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Screening for depression in cancer patients receiving radiotherapy: Feasibility and identification of effective tools on NRG Oncology RTOG 0841

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Abstract

BACKGROUND—Brief tools are needed to screen for depressive symptoms among oncology outpatients.

METHODS—Patients starting radiotherapy for first diagnosis of any tumor completed distress screening tools including the Patient Health Questionnaire (PHQ-9; PHQ-2), the National Comprehensive Cancer Network-Distress Thermometer (NCCN-DT), and the Hopkins Symptom Checklist (HSCL-25). Patients exceeding validated cutoff scores and a systematic sample of patients who screened negative completed the Structured Clinical Interview for DSM-IV (SCID) Mood Disorder modules via telephone.

RESULTS—463 patients from 35 community-based and 2 academic radiation oncology sites were recruited. Of 455 eligible, 66% were women (n=299) with breast (45%), GI (11%), lung (10%), gynecologic (6%), or other (27%) cancers. Seventy-five (16.5%) exceeded screening cut-offs for depressive symptoms. Of these, 42 patients completed the SCID. An additional 37 who screened negative completed the SCID. Among 79 patients completing a SCID, 8 (10.1%) met criteria for major depression, 2 (2.5%) for Dysthymia, and 6 (7.6%) for Adjustment disorder. The PHQ-2 demonstrated good psychometric properties for screening for mood disorders, using a cut-off score = 3 (ROC area under the curve=0.83) and was comparable to the PHQ-9 (> 9; AUC=0.85). The NCCN-DT did not detect depression (AUC=0.59).

CONCLUSION—The PHQ-2 demonstrated good psychometric properties to screen for mood disorders, which were equivalent to the PHQ-9 and superior to the NCCN-DT. These findings support using the PHQ-2 to identify patients in need of further assessment for depression, a low prevalence but clinically significant comorbidity. Findings can inform implementation of distress screening accreditation standards.

Precis

Addressing psychosocial needs has been increasingly recognized as an integral component of quality cancer care and the association between depression and cancer outcomes underscores the importance of identifying effective strategies for the detection of mood disorder among survivors. The Personal Health Questionnaire (PHQ)-2 demonstrated good psychometric properties to screen for mood disorders, which were equivalent to the longer PHQ-9 and superior to the National Comprehensive Cancer Network Distress Thermometer (NCCN-DT).

Keywords

depression; depression screening; distress; distress screening; mood disorders

INTRODUCTION

The Institute of Medicine (IOM) report “Cancer care for the whole patient” reviewed the nature and extent of unmet psychosocial needs among cancer survivors, including negative consequences for cancer treatment outcomes.¹ The IOM report listed “identifying each patient’s psychosocial health needs” as a requirement to ensure the provision of quality cancer care. Distress screening has increasingly been identified as an important component of quality cancer care.² The National Comprehensive Cancer Network (NCCN) Distress

Management clinical practice guidelines were one of the first to recommend routine distress screening in oncology care settings.³ The American Society of Clinical Oncology (ASCO) added psychosocial care including distress screening to the core set of quality indicators as part of the Quality Oncology Practice Initiative (QOPI) in 2008.⁴ The American College of Surgeons Commission on Cancer now requires sites to implement distress screening programs to meet accreditation standards.^{5,6}

Distress is broadly defined by the NCCN as “a multifactorial unpleasant emotional experience of a psychological (cognitive, behavioral, emotional), social and/or spiritual nature that may interfere with the ability to cope with cancer, its physical symptoms and its treatment” including depression.³ Estimates of the prevalence of depression among cancer patients vary considerably depending on the methodology used to define depression and the sample characteristics (e.g. active treatment, post-treatment surveillance, palliative care). A recent meta-analysis estimated that 8–24% of cancer patients in non-palliative care settings experience depression based on pooled mean prevalence estimates.⁷ Estimates from meta-analytical pooled prevalence based on studies that defined depression using psychiatric interviews were 25% in palliative care settings and 21% among oncology settings.⁸ While depression is less prevalent than anxiety among adults with cancer,^{8,9} the presence of depressive symptoms has been associated with poorer cancer outcomes. A meta-analysis of 25 independent studies found a 39% increase in mortality among cancer patients meeting diagnostic criteria for depression and a 25% increase in mortality risk among those with depressive symptoms, after controlling for prognostic variables.¹⁰ The slope of depressive symptoms over time was predictive of survival among metastatic breast cancer patients. Women who reported decreased depression scores over a 12 month period had longer median survival than women with increased depression.¹¹ The association between depression and cancer outcomes underscores the importance of implementing effective strategies for the detection and management of cancer patients with symptoms of depression.

The primary objective of this trial was to assess the feasibility of a screening procedure to detect mood disorders, including major depression, among cancer patients receiving definitive or palliative radiotherapy in community-based radiation oncology settings. The sensitivity and specificity of commonly used screening measures to detect mood disorders were evaluated. Secondary objectives of this study were to estimate the prevalence of mood disorders among cancer patients receiving definitive or palliative radiotherapy, to characterize the nature of clinical services received to manage depression, and to obtain patient preferences for and barriers to psychosocial care.

METHODS

Patients

Eligibility criteria included patients ≥ 21 years of age with their first diagnosis of any cancer type; cancer stage I-IV, who were within 2 weeks of starting radiotherapy; telephone access; and fluent in English. Patients currently taking medication for depression or anxiety and those with a pre-existing diagnosis of depression were eligible. Participants with symptoms consistent with a psychotic disorder or considered to potentially be at risk for suicide based on staff clinical judgment were excluded from participating due to ethical considerations.

Procedures

This study was conducted through the NCI-funded Radiation Therapy Oncology Group (RTOG) 0841 trial. Participating sites were required to have the NCI designation as a Community Clinical Oncology Program (CCOP), with the exception of two academic sites (study investigators' institutions). This study was approved by each participating site's institutional review board. Informed consent was obtained from all participants. Participating sites were required to complete a questionnaire describing the availability of psychosocial care at their site. This questionnaire was based on a survey conducted by Jacobsen and Ransom¹² to quantify implementation of National Comprehensive Cancer Network (NCCN) Distress Management guidelines at NCCN institutions.

As shown in Figure 1, participants completed depression screening measures at the time of study enrollment. Staff at participating sites administered the screening and scored responses. Assessment results and participant's information were provided to the RTOG coordinating center. Participants who exceeded clinical cut-off scores on screening measures completed an in-depth assessment administered by telephone. A systematic sample of participants who screened negative also completed the telephone-based assessment. Participants meeting criteria for a mood disorder completed a three month follow-up telephone-based assessment.

Measures

Socio-demographic characteristics were obtained through patient questionnaire. Functional status and disease variables, including cancer site, stage and treatment, were extracted from participant medical records at the time of patient enrollment. Participants completed several patient-reported outcomes (PROs) measures to screen for depression, described below.

Depression Screening Measures

Personal Health Questionnaire (PHQ)—The PHQ-9 is a 9-item scale composed of questions that correspond to Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) diagnostic criteria for a major depressive episode. PHQ-9 scores range from 0–27, a higher score indicates greater depression. The PHQ-9 has been shown to be efficient and valid as both a means of identifying depressed patients as well as sensitively measuring change in symptoms over time.^{13,14} The two items which comprise the PHQ-2 are contained within the PHQ-9.^{15,16} The PHQ-2 consists of the two main criteria for a major depressive episode, specifically depressed mood and anhedonia with a minimum duration of 2 weeks. PHQ-2 scores range from 0 to 6.

Hopkins Symptom Checklist (HSCL)—The 25-item version¹⁷ of the HSCL consists of a subset of items from the Symptom Checklist-90.¹⁸ HSCL-25 scores range from 0–100, higher scores indicate elevated depression. The HSCL-25 is highly correlated with the 58-item version of the HSCL.¹⁷ The HSCL-25 has been widely used to screen for depression among cancer patients¹⁷ and has demonstrated excellent reliability (Cronbach's alpha >.90) and validity across a variety of general and medical populations.¹⁹

National Comprehensive Cancer Network – Distress Thermometer (NCCN-DT)

—The NCCN-DT consists of a single item with instructions to rate distress over the past week on a scale from 0–10, with higher scores indicating higher distress. The NCCN recommends using a score of 4 as a cut-off for distress. The NCCN-DT has demonstrated good sensitivity and specificity for general distress.³

Participants also completed a 15-item version of the Health Status Questionnaire.^{20,21} Results are not included in this report.

Telephone-Based Assessment Measure

Structured Clinical Interview for DSM-IV—The Structured Clinical Interview (SCID)²² for DSM-IV was administered via telephone by trained, doctoral-level clinical psychologists. SCID modules to assess current major depressive episode, dysthymic disorder, bipolar disorder, and adjustment disorder were administered. Training and supervision for SCID interviewers followed recommended procedures²³ including reviewing the SCID user's guide, viewing SCID training videotapes, and rating a pre-recorded interview administered by an expert interviewer. Study interviewers resolved questions related to SCID administration, scoring, and interpretation with the study chair. Administration of the SCID was required within 4 weeks of completion of depression screening measures.

Participants also completed measures assessing current psychosocial care, preferences for psychosocial care, and barriers to receive care.

Sample size calculations

The primary endpoint was the feasibility of implementing the screening procedure. It was hypothesized that the screening procedure would be demonstrated to be acceptable to patients and efficient at identifying patients with a mood disorder. The acceptability of the screening procedure was defined as the percentage of registered patients that successfully completed the depression screening measures (PHQ-9 and HSCL-25). The efficiency of the screening procedure was operationalized as the percentage of patients 1) who screened positive on the PHQ-9 or HSCL-25 and 2) of those, who met DSM-IV criteria for a current mood disorder based on SCID interview. The screening procedure was defined as unacceptable if more than 25% of patients failed to complete the PHQ-9 and the HSCL-25. Screening would be deemed inefficient if less than 34% of patients exceed clinical cut-offs on the PHQ-9 or the HSCL-25. Based on an estimated 15% attrition rate, screening would also be deemed inefficient if less than 33% of patients who screened positive for depressive symptoms were diagnosed with a mood disorder. Given the unacceptable (null hypothesis) and acceptable (alternative hypothesis) rates listed in Table I, there will be 89% power to declare the screening tool successful at the 0.07 significance level. It was estimated screening 400 patients would provide adequate power to evaluate the primary endpoint.

Statistical Methods

Descriptive statistics, such as frequencies, mean, and median were used to display patient characteristics and screening and interview data. Specificity and sensitivity were assessed for

each screening tool using the SCID interview to determine depression. ROC curves, specifically area under the curve (AUC), were used to assess the accuracy of each measure in screening for depression, with an AUC=0.5 indicating the accuracy is similar to pure chance while a AUC=1.0 indicates perfect accuracy.

Clinical cut-off scores for depression screening measures

An incomplete screen was defined as 1 unanswered items on the PHQ-9 or 3 unanswered items on the 25-item HSCL-25. A PHQ-9 score 10 or a HSCL-25 score 44 was categorized as a positive screen, per established clinical cut-offs.

Managing severe distress and suicidal ideation

Detailed procedures for the management of patient-reported severe distress or suicidal ideation were included in the protocol and were approved by local IRBs for participating sites. All sites were required to provide a document listing on-site and local psychosocial resources to RTOG Headquarters prior to enrolling any patients, which were maintained on a password-protected web-site established for this study. This provided on-site staff and telephone interviewers with immediate access to referral information for distressed participants. If a participant reported a PHQ-9 score of 20–27 or an HSCL-25 total score of 65–100 during the depression screening, the site was required to document the clinical response and provide RTOG Headquarters with this documentation. Participant reported suicidal ideation on the PHQ-9, HSCL-25, or during a SCID interview mandated an evaluation of risk by site staff or telephone interviewers along with documentation of participant's risk and the clinical response, provided to RTOG Headquarters. Telephone interviewers (SCID interviewers) obtained the participant's location at the beginning of the interview in the event the participant reported risk of self-harm, requiring the interviewer to notify local police. Telephone interviewers had access to the RTOG study-specific web-site in order to access local referral information as needed during study interviews.

RESULTS

463 patients were accrued from May 28, 2009 to March 11, 2011 from 37 sites, including 35 CCOP sites and 2 academic cancer centers. Of the 463 participants, 8 were ineligible (6 were DCIS breast cancer and 2 lacked verifying baseline information) and not included in the analysis. Results are based on 455 participants. Patients' demographic and medical characteristics are presented in Table 2.

Feasibility of Implementing the Screening Procedure

All eligible participants enrolled (n=455) completed all depression screening measures, with no missing items. The 100% completion rate supports the acceptability of depression screening. A total of 27 participants (3.7%) reported highly elevated scores on the PHQ-9 or HSCL-25, requiring a documented clinical response from participating sites. Furthermore, 13 of these 27 patients (2.9%) reported suicidal ideation on the PHQ-9, HSCL-25, or during a SCID interview, requiring evaluation of risk by site staff or telephone interviewers along with documentation of participant's risk and the clinical response.

Depression screening

A total of 75 participants (16.5%) exceeded clinical cut-off scores on depression screening measures. Of these participants, 35 (46.7%) exceeded the clinical cut-off score on both the PHQ-9 and HSCL-25, 6 (8.0%) only exceeded the PHQ-9 cut-off, and 34 (45.3%) only exceeded the cut-off score on the HSCL-25. Descriptive statistics for the PHQ-9, PHQ-2, HSCL-25, and NCCN-DT are presented in Table 3.

SCID-Diagnosed Mood Disorders

A total of 79 SCID interviews were administered within 4 weeks of administration of depression screening measures. SCID interviews were administered to a combined sample of participants who exceeded depression screening cut-offs ($n=42$) and a systematic sample of participants who screened negative ($n=37$) as seen in Table 4. This represents 52.4% of interviews required. Missing interviews were due to inability to contact the patient (26%), patient declining interview (7%), a temporary regulatory hold (12%), and unknown (3%). Among the 79 participants who completed a SCID, of which 42 were positively screened, 16 met criteria for a mood disorder representing 3.5% of the total study sample. A total of 2 participants (2.5%) met criteria for dysthymia, 6 for an adjustment disorder (7.6%), and 9 for major depression (11.4%). One patient was diagnosed with both major depression and dysthymia. No patients were diagnosed with mania, hypomania, or a general medical condition or substance use causing mood-related symptoms.

Sensitivity and specificity of screening measures

Figure 2 illustrates the sensitivity and specificity of the screening measures in detecting any mood disorder. The HSCL-25 had the highest sensitivity rate (0.88) but had a lower specificity rate (0.59). The NCCN-DT has the lowest specificity rate (0.52) with a higher sensitivity rate of 0.80. The PHQ-9 had sensitivity and specificity rates of 0.69 and 0.79, respectively, while the PHQ-2 had sensitivity and specificity rates of 0.63 and 0.86, respectively. As shown in this figure, the PHQ-9 area under the curve (AUC) = 0.85 representing good accuracy in classifying participants as true positives or true negatives. The PHQ-2 also maintained good accuracy (AUC = 0.83) while being a much shorter tool compared to the PHQ-9. As shown in Figure 3, a PHQ-2 cut-off of 3 or 4 maximizes sensitivity and specificity. The HSCL-25 AUC = 0.80, indicating fair-good accuracy. The NCCN-DT AOC = 0.59 indicating poor accuracy in classifying patients with regard to the presence of mood disorders.

Psychosocial Care

Among the 36 respondents who screened positive on the PHQ-9 or HSCL and completed the telephone assessment, 66.7% ($n=24$) reported current care for mood-related concerns. Oncologists and nurses were the most common providers (32%), followed by mental health (17.9%), and primary care providers (15.4%). Counseling on-site (89.8%) or off-site (73.0%), and patient educational materials on managing depression (82.1%) were the most highly preferred psychosocial services. The most common barriers to psychosocial care included daily responsibilities (25.6%), physical symptoms (18.2%), feeling that distress

severity does not warrant psychosocial care (18.0%), and difficulty with time off of work (15.4%).

DISCUSSION

Screening for depression among adults receiving care in community-based radiation oncology settings is highly feasible, as evidenced by the depression screening measure completion rate. This finding was observed even among community-based radiotherapy settings that reportedly do not have distress screening procedures in place. Among a large sample of participants, a total of 16% of participants exceeded clinical cut-off scores on standardized depression screening measures which is consistent with prior findings.²⁴ Upon further assessment, a much lower proportion of patients met DSM-IV criteria for mood disorders. The current results are consistent with the lower-bound estimates of the prevalence of depression from a meta-analysis, which calculated the approximate rates of depression of 5–16% for outpatients.²⁵ Studies that employed a similar methodology in using expert interviewers to define depression estimated a lower prevalence of depression and mood disorders.²⁵ Prevalence estimates from RTOG 0841 must be interpreted cautiously, as this was not designed as an epidemiological study and the low participation rate (53%) in diagnostic interviews may have led to an underestimation of the prevalence of mood disorders.

One of the most compelling findings from this trial was the comparability of the PHQ-9 and the significantly shorter PHQ-2 in accurately categorizing participants with regard to the presence or absence of a current mood disorder. Both the PHQ-9 and the PHQ-2 have good accuracy in discriminating cancer patients with a mood disorder from those who do not meet DSM-IV criteria for a mood disorder, including major depression, dysthymia, and adjustment disorder. Findings suggest the PHQ-2 can be used to screen for mood disorders, without sacrificing psychometric properties of the longer PHQ-9, thus minimizing patient and staff burden. No participants met criteria for bipolar disorder. This finding is timely given the recent trend to incorporate psychosocial care as a “core” cancer care quality indicator and the American College of Surgeons Commission on Cancer distress screening accreditation requirement.^{5,6} The longer 25-item HSCL did not offer any additional precision with regard to accurately classifying participants with regard to the presence or absence of a mood disorder. In contrast, the NCCN-DT has poor accuracy to detect mood disorders. Using the NCCN-DT to detect mood disorders is akin to using a thermometer to quantify a patient’s body weight; the NCCN-DT simply does not accurately measure mood disorders including depression. Previous research has established that the NCCN-DT can adequately detect clinically significant anxiety,²⁶ however, it research has shown that depression, not anxiety, is associated with poorer significant outcomes such as survival. Sites using the NCCN-DT to screen for distress should also administer the PHQ-2 to be sure to capture clinically significant mood disturbances.

The majority of patients who screened positive for mood-related symptoms (70%) reported current care for mood-related concerns. The flip side of this finding is that 30% of participants with elevated symptoms are not currently receiving care. This finding supports the need to implement systematic distress screening with in-depth assessment and/or referral

for participants who screen positive. Cancer center-based oncology providers were identified as the most common sources of psychosocial care, followed by mental health and primary care providers. This is consistent with a strong preference for on-site counseling as the most preferred mode of psychosocial care delivery. The most common patient-related barriers to receiving psychosocial care (daily responsibilities, physical symptom burden) can be addressed through psychosocial care at the point of cancer care delivery, and through utilizing non-traditional strategies for psychosocial care delivery such as eHealth and mHealth approaches.²⁷

Limitations of this study include the low SCID completion rate among participants who screened positive. Missing interviews due to inability to contact the participant may introduce bias, if participants with more severe distress were more difficult to reach. An additional limitation is the disproportionate representation of breast cancer patients and women in this sample, potentially limiting generalizability.

In summary, the PHQ-2 is a feasible approach to screen for mood-related symptoms among cancer patients receiving treatment in community-based radiation oncology practices. Given the widespread use of radiotherapy to treat cancer, the brief and accurate detection of patients experiencing mood disorders in radiation oncology settings can lead to the improved detection and management of distress. The PHQ-2 is an effective tool for identifying cancer patients with mood disorders, is comparable to the longer PHQ-9, and superior to the widely used NCCN-DT.

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Conflicts of Interest: Dr. Wagner reports personal fees from Gilead Inc., outside the submitted work. Dr. Pugh reports grants from Pennsylvania Department of Health (CURE grant), during the conduct of the study.

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Figure 1.
Study procedures

Figure 2.
Receiver Operator Characteristic (ROC) Curve of screening measures

Figure 3.
ROC Curve of PHQ-2

Table 1

Acceptable and Unacceptable Rates for Screening Procedure

	Promising Rates under H_1	Discouraging Rates under H_0	Decision Rule for Declaring Screening Procedure Success
Patients (Pts) registered to trial	$p_0=1.00$	$p_0=1.00$	--
1) Pts completing questionnaires (acceptability)	$p_1=0.80$	$p_1=0.75$	76%
2) Pts screening positive (efficiency I)	$p_2=0.40p_1$	$p_2=0.33p_1$	34%
Pts contacted for diagnostic evaluation	$p_d=0.85p_2$	$p_d=0.85p_2$	--
3) Pts diagnosed as depressed (efficiency II)	$p_3=0.40p_d$	$p_3=0.33p_d$	33%
Probability of declaring screening procedure successful	Power = 0.89 (1 - p_3)	$\alpha = 0.07$ (p_3)	

Note: All 3 decision rules must be met for screening procedure to be considered successful

Table 2

Demographic and medical characteristics

Demographic and medical characteristics (n=455)	
Age (years)	
Median	59
Min - Max	23 – 88
Q1 – Q3	50 – 69
Gender	
Male	156 (34.3%)
Female	299 (65.7%)
Race	
American Indian/Alaska Native	2 (0.4%)
Asian	5 (1.1%)
Black or African American	66 (14.5%)
More than one race	3 (0.7%)
White	379 (83.3%)
Ethnicity	
Hispanic or Latino	15 (3.3%)
Not Hispanic or Latino	431 (94.7%)
Unknown (Individuals not reporting ethnicity)	9 (2.0%)
Psychotropic Medication	
No	392 (86.2%)
Yes	63 (13.8%)
Primary Tumor Site	
Brain	5 (1.1%)
Breast	206 (45.3%)
Colorectal	23 (5.1%)
GI, other	26 (5.7%)
Gynecologic	27 (5.9%)
Lung	45 (9.9%)
Other	118 (25.9%)
Not specified	5 (1.1%)
Stage	
I	164 (36.0%)
II	126 (27.7%)
III	85 (18.7%)
IV	42 (9.2%)
Unknown	38 (8.4%)
Palliative Radiotherapy	
No	419 (92.1%)
Yes	36 (7.9%)
Chemotherapy	

Demographic and medical characteristics (n=455)	
No	335 (73.6%)
Yes	120 (26.4%)
Q1 = first quartile; Q3 = third quartile	

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Table 3

Descriptive characteristics for the PHQ-9, PHQ-2, HSCL-25, and NCCN-DT

Baseline Screening Measures (n=455)	
PHQ-9	
Mean	3.5
Std. Dev.	4.3
Positive	41 (9.0%)
Negative	414 (91.0%)
PHQ-2	
Mean	0.7
Std. Dev.	1.2
Positive	36 (7.9%)
Negative	419 (92.1%)
NCCN-DT	
Mean	2.5
Std. Dev.	2.6
Positive	134 (30.5%)
Negative	305 (69.5%)
HSCL-25	
Mean	34.9
Std. Dev.	9.7
Positive	69 (15.2%)
Negative	386 (84.8%)

Table 4**Screening Procedure Feasibility**

Screening Measures Completed after Registration	
Yes	455 (100.0%)
Results on Screening Measures (PHQ-9/HSCL-25)	(n=455)
Positive for depressive symptoms	75 (16.5%)
Negative for depressive symptoms	380 (83.5%)
Number of SCID Interviews Required – All patients *	(n=150)
Interview completed	79 (52.4%)
Not evaluated, patient contacted, declined interview	10 (6.7%)
Not evaluated, temporary IRB hold on contact attempts	18 (12.1%)
Not evaluated, patient unable to be contacted	38 (25.5%)
Unknown†	5 (3.3%)
Number of SCID Interviews Required – Negative patients	(n=75)
Interview completed	37 (49.3%)
Not evaluated, patient contacted, declined interview	3 (4.0%)
Not evaluated, temporary IRB hold on contact attempts	11 (14.7%)
Not evaluated, patient unable to be contacted	21 (28.0%)
Unknown	3 (4.0%)
Number of SCID Interviews Required – Positive patients	(n=75)
Interview completed	42 (56.0%)
Not evaluated, patient contacted, declined interview	7 (9.3%)
Not evaluated, temporary IRB hold on contact attempts	7 (9.3%)
Not evaluated, patient unable to be contacted	17 (22.7%)
Unknown	2 (2.7%)
Number of SCID Interviews Completed	(n=79)
Patients diagnosed with major depression	16 (20.3%)

* Systematic sample of 20% of negative screen patients were scheduled for interviews (n=75/380) as well as positive patients (n=75).

SCID: Structured Clinical Interview for DSM-IV

PHQ-9: Patient Health Questionnaire, 9 item

HSCL-25: Hopkins Symptom Checklist, 25 item