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Latent Classes of Symptoms related to Clinically Depressed Mood in Adolescents

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Abstract

Background: The diagnosis of major depressive disorder (MDD), according to the *Diagnostic and Statistical Manual of Mental Disorders,* is based only on adult symptomatology of depression and not adapted for age and gender. This may contribute to the low diagnostic specificity and validity of adolescent MDD. In this study, we investigated whether latent classes based on symptoms associated with depressed mood could be identified in a sample of adolescents seeking psychiatric care, regardless of traditionally defined diagnostic categories.
Methods: Self-reports of the Strengths and Difficulties Questionnaire and the Development and Well-Being Assessment were collected consecutively from all new patients between the ages of 13 and 17 years at two psychiatric outpatient clinics in Stockholm, Sweden. Those who reported depressed mood at intake yielded a sample of 21 boys and 156 girls. Latent class analyses were performed for all screening items and for the depression-specific items of the Development and Well-Being Assessment.
Results: The symptoms that were reported in association with depressed mood differentiated the adolescents into two classes. One class had moderate emotional severity scores on the Strengths and Difficulties Questionnaire and mainly symptoms that were congruent with the *Diagnostic and Statistical Manual of Mental Disorders* criteria for MDD. The other class had higher emotional severity scores and similar symptoms to those reported in the first class. However, in addition, this group demonstrated more diverse symptomatology, including vegetative symptoms, suicidal ideation, anxiety, conduct problems, body dysmorphic symptoms, and deliberate vomiting. The classes predicted functional impairment in that the members of the second class showed more functional impairment.
Limitations: The relatively small sample size limited the generalizability of the results of this study, and the amount of items included in the analysis was restricted by the rules of latent class analysis. No conclusions about gender differences between the classes could be could be drawn as a result of the low number of boys included in the study.
Conclusions: Two distinct classes were identified among adolescents with depressed mood. The class with highest emotional symptom severity score and the most functional impairment had a more diverse symptomatology that included symptoms that were not congruent with the traditional diagnostic criteria of MDD. However, this additional symptomatology is clinically important to consider. As a result, the clinical usefulness of the *Diagnostic and Statistical Manual of Mental Disorders* during the diagnostic process of adolescent depression is questioned.

Keywords: Adolescent major depressive disorder, diagnostic validity, *Diagnostic and Statistical Manual of Mental Disorders,* latent class analysis

Introduction

Depression is one of the most common mental health disorders among the adolescent population; it has a cumulative prevalence of 25% by the end of adolescence, and the prevalence of mild to moderate depression seems to be increasing (1;2). Depression during adolescence results in secondary problems, such as the loss of social, cognitive, and interpersonal skills; social problems; poor school performance; substance abuse; and difficulties with family and peer relationships. Adolescent depression is also related to a significantly increased risk of self-harm and suicide (1). The early onset of depressive symptoms in general is known to be associated with increased risk for suicide, increased treatment use, and psychiatric comorbidity as compared with the adult onset of major depressive disorder (MDD) (3).

Neurodevelopmental aspects are important to consider in relation to adolescent depression. These include the course of adolescent brain maturation (including pruning), the maturation of the serotonergic and noradrenergic systems, and the mechanisms of hormonal impact on emotional regulation and stress sensitivity, which influence the expression of depression symptoms during puberty (4;5). In addition, genetic effects on symptoms of anxiety and depression are developmentally dynamic from middle childhood to young adulthood, thereby demonstrating both genetic innovation and genetic attenuation (6). A life-trajectory perspective of depression is important, because early exposure to environmental factors (e.g., developmental trauma, neglect, insecure attachment) may alter normal brain development and cause the dysregulation of affect and attention; these factors can result in an increased risk of depression, anxiety disorders, and attention-deficit/hyperactivity disorder later in childhood and during adolescence (7;8). The diagnostic criteria of the fourth and fifth editions of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV and DSM-5) for MDD do not take age into consideration, despite that fact that the symptomatology of depression changes across the life span and seems to have a specific phenotype during adolescence that is quite different from the adult clinical symptomatology.

There are specific concerns regarding the clinical use of DSM-IV and DSM-5 for the diagnosis of adolescent depression:

1. The diagnosis of MDD during childhood and adolescence can be based only upon unspecific symptom criteria, which may contribute to an adverse effect on diagnostic specificity and treatment (9). Depressed mood and anhedonia are the two cardinal symptoms of MDD in adults. However, for children and adolescents, depressed mood may be substituted with irritable mood, which is not specific to MDD. Because only one of the cardinal symptoms is necessary for a diagnosis of MDD according to the DSM-IV and DSM-5, the MDD diagnosis can potentially be based on irritability and other symptoms that may occur with other psychiatric or somatic disorders as well.

2. The symptom criteria of MDD are broadly defined and include reversed conditions. For example, a change in appetite and weight may be either weight loss/decreased appetite or weight gain/increased appetite; sleep problems may be early awakening, insomnia, late sleep phase, or hypersomnia. In addition, psychomotor inhibition and agitation are both MDD criteria. The broad definition of MDD leaves questions unanswered with regard to the diagnostic boundaries of the disorder (3).

3. Psychiatric comorbidities are especially prevalent during adolescence (10). From a clinical point of view, it is often not clear which of the symptoms presented are expressions of adolescent MDD and which are expressions of psychiatric comorbidities, because many of the symptoms are unspecific and overlap among different diagnostic entities (11;12). Concentration difficulties, restlessness, hyperactivity, and a decrease in impulse control commonly coexist with MDD. In addition, the differential diagnosis of attention-deficit/hyperactivity disorder and conduct disorder may be difficult, especially in children (10;13). Self-harming behavior (14), eating disorders (15), and substance abuse (16) frequently appear with MDD during adolescence. Generalized anxiety disorder and MDD often coexist and show diagnostic criteria overlap with regard to symptoms such as fatigue, concentration difficulties, irritability, and sleep disturbances (17-19).

One example that illustrates a potentially counterproductive consequence of the clinical application of the DSM-IV and DSM-5 system for the diagnosis of adolescent psychiatric problems is the case of developmental trauma. From a neuroscientific and developmental point of view, it is known that early diverse life events cause limbic hyperactivation and hypercortisolemia and it is hypothesized that this is linked to damage of hippocampal neurons and depressive illness later in life (8;20-23). Following this trajectory, the pathophysiological processes involved may cause a diverse symptomatology that includes concentration difficulties, anxiety, and impulsivity. Secondary behavioral problems that are intended to self-sooth the primary problems (e.g., self-harming, behavioral problems, alcohol and drug abuse) are also common (7). From this perspective, the DSM categorization may not necessarily be clinically helpful; on the

contrary, it may complicate the situation for the patient with multiple psychiatric comorbidities. Future adolescent depression research should optimally aim to develop treatments that target the underlying neurodevelopmental dysfunction.

Gender-specific symptom criteria are also lacking in the DSM system, which may have implications for nosology and therapeutics. Differences in genetic risk factors for anxiety and depression in males and females may increase during development (6). Depressive symptoms in combination with features such as emotional instability and dysregulation, low impulse control, and elevated stress reactivity demonstrate increased prevalence at the onset of puberty, with a major predominance in girls; this is hypothesized to be related to estrogen effects and cortisol receptor sensitivity in the brain (24-27). In Sweden, the prevalence of self-assessed anxious and depressive symptoms as well as hospitalization for anxiety, depression, and suicide attempts have shown a more rapid and dramatic increase among adolescent females as compared with males during the last decade (28). In adults, women have a higher documented frequency of comorbid depression and anxiety disorders and a three-fold higher prevalence of atypical depression (29;30). To identify gender-specific trajectories of depressive symptomatology and to define how the phenotype changes across the life span, we need to study which symptoms are associated with the depressive core symptoms during a defined age range and across genders.

The primary aims of this study were to investigate which psychiatric symptoms are associated with depressed mood (regardless of traditionally defined diagnostic categories) in a sample of adolescents seeking psychiatric care and to investigate whether age-specific latent classes based on these symptoms could be identified. This analysis may help to define age-specific combinations of symptoms related to depressed mood while disregarding traditional diagnostic systems that are based on adult symptomatology. This may increase the chance of linking neuromechanisms to corresponding symptomatology and behavioral dysfunction, which may ultimately be useful for the development of targeted and effective treatment (31;32).

Our first hypothesis was that latent class analysis (LCA) could identify particular classes of individuals on the basis of their symptom profile. In other words, we wanted to determine whether the symptoms may form meaningful classes, independently of prior theoretical expectations. LCA is a statistical method for identifying unmeasured class membership among subjects with the use of categorical and continuous observed variables. LCA can help to define subcategories of depression, such as depressed mood with self-harming behavior, depressed mood with eating problems, or depressed mood with sleeping problems. LCA has previously been used with both large population-based samples (e.g., to define latent classes of episodic mania-like symptoms in children and adolescents (33), to assess variations in depression symptoms over the life courses of adults (34)) and smaller clinical samples (e.g., to assess treatment engagement (35), to determine diagnostic subgroups of patients with post-traumatic stress disorder (36)). Our second hypothesis was that the identified classes would be differentially predictive of social impairment. Finally, we hypothesized that the genders would be unevenly distributed between the classes.

Methods

Description of the sample and the data collection procedure

The diagnostic self-assessment data for this study, which are discussed later in this article, were originally collected for a larger project that took place during 2009 and 2010. That study aimed to compare the efficacy of different intake procedures for new patients seeking help at the Stockholm Child and Adolescent Psychiatry Clinic, which is a public health care setting (37). Two outpatient clinics that covered two geographically different areas of Stockholm were assigned to let all new patients between the ages of 6 and 17 years old and their parents complete an intake procedure with the Strengths and Difficulties Questionnaire (SDQ) (38) and the Development and Well-Being Assessment (DAWBA) (39). Seven hundred and thirty-six patients and their parents were recruited consecutively and asked to complete the online versions of the SDQ and DAWBA at home before their first visit to the clinic. In the present study, we included the SDQ and DAWBA self-reports from all teenagers between the ages of 13 and 17 years who reported depressed mood (N = 177). The formulation in DAWBA that reflects depressed mood is "very sad, miserable, unhappy or tearful." Depressed mood was chosen as the inclusion criteria for this study, because it is the most obvious and specific attribute of depressive disorders and regarded as a cardinal symptom of MDD. According to the DSM system, depressed mood can be exchanged for irritable mood in adolescents; however, because irritable mood is prevalent but non-specific to depression, it is inadequate as an inclusion criterion (9). Anhedonia, which is the other cardinal symptom of depression, is highly prevalent among depressed adolescents, but its extent is quite variable (40) and therefore also not a good inclusion criterion. The high variability of anhedonia with teenage depression could result in

contrasting MDD phenotypes, which we wanted to capture in the LCA.

The Regional Ethical Review Board in Stockholm, Sweden, approved the study, and the research was conducted in accordance with the Helsinki Declaration as revised 1989.

Measures

The SDQ is a 25-item scale with subscales that reflect hyperactivity and inattention, behavior problems, emotional symptoms, peer problems, and pro-social behavior. The SDQ may also generate a total difficulties score by summarizing the scores of the subscales (except the pro-social subscale). The SDQ total impact score measures overall distress and social impairment caused by all mental health problems, specifically in the domains of family, school, learning, and leisure (41). The SDQ is considered psychometrically valid (42-44), and it is frequently used in the Nordic countries (45). In this study, the SDQ was administered before the DAWBA and used to ensure that the skipping rules were not overused (this is discussed in more detail later in this article). The SDQ was also used for the assessment of total difficulties and social impairment.

The DAWBA (39) is an Internet-based semi-structured interview that is compatible with the diagnostic criteria of the DSM-IV. Detailed information about the DAWBA is available from http://www.dawba.info; this includes online and downloadable versions of the measures and demonstrations of the clinical rating process. In this study, the DAWBA was used as a way to collect data about which symptoms were associated with depressed mood in adolescents who seek psychiatric care; the purpose was not to use it as a diagnostic tool. The DAWBA assesses separation anxiety; fears of specific things or situations; panic attacks and agoraphobia; post-traumatic stress; compulsions and obsessions; generalized anxiety; depression; attention and activity; conduct problems; and dieting, weight, and body/shape concerns. However, it does not address psychotic or autistic features or problems related to alcohol and drug abuse. The DAWBA focuses on current rather than lifetime problems. Each section starts with screening questions that allow the person completing the assessment to skip to the next section if the screening question is answered in the negative. If the screening is positive, additional specific questions are asked. Most sections of the DAWBA can only be skipped if the initial screening questions are negative and if the relevant SDQ score is close to average (i.e., <80th centile). This double requirement prevents "respondent fatigue," which could result in too many sections being skipped (39). The depression section has screening questions for depressed mood, irritable mood, and anhedonia. If any of these three cardinal symptoms for MDD are rated positively, specific questions about other depression criteria follow (Table 1). The eating disorder section also has several screening questions about body dysmorphic symptoms, shame in relation to eating, deliberate vomiting, worries related to eating, and self-blame in relation to overeating.

Depressed mood was used as the inclusion criterion for the study; irritable mood, anhedonia, and depression-specific items were also included as items in the analyses. Because two of the depression-specific items dealt with weight and appetite, we decided to have those two included in the LCA; in other words, not all five of the eating disorder screening questions were included due to limitations regarding the number of items allowed in the LCA. In summary, depressed mood was analyzed in relation to all other screening items except the five eating disorder items and in relation to the depression-specific items of the DAWBA.

TABLE 1. The probability of having each of the self assessed symptoms, if belonging to class 1 or 2 respectively. Probabilities of >70% are marked in bold

	Class 1 n = 101	Class 2 n = 79
Irritability	.64	**.89**
Loss of interest	**.86**	**.97**
Tired/no energy	**.88**	**.99**
Change of appetite	.53	**.97**
Change of weight	.21	**.86**
Sleeping difficulties	.62	**.85**
Sleep more than normal	.29	.48
Agitation	.46	.65
Feelings of worthlessness	**.74**	**.96**
Concentration difficulties	**.77**	**.96**
Suicidal ideation	.53	**.90**
Concurrent or previous thoughts or action of self harming	**.76**	**.97**
Specific fears	.60	**.90**
Symptoms of separation anxiety	.23	**.72**
Symptoms of social anxiety	.34	**.77**
Panic attacks during the last four weeks	.41	**.79**
Symptoms of agoraphobia	.36	**.72**
Experience of traumatic event	.35	.53
Symptoms of obsessive compulsive thoughts or behavior	.23	.51
Symptoms of generalized anxiety	**.91**	**.96**
Symptoms of hyperactivity	.35	.52
Conduct problems	.53	**.72**

The DAWBA has been translated to Swedish, and the Swedish version has been retranslated back into English and approved by Professor Goodman, who is the originator of the DAWBA. The Swedish DAWBA is in clinical use in several settings throughout Sweden, but no Swedish validation studies of this tool have yet been published (37). In Norway, the DAWBA has been shown to generate realistic estimates of the prevalence of psychiatric illness as well as a high predictive validity when used

in public health settings (46). Good to excellent inter-rater reliability has been reported in Norwegian studies, with a $\varkappa$ value of 0.86 to 0.91 for any diagnoses and a $\varkappa$ value of 0.57 to 0.93 for emotional diagnoses (47). Another Norwegian study also demonstrated that experienced clinicians can assign reliable diagnoses and assess severity on the basis of DAWBA data that is collected online (48).

Statistical analyses

LCA simultaneously defines the structure and estimates the probabilities of membership in a certain class (49). LCA assumes the presence of discrete classes or groupings rather than dimensions. For example, it can be used to categorize people on the basis of their depressive symptoms into different subtypes of depressive symptomatology (i.e., latent classes). This can help to define subcategories of depression, such as depressive symptoms with self-harming behavior, depressive symptoms with eating problems, and depressive symptoms with sleeping problems. One can seek to explore the consequences of such a class membership: for instance, one may consider whether membership in the class of depressive symptomatology in combination with eating problems predicts other variables. There are different indices that can be used to evaluate how many classes are needed to best describe the data. Nylund and colleagues simulated multiple models and concluded that the Bayesian information criterion (BIC) performs best, irrespective of the number of classes and the sample size (50). BIC is a comparative measure that allows us to compare the fit of models with different numbers of classes. The model with the best fit has the lowest BIC value. LCA has specific limitations with regard to the number of included items in relation to sample size, and these limitations cannot be exceeded. In the current study, all individuals included in the LCA had a potential probability of 0 to 1 to endorse a specific item or symptom given their class membership. The cutoff for scoring positive on a symptom was 0.7 (i.e., a >70% probability of answering "yes"), given class membership. The Student *t*-test was used to evaluate mean differences in emotional symptoms, conduct problems, hyperactivity, peer problems, pro-sociability, and impact on function as measured with the SDQ. The frequencies of having symptoms specific to eating disorders were calculated for the total group to further investigate the findings of the LCA results. The relative risk ratios of having symptoms specific to eating disorders on the basis of class membership were also calculated retrospectively.

Results

To estimate the amount of classes that best described the data, six models were tested with BIC. The model with two distinct classes showed the best fit for the data (Table 2). The sample included 21 boys and 156 girls, with a mean age of 15.0 years for the boys (standard deviation, 1.38; range, 13 to 17 years) and 15.4 for the girls (standard deviation, 1.37; range, 13 to 17 years).

TABLE 2. "Model-fit" using the Bayesian Information Criterion model (BIC) to test which amount of classes from 1 to six, that constitutes the best fit for the data (lowest BIC score)

Classes	BIC
1	2550.83
2	**2416.60**
3	2476.14
4	2561.74
5	2613.75
6	2705.55

LCA showed that, if an individual belonged to Class 1 (n = 99), the probability was high (>70%) that he or she would have symptoms of generalized anxiety, tiredness/loss of energy, loss of interest, concentration difficulties, previous or concurrent thoughts of self-harming or actual self-harming behavior, and feelings of worthlessness in addition to the predefined depressed mood (see Table 1).

In Class 2 (n = 78), there was an even higher probability of having the same symptoms as those exhibited by the individuals in Class 1. However, what differed between the classes was the higher probability of the members of Class 2 having a greater diversity of symptoms. In addition to depressed mood and the previously described symptoms, changes of appetite and weight, suicidal ideation, irritability, sleeping problems, symptoms of anxiety expressed as specific fears, separation anxiety, social anxiety, panic attacks and agoraphobia, and conduct problems were also reported among members of Class 2 (see Table 1). There was a lower probability (≤64%) of problems with excessive sleeping, agitation, obsessive-compulsive symptoms, and hyperactivity in both classes, and members of both groups often self-reported having experienced or witnessed adverse or traumatic events (see Table 1).

Symptom scores for self-assessment with the SDQ differed significantly between the classes. Members of Class 2 showed higher symptom severity for emotional symptoms, conduct problems, hyperactivity, and peer problems and lower scores for pro-social behavior. The total difficulties scores and impact scores were

significantly higher for members of Class 2 (see Table 3).

TABLE 3. T-tests showing differences of mean-values of symptom severity between Class 1 and Class 2 assessed by Strengths and Difficulties Questionnaire (SDQ), including the subscales, the total difficulties score and impact on function

	Class 1 n = 99	Class 2 n = 78	
	Mean (SD)		t-value
SDQ-total	17.2 (5.2)	22.7 (5.3)	6.9***
SDQ-emotional symptoms	5.8 (2.1)	8.0 (1.6)	8.1***
SDQ-conduct problems	3.2 (2.0)	4.0 (2.1)	2.6**
SDQ-hyperactivity	5.3 (2.6)	6.9 (2.2)	4.3***
SDQ-peer problem	2.9 (2.1)	3.8 (2.0)	3.2**
SDQ-pro-social	7.4 (1.9)	7.4 (2.0)	0.1ns
SDQ-impact on function	4.2 (2.7)	5.6 (2.6)	3.4***

*** p < .001, ** p < .01, * p < .05; SD=standard deviation; ns=non-significant

Because problems with appetite and weight changes, which were both assessed by the depression-specific questions, demonstrated a major difference between the two classes, we decided to take a closer look at the five screening questions for eating disorders that were not included in the original LCA. We retrospectively analyzed how the answers to these five items were distributed between the two latent classes. It was discovered that members of Class 2 had more than double the risk of having body dysmorphic symptoms, shame related to eating behavior, self-induced vomiting, increased worrying about eating, and self-accusations involving overeating as compared with Class 1 (Table 4).

TABLE 4. Percentage of individuals in each class who has symptoms related to eating disorders and the relative risk of having the symptom when class 1 is used as reference

	Class 1 N = 88	Class 2 N = 73	OR (95 % CI)
1. Have you ever thought you were fat even when other people told you that you were very thin?	59.1% (52)	76.7% (56)	2.15 (1.07-4.32)
2. Would you be ashamed if other people knew how much you eat?	31.8% (28)	54.8% (40)	2.53 (1.32-4.83)
3. Have you ever deliberately made yourself vomit (throw up)?	31.8% (28)	54.8% (40)	2.53 (1.32-4.83)
4. Do worries about eating (what? where? how much?) really interfere with your life?	36.4% (32)	67.1% (49)	3.42 (1.77-6.64)
5. If you eat too much, do you blame yourself a lot?	59.1% (52)	76.7% (56)	2.15 (1.07-4.32)

Discussion

This study aimed to investigate which psychiatric symptoms were associated with depressed mood, regardless of traditionally defined diagnostic categories and whether age-specific diagnostic latent classes that were based on these symptoms could be identified. This is of importance because the diagnostic entity of MDD as defined by adult DSM criteria does not well match the symptomatology that adolescents present in conjunction with depressed mood; in addition, the boundaries of how these symptoms are expressed among individuals with comorbid disorders are not clear cut (10;15;51). We investigated whether age-specific diagnostic latent classes could be identified on the basis of a broad variety of symptoms, including symptoms that are not traditionally regarded as depression criteria. Some of these have, in previous research, been shown to frequently co-occur with depressive problems in adolescents, such as attention-deficit/hyperactivity disorder, anxiety, and eating disorders (13;15;52;53). Our study yielded two main results. First, LCA of the psychiatric symptoms differentiated the adolescents with depressed mood into two distinct classes that differed with regard to emotional symptom severity and diversity of symptoms. Second, the classes predicted social impairment; Class 2 had higher general symptom severity and greater impact on function related to family, school, learning, and leisure. Our third hypothesis that the genders would be unevenly distributed between the classes was not confirmed as a result of the relatively small number of boys included in the study.

The results of the LCA that included a broad range of psychiatric symptoms in adolescents with depressed mood and who were seeking psychiatric care differentiated the adolescents into two distinct classes, which supported our first hypothesis. Class 1 had symptoms that reflected the established DSM criteria for MDD, such as tiredness/loss of energy, loss of interest, concentration difficulties, previous or concurrent thoughts of self-harm or actual self-harming behavior, and feelings of worthlessness. Class 2, on the other hand, had all of the same symptoms as Class 1 in addition a more diverse symptomatology that included irritability, suicidal ideation, conduct problems, symptoms of anxiety expressed as specific fears, separation anxiety, social anxiety, and panic attacks and agoraphobia. Class 2 also had a high probability of having vegetative symptoms, such as changes of appetite and weight and sleeping problems. Members of Class 2 also had a higher risk of having body dysmorphic symptoms, deliberate vomiting, increased worrying, and shame related to eating. These findings are in line with previous studies that have demonstrated that binge eating is related to emotional dysregulation (54) and that the comorbidity of depressed mood and eating-related symptoms is high in this age group (15). There was also a high probability of sleeping problems among the members of Class 2. Sleeping problems should be carefully addressed at intake, because they may have a reciprocal relationship with emotional dysregulation and explain the increase in

self-reported tiredness and concentration difficulties (55;56).

Our second hypothesis that the latent classes of adolescent depression are predictive of symptom severity and social impairment was also supported by our findings. Indeed, one may speculate that the symptomatology of Class 1 represents a milder form of depression, with its own trajectory, and that the more severe Class 2 (as defined by the emotional subscale of SDQ) describes the age-specific symptom profile of melancholic depression, with more suicidal ideation and vegetative symptoms. If that is the case, it is of clinical importance to recognize the diversity of symptoms that present with adolescent melancholic depression as compared with the typical adult features. According to our data, symptoms related to severe depression during adolescence include conduct problems, anxiety and panic attacks, agoraphobia, specific fears, social as well as generalized anxiety, and symptoms related to eating and sleeping. Binge eating and deliberate vomiting often occur in adolescents of normal weights; these features are closely related to shame and should be specifically asked about during intake. Sleep disturbances in adolescents are also important to identify and treat, because they are related to an increased risk of suicide (57).

It has been suggested that adolescent melancholic depression may be a discrete category at the extreme end of the depression spectrum (58). If melancholic depression during adolescence is defined by the symptoms demonstrated by the members of Class 2, then this may be a possibility in line with our findings. Interestingly, anhedonia - which is a cardinal symptom of adolescent MDD according to DSM and regarded as a typical feature of melancholic depression in adults - occurred very frequently in both classes. However, irritability - which is also regarded as a cardinal symptom of adolescent depression - was not reported as frequently, and it was predominantly found in the members of the more severely depressed group. The notion that adolescent MDD is a purely dimensional construct (58) was not supported by our data.

Unfortunately, our third hypothesis regarding gender distribution across the classes could not be confirmed as a result of the relatively small number of boys included in the study. The ratio of boys and girls in the total sample was 21 to 156, which mirrors the gender distribution of depressed teenage patients in child psychiatry treatment in Sweden (59). It may also be the case that teenage boys with depression have a different symptom profile that includes substance abuse as well as behavioral and conduct problems that make them less inclined to seek psychiatric care (60). Suicide rates are four times higher among boys as compared with girls between the ages of 16 and 18 years in the United States, but girls have higher rates of suicidal ideation and attempted suicide (61).

The lack of adaptation for ontogenetic aspects and age in the MDD diagnostic criteria of DSM-IV and DSM-5 may contribute to a low diagnostic specificity and validity for MDD during adolescence. Consequently, the DSM system may have limited the opportunity to identify trajectories of the progression of depressive problems across adolescence into young adulthood and thus hampered the ability to estimate prognosis and to develop efficient treatment (62). Furthermore, when treatments that are shown to be effective for adult MDD are applied to adolescent MDD defined by adult criteria, there is considerable risk that young people who are not suffering from MDD will receive antidepressant medication. In fact, selective serotonin reuptake inhibitor treatment of adolescent MDD (as defined by the DSM system) has not demonstrated clear evidence of the reduction of depressive symptoms as compared with placebo, and it is not known whether selective serotonin reuptake inhibitors decrease the risk of suicide in this population (32;63). The situation may look different if new treatments for adolescent depression were targeted for populations that were defined by age-appropriate symptom profiles and their underlying pathophysiologies.

The rationales of the DSM-IV and DSM-5 diagnostic systems have recently been heavily debated, and the National Institute of Mental Health has launched a strategic plan (Strategy 1.4) to develop new ways of classifying mental disorders on the basis of dimensions of observable behavior as well as neurobiological measures. (For the full text of this plan, visit http://www.nimh.nih.gov/about/strategic-planning-reports/index.shtml.) The Research Domain Criteria Project of the National Institute of Mental Health aims to establish construct validity for dimensions of psychopathology by promoting clinical research in which subjects are recruited transdiagnostically on the basis of the specific research question. Developmental and gender aspects are not included in these criteria, but it is stated that an intended focus is to enhance a systematic integration of developmental aspects and interactions with the environment and their relationship to specific brain circuits and functions.

A limitation of this study is its relatively small sample size. The results have to be replicated with the use of larger samples and recruited from more diverse locations to be generalizable. The relatively small sample size also limited the amount of items that could be included in the LCA. The small

number of boys in the study made comparisons between genders underpowered, and no conclusions could be drawn regarding symptom differences between boys and girls. Another limitation is that the DAWBA does not assess autistic and psychotic symptoms or alcohol and drug abuse. These problems may have been co-occurring among individuals with depressed mood in this study's cohort, but they have not been taken into consideration during our analysis.

In summary, LCAs of psychiatric symptoms in teenagers with depressed mood showed two distinct classes. One group demonstrated tiredness/loss of energy, feelings of worthlessness, concentration difficulties, previous or concurrent thoughts of self-harming or actual self-harming behavior, generalized anxiety, and less functional impairment as compared with the other group. The second group had similar symptoms but greater symptom variations, including vegetative symptoms and suicidal ideation; this group's members also had greater functional impairment. No conclusions about gender distribution could be drawn as a result of the small number of boys included in the study. These findings show that age-specific symptoms outside of the traditionally defined MDD criteria are important to consider during the diagnostic process for teenage depression, and they point to the difficulty of defining adolescent MDD as a precise diagnostic entity when employing adult DSM-IV and DSM-5 standards. The clinical utility of the DSM-IV and DSM-5 systems for the diagnosis of teenage depression is limited as a result of the low diagnostic validity and specificity of the symptom criteria for this age group. Future studies of teenage depression should be based on dimensions of psychopathology and their behavioral aspects as recognized by transdiagnostic investigations. However, both developmental and gender aspects as well as interaction with the environment must be taken into consideration to gain a better understanding of the trajectories of symptom expression and disease progression across the life span and, ultimately, to aid in the development of targeted prevention and treatment.

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