDS).

Unfortunately, not the complete spectrum of depressive symptoms as represented in the Inventory of Depressive Symptoms (IDS), for instance, can be used for methodological reasons of having to limit the number of variables for CA. This is one of the limitations of the present study. Moreover, the representativeness of responding psychiatrists remains unclear since no detailed biographic variables or variables on the setting of participating psychiatrists were obtained and the database used did not contain information on age and gender of psychiatrists. One further limitation of the present study is the low response rate of only 28.5% of psychiatrists and the lack of information on differences between groups of psychiatrists responding and not responding. However, compared to other reports targeting the analysis of the relative importance of different symptoms for diagnosis and severity assessment of depressive disorder (Hummel et al., 2012; Danner et al., 2011) by means of an AHP, the group is still rather large.



**FIGURE 3** Similar to Figure 1, but the average overall rating of severity by participants is marked with a dotted pentagram



**FIGURE 4** The predictive capacity of the model from conjoint analysis was analyzed for two case vignettes ( $n = 42$  participants). The degree of severity was to be rated on a 4-step scale from no depression to mild, moderate, and severe depression. (-1, severity was rated one degree less severe than predicted from model; 0, degree of severity was rated as predicted from model; 1, severity was rated one degree more severe than predicted from model; 2, severity was rated two degrees more severe than predicted from model)

The depressive symptom given the highest relevance by practicing psychiatrists was mood. This is not surprising as it represents the very core symptom of depressive disorder. The second most important symptom practicing psychiatrists prefer in severity judgment was suicidality. This is somewhat surprising as it has been hypothesized in a prior study that suicidality is less central to the diagnosis of depressive disorder than vegetative symptoms (Buchwald & Rudick-Davis, 1993). Moreover, the large discrepancy between the importance of suicidality and vegetative symptoms is surprising because in subjects with high risk for suicide the presence of vegetative symptoms is frequent (McGirr et al., 2007; McCall et al., 2010). One possible explanation is that overlooking suicidality poses an immediate threat to the life of the patient and an indirect threat to the practicing psychiatrist due to potential litigation consequences.

Other than suicidality, neither mood, nor vegetative or cognitive functions, nor social function suffice to dominate the overall severity assignment when a threshold with severe feature presentation is reached. This questions the current algorithms for diagnosis of major depressive disorder where e.g. suicidality and vegetative functions are of equal importance for both, diagnosis and overall severity judgment. Future studies will need to investigate in greater detail whether different relevance of symptoms contributes to the low inter-rater reliability of the clinical diagnosis of major depressive disorder (Regier et al., 2013).

Somewhat surprisingly the relevance of everyday functioning for the assignment of severity of disease by clinical psychiatrists was low. However, this falls in line with a recent demand to keep the rating of diseases severity and disability separate and to base the assessment of severity on the development of disease, its spread, or continuity (Ustün & Kennedy, 2009). The reason behind this is to avoid co-linearity which would be imposed when disability parameters would be included in the algorithm to determine severity.

## 5 | CONCLUSION

The results of the present study raise various issues for clinical practice. Diagnosis and appraisal of therapeutic efficacy are subject to

preferences by clinical psychiatrists and prevalence and therapeutic efficacy may be over- or under-estimated unless these differences in preferences are taken into account. Surprisingly, everyday functioning is less important for appraisal of severity of depressive disorder than clinical symptoms. Moreover, different relevance of symptoms in the diagnostic process may blur the view on subtypes of depressive disorder that may or may not go hand-in-hand with specific symptoms. Future studies will need to disentangle the preferences of psychiatrists in the diagnostic process and the nosology of depressive disorder.

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## DECLARATION OF INTEREST STATEMENT

MR and AB partake in advisory boards and speaker's boards of companies developing or selling drugs used in the treatment of depressive disorder (MR: Servier, Germany and Lundbeck, Germany; AB: Lundbeck, Germany).

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## SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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