Cross-Sectional Associations Among Symptoms of Pain, Irritability, and Depression and How These Symptoms Relate to Social Functioning and Quality of Life:

Findings From the EMBARC and STRIDE Studies and the VitalSign[6] Project

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ABSTRACT

Objective: The aim of this report was to evaluate the psychometric properties of the Pain Frequency, Intensity, and Burden Scale (P-FIBS), a brief measure of pain, as well as the association of pain with irritability and depression and how these symptoms relate to functional impairments.

Methods: Participants of 2 randomized controlled trials (Establishing Moderators and Biosignatures of Antidepressant Response in Clinical Care [EMBARC; n = 251 with *DSM-IV* diagnosis of major depressive disorder; study duration: August 2011–December 2015] and STimulant Reduction Intervention Using Dosed Exercise [STRIDE; n = 302 with *DSM-IV* diagnosis of stimulant abuse or dependence; study-duration: July 2010–February 2013]) and treatment-seeking patients in primary care clinics from an ongoing quality-improvement project (VitalSign[6]; n = 4,370; project duration: August 2014–July 2019) were included. Psychometric properties of the P-FIBS were evaluated with confirmatory factor and item response theory analyses in EMBARC and VitalSign[6]. The approach of Baron and Kenny was used to assess whether irritability accounted for the effect of pain on depression.

Results: Cronbach α (0.84–0.89) and model fits for single-factor structure of P-FIBS were acceptable. Pain was positively correlated with irritability ($r = 0.22–0.29$) and depression ($r = 0.10–0.33$). Irritability accounted for 40.7%–65.5% of the effect of pain on depression. Higher irritability and depression were associated with poorer social functioning, quality of life, and productivity in work- and non–work-related activities. Pain was associated with non–work-related activity impairments even after controlling for irritability and depression.

Conclusions: The P-FIBS is a brief and reliable measure of pain. Irritability is associated with pain and accounts for a large proportion of the effect of pain on depression. Symptoms of pain, irritability, and depression are associated with functional impairments.

Trial registration: ClinicalTrials.gov identifiers: NCT01407094 (EMBARC), NCT01141608 (STRIDE).

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Pain and depression are the two leading causes of disability in the United States[1] and are commonly reported by patients who seek care in primary care and psychiatric practices.[2] They are often comorbid; two-thirds of patients with major depressive disorder (MDD) report experiencing at least one chronic painful physical condition such as presence of pain in the abdomen, shoulders, neck, back, extremities, or chest; headaches; or migraine for 3–6 months.[3,4] Comorbidity with pain, in turn, is associated with higher severity of overall depression.[4–6] Patients with MDD are also 2.5 times more likely to receive chronic opioid medications than their peers without mental illnesses.[7] Together, these findings argue for systematic assessment of pain and depression.

Irritability is an important feature that is associated with both pain and depression but often goes unrecognized. It is unique among symptoms associated with depression, as irritability is considered a criterion symptom for diagnosis of MDD in adolescents but not in adults.[8] Yet, it is widely prevalent and is associated with poor long-term outcomes,[9–12] including higher rates of suicide attempt and completed suicide.[12,13] Among physiologic causes of irritability, pain has gained recent attention.[14] In fact, a recent study[15] of outpatients with chronic pain found that irritability was significantly associated with severity of pain and life interference due to pain. However, the association between pain and irritability and how they relate to depression remain unclear. Additionally, depression is associated with impairments in multiple facets of life, including work productivity,[16,17] psychosocial functioning,[18,19] quality of life,[20,21] and routine day-to-day activities.[22,23] In a previous report,[4] presence of pain and depression was shown to be associated with poorer quality of life as compared to either of these conditions alone. However, the impact of irritability on measures of functional

Clinical Points

- The Pain Frequency, Intensity, and Burden Scale (P-FIBS) is a brief and reliable measure of pain.
- In 3 separate samples of adults, irritability was associated with pain and accounted for 40.7%–65.5% of the effect of pain on depression.
- Higher irritability was associated with greater functional and quality of life impairments even after accounting for the severity of concurrent pain and depression.

impairments, especially after accounting for symptoms of depression and pain, remains poorly understood.

This report seeks to understand the association between pain and irritability and how they relate to depression in 3 separate samples of adults. This report also seeks to evaluate the impact of these symptoms (pain, irritability, and depression) on measures of social functioning and/or quality of life. Two of these samples are from randomized controlled trials (RCTs) of adults with MDD (Establishing Moderators and Biosignatures of Antidepressant Response in Clinical Care [EMBARC][24,25]) and stimulant use disorder (STimulant Reduction Intervention Using Dosed Exercise [STRIDE][26]). The third sample included treatment-seeking outpatients in primary care clinics who screened positive for depression as part of an ongoing quality improvement project, VitalSign[6], to screen for and manage depression using the Primary Care First (PCP-First) approach.[27]

To measure pain, this report used the recently developed Pain Frequency, Intensity, and Burden Scale (P-FIBS), which is a brief self-report measure that not only assesses intensity of pain, but also evaluates frequency of pain, interference in daily life due to pain, and use of medication or other treatments to manage pain.[28] This scale was developed to address the modest accuracy of commonly used numerical rating scales for pain[29] and to provide a multidimensional assessment of pain.[28] In the STRIDE study, the P-FIBS was shown to have sound psychometric properties and a single-factor structure.[28] Therefore, this current report first evaluated the psychometric properties of the P-FIBS using confirmatory factor analysis and exploratory item response theory (IRT) analyses in 2 separate samples of adults (EMBARC and VitalSign[6]) and then asked the following specific questions in all 3 samples (EMBARC, STRIDE, and VitalSign[6]):

1. Is pain associated with irritability and depression?
2. Does irritability account for the effect of pain on depression?
3. Are these symptoms (pain, irritability, and depression) associated with social functioning and quality of life?

While symptom severity measures were available in all 3 samples, the EMBARC and STRIDE studies collected only measures of social functioning and quality of life, respectively, whereas the VitalSign[6] project collected only measures of productivity in work- and non–work-related activities.

METHODS

Participants

EMBARC. As previously described,[24,25] the EMBARC study (NCT01407094) enrolled 309 participants with MDD at 4 sites from August 2011 to December 2015. Of these, 10 were in a feasibility sample and 3 were randomized but were not eligible for the study.[24] Of the 296 participants with MDD who were randomized either to sertraline or to placebo, 45 did not complete the measures of either pain (P-FIBS) or irritability at baseline. Thus, the analytic sample for this report included baseline data from 251 participants with MDD. Institutional review boards (IRBs) at each site approved the study, and all participants provided written informed consent prior to completing any study-related procedures. The inclusion and exclusion criteria have been described previously[24] and are listed in detail at https://clinicaltrials.gov/ct2/show/NCT01407094. Briefly, participants were 18–65 years of age, met criteria for current episode of MDD on Structured Clinical Interview for *DSM-IV* Axis I Disorders (SCID),[30] scored ≥ 14 on the 16-item Quick Inventory of Depressive Symptomatology Self-Report (QIDS-SR)[31] at both screening and randomization visits, did not meet criteria for any failed antidepressant trial in the current episode based on Massachusetts General Hospital Antidepressant Treatment Response Questionnaire,[32] and agreed to and were eligible for all biomarker procedures (electroencephalography, psychological testing, magnetic resonance imaging, and blood draws). Participants were excluded if they did not tolerate sertraline or bupropion in the past, were pregnant/breastfeeding/planning to become pregnant, were medically or psychiatrically unstable, met *DSM-IV* criteria for psychotic/bipolar disorder in lifetime or substance abuse in past 2 months or substance dependence in past 6 months, or were on treatment with prohibited concomitant medications (antipsychotics, anticonvulsants, mood stabilizers, central nervous system stimulants, daily benzodiazepines or hypnotics, or antidepressants).

STRIDE. The STRIDE study (NCT01141608) recruited 18- to 65-year-old patients (n = 302) with stimulant abuse or dependence (per *DSM-IV*) who were in residential addiction treatment programs for a 36-week-long study from July 2010 to February 2013.[26,33] This report used data from the baseline visit only. The IRBs associated with each of the participating addiction treatment programs approved the study. Individuals provided written informed consent prior to completing any study-related procedures. Eligible participants reported use of stimulants within 30 days prior to admission to the program, agreed to complete the residential program, met past-year *DSM-IV* criteria for stimulant abuse or dependence, and were cleared to exercise via a protocol-defined stress test with additional medical clearance if body mass index was > 40 kg/m^2. Exclusion criteria included (1)

evidence of a general medical condition or other abnormality contraindicating exercise; (2) past-year opioid dependence; (3) being considered a high risk for suicide and/or study non-completion due to the need for psychiatric hospitalization; (4) current psychotic disorder; (5) pregnancy; (6) aerobically exercising more than 3 times per week for 20 minutes or more, consistently for the 3 months prior to study enrollment; (7) prescribed β–blockers or any opioid replacement therapies, and (8) anticipated circumstances making study completion unlikely or hazardous. As previously reported, 69 (22.85%) of 302 participants in STRIDE met the *DSM-IV* criteria for a current major depressive episode using the Mini-International Neuropsychiatric Interview (MINI).[34] Additionally, 16 (5.30%) of 302 participants in STRIDE had score ≥ 11 on the clinician-rated version of QIDS (QIDS-C).[33]

***VitalSign*[6].** As previously described,[27,35] the VitalSign[6] is an ongoing quality improvement project to improve recognition, treatment, and outcomes of patients with depression using the Primary Care First (PCP-First) model. This model incorporates health information technology tools through an electronic health records (EHR)–integrated web application and facilitates the following 5 components: (1) screening, (2) diagnosis, (3) treatment selection, (4) treatment implementation, and (5) treatment revision. A web-based application is used for screening of patients at participating clinics for depression using the 2-item Patient Health Questionnaire (PHQ-2).[36] Those who screen positive (PHQ-2 score > 2)[37] complete the 9-item PHQ (PHQ-9). The analytic sample for this report is based on deidentified data obtained from adults (aged ≥ 18 years) who completed assessments of pain and irritability after screening positive for depression from August 2014 to July 2019 (n = 4,370). This report used data from the baseline visit only. The study was reviewed and approved by the IRB of University of Texas Southwestern Medical Center at Dallas with a waiver of the need to obtain informed consent from individual patients.

Measurements

Pain. The P-FIBS is a 4-item self-report measure. Each individual item is rated on a 9-point Likert scale corresponding to scores of 0, 1, 2, 3, 4, 5, 6, 7, and 8 for a total score range of 0–32. In a previous report[28] using the STRIDE study, the Cronbach α of P-FIBS was 0.90, and each item showed high correlation with the total score. In the same report, a principal component analysis found that only the first component had an eigenvalue greater than 1, suggesting that the P-FIBS is unidimensional. Strong construct validity was demonstrated by strong correlations with the physical component and bodily pain scales of the 36-item Short Form Health Survey (SF-36).[28]

Irritability. The 5-item irritability domain of the Concise Associated Symptom Tracking scale (CAST-IRR) is a self-report measure with the following individual items: "I wish people would just leave me alone," "I feel very uptight," "I find myself saying or doing things without thinking," "Lately everything seems to be annoying me," and "I find people get on my nerves easily." Each individual item is rated on a 5-point Likert scale with responses of "strongly disagree," "disagree," "neither agree nor disagree," "agree," and "strongly agree" corresponding to scores of 1, 2, 3, 4, and 5, respectively, and a total score of 5–25. In previous reports,[38,39] the Cronbach α of the CAST-IRR was 0.77–0.83.

Depression. Depression measures for each sample examined the 9 criterion symptoms of a major depressive episode (MDE). Specifically, for the EMBARC study, the QIDS-SR was used.[31] Of the 16 items (each item has 4 choices that are scored from 0 to 3) in the QIDS-SR, 9 items (corresponding to the 9 symptom criteria of an MDE[8]) are used to calculate the total score, which can range from 0 to 27.[31] In the STRIDE study, the QIDS-C was used. Individual items of the QIDS-C correspond to those of the QIDS-SR and are scored in an identical fashion.[31] In the VitalSign[6] project, patients completed the PHQ-9 after screening positive for depression (PHQ-2 score > 2). The PHQ-9 is a self-report measure that assesses the 9 symptom criteria that define an MDE.[37] Each PHQ-9 item is scored from 0 to 3; total score ranges between 0 and 27, and symptom severity is categorized as minimal (0–4), mild (5–9), moderate (10–14), severe (15–19), and very severe (20–27).[37]

Measures of functioning and quality of life. In the EMBARC study, the 24-item short version of the Social Adjustment Scale Self-Report (SAS-SR)[40] was used to measure functioning in the past 2 weeks at work (as either a paid worker, an unpaid homemaker, or a student), in social and leisure activities, in relationships with extended family, with marital partner, with children, and in role within the family unit.[24] In a previous study,[40] this short version of the SAS-SR was highly correlated to the full 54-item version (Pearson *r* ranging from 0.89 to 0.95). The overall mean score on the SAS-SR short version was used in this report, with higher score indicating poorer social functioning. The 14-item Short Form version of the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q-SF) was used to measure overall satisfaction with different aspects of life in the STRIDE study.[26,41,42] Each item of the Q-LES-Q-SF is rated on a 5-point scale, and the sum of these 14 items is expressed as a percentage of maximum score possible (range, 0–100). Higher scores are indicative of better quality of life. The Work Productivity and Activity Impairment questionnaire (WPAI) was used to assess productivity in work- and non–work-related activities in the VitalSign[6] project.[27,43] The items of the WPAI include employment status (item 1), number of hours missed from work in the last week due to health reasons (range 0–80; item 2), number of hours missed from work due to other reasons such as vacation (item 3), number of hours worked in the last week (range 0–80; item 4), impairment resulting from health conditions while working using a scale of 0 to 10 in which 0 indicates no impairment (item 5), and impairment in regular daily activities other than work or job (item 6). The overall work productivity loss was computed the basis of scores for items 2, 4, and 5, per Reilly et al,[43] only in patients who were employed (per response to item 1). The impairment in non–work-related daily activities was computed in both

employed and unemployed individuals using scores for item 6. Both scores (productivity in work- and non–work-related activities) are expressed as percentages, with higher scores reflecting greater impairment.

Statistical Analyses

Descriptive statistics were used to describe the samples for the EMBARC and STRIDE studies and the VitalSign[6] project. As initial psychometric properties of the P-FIBS were previously tested in the STRIDE study,[28] data from EMBARC study and VitalSign[6] project were used in this report to validate the single-domain structure of the P-FIBS using confirmatory factor analysis as implemented with PROC CALIS in SAS 9.4 (released November 2016; SAS Institute). Acceptable model fit was defined a priori as goodness of fit index (GFI) ≥ 0.90, comparative fit index (CFI) ≥ 0.90, and root mean square error of approximation (RMSEA) ≤ 0.08.[44] Separate item response theory (IRT) analyses based on the graded response model[45] for the EMBARC study and VitalSign[6] project were used to evaluate the performance of individual items. The slope for each item provides an estimate of that item's ability to discriminate between differences in levels of that item, and the thresholds indicate the item's sensitivity at difference levels. Specifically, threshold 1 compares selecting 0 versus 1, 2, 3, 4, 5, 6, 7, 8; threshold 2 compares selecting 0, 1 versus 2, 3, 4, 5, 6, 7, 8; threshold 3 compares selecting 0, 1, 2 versus 3, 4, 5, 6, 7, 8; threshold 4 compares selecting 0, 1, 2, 3 versus 4, 5, 6, 7, 8; threshold 5 compares selecting 0, 1, 2, 3, 4 versus 5, 6, 7, 8; threshold 6 compare selecting 0, 1, 2, 3, 4, 5 versus 6, 7, 8; threshold 7 compares selecting 0, 1, 2, 3, 4, 5, 6, versus 7, 8; and threshold 8 compares selecting 0, 1, 2, 3, 4, 5, 6, 7 versus 8.[46] The Cronbach α coefficient was calculated to evaluate the internal consistency of the P-FIBS for both the EMBARC study and the VitalSign[6] project.[47]

Age, sex, race, and ethnicity were included as covariates in all regression analyses given their association with severity of depression in the National Health Interview Survey.[48] Additionally, association of these features (age, sex, race, and ethnicity) with symptom measures (pain, irritability, and depression) was evaluated. In all 3 samples (EMBARC, STRIDE, and VitalSign[6]), Pearson r correlation coefficients were estimated to evaluate the association of the P-FIBS with measures of irritability and depression. In all 3 samples (EMBARC, STRIDE, and VitalSign[6]), the approach described by Baron and Kenny[49] was used to evaluate whether irritability accounts for the effect of pain on depression. This approach uses 3 separate linear regression models to evaluate how much of the predictive ability of a variable (pain in this report) for an outcome (depression in this report) is accounted for by a third variable (irritability). In this report, depression was the dependent variable and pain was the independent variable of interest in the first regression model. In the second regression model, irritability was the dependent variable and pain was the independent variable of interest. In the third and final regression model, depression was the dependent variable and both pain and irritability were independent variables of interest. Linear regression analyses evaluated the association of symptom measures (pain, irritability, and depression) with those of social functioning (SAS-SR short version score) in the EMBARC study, quality of life (Q-LES-Q-SF score) in STRIDE study, and productivity in work- and non–work-related activities (from the WPAI) in the VitalSign[6] project. The scores of symptom measures were standardized (z-transformed with mean of 0 and standard deviation of 1) to facilitate the comparison of β estimates for each symptom measure.

All analyses were done using SAS 9.4, and threshold for statistical significance was set at $P < .05$ without adjustment for multiple comparisons.

Table 1. Sociodemographic and Clinical Variables of Samples Included in This Report[a,b]

Variable	EMBARC (N = 251)		STRIDE (N = 302)		VitalSign[6] (N = 4,370)	
Categorical	n	%	n	%	n	%
Sex*						
Male	86	34.3	181	59.9	960	25.4
Female	165	65.7	121	40.1	2,824	74.6
Race$						
White	166	66.1	148	49.0	298	17.2
Black	47	18.7	135	44.7	1,032	59.7
Other	38	15.2	19	6.3	399	23.1
Ethnicity#						
Hispanic	50	19.9	31	10.3	930	49.1
Non-Hispanic	201	80.1	271	89.7	964	50.9
Continuous	Mean	SD	Mean	SD	Mean	SD
Age in years	36.4	13.1	39.0	10.8	42.8	13.3
P-FIBS	8.8	7.0	5.0	6.9	15.6	9.6
CAST-IRR	16.2	4.0	10.82	4.20	15.4	5.3
QIDS-SR	18.1	2.8	NA	NA	NA	NA
QIDS-C	NA	NA	5.4	3.0	NA	NA
PHQ-9	NA	NA	NA	NA	14.3	5.8

[a]The n values shown represent the analytic samples for this report. Pain was assessed with the P-FIBS, and irritability was assessed with the CAST-IRR in all 3 samples. Depression was assessed with the QIDS-SR in EMBARC, with the QIDS-C in STRIDE, and with the PHQ-9 in the VitalSign[6] project.
*Missing n = 586 in the VitalSign[6] project.
$Missing n = 2,641 in the VitalSign[6] project.
#Missing n = 2,476 in the VitalSign[6] project.
Abbreviations: CAST-IRR = 5-item irritability domain of the Concise Associated Symptom Tracking scale; EMBARC = Establishing Moderators and Biosignatures of Antidepressant Response for Clinical Care for Depression; NA = not available; P-FIBS = Pain Frequency, Intensity, and Burden Scale; PHQ-9 = 9-item Patient Health Questionnaire; QIDS-C = Quick Inventory of Depressive Symptomatology Clinician-Rated; QIDS-SR = QIDS Self-Report; STRIDE = STimulant Reduction Intervention Using Dosed Exercise.

RESULTS

Table 1 describes the demographic and clinical characteristics of the 3 samples. While participants in the EMBARC study and patients in the VitalSign[6] project were predominantly female, the majority of participants in STRIDE were male. Scores on the P-FIBS were numerically higher in patients in the VitalSign[6] project (mean [SD] = 15.6 [9.6]) than those in both the EMBARC (mean [SD] = 8.8 [7.0]) and STRIDE (mean [SD] = 5.0 [6.9]) studies. Participants in the EMBARC study and patients in the VitalSign[6] project had numerically higher mean severity of depressive symptoms than participants in the STRIDE study (see Table 1).

Table 2. Pain Frequency, Intensity, and Burden Scale (P-FIBS) Items and Their Responses in the EMBARC Study and VitalSign[6] Project[a]

Item and Response	EMBARC		VitalSign[6]	
Item 1. How frequently have you experienced pain in the past week?	n	%	n	%
0: Never	44	17.5	487	11.1
1: Almost some of the days	36	14.3	172	3.9
2: Some of the days	66	26.3	904	20.7
3: Almost half of the days	9	3.6	125	2.9
4: About half of the days	17	6.8	431	9.9
5: Almost most of the days	20	8.0	126	2.9
6: Most of the days	17	6.8	688	15.7
7: Almost everyday	23	9.2	145	3.3
8: Everyday	19	7.6	1292	29.6
Item 2. How would rate the intensity of your pain in the past week?	n	%	n	%
0: No pain	43	17.1	512	11.7
1: None to mild pain	27	10.8	143	3.3
2: Mild pain	53	21.1	736	16.8
3: Mild to moderate pain	43	17.1	171	3.9
4: Moderate pain	35	13.9	992	22.7
5: Moderate to severe pain	35	13.9	444	10.2
6: Severe pain	11	4.4	754	17.3
7: Severe to unbearable pain	2	0.8	285	6.5
8: Unbearable pain	2	0.8	333	7.6
Item 3. How much did pain interfere with your daily life in the past week?	n	%	n	%
0: Never	92	36.7	724	16.6
1: Almost some of the days	40	15.9	276	6.3
2: Some of the days	56	22.3	935	21.4
3: Almost half of the days	16	6.4	142	3.3
4: About half of the days	16	6.4	496	11.4
5: Almost most of the days	13	5.2	117	2.7
6: Most of the days	5	2.0	730	16.7
7: Almost everyday	6	2.4	130	3.0
8: Everyday	7	2.8	820	18.8
Item 4. How often did you use medication or other treatment to manage your pain in the past week?	n	%	n	%
0: Never	136	54.2	1392	31.9
1: Almost some of the days	40	15.9	294	6.7
2: Some of the days	46	18.3	918	21.0
3: Almost half of the days	5	2.0	87	2.0
4: About half of the days	7	2.8	317	7.3
5: Almost most of the days	3	1.2	51	1.2
6: Most of the days	3	1.2	424	9.7
7: Almost everyday	4	1.6	63	1.4
8: Everyday	7	2.8	824	18.9

[a]Item level responses for P-FIBS in STRIDE were reported previously by dela Cruz and colleagues.[28]

Abbreviations: EMBARC = Establishing Moderators and Biosignatures of Antidepressant Response for Clinical Care for Depression; P-FIBS = Pain Frequency, Intensity, and Burden Scale; STRIDE = STimulant Reduction Intervention Using Dosed Exercise.

Pain was positively correlated with age in all 3 samples (EMBARC: $r = 0.30$, $P < .0001$; STRIDE: $r = 0.21$, $P = .0003$; VitalSign[6]: $r = 0.17$, $P < .0001$). Irritability was negatively correlated with age in EMBARC ($r = -17$, $P = .008$) and in VitalSign[6] ($r = -0.10$, $P < .0001$) but not in STRIDE ($r = -0.06$, $P = .32$). Depression and age were not significantly associated in any of the 3 samples ($r = -0.09$ to -0.02, all $P > .10$). Irritability was lower in Black participants versus others ($\beta = -2.37$, SE = 1.00, $P = .018$) in the STRIDE study and in male versus female participants and in Hispanic versus non-Hispanic participants ($\beta = -2.35$, SE = 0.24, $P < .0001$) in the VitalSign[6] project ($\beta = -0.66$, SE = 0.20, $P = .0008$) and was higher among White participants versus others ($\beta = -1.07$, SE = 0.40, $P = .008$) in the VitalSign[6] project. Depression severity was lower in Black participants versus others ($\beta = -1.89$, SE = 0.72, $P = .009$) in the STRIDE study and in male versus female participants ($\beta = -0.76$, SE = 0.22, $P = .0005$), and in Hispanic versus non-Hispanic participants ($\beta = -1.83$, SE = 0.26, $P < .0001$) in the VitalSign[6] project. Pain severity was higher in White participants versus others ($\beta = 3.44$, SE = 0.74, $P < .0001$) and in non-Hispanic versus Hispanic participants ($\beta = 3.35$, SE = 0.44, $P < .0001$) in the VitalSign[6] project as well as in female versus male participants ($\beta = 1.92$, SE = 0.92, $P = .038$) and in White versus Black participants ($\beta = 3.65$, SE = 1.40, $P = .01$) in the EMBARC study.

Psychometric Properties of the P-FIBS

See Table 2 for specific items of the P-FIBS and corresponding participant responses. Cronbach α of the P-FIBS in the EMBARC study and the VitalSign[6] project was 0.84 and 0.89, respectively. On confirmatory factor analysis, model fit for single-factor structure of the P-FIBS was adequate in both EMBARC (GFI > 0.99, CFI = 1.00, and RMSEA = 0.00) and VitalSign[6] (GFI > 0.99, CFI = 1.00, and RMSEA = 0.00). Only the first factor had an eigenvalue exceeding 1.00 in polychoric correlation matrices from IRT analyses supporting their unidimensionality. The eigenvalue of the first factor in EMBARC and VitalSign[6] was 3.08 and 3.25, respectively. Furthermore, the slope exceeded 1.0 for each item, indicating that these items provided adequate discriminability. Table 3 presents the slopes and difficulty thresholds for each item. As a measure of construct validity, P-FIBS scores were markedly higher (Cohen *d* effect size = 0.95) in participants in the EMBARC study who reported back pain (n = 90, mean [SD] = 12.6 [6.2]) than those with no back pain (n = 161, mean [SD] = 6.6 [6.4]).

Is Pain Associated With Irritability and Depression?

Pain was positively correlated with irritability (EMBARC: $r = 0.22$, $P = .0006$; STRIDE: $r = 0.29$, $P < .0001$; and VitalSign[6]: $r = 0.26$, $P < .0001$) and depression (EMBARC: $r = 0.10$, $P = .11$; STRIDE: $r = 0.20$, $P = .0005$; and VitalSign[6]: $r = 0.33$, $P < .0001$). Even after controlling for age, sex, race, and ethnicity, higher levels of pain were associated with higher levels of irritability in EMBARC ($\beta = .19$, $t_{1,244} = 5.11$, $P < .001$), STRIDE ($\beta = .18$, $t_{1,292} = 5.50$, $P < .001$) and VitalSign[6] project ($\beta = .13$, $t_{1,1885} = 11.08$, $P < .001$). The association between pain and depression was significant in STRIDE ($\beta = .09$, $t_{1,292} = 3.86$, $P < .0001$) and the VitalSign[6] project ($\beta = .11$, $t_{1,1885} = 11.08$, $P < .001$) but not in EMBARC ($\beta = .05$, $t_{1,244} = 1.83$, $P = .07$).

Does Irritability Account for the Effect of Pain on Depression?

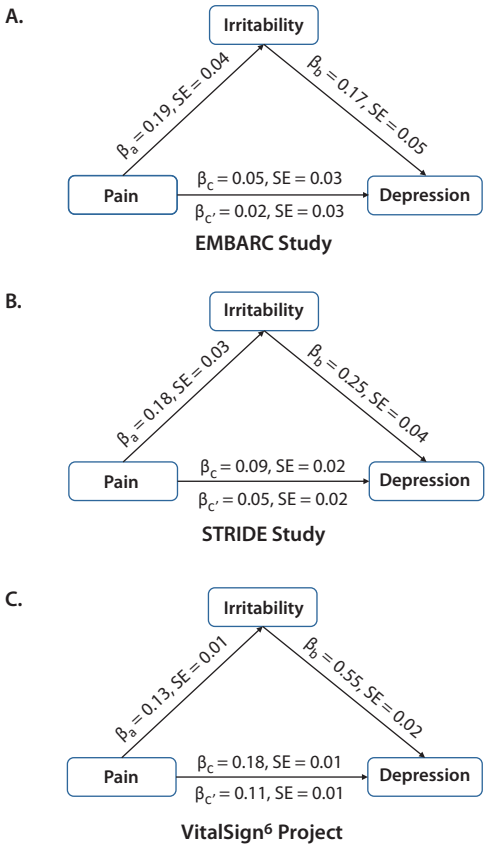
Regression models, per the approach of Baron and Kenny, demonstrated that irritability significantly accounted for the effect of pain on depression in EMBARC (Sobel test statistics = 3.03, $P = .002$), STRIDE (Sobel test statistics = 4.19, $P < .001$) and VitalSign[6] (Sobel test statistics = 10.14, $P < .001$). As shown in Figure 1, the magnitude of positive association

Table 3. Parameters Obtained From Item Response Theory Analyses of the P-FIBS From the EMBARC Study and VitalSign[6] Project

Item and Parameter	EMBARC		VitalSign[6]	
Item 1. How frequently have you experienced pain in the past week?	β	SE	β	SE
Slope	4.08	0.46	4.95	0.15
Threshold 1	−1.06	0.11	−1.34	0.03
Threshold 2	−0.39	0.09	−1.06	0.03
Threshold 3	0.37	0.08	−0.31	0.02
Threshold 4	0.46	0.08	−0.23	0.02
Threshold 5	0.63	0.09	0.04	0.02
Threshold 6	0.83	0.09	0.11	0.02
Threshold 7	1.04	0.10	0.51	0.02
Threshold 8	1.43	0.13	0.60	0.02
Item 2. How would rate the intensity of your pain in the past week?	β	SE	β	SE
Slope	4.89	0.62	4.14	0.11
Threshold 1	−1.07	0.11	−1.34	0.03
Threshold 2	−0.52	0.09	−1.10	0.03
Threshold 3	0.13	0.08	−0.42	0.02
Threshold 4	0.54	0.08	−0.31	0.02
Threshold 5	0.91	0.09	0.30	0.02
Threshold 6	1.51	0.13	0.56	0.02
Threshold 7	1.95	0.19	1.13	0.03
Threshold 8	2.12	0.23	1.46	0.03
Item 3. How much did pain interfere with your daily life in the past week?	β	SE	β	SE
Slope	4.13	0.54	4.93	0.15
Threshold 1	−0.26	0.09	−1.00	0.03
Threshold 2	0.18	0.08	−0.74	0.02
Threshold 3	0.75	0.09	−0.11	0.02
Threshold 4	0.95	0.10	−0.02	0.02
Threshold 5	1.19	0.11	0.28	0.02
Threshold 6	1.43	0.13	0.35	0.02
Threshold 7	1.57	0.14	0.83	0.02
Threshold 8	1.83	0.17	0.93	0.02
Item 4. How often did you use medication or other treatment to manage your pain in the past week?	β	SE	β	SE
Slope	1.40	0.21	1.66	0.05
Threshold 1	0.18	0.12	−0.68	0.03
Threshold 2	0.80	0.15	−0.43	0.03
Threshold 3	1.83	0.25	0.31	0.03
Threshold 4	2.01	0.28	0.38	0.03
Threshold 5	2.31	0.32	0.65	0.03
Threshold 6	2.47	0.35	0.70	0.03
Threshold 7	2.66	0.38	1.15	0.04
Threshold 8	3.02	0.45	1.22	0.04

Abbreviations: EMBARC = Establishing Moderators and Biosignatures of Antidepressant Response for Clinical Care for Depression; P-FIBS = Pain Frequency, Intensity, and Burden scale; STRIDE = STimulant Reduction Intervention Using Dosed Exercise.

Figure 1. Irritability Accounts for the Effect of Pain on Depression in (A) the EMBARC Study, (B) the STRIDE Study, and (C) the VitalSign[6] Project[a]



[a]Pain, measured with the P-FIBS, was the independent variable of interest, and irritability, measured with the CAST-IRR, was the moderating variable in all 3 analyses. Depression, the outcome variable, was measured with the QIDS-SR in Establishing Moderators and Biosignatures of Antidepressant Response for Clinical Care for Depression (EMBARC) study, with the QIDS-C clinician version in the STRIDE study, and PHQ-9 in the VitalSign[6] project.

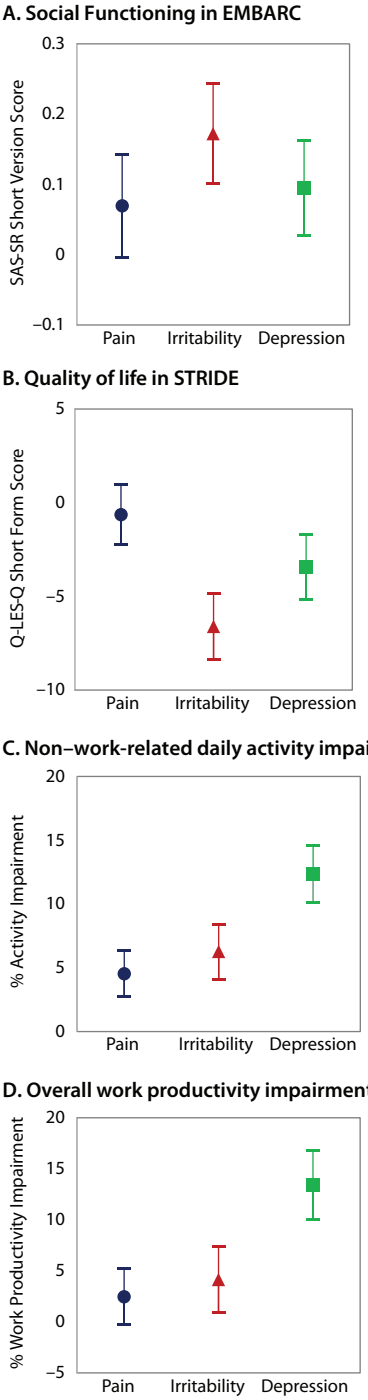
Abbreviations: CAST-IRR = 5-item irritability domain of the Concise Associated Symptom Tracking scale; EMBARC = Establishing Moderators and Biosignatures of Antidepressant Response for Clinical Care for Depression; P-FIBS = Pain Frequency, Intensity, and Burden Scale; PHQ-9 = 9-item Patient Health Questionnaire; QIDS-C = Quick Inventory of Depressive Symptomatology Clinician-Rated; QIDS-SR = QIDS Self-Report; STRIDE = STimulant Reduction Intervention Using Dosed Exercise.

(β_c) between pain and depression scores (ie, higher levels of pain were associated with higher levels of depression) were significantly reduced after the inclusion of irritability (β_c') in the model (β_c [SE] vs β_c' [SE] was 0.05 [0.03] vs 0.02 [0.03] in EMBARC, 0.09 [0.02] vs 0.05 [0.02] in STRIDE, and 0.18 [0.01] vs 0.11 [0.01] in VitalSign[6], respectively). Irritability accounted for 65.5%, 50.4%, and 40.7% of the effect of pain on depression in EMBARC, STRIDE, and VitalSign[6], respectively.

Are These Symptoms (Pain, Irritability, and Depression) Associated With Social Functioning and/or Quality of Life?

See Figure 2 for β estimates and 95% CIs. Higher irritability was associated with poorer social functioning ($t_{1,225} = 4.73$, $P < .0001$) in EMBARC, lower quality of life ($t_{1,293} = -7.39$, $P < .0001$) in STRIDE, and impaired productivity in work- ($t_{1,437} = 2.50$, $P = .013$) and non–work-related ($t_{1,838} = 5.75$, $P < .0001$) activities in VitalSign[6], even after controlling for the severity of concurrent pain and depression. Higher depression was associated with poorer social functioning ($t_{1,225} = 2.75$, $P = .006$) in EMBARC, lower quality of life ($t_{1,293} = -3.83$, $P = .0002$) in STRIDE, and impaired productivity in work- ($t_{1,437} = 7.71$, $P < .0001$) and non–work-related ($t_{1,838} = 10.98$, $P < .0001$) activities in VitalSign[6], even after controlling for the severity of concurrent pain and irritability. Pain was associated with non–work-related activity impairments ($t_{1,838} = 4.98$, $P < .0001$) in VitalSign[6] but not with work productivity

Figure 2. Association Between Symptoms of Pain, Irritability and Depression and Measures of (A) Social Functioning, (B) Quality of Life, (C) Non–Work-Related Activity Impairment, and (D) Work Productivity Impairment[a]



[a]This figure presents the β estimates and their 95% CIs (represented by the error bars) of the association between symptom measures (pain, irritability, and depression) and measures of social functioning (measured with the 24-item Short Version of the SAS-SR) in the EMBARC study, quality of life (measured with the 14-item short form version of the Q-LES-Q) in the STRIDE study, and productivity in work- and non–work-related activities (measured with the WPAI) in the VitalSign[6] project.

Abbreviations: EMBARC = Establishing Moderators and Biosignatures of Antidepressant Response for Clinical Care for Depression; Q-LES-Q = Quality of Life Enjoyment and Satisfaction Questionnaire, SAS-SR = Social Adjustment Scale Self-Report, STRIDE = STimulant Reduction Intervention Using Dosed Exercise, WPAI = Work Productivity and Activity Impairment scale.

impairment ($t_{1,\ 437} = 1.76$, $P = .08$) in VitalSign[6], social functioning ($t_{1,\ 225} = 1.87$, $P = .06$) in EMBARC, or quality of life ($t_{1,\ 293} = -0.77$, $P = .44$) in STRIDE after controlling for severity of concurrent irritability and depression.

DISCUSSION

This report validated the psychometric properties of a scale for measurement of pain in 2 large samples. Furthermore, in 3 large samples of adults, irritability was significantly associated with pain and accounted for 40.7%–65.5% of the effect of pain on depression. Additionally, symptoms of pain, irritability, and depression were associated with poorer social functioning, quality of life, and productivity in work and non–work-related activities. Together, these findings support the utility of the P-FIBS, an easy-to-administer self-report measure of pain, and the importance of irritability as a feature of illness in adults with pain and depression.

This study adds to the initial findings of dela Cruz and colleagues[28] that P-FIBS has strong psychometric properties. This point is particularly relevant given the significant racial and ethnic diversity and broad diagnostic criteria (adults with MDD, adults with serious substance use, and adults in primary care clinics who were screened for depression as part of their routine clinical care) of samples included in this report. The associations between pain and irritability were similar in magnitude to those reported by Holtzman et al[15] in which the intensity of pain had correlation ranging from 0.29 to 0.34 for different measures of irritability. Holtzman and colleagues[15] also found that patients with chronic pain had moderately higher levels of irritability as compared to healthy adults. Therefore, this report extends these prior findings by demonstrating that irritability accounts for a large proportion of the effect of pain on symptoms of depression in 3 separate samples of adults and adds to the emerging literature on irritability as an important feature of illness in adults with depression.[9–11,50]

Findings of this report also extend the understanding of how symptoms of irritability and pain relate to social functioning, quality of life, and productivity in work- and non–work-related activities even after accounting for the severity of depression. Specifically, irritability was significantly associated with all of the functional measures evaluated in this report while pain was associated only with impairments in non–work-related daily activities. Comparison of β estimates of the symptom measures offered additional insights. For example, in the VitalSign[6] project, the association of depression with impairments in work and non–work-related productivity was 2–3 times stronger than the association of irritability with these productivity measures. However, in the EMBARC and STRIDE studies, the association of irritability with measures of social functioning and quality of life was 1.5–2 times stronger than the association of depression with these measures. Future longitudinal studies are needed to understand how changes in these symptom measures relate to each other and

to changes in functioning and quality of life. Furthermore, studies of psychosocial treatments that have been shown to improve depression,[51,52] pain,[53,54] and irritability[55,56] are needed to understand how improving irritability in individuals with chronic pain improves their mental well-being. Findings of this report may be relevant to clinical practice and research. First, while the numerical rating scale is one of the most commonly used pain assessments, it examines only intensity of pain and fails to assess frequency, impairment, and treatment necessity. By assessing these features, the P-FIBS provides a multidimensional assessment of pain. Second, systematic assessment of irritability may improve clinical care of patients with pain and depression. Pain and depression are now considered critical components in health care, with pain often considered the fifth vital sign[57] and now depression being considered the sixth vital sign.[58] Importantly, advances in health information technology may facilitate these assessments as evidenced by the VitalSign[6] project, in which pain, depression, and irritability measures were collected at each visit from patients as part of their routine clinical care.[27,35]

Research efforts are necessary to understand the reasons why irritability accounts for the effect of pain on depression. Inflammation is common to both pain and depression[59] and may underlie the increased sensitivity to sensory stimuli that is associated with irritability.[14] Other mechanisms, including changes in neuroplasticity, such as those mediated by changes in brain-derived neurotrophic factor, have been implicated in the pathophysiology of both pain and depression.[60] Ketamine, a dissociative anesthetic that is used for pain and improves depression,[60,61] was recently shown to improve irritability[62] and may be used as a pharmacologic probe to understand the biological mechanisms that link pain to irritability and depression as well as to develop treatment interventions that specifically target irritability.

There are several limitations of this report. Utility of the P-FIBS as compared to other measures of pain (such as the pain visual analog scale or the numerical rating scale) was not evaluated. Additionally, the discriminative value of the P-FIBS in individuals with chronic pain conditions have not been tested. The EMBARC and STRIDE studies as well as the VitalSign[6] project were not designed to evaluate the associations among pain, irritability, and depression. Therefore, these results should be considered preliminary and require further validation. Associations of pain with irritability and depression were assessed in a cross-sectional fashion, and future longitudinal studies are needed to assess how changes in these symptoms relate to each other. Furthermore, irritability was assessed with self-report measures that should be supplemented with reports from others such family members, friends, and coworkers[63,64] and include overt behaviors such as anger attacks.[65,66]

In conclusion, the P-FIBS is a brief self-report measure of pain that can be administered easily in routine clinical practice. Furthermore, irritability is associated with pain and accounts for a large proportion of the effect of pain on depression. Together, these findings support systematic assessment of irritability in adults with pain and depression.

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