Published in final edited form as:

Arthritis Care Res (Hoboken). 2020 May ; 72(5): 669–678. doi:10.1002/acr.23898.

Depression Subtypes in Persons with or at Risk for Symptomatic Knee Osteoarthritis

Alan M. Rathbun, PhD, MPH^{1,2,*}, Megan S. Schuler, PhD³, Elizabeth A. Stuart, PhD⁴, Michelle D. Shardell, PhD⁵, Michelle S. Yau, PhD, MPH⁶, Joseph J. Gallo, MD, MPH⁴, Alice S. Ryan, PhD^{1,2}, Marc C. Hochberg, MD, MPH^{1,2}

¹VA Maryland Health Care System, Baltimore, MD USA

²University of Maryland School of Medicine, Baltimore, MD, USA

³RAND Corporation, Boston, MA, USA

⁴Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA

⁵National Institute on Aging, Baltimore, MD, USA

⁶Institute for Aging Research, Hebrew SeniorLife, Boston, MA, USA

Abstract

Objective: To identify depression subtypes in participants with or at-risk for symptomatic knee osteoarthritis (OA) and to evaluate differences in pain and disability trajectories between groups.

Methods: Participants (n=4486) were enrolled in the Osteoarthritis Initiative. Latent class analysis (LCA) was applied to the 20-Item Center for Epidemiological Studies Depression Scale measured at baseline to identify groups with similar patterns of depressive symptoms, and subtypes were assigned using posterior probability estimates. The relationships between depression subtypes and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain and disability subscales were modeled over four years and were stratified by baseline knee OA status [symptomatic (n=1626) or at-risk (n=2860)].

Results: Four subtypes were identified: Asymptomatic (80.6%), Catatonic (5.3%), Anhedonic (10.6%), and Melancholic (3.5%). Catatonic and Anhedonic subtypes were differentiated by symptoms corresponding to psychomotor agitation and the inability to experience pleasure, respectively. The Melancholic subtype expressed symptoms related to reduced energy and movement, anhedonia, and other somatic complaints. Detectable mean differences in pain and disability compared to the Asymptomatic group were observed for the Anhedonic (1.52.3 WOMAC units) and Melancholic (4.8–6.6 WOMAC units) subtypes, and associations were generally larger in persons with symptomatic knee OA relative to those at-risk.

* **Corresponding Author:** Alan M. Rathbun, PhD, MPH, Howard Hall Suite 200, 660 W. Redwood Street, University of Maryland School of Medicine, Baltimore, MD 21201; Phone: (410) 706-5151; Fax: (410) 706-4433; arathbun@som.umaryland.edu.

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Conclusion: Among persons with or at-risk for symptomatic knee OA, there is evidence of depression subtypes characterized by distinct clusters of depressive symptoms that have differential effects on reports of pain and disability over time. Thus, findings imply depression interventions could be optimized by targeting the specific symptomology these subtypes exhibit.

INTRODUCTION

Osteoarthritis (OA) is the most common joint disorder in the United States (US); symptomatic knee OA affects approximately 9.3 million American adults and 10% of men and 13% of women aged 60 years or older (1, 2). Knee OA represents a failure of normal joint repair and is often accompanied by symptoms of pain and disability (3). Worsening OA disease severity may lead to the development of psychiatric comorbidity, particularly depressive symptoms, which can exacerbate the course of pain, disability, and disease progression (4–8). The bidirectional relationship between OA disease severity and depressive symptoms may influence the severity of both, thus complicating medical management and contributing to higher health care costs, decreased quality of life, and greater mortality (9–11).

Depression presenting in chronic diseases is difficult to recognize; indeed, depressive symptoms in arthritis patients are under-diagnosed (12, 13). A contributing factor to the under-recognition of depression in OA patients is the overlapping somatic symptomology between the conditions; resultantly, many individuals are only treated for their chronic disease and not depressive symptoms (12). A meta-analysis estimated that depressive symptoms are present in 18.5% of adults with knee OA, a prevalence that is more than double that in the US general population and has remained unchanged over time, despite increases in depression treatment rates (14–16). Depression treatment in American adults predominantly consists of pharmacotherapy using antidepressant medications (15). However, many patients do not achieve symptomatic remission, and non-response is even more pervasive in those with chronic diseases (10, 17).

Increasingly, major depressive disorder is recognized to be heterogenous with respect to clinical presentation (12). Official classifications and corresponding treatments for major depressive disorder have traditionally used a “one size fits all” approach, yet it is becoming more accepted that such definitions and management strategies do not accurately reflect the immense heterogeneity of depressive symptomology (12, 18). In the research and clinical setting, depressive symptoms are generally evaluated in terms of symptom count or a dichotomous indicator, which does not differentiate patients with disparate symptomology (18). By contrast, nascent research has begun utilizing the “Depression Symptomics” framework, a methodology that evaluates how different constellations of depressive symptoms cluster and differentially impact health, well-being, and medical management (19).

Currently, variability in depressive symptoms among OA patients and the implications of distinct depression profiles on OA disease severity is poorly understood. Understanding heterogeneity in depressive symptoms among persons with or at-risk for symptomatic knee OA could lead to more personalized interventions that target individuals’ symptomatic

profiles in order to improve clinical outcomes for both conditions. Study objectives were to 1) identify depression subtypes in persons with or at-risk for symptomatic knee OA based on patterns of depressive symptoms and 2) examine the impact of depression subtypes on pain and disability stratified by individuals with or at-risk symptomatic knee OA.

MATERIALS & METHODS

Study Data & Sample

The sample included participants from the Osteoarthritis Initiative (OAI), an observational cohort study designed to identify risk factors and biomarkers for the onset and progression of knee OA, and methodologic details have been published previously (20). Institutional Review Boards at each site approved the OAI study, and all participants provided informed consent. The OAI cohort (n=4,796) was restricted to participants (n=4,486) with baseline symptomatic knee OA data and baseline radiographs that were read centrally at Boston University by trained, certified, radiologic technicians (21). This sample (Figure 1) was used to examine heterogeneity in baseline depressive symptoms, and there were 1,626 and 2,860 persons with or at-risk (respectively) for symptomatic knee OA at baseline, defined as “pain most days of a month in past 12 months” (20). Only one knee per participant selected by random sampling was included in the analysis. Participants with complete baseline data and at least one follow-up observation were used for longitudinal analyses. Complete data on covariates and outcomes at study enrollment were available for 4,300 participants, and information on pain and disability during follow-up were available for 4,204, 4,043, 3,990, and 3,970 participants at the first, second, third, and fourth annual follow-up visits, respectively, in persons with fully observed baseline data. Depressive episodes last between 6 to 12 months, and a four year follow-up period provided sufficient time to examine associations between baseline depression subtypes and pain and disability (22).

Depressive Symptoms

The 20-Item Center for Epidemiologic Studies Depression (CES-D) scale was used to assess an array of depressive symptoms: psychomotor agitation/retardation, poor appetite, restless sleep, sadness, feelings of loneliness, social interactions, impaired concentration, and anhedonia (23). CES-D items have a reference time frame corresponding to the occurrence of depressive symptoms in the prior week, and response options ranging from 0 to 3, where increasing score is representative of greater symptomatic frequency (23). Binary indicators were created for each symptom, classifying individuals responding “2” (i.e., *occasionally or a moderate amount of time*) or “3” (i.e., *most or all of the time*) as having a given symptom, an approach which has been used in prior research (24). These 20 binary symptom indicators were used to identify depression subtypes.

Pain and Disability

The Western Ontario and McMaster Universities Arthritis Index (WOMAC; Likert version 3.1) was used to assess knee OA disease severity. The WOMAC assessed three distinct domains: stiffness (2 items), pain (5 items), and disability (17 items) (25). WOMAC item-responses are on a Likert scale, ranging from zero (“none”) to four (“extreme”), with higher scores indicating greater severity. Item scores are summed across subscales to calculate

summary scores for each domain. In the current study, pain and disability subscales were used as outcomes and assessed at baseline and four annual follow-up visits. Pain and disability scores were rescaled to range from 0–100 so that estimates can be compared to minimal perceptible clinical differences. Clinically significant differences on rescaled WOMAC pain and disability scores are approximately 9.7 and 9.3 units, respectively (26).

Confounders

Potential confounders measured at study baseline were selected a priori based on review of the research literature. Sociodemographic and behavioral measures were age (years), sex, race (white or non-white), marital status (married, widowed, divorced, separated, or never married), educational attainment (high school, college graduate, or graduate degree), health insurance (insured or uninsured), employment (employed or unemployed), alcohol consumption (none, minimal, or moderate), and smoking (never, former, or former). Clinical characteristics included body mass index (BMI; kilograms per meters squared), comorbidity, history of knee injuries, use of analgesic medications, OA disease severity (Kellgren-Lawrence [K-L] grade) and total WOMAC score. Comorbidity was measured using the Charlson Comorbidity Index, a composite scale comprising 22 different comorbid conditions that does not incorporate major depression (27). History of knee injuries was assessed as “ever injured badly enough to limit ability to walk for at least two days.” Analgesic medications were operationalized as the use of acetaminophen, nonsteroidal anti-inflammatory drugs, or opioids within the previous 30 days. K-L grade is an ordinal scale ranging from zero to four, and higher values represent worse structural disease (28).

Latent Class Analysis

Latent class analysis (LCA) is an approach that identifies subgroups (i.e., classes) based on multiple indicators of a given construct (e.g., depression) and was used to identify classes of individuals with similar patterns of depressive symptoms (29). LCA assumes mutually exclusive and exhaustive classes of individuals that are differentiated within a population by values of observed indicators (29). The LCA model estimates the prevalence of each class in the overall sample and item-response probabilities within each class; namely, the probabilities of endorsing each indicator given membership in a specific class (29). For each individual, posterior class probabilities are estimated to provide a person’s likelihood of membership in each subtype, given their indicator response pattern (29).

LCA models were implemented sequentially with one to six classes and were evaluated regarding fit, parsimony, and clinical interpretability. Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) fit statistics were used to compare LCA models with different numbers of classes (30, 31). Model uncertainty was assessed using relative entropy, with values ranging from zero to one, and higher estimates indicate greater classification certainty. Class prevalence estimates and item-response probabilities were used to qualitatively examine and describe the different classes and select the optimal number of depression subtypes. LCA model fitting was conducted in the overall study sample (n=4486) and then stratified by participants with (n=1626) or at-risk (n=2860) for symptomatic knee OA to assess measurement invariance. LCA estimation allows missing values in response variables and were assumed to be missing at random. After identifying the optimal LCA

model, posterior probability estimates were used to assign individuals to the subtype for which they had the highest probability of membership. Chi-square tests and analysis of variance were used to evaluate between-group differences in baseline covariates by depression subtype. Analyses were conducted using R statistical software (version 3.4.1).

Propensity Scores

Multiple-group propensity score weights were used to balance between-group differences in potential baseline confounders by depression subtype in order to promote causal interpretations regarding their effect on pain and disability (32). Propensity score weights were estimated using boosted regression, which has been shown to outperform other methods of estimation concerning bias reduction (32). The generalized boosted model is a flexible machine learning estimation routine that fits multiple regression trees to account for potentially complex and non-linear relationships between exposure and covariates without overfitting data (32). The boosting algorithm optimizes balance on covariates across groups; indicators for missing covariates were automatically included in the propensity model, such that depression subtypes were balanced regarding observed covariates as well as missing data patterns (32). Given that longitudinal analyses were stratified by symptomatic knee OA status at baseline, weights were estimated separately in at-risk and symptomatic OIA participants. Propensity score weights in the subsamples were stabilized with the marginal probability for each depression subtype. Standardized covariate differences were used to assess balance in the weighted and unweighted samples, and differences of 0.2 standard deviations were considered evidence of imbalance.

Weighted Estimating Equations

Weighted estimating equations (WEE) were used to assess the relationship between depression subtype and pain and disability over four years stratified by participants with and at-risk for symptomatic knee OA. WEE account for missing data using weighting, where weights are the inverse probability of observation conditional on predictors of missing data and were stabilized using the time-specific marginal probabilities for response. Final weights were the product of the time-invariant propensity score weights and time-specific non-response weights. WEE were implemented using survey analysis methods that are appropriate for clustered data and can be used to estimate population-average exposure effects while accounting for between-person heterogeneity in standard error estimates. Models included categorical indicators for depression subtype, follow-up time, and their interaction to determine whether there were differences in pain and disability across subtypes over time. Differences in pain and disability by depression subtype at each time point were estimated with 95% confidence intervals (CI), and an alpha level of 0.05 was used to define statistical significance.

RESULTS

Depression Subtypes

A four-class LCA model was chosen based on clinical interpretability of the subtypes, prevalence estimates, and fit statistics. Indicators of model fit implied that a five-class model provided a more optimal solution; however, the fifth class was not uniquely distinct when

compared to one of the other identified subtypes. Moreover, class prevalence structure and item-response probabilities were consistent by symptomatic knee OA status at baseline, and the relative model entropy of 0.86 indicated a high degree of classification certainty. Four depression subtypes (Table 1) were identified: Asymptomatic (80.6%), Catatonic (5.3%), Anhedonic (10.6%), and Melancholic (3.5%). CES-D score was lowest (Table 2) in Asymptomatic participants, comparable between the Catatonic and Anhedonic subtypes, and highest in the Melancholic group. Similarly, the proportions of individuals meeting CES-D screening criteria for probable depression were 0.4%, 36.7%, 36.2%, and 100% for the Asymptomatic, Catatonic, Anhedonic, and Melancholic subtypes, respectively.

The Asymptomatic group was the most prevalent subtype and had low item-response probabilities for every depressive symptom. The second most common subtype was the Anhedonic group, which was characterized by high item-response probabilities for symptoms corresponding to the inability to experience pleasure and happiness. The Catatonic subtype was the third highest in prevalence and was more likely to endorse symptoms related to psychomotor agitation and somatic complaints; in particular, decreased energy and movement, difficulty concentrating, and restless sleep. The least common subtype was the Melancholic group that had high item-response probabilities for the widest spectrum of symptoms, including sadness, loneliness, anhedonia, psychomotor agitation, and other somatic complaints.

Subtype Characteristics

When compared to those classified as Asymptomatic, other subtypes, particularly Catatonic and Melancholic, were more likely to be female, non-white, not married, and of lower socioeconomic status as measured by educational attainment and employment and health insurance status. Age was comparable across the Asymptomatic, Catatonic, and Anhedonic subtypes but lower in the Melancholic group (57 years versus 61 years). The Catatonic, Anhedonic, and Melancholic subtypes had a higher likelihood of being current smokers but were less likely to consume alcohol than the Asymptomatic group. In addition, Asymptomatic participants had fewer comorbid conditions, lower BMI, lower probability of symptomatic knee OA, and less analgesic medication use compared to every other subtype. Similarly, K-L grade and total WOMAC score were worse in the Catatonic, Anhedonic, and Melancholic subtypes compared to the Asymptomatic group. Subtype characteristics and covariate trends of the overall sample were similar to the stratified samples (Supplementary Table 1 and Supplementary Table 2, respectively). In general, propensity score weights reduced the magnitude of between-subtype standardized covariate differences at baseline below 0.2 standard deviations (Supplementary Table 3 and Supplementary Table 4, respectively).

OA Pain and Disability

In persons at-risk for symptomatic knee OA, the Asymptomatic group had almost no change in pain and disability, while other subtypes generally sustained small increases (Figure 2B & 2D). Time-specific differences in outcomes were smallest in magnitude between the Catatonic and Asymptomatic groups, ranging over four years from -0.20 (95% CI: -2.23 , 1.84) to 1.66 (95% CI: -0.59 , 3.91) for pain and -1.06 (95% CI: -2.69 , 0.57) to 0.70 (95%

CI: -1.07, 2.48) for disability (Table 3). However, the between-subtype differences in pain and disability for the Anhedonic and Asymptomatic groups increased in magnitude from baseline (0.45 [95% CI: -0.73, 1.64] and -0.17 [95% CI: -1.17, 0.82], respectively) and were as high as 2.28 (95% CI: 0.33, 4.22) and 2.63 (95% CI: 0.92, 4.35) during follow-up, respectively. Similarly, the Melancholic subtype had worse outcomes across all four annual follow-up visits, but the time-specific differences in pain and disability were not statistically significant.

Among participants with symptomatic knee OA, every group experienced improvement from baseline except the Melancholic subtype, which had persistently greater pain and disability during the follow-up period (Figure 2A & 2C, respectively). When compared to the Asymptomatic group, time-specific differences in pain and disability among the Catatonic and Anhedonic subtypes were small in magnitude and generally 1 rescaled WOMAC units (Table 4). By contrast, differences in pain between the Melancholic and Asymptomatic groups increased from 0.47 (95% CI: -3.68, 4.62) at baseline to 4.79 (95% CI: -1.77, 11.35) at the fourth annual follow-up visit. Similarly, differences in disability increased from 2.80 (95% CI: -1.84, 7.44) at baseline to time-specific differences as large as 6.56 (95% CI: 1.72, 11.40) rescaled WOMAC units in the Melancholic subtype during follow-up.

DISCUSSION

The current study identified four distinct depression subtypes based on patterns of depressive symptoms in persons with or at-risk for symptomatic knee OA. Consistent with a previous meta-analysis, findings indicate that approximately 80% of OAI participants expressed few symptoms of depression (16). However, findings demonstrated moderate heterogeneity in the 20% of participants reporting more depressive symptoms at baseline, and these subtypes were qualified as Catatonic, Anhedonic, and Melancholic. Moreover, detectable effects on pain and disability across four years of follow-up were limited to the Anhedonic and Melancholic subtypes and were largest in persons with symptomatic knee OA who exhibited both somatic and cognitive symptomology. These results imply there is variability in both the expression and severity of depressive symptoms among participants with or at-risk for symptomatic knee OA that may lead to differences in knee OA outcomes.

Few studies have examined depressive symptom heterogeneity in patients with chronic physical diseases, and the current study highlights three symptomatic depression subtypes identified in the OAI cohort (33). The Catatonic and Anhedonic subtypes were differentiated by somatic and cognitive symptoms, while the Melancholic group had a broader constellation of symptomology. Prior work in cancer patients identified a mild depression subtype presenting with concentration and sleep problems and psychomotor agitation that is like the Catatonic group reported in the current study (34). Research also provides support for a non-dysphoric (i.e., without sadness) depression subtype in older adults typified by slowness of movement, but unlike the Catatonic group, exhibited other cognitive symptoms (35–37). Anhedonic subtypes epitomized solely by the absence of happiness have not been widely reported (38). Research conducted in the general population derived an Anhedonic subtype with similar characteristics to current results: older age and more proportionate sex

distribution (39). However, that study suggested the Anhedonic class had fewer future depressive episodes and stressful events than other subtypes; surprising, given Anhedonia is associated with chronic stress and is a risk factor for major depression (39, 40). Subtypes comprised of cognitive and somatic symptoms are consistently reported, and melancholic depression characterized by sadness, anhedonia, decreased energy and movement, difficulty concentrating, restless sleep, and other physical and emotional problems has been identified in general population and elderly samples (33, 41, 42). Melancholic depression is a more severe phenotype, evidenced by higher CES-D scores satisfying screening criteria for every participant in this group, and is associated with an almost two-fold response time to pharmacological treatment compared to other subtypes (43). Nonetheless, one third of individuals in the Catatonic and Anhedonic groups screened positive for probable depression, and these subtypes not only represent differences in severity, but illustrate different patterns of symptomology and may explain (in part) why almost 60% of depressed OA patients do not receive mental health care (44).

Differences in pain and disability by depression subtype further highlight the difficulty in managing psychosomatic factors in knee OA patients. The Catatonic subtype was the only group that did not experience significantly greater pain and disability than Asymptomatic participants. This finding is contrary to research showing that older adults who report somatic symptoms of depression but deny feelings of sadness are at an increased risk for functional impairment (35). Perhaps the Catatonic subtype represents a mild phenotype, but it may also indicate somatic symptom overlap, where CES-D items detect symptomology of knee OA or another unrelated medical condition (e.g., fatigue) that is not predictive of pain and disability (34, 45, 46). By contrast, participants at-risk for symptomatic knee OA in the Anhedonic subtype had statistically greater pain and disability (1.5–2.3 WOMAC units) compared to Asymptomatic individuals that was small in magnitude and not clinically significant. However, prior research indicates that OAI participants experience minimal changes in their knee OA symptoms; therefore, psychosomatic factors that contribute to persistently higher disease severity may be relevant at the population level (47). The cognitive symptoms of the Anhedonic subtype may represent perseverative thought, a process of repetitive pessimistic thinking associated with negative affect and other traits closely-related to depression, which could act as a response-shift and lead to reports of worse pain and disability (48). Alternatively, the Anhedonic subtype may constitute a mild mood disorder which, following the onset of a chronic physical disease, decompensates in to melancholic depression in some individuals with symptomatic knee OA. This premise is supported by persistently higher disease severity (4.8–6.6 WOMAC units) among symptomatic knee OA participants in the Melancholic subtype, perhaps indicative of substantive increases in pain severity and decreased physical performance associated with a greater number and spectrum of depressive symptoms (49). Unfortunately, it is not possible to determine causality regarding knee OA and depression in the current study, and the melancholic subtype may represent more severe depressive symptoms that are a consequence of pain, disability, or other related factors. Notwithstanding, Anhedonia, and to a larger extent, Melancholic depression, may be a modifiable risk factor for worsening knee OA disease severity and potential target for intervention.

There are limitations that should be considered when interpreting study results. First, the 20-Item CES-D lacks assessments of symptoms (e.g., hallucinations, risk taking behaviors, etc.) commonly found in Psychotic and Atypical depression subtypes (23). Nevertheless, the CES-D is a valid and reliable measure of depressive symptoms in persons with knee OA that has been used in prior OAI studies on depression (6, 7, 49). Second, a three-step design was used, where the measurement model was estimated, participants were assigned to a subtype, and a structural model of outcomes was fit; an approach that may lead to misclassification of class assignment. However, relative model entropy suggested a minimal level of class uncertainty and any resulting bias would attenuate associations to the null. Lastly, the potential for confounding by unmeasured factors, such as depression treatments, cannot be eliminated here and is the case for all observational studies. These limitations are mitigated by the study's strengths. First, this is one of the largest LCA studies on depression heterogeneity in persons with or at-risk for chronic musculoskeletal disorders. Second, modern statistical techniques that leveraged machine learning and inverse probability weighting methods were used to overcome model misspecification when adjusting for potential confounders and missing data. Finally, the OAI is a well-documented, prospective cohort, and measured comprehensive sociodemographic and clinical characteristics relevant to assessments of depression subtypes and their influence OA pain and disability.

To conclude, study findings indicate that depression subtypes among individuals with or at-risk for symptomatic knee OA are differentiated primarily by psychomotor agitation, anhedonia, and other somatic complaints. Moreover, Anhedonic and Melancholic depression subtypes may be risk factors for increased pain and disability in persons who develop and experience symptomatic knee OA. These results demonstrate the advantages of using a datadriven approach to identify distinct depression subtypes that represent unique clinical phenotypes presenting with different spectrums of symptoms. Consistent with clinical recommendations, our findings support the need for depression screening in knee OA patients during primary care and rheumatology encounters with simple, reliable, and valid instruments (e.g., 2-item Patient Health Questionnaire) (50). If depression screening becomes routine in patients with musculoskeletal disorders, more comprehensive symptomatic assessments could be conducted after referral to mental health professionals, where patients then receive treatments that are tailored to their specific depressive symptomology. However, the feasibility and cost-effectiveness of more complex assessment methods in the secondary care setting that are required for depression subtype identification are unknown. Ultimately, findings highlight the difficulty of using standard depression treatments in individuals with musculoskeletal disorders, and protocols that address the specific symptomatology of different subtypes of depression that may present in knee OA patients are needed.

ACKNOWLEDGEMENTS

The OAI is a public-private partnership comprised of five contracts (N01-AR-2-2258; N01-AR-2-2259; N01-AR-2-2260; N01-AR-2-2261; N01-AR-2-2262) funded by the National Institutes of Health, a branch of the Department of Health and Human Services, and conducted by the OAI Study Investigators. Private funding partners include Merck Research Laboratories; Novartis Pharmaceuticals Corporation, GlaxoSmithKline; and Pfizer, Inc. Private sector funding for the OAI is managed by the Foundation for the National Institutes of Health. This manuscript was prepared using an OAI public use data set and does not necessarily reflect the opinions or views of the OAI investigators, the NIH, or the private funding partners.

Funding: This study was supported by the Rheumatology Research Foundation's Scientist Development Award. The sponsor had no role in the study design, collection, analysis and interpretation of data; in the writing of the manuscript; and in the decision to submit the manuscript for publication.

Disclosures: Dr. Alan M. Rathbun is supported by a grant from the Rheumatology Research Foundation. Drs. Megan S. Schuler, Elizabeth A. Stuart, Michelle D. Shardell, Michelle S. Yau, Joseph J. Gallo, Alice S. Ryan, and Marc C. Hochberg have no conflicts of interest to declare.

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SIGNIFICANCE & INNOVATION

- Depressive symptoms in persons with or at-risk for symptomatic knee OA present as one of four unique subtypes
- Depression subtypes are differentiated primarily by psychomotor agitation, anhedonia, and other somatic complaints
- Anhedonic and Melancholic depression subtypes may be risk factors for increased pain and disability
- Results highlight the need for protocols designed to address the specific symptomatology of different depression subtypes

Figure 1.
Study sample flow diagram

Figure 2.

Pain (A and B) and disability (C and D) trajectories by baseline depression subtypes among participants with (A and C) or at-risk (B and D) for symptomatic knee OA.

Table 1.

Baseline CES-D item response probabilities by depressive symptom subtype among participants who had or were at risk for knee osteoarthritis.

CES-D Item	Asymptomatic	Catatonic	Anhedonic	Melancholic
1. I was bothered by things that don't usually bother me.	0.005	0.126	0.019	0.392
2. I did not feel like eating; my appetite was poor.	0.002	0.085	0.015	0.158
3. I felt that I could not shake off the blues even with help from my family and friends.	0.004	0.076	0.014	0.529
*4. I felt that I was just as good as other people.	0.085	0.125	0.500	0.425
5. I had trouble keeping my mind on what I was doing.	0.018	0.268	0.057	0.502
6. I felt depressed.	0.002	0.078	0.024	0.742
7. I felt that everything I did was an effort.	0.009	0.319	0.049	0.641
*8. I felt hopeful about the future.	0.073	0.257	0.752	0.847
9. I thought my life had been a failure.	0.002	0.026	0.024	0.298
10. I felt fearful.	0.004	0.052	0.009	0.290
11. My sleep was restless.	0.116	0.460	0.206	0.661
*12. I was happy	0.033	0.274	0.722	0.882
13. I talked less than usual.	0.011	0.190	0.056	0.390
14. I felt lonely.	0.013	0.127	0.050	0.537
15. People were unfriendly.	0.004	0.033	0.015	0.119
*16. I enjoyed life.	0.011	0.141	0.617	0.773
17. I had crying spells.	0.001	0.038	0.011	0.192
18. I felt sad.	0.002	0.054	0.023	0.585
19. I felt that people disliked me.	0.005	0.037	0.015	0.141
20. I could not get "going."	0.005	0.264	0.066	0.592

* Indicates CES-D item was reversed scored.

Table 2.

Baseline sample characteristics by depressive symptom subtype before propensity score weighting.

Variable (mean (sd) or n (%))	Asymptomatic (n=3,615)	Catatonic (n=239)	Anhedonic (n=474)	Melancholic (n=158)	P Value
Age	61.24 (9.09)	61.06 (9.37)	61.87 (9.81)	57.44 (8.27)	<0.001
Female	2054 (56.8)	157 (65.7)	283 (59.7)	113 (71.5)	<0.001
White	630 (17.4)	82 (34.6)	122 (25.7)	53 (33.5)	<0.001
Marital status					<0.001
<i>Married</i>	2537 (70.8)	124 (52.1)	267 (56.3)	75 (47.8)	
<i>Widowed</i>	250 (7.0)	30 (12.6)	59 (12.4)	13 (8.3)	
<i>Divorced</i>	467 (13.0)	41 (17.2)	80 (16.9)	34 (21.7)	
<i>Separated</i>	45 (1.3)	11 (4.6)	11 (2.3)	8 (5.1)	
<i>Never Married</i>	285 (8.0)	32 (13.4)	57 (12.0)	27 (17.2)	
Education					<0.001
<i>No Degree</i>	1265 (35.3)	137 (57.6)	252 (53.2)	97 (61.4)	
<i>College Degree</i>	1111 (31.0)	53 (22.3)	123 (25.9)	37 (23.4)	
<i>Graduate Degree</i>	1208 (33.7)	48 (20.2)	99 (20.9)	24 (15.2)	
Employment	2272 (62.9)	133 (55.6)	279 (59.0)	88 (55.7)	0.022
Health insurance	3507 (97.9)	219 (92.0)	442 (94.0)	138 (87.3)	<0.001
Smoking					<0.001
<i>Never</i>	1944 (54.6)	104 (43.9)	232 (49.5)	78 (50.0)	
<i>Current</i>	177 (5.0)	29 (12.2)	41 (8.7)	30 (19.2)	
<i>Former</i>	1438 (40.4)	104 (43.9)	196 (41.8)	48 (30.8)	
Alcohol consumption					0.015
<i>None</i>	641 (17.9)	55 (23.1)	104 (22.0)	42 (26.6)	
<i>Minimal</i>	2634 (73.5)	163 (68.5)	338 (71.5)	105 (66.5)	
<i>Moderate</i>	307 (8.6)	20 (8.4)	31 (6.6)	11 (7.0)	
Charlson comorbidity	0.34 (0.78)	0.54 (1.04)	0.54 (1.04)	0.68 (1.03)	<0.001
BMI	28.40 (4.68)	29.33 (5.27)	29.17 (5.14)	29.94 (5.79)	<0.001
Symptomatic knee OA	1224 (33.9)	116 (48.5)	202 (42.6)	84 (53.2)	<0.001
K-L grade					<0.001
<i>0</i>	1455 (40.2)	74 (31.0)	163 (34.4)	52 (32.9)	
<i>1</i>	650 (18.0)	42 (17.6)	81 (17.1)	32 (20.3)	
<i>2</i>	916 (25.3)	61 (25.5)	127 (26.8)	52 (32.9)	
<i>3</i>	484 (13.4)	54 (22.6)	79 (16.7)	19 (12.0)	
<i>4</i>	110 (3.0)	8 (3.3)	24 (5.1)	3 (1.9)	
History of knee injury	938 (26.2)	69 (29.0)	133 (28.4)	48 (30.4)	0.419
Analgesic use	1238 (34.3)	108 (45.6)	196 (41.4)	95 (60.5)	21.97 <0.001
WOMAC	10.18 (13.17)	17.40 (18.81)	15.51 (17.64)	(20.28)	<0.001
CES-D score	4.03 (3.56)	13.92 (4.59)	13.85 (4.47)	28.97 (7.2)	<0.001
CES-D score 16	15 (0.4)	87 (36.7)	170 (36.2)	158 (100.0)	<0.001

BMI: Body mass index; CES-D: Center for Epidemiologic Studies Depression scale; K-L grade: Kellgren-Lawrence grade; OA: Osteoarthritis; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index.

Table 3.

Time-specific differences (Reference=Asymptomatic) in pain and disability by baseline depression subtype among participants at-risk for symptomatic knee OA.

Time Point	Catatonic			Anhedonic			Melancholic		
	β	95% CI	P	β	95% CI	P	β	95% CI	P
Pain									
Baseline	0.01	-1.74, 1.76	0.994	0.45	-0.73, 1.64	0.451	-1.02	-3.17, 1.12	0.349
Year One	1.54	-0.91, 4.00	0.219	1.59	0.07, 3.12	0.041	2.77	-1.99, 7.53	0.254
Year Two	0.32	-2.02, 2.66	0.790	0.97	-0.62, 2.57	0.231	0.40	-2.73, 3.53	0.802
Year Three	1.66	-0.59, 3.91	0.148	2.28	0.33, 4.22	0.022	2.59	-2.23, 7.42	0.292
Year Four	-0.20	-2.23, 1.84	0.850	1.56	-0.12, 3.23	0.069	1.95	-1.87, 5.77	0.316
Disability									
Baseline	-0.26	-1.79, 1.26	0.734	-0.17	-1.17, 0.82	0.737	0.50	-1.78, 2.78	0.667
Year One	0.70	-1.07, 2.48	0.437	1.12	-0.16, 2.40	0.087	4.17	-0.52, 8.86	0.082
Year Two	-0.20	-1.75, 1.34	0.798	1.70	0.17, 3.23	0.030	0.80	-2.19, 3.80	0.599
Year Three	0.32	-1.57, 2.21	0.742	2.63	0.92, 4.35	0.003	1.55	-1.55, 4.64	0.327
Year Four	-1.06	-2.69, 0.57	0.204	1.57	0.00, 3.14	0.050	2.12	-1.73, 5.96	0.281

Table 4.

Time-specific differences (Reference=Asymptomatic) in pain and disability by baseline depression subtype among participants with symptomatic knee OA.

Time Point	Catatonic			Anhedonic			Melancholic		
	β	95% CI	P	β	95% CI	P	β	95% CI	P
Pain									
Baseline	-1.51	-5.06, 2.04	0.404	0.39	2.31, 3.09	0.779	0.47	-3.68, 4.62	0.824
Year One	-0.14	-3.96, 3.68	0.942	0.57	-2.32, 3.46	0.701	1.33	-3.40, 6.05	0.582
Year Two	-0.33	-4.34, 3.69	0.873	0.95	-2.18, 4.08	0.551	4.25	-0.45, 8.95	0.077
Year Three	-0.17	-4.07, 3.72	0.932	-0.64	-3.58, 2.30	0.668	2.98	-2.49, 8.44	0.286
Year Four	0.82	-3.34, 4.98	0.699	-0.31	-3.18, 2.55	0.830	4.79	-1.77, 11.35	0.152
Disability									
Baseline	1.27	-2.07, 4.60	0.457	0.48	-2.17, 3.12	0.723	2.80	-1.84, 7.44	0.237
Year One	0.58	-3.12, 4.27	0.760	1.24	-1.60, 4.08	0.393	2.76	-1.74, 7.27	0.230
Year Two	-0.54	-4.26, 3.19	0.778	-0.08	-2.80, 2.64	0.954	4.82	0.31, 9.33	0.037
Year Three	-0.01	-3.57, 3.54	0.994	0.14	-2.68, 2.96	0.921	6.56	1.72, 11.40	0.008
Year Four	1.21	-2.92, 5.34	0.567	0.31	-2.32, 2.94	0.817	5.35	-0.90, 11.60	0.094