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Depression is not a consistent syndrome: an investigation of unique symptom patterns in the STAR*D study

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Abstract

Background—The DSM-5 encompasses a wide range of symptoms for Major Depressive Disorder (MDD). Symptoms are commonly added up to sum-scores, and thresholds differentiate between healthy and depressed individuals. The underlying assumption is that all patients diagnosed with MDD have a similar condition, and that sum-scores accurately reflect the severity of this condition. To test this assumption, we examined the number of DSM-5 depression symptom patterns in the "Sequenced Treatment Alternatives to Relieve Depression" (STAR*D) study.

Methods—We investigated the number of unique symptom profiles reported by 3,703 depressed outpatients at the beginning of the first treatment stage of STAR*D.

Results—Overall, we identified 1,030 unique symptom profiles. Of these profiles, 864 profiles (83.9%) were endorsed by five or fewer subjects, and 501 profiles (48.6%) were endorsed by only one individual. The most common symptom profile exhibited a frequency of only 1.8%. Controlling for overall depression severity did not reduce the amount of observed heterogeneity.

Limitations—Symptoms were dichotomized to construct symptom profiles. Many subjects enrolled in STAR*D reported medical conditions for which prescribed medications may have affected symptom presentation.

Conclusions—The substantial symptom variation among individuals who all qualify for one diagnosis calls into question the status of MDD as a specific consistent syndrome and offers a potential explanation for the difficulty in documenting treatment efficacy. We suggest that the analysis of individual symptoms, their patterns, and their causal associations will provide insights that could not be discovered in studies relying on only sum-scores.

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Conflict of interest

None.

Contributors

Both authors analyzed the data, managed the literature searches, contributed to the manuscript, and approved the final manuscript.

Keywords

depression symptoms; DSM; heterogeneity; major depressive disorder; STAR*D

Introduction

Major Depressive Disorder (MDD) is a highly prevalent, recurrent, and debilitating condition (Kessler et al., 2005, 2003; McClintock et al., 2010). Despite decades of research, its causes and very nature remain objects of debate, and available treatments are ineffective for many patients (Khan et al., 2002; Kirsch et al., 2008; Pigott et al., 2010). In one of the largest clinical trials, the "Sequenced Treatment Alternatives to Relieve Depression" (STAR*D) (Fava et al., 2003; Rush et al., 2004), only about one fourth of the patients enrolled achieved remission during the first treatment stage.

One potential explanation for such disappointing findings is *covert heterogeneity*. The current disease category depression is commonly regarded as a consistent syndrome, justifying the use of symptom sum-scores and thresholds: the number of symptoms is the main focus, while specific symptoms are ignored. This approach, however, may obfuscate dramatic differences among depressed individuals in their endorsed symptoms (Faravelli et al., 1996; Parker, 2005). Here we test the hypothesis of covert heterogeneity by examining the number of unique symptom profiles in STAR*D.

The Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (APA, 2013) describes nine MDD symptoms: 1) depressed mood, 2) diminished interest / pleasure, 3) weight / appetite increase / decrease, 4) insomnia / hypersomnia, 5) psychomotor agitation / retardation, 6) fatigue or loss of energy, 7) feelings of worthlessness or inappropriate guilt, 8) diminished ability to think or concentrate, or indecisiveness, and 9) recurrent thoughts of death or recurrent suicidal ideation. In order to meet the criteria for depression, an individual has to exhibit five or more symptoms, at least one of which must be either symptom one or two.

It is of note that all symptoms except depressed mood are compounds that include at least two sub-symptoms, and three of the criterion symptoms (sleep, weight/appetite, psychomotor) can be met by either increases or decreases. This means that two individuals who qualify for a diagnosis of MDD may not have a single symptom in common. Taking only the 9 DSM-5 criterion symptoms into account, 227 unique symptom profiles exist that all qualify for a diagnosis of MDD. Considering the extremes of sleep, appetite and psychomotor changes separately increases the number of unique profiles to 945, and taking into account sub-symptoms of all eight compounds leads to 16,400 different profiles that qualify for a diagnosis of MDD.

Huge possible variations in MDD profiles do not, however, necessarily imply a large variety of actual symptom profiles. Our analysis uses data from 3,703 participants in the first treatment stage of the STAR*D study to assess the degree of symptom heterogeneity in a large representative sample of depressed outpatients.

Method

Study description

Dataset version 3.0 from the NIH-supported STAR*D study (Fava et al., 2003; Rush et al., 2004) was analyzed for this report. STAR*D was a multisite randomized clinical trial conducted in the USA to investigate which of several treatment options would be most effective for nonpsychotic MDD outpatients. The first treatment stage enrolled 4,041 patients; all participants received citalopram, a selective serotonin reuptake inhibitor (SSRI) antidepressant. The data analyzed in this report were obtained from 3,703 individuals who were queried by telephone during the first week of the first treatment stage. STAR*D was approved and monitored by the institutional review boards at each of the 14 participating institutions, a national coordinating center, a data coordinating center, and the data safety and monitoring board at the NIMH. All participants provided written informed consent at study entry.

Participants

STAR*D used relatively inclusive selection criteria in order to obtain a highly representative sample of patients seeking treatment for MDD. Participants had to be between 18 and 75 years, fulfill DSM-IV criteria for single or recurrent nonpsychotic MDD, and have at least moderately severe depression corresponding to a score of at least 14 on the 17-item Hamilton Rating Scale for Depression (HAM-D) (Hamilton, 1960). Participants with a history of bipolar disorder, schizophrenia, schizoaffective disorder, or psychosis were excluded, as were patients with current anorexia, bulimia, or primary obsessive compulsive disorder. Further exclusion criteria were a history of inability to tolerate antidepressant medication, lack of response to an adequate trial of SSRI in the current episode of MDD, or failure to respond to 16 or more sessions of cognitive therapy in the current episode of MDD. Additional details about design, methods, and exclusion criteria of STAR*D are described elsewhere (Fava et al., 2003; Rush et al., 2004).

Outcome measures

None of the screening instruments used in STAR*D measured all DSM-5 criterion symptoms and the sub-symptoms of the three contrasting compound symptoms. The Quick Inventory of Depressive Symptoms (QIDS-16; Rush et al., 2003), however, met most of our requirements: it provides information on all DSM criterion symptoms, and assesses the direction of effects in two of the three contrasting domains (insomnia vs. hypersomnia; psychomotor agitation vs. retardation; the directions of weight and appetite problems were not scored). Each QIDS-16 item yields a score between 0 and 3, 0 indicating no problems, 3 indicating severe problems. We averaged three different QIDS-16 insomnia items into one insomnia symptom to avoid artificially inflating the number of symptom profiles. Overall, twelve symptoms were used in the analysis (Table 1). All symptoms were dichotomized into absent (scores 0 and 1) vs. present (scores 2 and 3) for the estimation of symptom profiles.

Statistical analysis

We examined the number of unique symptom profiles in the sample of 3,703 MDD outpatients. A profile is defined by any unique combination of symptoms; neither of the two DSM-5 MDD core symptoms 'low mood' or 'loss of interest' were required to define a profile. This closely resembles the way participants are selected for inclusion in depression studies: screening instruments such as the HAM-D or the BDI (Beck et al., 1988) are employed, and any sum-score above a certain threshold leads to inclusion, irrespective of the presence of DSM-5 core symptoms. Overall, the presence or absence of 12 symptoms makes 4,096 profiles possible.

In addition, we analyzed the subsample of participants who had the overall median number of symptoms in order to see if the heterogeneity in symptom profiles mainly reflects severity differences among subjects (i.e. we controlled for severity).

Results

The mean age of the 3,703 patients was 41.2 (*SD* = 13.2), and 63% were female. Detailed demographic information on this exact sample are reported elsewhere (Fried and Nesse, 2014). On average, participants exhibited 6 symptoms (mean symptom number = 6.03; *SD* = 2.75). Mean and median levels for each symptom are presented in Table 1; the three most commonly endorsed symptoms were sad mood, loss of energy, and concentration problems, the three symptoms with the lowest severities were hypersomnia, suicidal ideation, and psychomotor retardation. It is noteworthy that there was considerable variation even amongst symptoms with comparably low mean values, such as hypersomnia.

Analysis of symptom profiles

Overall, we identified 1,030 unique symptom profiles, with an average of 3.6 individuals per profile. Of these profiles, 864 (83.9%) were reported by five or fewer participants, and 501 (48.6%) were reported by only one individual. Of the 3,703 persons in the study, 1,527 (41.2%) shared their profile with 5 or fewer other individuals, and 501 participants (13.5%) showed unique symptom profiles that were different from those of all other individuals.

Figure 1 illustrates the frequencies of the 30 most common symptom profiles, describing 888 subjects (24%). Details on the ten most frequent profiles are presented in Table 2. For instance, participants in the most common group 'A' reported low levels on all symptoms (this is possible due to the dichotomization of responses into an absent and present category), and individuals with the second most common profile 'B' reported all symptoms except for hypersomnia and suicidal ideation. The 9th cluster 'I' and subsequent profiles each applied to less than 1% of the subjects.

Subgroup analysis

To examine whether observed heterogeneity simply reflected severity differences between participants, we investigated the number of unique symptom profiles in patients with similar overall depression severity. If severity differences among MDD patients were responsible for the dramatic heterogeneity, the number of unique profiles in a population with equal

overall severity should be greatly reduced. To that end, we repeated the analysis with 569 participants who reported exactly 6 symptoms, the median number in the full sample. In this subsample, we identified 188 unique symptom profiles, about 3 patients per profile. Out of these 188 profiles, 162 (86.2%) were endorsed by 5 or less participants, and 97 (51.6%) were endorsed by only one person. Severity differences of subjects diagnosed with MDD in STAR*D do not account for the large inter-individual differences in symptom profiles.

Discussion

The analysis of symptom profiles of 3,703 depressed outpatients in the STAR*D study reveals pronounced heterogeneity. The most common symptom profile was endorsed by only about 2% of subjects, and roughly 14% of the participants exhibited unique profiles not shared with a single other person in the study. Controlling for depression severity did not change the results.

Our main finding can be interpreted in several ways. The first is to attribute it to an artifact of the method. However, instead of using all possible permutations of symptom combinations, the analysis was limited to 12 symptoms. Also, instead of rating symptom severity on the original 4-level scale, all symptoms were collapsed to a present or absent code, further reducing the number of possible profiles. The results could have shown most patients fitting into a few common patterns, but no single pattern applied to even 2% of subjects.

A second possibility is that depression is a distinct disease entity with protean manifestations, similar to syphilis or lupus erythematous. From this point of view, symptomatic variability among MDD patients is unimportant because all symptoms have the same underlying cause. In such common cause models, symptoms are passive and interchangeable results of an underlying disorder, and diverse symptom profiles do not undermine the unity of the disorder (Schmittmann et al., 2013). While this theory remains possible for depression, it does not perform well in direct tests (Cramer et al., 2013; Fried et al., 2013), and is increasingly unlikely in view of the inability to find replicated biomarkers (Hek et al., 2013; Kapur et al., 2012; Tansey et al., 2012). Nonetheless, the idea that all depression has a single cause remains deeply entrenched in psychiatry. Mental disorders are widely understood to be brain dysfunctions, which explains the motivation underlying the NIMH's recent decision to solely fund studies investigating the neurobiological roots of mental disorders (Reardon, 2014). If depression symptoms are passive and interchangeable consequences of a latent disorder (similar to symptoms of infectious diseases), identifying and treating the underlying problem is unquestionably the correct way to proceed.

A third possibility is that depressed patients suffer from numerous syndromes that differ in etiology, symptom presentation, and biological predisposition. If this is correct, then usually unrecognized differences among MDD patients may help to account for inconsistent findings and recent disappointing results such as the questionable reliability of depression diagnosis in the DSM-5 field trials (Regier et al., 2013), the striking lack of progress in identifying biomarkers associated with depression diagnosis or treatment response (Hek et al., 2013; Kapur et al., 2012; Tansey et al., 2012), and the low efficacy of antidepressants in

clinical trials (Kirsch et al., 2008; Pigott et al., 2010). A growing body of evidence supports this interpretation: individual depression symptoms differ in important aspects such as risk factors (Fried et al., 2013), genetic background (Kendler et al., 2013; Myung et al., 2012), precipitants (Keller and Nesse, 2006; Keller et al., 2007), associations with personality traits, comorbidities, and demographic characteristics (Lux and Kendler, 2010), and their impact on functioning (Faravelli et al., 1996; Fried and Nesse, 2014; Tweed, 1993). There is also evidence that certain symptoms are more heritable than others (Jang et al., 2004), that specific symptoms and symptom patterns predict response in treatment studies (Fava et al., 2008; Uher et al., 2012), and that biomarkers may well exist for specific symptoms or symptom configurations (Kendler et al., 2013; Myung et al., 2012). Overall, these findings make it unlikely that depression is a single disorder with a variety of equivalent symptoms. Considering that DSM MDD criterion symptoms were determined largely by clinical consensus instead of empirical evidence (Kendler and Zachar, 2008; Lux and Kendler, 2010; Zimmerman et al., 2006a), it may not be surprising that they do not represent a consistent syndrome. Today's DSM symptoms closely resemble the ones proposed over 40 years ago, and numerous critical calls for a psychometric re-evaluation of depression have had little impact (Andrews et al., 2007; Lux and Kendler, 2010; McGlinchey et al., 2006; Zimmerman et al., 2006b).

A final possibility is a refinement of the above interpretation; depression symptoms may be, like the symptoms of a cold, different potentially useful responses aroused by different aspects of bad situations (Keller and Nesse, 2006). The inconsistency of depression symptoms within individuals across time supports this possibility (Oquendo et al., 2004). It also fits a biological view of higher and lower mood states as useful in situations characterized by greater or less propitiousness (Nesse and Stein, 2012). Different symptom profiles could reflect variations in the kinds of resources pursued, as documented in work by Keller et al. (Keller and Nesse, 2006, 2005; Keller et al., 2007), or different reasons why a goal cannot be reached, such as a specific obstacle, or lack of any strategy for reaching a goal (Nesse, 2009). This perspective provides a framework for distinguishing depression symptoms that arise from primary brain changes from those aroused by life situations, inflammation, or some other stimulus that normally causes low mood (Nesse and Stein, 2012).

Implications

The finding of pronounced heterogeneity has practical research implications. The most important is that using sum-scores as a proxy for depression severity may be unjustified. Sum-scores may provide an estimate of overall psychopathological load, but individual depression symptoms differ in their impact on impairment of psychosocial functioning (Fried and Nesse, 2014; Tweed, 1993), can be more informative about global functioning than symptom sum-scores (Faravelli et al., 1996), and depression can be very severe even when only a few symptoms are present (Gotlib et al., 1995; Solomon et al., 2001).

Another implication is that individuals with similar sum-scores can have very different syndromes; we may eventually find that scores on instruments such as the BDI or the HAM-D provide descriptions of depression as inadequate as the count of broken bones in a trauma

victim. Assuming that an individual's depression is adequately described by a sum-score may conceal important clinical insights.

The third implication is for attempts to create meaningful subtypes of depression, such as neurotic, psychotic, melancholic, atypical, and anxious depression. On the one hand, it has been argued that depressive disorders can be understood as dimensional – the so-called unitary position that led to the DSM-III categories "minor depression" and "major depression"; from this perspective, mood disorders can be differentiated by the severity of the syndrome alone. Others have posited qualitative differences between different depressive states (for an overview, see Faravelli et al., 1996; Parker, 2005; Roth, 2001). Unfortunately, there has been limited success in identifying external validators for such qualitative subtypes (Davidson, 2007; Melartin et al., 2004; Pae et al., 2009; Young et al., 1987), and the debate about the number and nature of depression subtypes continues (Baumeister et al., 2011; Lichtenberg and Belmaker, 2010; van Loo et al., 2012). In addition to theory-driven approaches, there is a vast literature on different data-driven techniques that have aimed to cluster individuals with MDD or depression symptoms into smaller and more homogeneous groups. Factor analyses (FA) have been employed to examine relationships between symptoms, and often lead to cognitive, affective, or somatic symptom dimensions. The results of factor analytic approaches, however, vary across different depression screening instruments, and factor solutions for the same instrument differ across samples (Brown et al., 1995; Furukawa et al., 2005; Helmes and Nielson, 1998; Shafer, 2006; Wood et al., 2010). Results also depend on the method of extraction (Widaman, 1993), and factoring techniques can come to divergent conclusions across subsamples of the same population (Furukawa et al., 2005). The Center for Epidemiologic Studies Depression Scale (CES-D) (Radloff, 1977) provides a good example: while some studies confirm the 4-factor structure of the original report by Radloff (Blazer et al., 1998; Iwata and Roberts, 1996), others identified 1-factor to 3-factor solutions as well as higher-order factor structures (Helmes and Nielson, 1998; Lee et al., 2008; Morin and Ninot, 2011; Wood et al., 2010). In contrast to FA, latent class analysis (LCA) has been used to detect groups of individuals with similar item-response patterns (i.e. symptom profiles) (e.g., Lamers et al., 2010). However, a recent review of the LCA literature in depression research revealed that latent classes are not consistent across studies, and that identified profiles mainly reflect overall severity differences instead of qualitatively different classes (van Loo et al., 2012). The authors concluded that "studies performed to date do not provide conclusive evidence for the existence of depressive symptom dimensions or symptomatic subtypes" (van Loo et al., 2012) (p. 1). Other data-driven methods include the cluster analysis (CA), a technique that groups participants by similarity of characteristics (e.g., Guidi et al., 2011), and the grade of membership (GOM) analysis that groups individuals by a multivariate item profile (similar to LCA, individuals are grouped based on their symptoms, but in contrast to the deterministic LCA that groups each person into one class, GOM analysis uses a fuzzy logic approach in which a person belongs to several pure types with a certain probability; e.g. Davidson et al., 1988). Opportunities remain for these methods to illuminate depression subtypes, but so far their contributions have been modest.

Examining *specific* depression symptoms – those in the DSM-5 and others such anxiety and anger that are highly prevalent in depressed individuals (Fava et al., 2008; Judd et al., 2013) – offers a way forward. We see two main opportunities for progress. One straightforward approach is to analyze the influences of specific depression symptoms in both clinical and research studies, instead of ignoring the information in this data (Fried et al., 2013; Hasler et al., 2004; Lux and Kendler, 2010; Van Praag, 2010). A more novel approach is to use psychopathological network models to examine the causal relations among symptoms (Borsboom and Cramer, 2013). From a network perspective, symptoms do not cluster because of a common cause – they cluster because they are connected in complex dynamic causal networks of direct and indirect influences; insomnia may lead to fatigue, which may in turn cause psychomotor and concentration problems, irrespective of the particular diagnosis a patient may have. The network theory predicts that the reason for the higher inter-correlation within these so-called somatic depression items is not a specific disease type that causes predominantly somatic symptoms, but that a somatic symptom likely leads to other somatic symptoms that may fuel each other in vicious circles of mutual influence.

Limitations

The results of this report have to be interpreted in the light of four limitations. First, in order to make the most conservative case, we used simple symptom profiles based on symptoms dichotomized into categories of present and absent. Most depressive symptoms are, however, continuous dimensions that range from the non-pathological to the clearly pathological (Persons, 1986). Second, while subjects were not taking antidepressant medication at the baseline of STAR*D, many reported other medical conditions for which prescribed medications may have affected depression symptoms. Third, the QIDS-16 used in this report assesses most MDD symptoms with only one question, so item wording may have biased the results. Future studies should aim to assess each individual MDD symptom as carefully as current studies assess diagnoses (e.g., sleep diaries, weight diaries, and concentration tests). Fourth, this report likely underestimates depression variability due to our focus on the DSM-5 criterion symptoms. It is well established that several symptoms not currently part of the DSM criteria, such as helplessness, anxiety, and anger, are prevalent and clinically relevant in depressed individuals (Fava et al., 2008; Judd et al., 2013; McGlinchey et al., 2006). Taking such symptoms into account will encourage closer attention to the substantial covert heterogeneity among patients who all share a diagnosis of MDD.

Conclusion

Overall, the dissatisfaction with the diagnostic criteria of MDD might best be reduced by acknowledging that it is not one coherent condition with a single cause. We suggest that the analysis of individual symptoms, their patterns, and their causal associations will provide substantial insights that could never be discovered by studies relying on sum-scores.

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References

Andrews G, Slade T, Sunderland M, Anderson T. Issues for DSM-V: simplifying DSM-IV to enhance utility: the case of major depressive disorder. Am. J. Psychiatry. 2007; 164:1784–1785. [PubMed: 18056230]

APA. Diagnostic and Statistical Manual of Mental Disorders. Fifth Edition. Washington, DC.: American Psychiatric Association; 2013.

Baumeister H, Hutter N, Bengel J, Härter M. Quality of life in medically ill persons with comorbid mental disorders: a systematic review and meta-analysis. Psychother. Psychosom. 2011; 80:275–286. [PubMed: 21646822]

Beck AT, Steer RA, Garbin MG. Psychometric properties of the Beck Depression Inventory: 25 years of evaluation. Clin. Psychol. Rev. 1988; 8:77–100.

Blazer DG, Landerman LR, Hays JC, Simonsick EM, Saunders WB. Symptoms of depression among community-dwelling elderly African-American and white older adults. Psychol. Med. 1998; 28:1311–1320. [PubMed: 9854272]

Borsboom D, Cramer AOJ. Network analysis: an integrative approach to the structure of psychopathology. Annu. Rev. Clin. Psychol. 2013; 9:91–121. [PubMed: 23537483]

Brown C, Schulberg HC, Madonia MJ. Assessing Depression in Primary Care Practice With the Beck Depression Inventory and the Hamilton Rating Scale for Depression. Psychol. Assess. 1995; 7:59–65.

Cramer AOJ, Borsboom D, Aggen SH, Kendler KS. The pathoplasticity of dysphoric episodes: differential impact of stressful life events on the pattern of depressive symptom inter-correlations. Psychol. Med. 2013; 42:957–965. [PubMed: 22093641]

Davidson J, Woodbury MA, Pelton S, Krishnan R. A study of depressive typologies using grade of membership analysis. Psychol. Med. 1988; 18:179–189. [PubMed: 3363037]

Davidson JRT. A history of the concept of atypical depression. J. Clin. Psychiatry. 2007; 68:10–15. [PubMed: 17348762]

Faravelli C, Servi P, Arends J, Strik W. Number of symptoms, quantification, and qualification of depression. Compr. Psychiatry. 1996; 37:307–315. [PubMed: 8879904]

Fava M, Rush AJ, Alpert JE, Balasubramani GK, Wisniewski SR, Carmin CN, Biggs MM, Zisook S, Leuchter A, Howland R, Warden D, Trivedi MH. Difference in treatment outcome in outpatients with anxious versus nonanxious depression: a STAR*D report. Am. J. Psychiatry. 2008; 165:342–351. [PubMed: 18172020]

Fava M, Rush AJ, Trivedi MH, Nierenberg A, Thase ME, Sackeim HA, Quitkin FM, Wisniewski S, Lavori PW, Rosenbaum JF, Kupfer DJ. Background and rationale for the sequenced treatment alternatives to relieve depression (STAR*D) study. Psychiatr. Clin. North Am. 2003; 26:457–494. [PubMed: 12778843]

Fried EI, Nesse RM. The Impact of Individual Depressive Symptoms on Impairment of Psychosocial Functioning. PLoS One. 2014; 9:e90311. [PubMed: 24587318]

Fried EI, Nesse RM, Zivin K, Guille C, Sen S. Depression is more than the sum score of its parts: individual DSM symptoms have different risk factors. Psychol. Med. 2013; 12:1–10.

Furukawa T, Streiner D, Azuma H, Higuchi T, Kamijima K, Kanba S, Ozaki N, Aoba A, Murasaki M, Miura S. Cross-cultural equivalence in depression assessment: Japan-Europe-North American study. Acta Psychiatr. Scand. 2005; 112:279–285. [PubMed: 16156835]

Gotlib IH, Lewinsohn PM, Seeley JR. Symptoms versus a diagnosis of depression: differences in psychosocial functioning. J. Consult. Clin. Psychol. 1995; 63:90–100. [PubMed: 7896995]

Guidi J, Fava Ga, Picardi A, Porcelli P, Bellomo A, Grandi S, Grassi L, Pasquini P, Quartesan R, Rafanelli C, Rigatelli M, Sonino N. Subtyping depression in the medically ill by cluster analysis. J. Affect. Disord. 2011; 132:383–388. [PubMed: 21458076]

Hamilton M. A rating scale for depression. J. Neurol. Neurosurg. Psychiatry. 1960; 23:56–62. [PubMed: 14399272]

Hasler G, Drevets WC, Manji HK, Charney DS. Discovering endophenotypes for major depression. Neuropsychopharmacology. 2004; 29:1765–1781. [PubMed: 15213704]

Hek K, Demirkan A, Lahti J, Terracciano A. A Genome-Wide Association Study of Depressive Symptoms. Biol. Psychiatry. 2013; 73(7):667–678. [PubMed: 23290196]

Helmes E, Nielson WR. An examination Epidemiological of the internal structure of the Center for Studies-Depression Scale in two medical samples. Pers. Individ. Dif. 1998; 25:735–743.

Iwata N, Roberts RE. Age differences among Japanese on the Center for Epidemiologic Studies Depression Scale: an ethnocultural perspective on somatization. Soc. Sci. Med. 1996; 43:967–974. [PubMed: 8888466]

Jang KL, Livesley WJ, Taylor S, Stein MB, Moon EC. Heritability of individual depressive symptoms. J. Affect. Disord. 2004; 80:125–133. [PubMed: 15207925]

Judd LL, Schettler PJ, Coryell W, Akiskal HS, Fiedorowicz JG. Overt Irritability/Anger in Unipolar Major Depressive Episodes: Past and Current Characteristics and Implications for Long-term Course. JAMA psychiatry. 2013:92093.

Kapur S, Phillips aG, Insel TR. Why has it taken so long for biological psychiatry to develop clinical tests and what to do about it? Mol. Psychiatry. 2012; 17:1174–1179. [PubMed: 22869033]

Keller MC, Neale MC, Kendler KS. Association of different adverse life events with distinct patterns of depressive symptoms. Am. J. Psychiatry. 2007; 164:1521–1529. [PubMed: 17898343]

Keller MC, Nesse RM. Is low mood an adaptation? Evidence for subtypes with symptoms that match precipitants. J. Affect. Disord. 2005; 86:27–35. [PubMed: 15820268]

Keller MC, Nesse RM. The evolutionary significance of depressive symptoms: different adverse situations lead to different depressive symptom patterns. J. Pers. Soc. Psychol. 2006; 91:316–330. [PubMed: 16881767]

Kendler KS, Aggen SH, Neale MC. Evidence for Multiple Genetic Factors Underlying DSM-IV Criteria for Major Depression. Am. J. Psychiatry. 2013; 70(6):599–607.

Kendler, KS.; Zachar, P. The incredible insecurity of psychiatric nosology. In: Parnas, J.; Kendler, KS., editors. Philosophical Issues in Psychiatry: Explanation, Phenomenology, and Nosology. Baltimore, MD: Johns Hopkins University Press; 2008. p. 368-387.

Kessler RC, Berglund P, Demler O, Jin R, Koretz D, Merikangas KR, Rush AJ, Walters EE, Wang PS. The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). JAMA. 2003; 289:3095–3105. [PubMed: 12813115]

Kessler RC, Chiu WT, Demler O, Merikangas KR, Walters EE. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. Arch. Gen. Psychiatry. 2005; 62:617–627. [PubMed: 15939839]

Khan A, Khan S, Brown Wa. Are placebo controls necessary to test new antidepressants and anxiolytics? Int. J. Neuropsychopharmacol. 2002; 5:193–197. doi: [PubMed: 12366872]

Kirsch I, Deacon BJ, Huedo-Medina TB, Scoboria A, Moore TJ, Johnson BT. Initial severity and antidepressant benefits: a meta-analysis of data submitted to the Food and Drug Administration. PLoS Med. 2008; 5:e45. [PubMed: 18303940]

Lamers F, de Jonge P, Nolen Wa, Smit JH, Zitman FG, Beekman ATF, Penninx BWJH. Identifying depressive subtypes in a large cohort study: results from the Netherlands Study of Depression and Anxiety (NESDA). J. Clin. Psychiatry. 2010; 71:1582–1589. [PubMed: 20673552]

Lee SW, Stewart SM, Byrne BM, Wong JPS, Ho SY, Lee PWH, Lam TH. Factor structure of the Center for Epidemiological Studies Depression Scale in Hong Kong adolescents. J. Pers. Assess. 2008; 90:175–184. [PubMed: 18444112]

Lichtenberg P, Belmaker RH. Subtyping major depressive disorder. Psychother. Psychosom. 2010; 79:131–135. [PubMed: 20185969]

Lux V, Kendler KS. Deconstructing major depression: a validation study of the DSM-IV symptomatic criteria. Psychol. Med. 2010; 40:1679–1690. [PubMed: 20059797]

McClintock SM, Husain MM, Greer TL, Cullum CM. Association between depression severity and neurocognitive function in major depressive disorder: a review and synthesis. Neuropsychology. 2010; 24:9–34. [PubMed: 20063944]

McGlinchey JB, Zimmerman M, Young D, Chelminski I. Diagnosing major depressive disorder VIII: are some symptoms better than others? J. Nerv. Ment. Dis. 2006; 194:785–790. [PubMed: 17041292]

Melartin T, Leskelä U, Rytsälä H, Sokero P, Lestelä-Mielonen P, Isometsä E. Co-morbidity and stability of melancholic features in DSM-IV major depressive disorder. Psychol. Med. 2004; 34:1443. [PubMed: 15724875]

Morin A, Ninot G. Psychometric properties of the Center for Epidemiologic Studies Depression Scale (CES-D) in French clinical and nonclinical adults. Rev. d'Épidémiologie Santé Publique. 2011; 59:327–340.

Myung W, Song J, Lim S-W, Won H-H, Kim S, Lee Y, Kang HS, Lee H, Kim J-W, Carroll BJ, Kim DK. Genetic association study of individual symptoms in depression. Psychiatry Res. 2012; 198(3):400–406. [PubMed: 22429480]

Nesse RM. Neuroscience is not enough, evolution is essential. Understanding Depression: A Translational Approach. 2009

Nesse RM, Stein DJ. Towards a genuinely medical model for psychiatric nosology. BMC Med. 2012; 10:1–9. [PubMed: 22216957]

Oquendo MA, Barrera A, Ellis SP, Li S, Burke AK, Grunebaum M, Endicott J, Mann JJ. Instability of symptoms in recurrent major depression: a prospective study. Am. J. Psychiatry. 2004; 161:255–261. [PubMed: 14754774]

Pae CU, Tharwani H, Marks DM, Masand PS, Patkar AA. Atypical depression: A comprehensive review. CNS Drugs. 2009; 23:1023–1037. [PubMed: 19958040]

Parker G. Beyond major depression. Psychol. Med. 2005; 35:467–474. [PubMed: 15856717]

Persons JB. The advantages of studying psychological phenomena rather than psychiatric diagnoses. Am. Psychol. 1986; 41:1252–1260. [PubMed: 3813184]

Pigott HE, Leventhal AM, Alter GS, Boren JJ. Efficacy and effectiveness of antidepressants: current status of research. Psychother. Psychosom. 2010; 79:267–279. [PubMed: 20616621]

Radloff LS. The CES-D Scale: A Self-Report Depression Scale for Research in the General Population. Appl. Psychol. Meas. 1977; 1:385–401.

Reardon S. NIH rethinks psychiatry trials. Nature. 2014; 507

Regier DA, Narrow WE, Clarke DE, Kraemer HC, Kuramoto SJ, Kuhl EA, Kupfer DJ. DSM-5 Field Trials in the United States and Canada, Part II: Test-Retest Reliability of Selected Categorical Diagnoses. Am. J. Psychiatry. 2013; 170(1):59–70. [PubMed: 23111466]

Roth M. Unitary or binary nature of classification of depressive illness and its implications for the scope of manic depressive disorder. J. Affect. Disord. 2001; 64:1–18. [PubMed: 11292515]

Rush AJ, Fava M, Wisniewski SR, Lavori PW, Trivedi MH, Sackeim HA, Thase ME, Nierenberg A, Quitkin FM, Kashner TM, Kupfer DJ, Rosenbaum JF, Alpert J, Stewart JW, McGrath PJ, Biggs MM, Shores-Wilson K, Lebowitz BD, Ritz L, Niederehe G. Sequenced treatment alternatives to relieve depression (STAR*D): rationale and design. Control. Clin. Trials. 2004; 25:119–142. [PubMed: 15061154]

Rush AJ, Trivedi MH, Ibrahim HM, Carmody TJ, Arnow B, Klein DN, Markowitz JC, Ninan PT, Kornstein S, Manber R, Thase ME, Kocsis JH, Keller MB. The 16-Item Quick Inventory of Depressive Symptomatology (QIDS), Clinician Rating (QIDS-C), and Self-Report (QIDS-SR): A Psychometric Evaluation in Patients with Chronic Major Depression. Biol. Psychiatry. 2003; 54(5):573–583. [PubMed: 12946886]

Schmittmann VD, Cramer AOJ, Waldorp LJ, Epskamp S, Kievit RA, Borsboom D. Deconstructing the construct: A network perspective on psychological phenomena. New Ideas Psychol. 2013; 31:43–53.

Shafer AB. Meta-analysis of the Factor Structures of Four Depression Questionnaires: Beck, CES-D, Hamilton, and Zung. J. Clin. Psychol. 2006; 62:123–146. [PubMed: 16287149]

Solomon A, Haaga DA, Arnow BA. Is clinical depression distinct from subthreshold depressive symptoms? A review of the continuity issue in depression research. J. Nerv. Ment. Dis. 2001; 189:498–506. [PubMed: 11531201]

Tansey KE, Guipponi M, Perroud N, Bondolfi G, Domenici E, Evans D, Hall SK, Hauser J, Henigsberg N, Hu X, Jerman B, Maier W, Mors O, O'Donovan M, Peters TJ, Placentino A, Rietschel M, Souery D, Aitchison KJ, Craig I, Farmer A, Wendland JR, Malafosse A, Holmans P, Lewis G, Lewis CM, Stensbøl TB, Kapur S, McGuffin P, Uher R. Genetic predictors of response to serotonergic and noradrenergic antidepressants in major depressive disorder: a genome-wide analysis of individual-level data and a meta-analysis. PLoS Med. 2012; 9:e1001326. [PubMed: 23091423]

Tweed DL. Depression-related impairment: estimating concurrent and lingering effects. Psychol. Med. 1993; 23:373–386. [PubMed: 8332654]

Uher R, Perlis RH, Henigsberg N, Zobel A, Rietschel M, Mors O, Hauser J, Dernovsek MZ, Souery D, Bajs M, Maier W, Aitchison KJ, Farmer A, McGuffin P. Depression symptom dimensions as predictors of antidepressant treatment outcome: replicable evidence for interest-activity symptoms. Psychol. Med. 2012; 42:967–980. [PubMed: 21929846]

Van Loo HM, de Jonge P, Romeijn J-W, Kessler RC, Schoevers RA. Data-driven subtypes of major depressive disorder: a systematic review. BMC Med. 2012; 10:156. [PubMed: 23210727]

Van Praag HM. Biological psychiatry: still marching forward in a dead end. World Psychiatry. 2010; 9:164–165. [PubMed: 20975860]

Widaman K. Common factor analysis versus principal component analysis: Differential bias in representing model parameters? Multivariate Behav. Res. 1993; 28:263–311. [PubMed: 26776890]

Wood AM, Taylor PJ, Joseph S. Does the CES-D measure a continuum from depression to happiness? Comparing substantive and artifactual models. Psychiatry Res. 2010; 177:120–123. [PubMed: 20207424]

Young MA, Keller MB, Lavori PW, Scheftner WA, Fawcett JA, Endicott J, Hirschfeld RM. Lack of stability of the RDC endogenous subtype in consecutive episodes of major depression. J. Affect. Disord. 1987; 12:139–143. [PubMed: 2955005]

Zimmerman M, McGlinchey JB, Young D, Chelminski I. Diagnosing major depressive disorder I: A psychometric evaluation of the DSM-IV symptom criteria. J. Nerv. Ment. Dis. 2006a; 194:158–163. [PubMed: 16534432]

Zimmerman M, McGlinchey JB, Young D, Chelminski I. Diagnosing major depressive disorder III: can some symptoms be eliminated from the diagnostic criteria? J. Nerv. Ment. Dis. 2006b; 194:313–317. [PubMed: 16699378]

Highlights

- We used a conservative approach to quantify the number of MDD symptom patterns.
- We identified 1,030 unique symptom profiles in 3,703 MDD outpatients.
- The most common profile exhibited a frequency of only 1.8%.
- 83.9% of the profiles were endorsed by five or fewer subjects.
- 48.6% of the profiles were endorsed by only one individual.

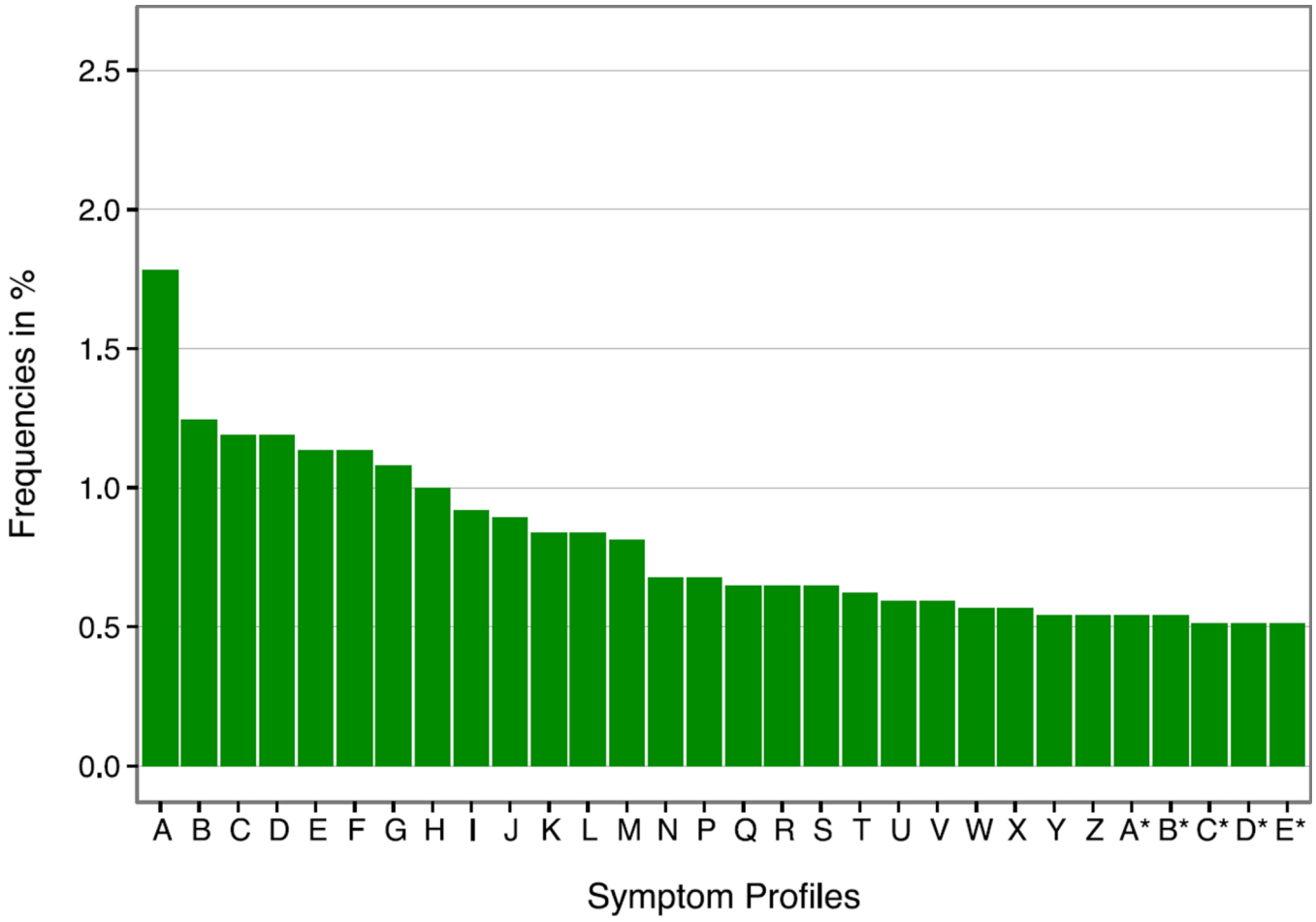

Figure 1.
Frequencies of the 30 most common depression symptom profiles during the beginning of the first treatment stage of the STAR*D study (*n* = 3,703).

Table 1

Depression symptoms

QIDS-16 symptoms	Mean	Median	SD
Sad mood	2.14	2	0.83
Loss of energy	2.00	2	1.15
Concentration problems	1.83	2	1.00
Insomnia	1.69	2	0.82
Loss of interest	1.69	2	1.11
Appetite problems	1.42	1	1.22
Self-blame	1.37	1	1.25
Weight problems	1.16	1	1.22
Psychomotor agitation	1.05	1	1.00
Psychomotor retardation	0.90	1	0.97
Suicidal ideation	0.74	1	0.85
Hypersomnia	0.44	0	0.83

Table 2

Detailed information about the ten most frequent symptom profiles

	Sad	Ene	Con	Ins	Int	App	Bla	Wei	Agi	Ret	Sui	Hyp	Freq(%)	Profile description
A													1.78	No symptoms
B	x	x	x	x	x	x	x	x	x	x			1.24	All but Sui & Hyp
C	x	x	x	x	x	x		x					1.19	Mixed profile
D	x	x	x	x	x	x	x	x					1.19	Mixed profile
E	x	x	x	x	x								1.13	Mixed profile
F	x	x	x	x	x		x						1.13	Mixed profile
G				x									1.08	Only Ins
H	x	x	x	x	x	x	x	x	x				1.00	All but Ret, Sui & Hyp
I	x	x	x	x									0.92	Mixed profile
J	x	x	x	x	x	x		x	x	x			0.89	All but Hyp, Bla & Sui

Cells with 'x' mark symptom presence.

Abbreviations: Sad, sadness; Ene, energy loss; Con, concentration problems; Ins, insomnia; Int, interest loss; App, appetite problems; Bla, self-blame; Wei, weight problems; Agi, psychomotor agitation; Ret, psychomotor retardation; Sui, suicidal ideation; Hyp, hypersomnia; Freq, frequency of profiles.