Depression and Comorbid Panic and Pain in Primary Care Patients

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ABSTRACT

ANGELA M. DEVEAUGH-GEISS: Depression and Comorbid
Panic and Pain in Primary Care Patients
(Under the direction of Suzanne L. West, PhD and William C. Miller, MD, PhD)

Depression is a common and debilitating condition. Though the goal of depression treatment is remission, many patients do not achieve this outcome.[1] This research focused on exploring how two common comorbid conditions, panic and pain symptoms, affect depression treatment outcomes in a primary care setting using data from an open-label longitudinal, comparative effectiveness study of three selective serotonin reuptake inhibitors.[2]

While baseline panic symptoms were not associated with depression outcomes (remission or partial response), persistent panic, or panic symptoms that were present at baseline and month 3, were associated with poorer depression outcomes, particularly remission. Although we used a screening question to assess panic symptoms, the probabilistic sensitivity analysis suggests that the results are robust to varying sensitivity and specificity within a large range of plausible values.

Baseline pain symptoms were associated with worse depression outcomes, with evidence of an incremental response with increasing pain severity. Furthermore, the improvement of pain in the first month of treatment was associated with better depression response. Though there is no available information on the minimal clinically important difference on the Patient Health Questionnaire-15 pain subscale, we explored two different

cut-points and found similar results with each. Furthermore, there was evidence that a more conservative cut-point resulted in a stronger association of pain improvement and depression outcomes, suggesting that even small changes in pain result in improved depression outcomes.

Across all analyses (panic and pain), there was evidence of incremental response, with a stronger association in the remission vs. nonresponse comparison and a weaker association in the partial response vs. nonresponse comparison.

These findings suggest that comorbid panic (particularly persistent panic) and pain symptoms are associated with worse depression outcomes in the maintenance phase of treatment. Furthermore, improvements in pain are associated with improved depression outcomes. Consequently, improvement in panic and pain symptoms may be important for improved depression outcomes and primary care physicians should be attuned to the presence of these symptoms when making treatment decisions.

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LIST OF ABBREVIATIONS

ARTIST	A Randomized Trial Investigating SSRI Treatment
BPHQ	Brief Patient Health Questionnaire
BPS	Bodily Pain Scale
DSM	Diagnostic and Statistical Manual
EMM	Effect measure modifier
FDA	Food and Drug Administration
GAD	Generalized Anxiety Disorder
IPT	Interpersonal therapy
IRB	Institutional review board
MCS	Mental Component Summary
MDD	Major depressive disorder
MDE	Major depressive episode
MOS	Medical Outcomes Study
NA	Not applicable
NCS	National Comorbidity Survey
NCS-R	National Comorbidity Survey-Replication
OCD	Obsessive Compulsive Disorder
OR	Odds ratio

PCP	Primary care provider
PHQ	Patient Health Questionnaire
PTSD	Post traumatic stress disorder
PRIME-MD	Primary Care Evaluation of Mental Disorders
RCI	Reliable Change Index
SAD	Social Anxiety Disorder
SCID	Structured Clinical Interview for DSM-IV
SCL-20	Symptom Checklist-20
SF-36	Short Form-36
SNRI	Serotonin Norepinephrine Reuptake Inhibitor
SSRI	Selective Serotonin Reuptake Inhibitor
STAR*D	Sequenced Treatment Alternatives to Relieve Depression

CHAPTER I

STATEMENT OF SPECIFIC AIMS

Depression is a common and debilitating condition affecting approximately 121 million people worldwide.[3] The goal for depression treatment is remission; however, a large "real world" antidepressant effectiveness trial demonstrated that approximately 30% of patients experienced remission regardless of treatment setting (primary vs. specialty care).[1]

Almost half of the outpatient care for depression is provided by primary care providers (PCPs)[4] and nearly 10% of primary care office visits are depression-related.[5] Additionally, the annual number of antidepressant visits is similar for psychiatrists and PCPs[6] and SSRIs are commonly prescribed in primary care settings.[7] Despite the prevalence of SSRI use in primary care, most of the available studies did not capture information on antidepressant treatment or did not study the effects of SSRIs. Furthermore, the average visit to a PCP lasts about 15 to 20 minutes[8, 9] and treatment for depression must compete with other demands. Therefore, given the time constraints of primary care practice, it is important to explore what factors affect depression treatment outcomes in this setting.

Comorbid anxiety (including comorbid panic disorder) and comorbid pain are common in depressed patients and may lead to poorer treatment outcomes.[10-13] While comorbid anxiety may be more common in depressed patients treated in primary care vs. specialty care, the prevalence of comorbid pain appears to be similar regardless of treatment setting.[10, 14, 15] However, most studies of depression and comorbid panic or pain focus on the treatment of depression in specialty care or clinical trials settings, which lack generalizability to primary care settings or to general clinical practice. This study expanded on previous research by utilizing a large, naturalistic study of depressed primary care patients. The objective of this study was to examine how panic symptoms, pain symptoms, and improvements in pain affect depression outcomes (remission, partial response, or nonresponse) in primary care patients treated for depression with one of three SSRIs (sertraline, paroxetine, or fluoxetine) at month 6, during the maintenance phase of depression treatment.

Specific Aim 1: To determine the effect of panic symptoms on depression treatment outcomes at month 6. Hypothesis 1: Depressed patients with panic symptoms will have worse outcomes than depressed patients without panic symptoms.

Specific Aim 2: To determine the effect of baseline pain symptoms on depression treatment outcomes at month 6. Hypothesis 2: Depressed patients with baseline pain symptoms will have worse outcomes than depressed patients without baseline pain symptoms.

Specific Aim 3: To determine the effect of early improvement in pain (baseline to month 1) on depression treatment outcomes at months 1 and 6. Hypothesis 3: Depressed

patients without early improvement in pain will have worse outcomes at months 1 and 6 than depressed patients with early improvement in pain.

To address these aims, we used existing data from A Randomized Trial Investigating SSRI Treatment (ARTIST).[2] ARTIST was a 9-month longitudinal effectiveness study comparing three SSRIs for the treatment of depression in a primary care setting (n=573). ARTIST included well-validated depression measures including the Mental Component Summary (MCS), the Patient Health Questionnaire-9 (PHQ-9), and the Symptom Checklist 20 (SCL-20). ARTIST also included measures of panic and pain; panic was measured using a screening question from the Brief Patient Health Questionnaire (BPHQ) and pain was measured using the Patient Health Questionnaire-15 (PHQ-15).

CHAPTER II

BACKGROUND AND SIGNIFICANCE

Depression

Diagnostic criteria for Major Depressive Disorder

A Major Depressive Episode (MDE) is characterized by a number of symptoms including depressed mood, loss of interest or pleasure, weight loss or gain, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue or loss of energy, feelings of worthlessness or excessive guilt, inability to concentrate, or recurrent thoughts of death.[16] The DSM-IV (Diagnostic and Statistical Manual of Mental Disorder, Fourth Edition) criteria for an MDE is the presence of 5 or more of these symptoms during the same 2-week period that represents a change from previous functioning and at least one of the symptoms is either depressed mood or loss of interest or pleasure.[16] Major depressive disorder (MDD) is the presence of a single MDE "that is not better accounted for by schizoaffective disorder and is not superimposed on schizophrenia, schizophreniform disorder, delusional disorder, or psychotic disorder not otherwise specified" and "there has never been a manic episode, a mixed-episode, or a hypomanic episode."[16]

Depression is common and debilitating

According to the National Comorbidity Survey-Replication (NCS-R), the lifetime prevalence of MDD in the United States is 16.2%.[17] Depression is not only common, it is

also debilitating. The World Health Organization Global Burden of Disease Study ranked depression the fourth most disabling disease in 1990.[18] Depression is expected to be the second leading cause of disability in the world by the year 2020; today, depression is the second leading cause of disability adjusted life years in those aged 15 to 44.[18]

Primary care is a key setting for the management of depression

Almost 10% of all primary care office visits are depression-related and PCPs provide nearly half the outpatient care for depressed patients.[4, 5] According to the 1995 and 1996 National Ambulatory Medical Care Survey, the annual number of antidepressant visits is similar for psychiatrists and PCPs.[6] However, the average visit to a PCP lasts approximately 15 to 20 minutes[8, 9, 19] and recognition and treatment of depression must compete with other demands.[20-23]

While several studies have shown that depression treated in primary care is different than depression treated in specialty care in terms of severity and presenting symptoms or demographics,[24-26] a direct comparison of the two treatment settings revealed that severity of depression was similar among patients treated in primary care vs. specialty care.[27, 28]

The goal of depression treatment is remission

Regardless of treatment setting, the goal of depression treatment is remission, or absence of depressive symptoms. However, a large "real world" antidepressant effectiveness trial demonstrated that approximately 30% of patients experience remission.[1] Remission rates were similar regardless of treatment setting - primary vs. specialty care. Therefore, in

order to achieve remission, it is important to understand what factors influence depression treatment outcome.

Depression and Comorbid Anxiety

Comorbid anxiety is common in depressed patients

Comorbid anxiety disorder [e.g., generalized anxiety disorder (GAD), obsessive-compulsive disorder (OCD), panic disorder, posttraumatic stress disorder (PTSD), and social anxiety disorder (SAD) (see Table 1)] or anxiety symptoms (symptoms of an anxiety disorder) are common in depressed patients. In the NCS and NCS-R, almost 60% of patients with lifetime MDD had a comorbid anxiety disorder with even more patients experiencing comorbid anxiety symptoms.[13] In depressed patients treated in a primary care setting, GAD and SAD appear to be the most common, although many patients suffer from comorbid panic disorder, which may be the most clinically important comorbid anxiety disorder.[29, 30]

Table 1. Characteristics of five common anxiety disorders[31]

Disorder	Characteristics
GAD	Chronic anxiety, exaggerated worry and tension
OCD	Recurrent, unwanted thoughts (obsessions) and/or repetitive behaviors (compulsions)
Panic Disorder	Unexpected repeated episodes of intense fear accompanied by physical symptoms (e.g., chest pain, heart palpitations, shortness of breath, dizziness, or abdominal distress)
PTSD	Anxiety that can develop after exposure to an event/ordeal in which grave physical harm occurred or was threatened
SAD	Overwhelming anxiety and excessive self-consciousness in everyday social situations

Many studies of depression and comorbid anxiety group the anxiety disorders together rather than looking at the effect of individual anxiety disorders or study patients with depression and high anxiety scores (e.g., patients with high scores on the Hamilton Depression Scale Anxiety/Somatization Factor). When anxiety disorders are grouped, it is impossible to examine the effect of individual anxiety disorders on depression treatment outcomes. When anxiety is defined as a high anxiety score, the focus of the study is on symptoms of anxiety rather than an anxiety disorder. Therefore, we included relevant background information on depression and comorbid anxiety defined as multiple anxiety disorders or anxious depression (depressed patients who report high levels of anxiety). When available, we included information specific to depression and comorbid panic disorder, the focus of the current study.

Anxiety may be more common in primary care vs. specialty care settings

In a large study conducted in both primary and specialty care (Sequenced Treatment Alternatives to Relieve Depression, STAR*D), anxious depression was significantly more common in women, Hispanics, non-single subjects, unemployed subjects, those with less schooling, those with more severe depression and those in primary-care settings; results were the same when the authors controlled for baseline depression severity.[14, 15] The high prevalence of comorbid anxiety in depressed primary care patients, along with the clinical importance of panic disorder, underscores the need to understand the effect of depression and comorbid panic, particularly in primary care patients.

Comorbid anxiety may be associated with poor depression outcomes

In specialty care settings or in population-based studies, there is evidence that depression and comorbid anxiety are associated with more severe depressive symptoms or more depressive symptoms[32-34] though not all studies support this difference.[35-37] Additionally, patients with depression and comorbid anxiety are less likely to experience response or remission, [38-42] have a lower rate of recovery,[33, 43] or have a slower response to treatment. [34, 44, 45] Additionally, the presence of subthreshold anxiety (anxiety that does not meet the DSM criteria for an anxiety disorder) may also lead to worse depression outcomes.[46] While there is no evidence that patients with depression and comorbid anxiety experienced higher rates of relapse/recurrence of their depressive episodes,[37, 45] patients with anxiety remaining at remission of the index episode of depression were found to have a shorter time to relapse/recurrence.[37]

Like patients with depression and comorbid anxiety, patients with depression and comorbid panic have more severe depression,[47-51] however there is some evidence to the contrary.[42] Additionally, patients with depression and comorbid panic may be less likely to experience recovery or experience a slower recovery[38, 42, 45, 48, 51-53] and have a more severe course of depression.[47, 54] In a study of patients visiting primary care or specialty care, depressed patients with comorbid anxiety were less likely to remit in the first year.[43] However, there is some evidence that depression and comorbid panic are not associated with worse depression outcomes.[38, 50] However, there is also evidence that patients with comorbid panic are less likely to respond[42] or experience a longer time to response.[51]

Primary care patients with depression and comorbid anxiety can be difficult to treat

Studies in primary care have evaluated several different interventions for patients with comorbid depression and anxiety with mixed results. Some studies suggest that the presence of comorbid anxiety is associated with greater depressive severity[55] or worse depression outcomes,[56] however, not all studies support a difference.[30] Additionally, patients with depression and comorbid anxiety are less likely to experience response/remission or experience slower recovery.[30, 55, 57, 58] While primary care patients with depression and comorbid anxiety were more likely to experience relapse of their depression, anxiety was not associated with relapse in a regression analysis which controlled for sex, age, chronic disease score, study group and intervention status.[59] Similarly, anxiety symptoms were an important predictor of shorter depression-free time and higher mean severity of depression symptomatology when considered alone, but anxiety was not an important predictor in the multiple regression analysis.[60]

Like depression and comorbid anxiety, studies in primary care settings have examined depression and comorbid panic with mixed results. Both panic attacks and panic disorder are associated with more severe depressive illness and greater disability.[61] Similarly, a lifetime history of panic disorder is associated with more severe depression,[62] greater impairment,[62] and poorer treatment response.[55, 63] However, not all evidence supports a difference in outcomes for patients with depression and comorbid panic vs. depression alone. While comorbid panic was associated with more severe depression, the presence of panic was not associated with response rates after 12 months of treatment[64] and panic was not associated with persistence of depression.[65]

Suicide is common among patients with depression and comorbid anxiety

It has been reported that, in patients with depression, the presence of comorbid panic attacks[66, 67] and lifetime anxiety disorders[68] are associated with an increased risk of suicide. In depressed primary care patients, the presence of comorbid panic disorder or panic attacks are associated with an increased risk of suicidal ideation[69] and patients with both depression and panic disorder have a higher rate of suicidal ideation than patients with either panic disorder or major depression alone.[70] With regard to suicide attempts, patients with both depression and panic disorder have a higher rate than patients with either panic disorder or major depression alone.[67, 71]

Limitations of the available longitudinal data on depression and comorbid anxiety

There are limitations to the available evidence on outcomes for primary care patients with depression and comorbid anxiety. Only three of the longitudinal studies included more than 250 patients[59, 61, 64] and only two of these studies was designed to look specifically at depression and comorbid panic.[61, 64] Furthermore, most of the studies either did not capture treatment information or evaluated treatments that are less commonly used in PC (Interpersonal therapy, nortriptyline). Table 2 presents each longitudinal primary care study along with a summary of the study design and the author's conclusions.

We expanded on the available evidence by utilizing a large sample (n=573) of primary care patients who were treated in a naturalistic manner (patients were randomized to treatment but could have changes and additions to their medication). We

explored outcomes during the maintenance phase of treatment (month 6) and whether adequacy of antidepressant treatment affected the results.

Table 2. Longitudinal studies of depression and anxiety in primary care

First Author, Title, Citation	Study Design (duration), Population, Intervention	Findings	Conclusions and Limitations
Conradi HJ. Prediction of the three-year course of recurrent depression in primary care patients: Different risk factors for different outcomes. Journal of Affective Disorders. 2007; 105: 1-3. 276-271.[72]	Prospective cohort study (3 years) 123 depressed primary care patients (18 to 70 years of age) Usual care vs. Usual care plus low-intensity psycho-educational prevention program	Higher anxiety (as measured by the anxiety scale of the SCL-90) was a predictor of shorter depression-free time and higher mean severity of depressive symptomatology during follow-up.	**Conclusions:** Suggests that depression and comorbid baseline anxiety symptoms are associated with shorter depression-free time and worse treatment outcomes. **Limitations:** Results differed in the multiple regression analysis and the bivariate analysis. Measured anxiety symptoms not the presence of specific anxiety disorders.
McIntyre RS. Residual Anxiety Symptoms in Depressed Primary Care Patients. Journal of Psychiatric Practice. 2007. 13 (2): 125-128.[56]	Prospective cohort study (8 weeks) 454 depressed primary care patients (18 years of age and older) Treatment chosen at the discretion of the PCP	The baseline composite anxiety ratio (anxiety score as measured by 6 Hamilton Depression Rating Scale (HAMD) items divided by total HAMD scores) did not correlate with the probability of depression remission at endpoint. There was an inverse correlation between anxiety ratio at endpoint and probability of remission at endpoint.	**Conclusions:** Suggests that depression and baseline comorbid anxiety symptoms are associated with worse treatment outcomes; improvement in anxiety symptoms appears to be associated with improved depression outcomes. **Limitations:** Only 8 weeks of follow-up, analyses did not control for treatment, completer analysis only.

First Author, Title, Citation	Study Design (duration), Population, Intervention	Findings	Conclusions and Limitations
Alexopoulos GS. Remission in depressed geriatric primary care patients: a report from the PROSPECT study. Am J Psychiatry, 2005. 162: 718-724.[58]	Prospective cohort study (4 months) 215 depressed primary care patients (60 years of age and older) PROSPECT intervention (first step: citalopram or IPT) vs. usual care	Patients with limitations in physical and emotional aspects of functioning, hopelessness, and anxiety were less likely to achieve remission.	**Conclusions:** Suggests that depression and comorbid anxiety are associated with worse treatment outcomes in the elderly. **Limitations**: Small sample size, only 4 months of follow-up, usual care consisted of educational materials (videotape and printed materials on geriatric depression and treatment)
Hegel MT. Impact of comorbid panic and posttraumatic stress disorder on outcomes in collaborative care for late-life depression in primary care. Am J Ger Psychiatry. 13 (1): 48-58.	Prospective cohort study (12 months) 1,801 depressed primary care patients (60 years of age and older) IMPACT intervention (collaborative, stepped-care approach)	Patients with PTSD had a more delayed response compared to patients without PTSD, patients with panic had similar outcomes to patients with no panic.	**Conclusions:** Suggests that depression and comorbid PTSD are associated with worse treatment outcomes in the elderly; there is no evidence that panic leads to worse outcomes. **Limitations**: panic and PTSD based on screening instruments and not clinical diagnoses, studied treatments that are not as commonly used in primary care as SSRIs.
Brown C. Factors associated with symptomatic improvement and recovery from major depression in primary care patients. Gen Hosp Psychiatry, 2000. 22: 242-250.[57]	Prospective, randomized controlled study (8 months) 181 primary care patients (18 to 64 years of age) IPT vs. nortriptyline vs. usual care	Patients with no history of panic or GAD who perceived internal control of health and were randomized to standardized treatment were more likely to recover by month 8 (controlling for baseline depression severity). Anxiety was not a predictor of recovery for patients treated with nortriptyline, although it was with IPT.	**Conclusions:** Suggests that depression and comorbid anxiety are associated with worse treatment outcomes. **Limitations:** small sample size, studied treatments that are not as commonly used in primary care as SSRIs.

First Author, Title, Citation	Study Design (duration), Population, Intervention	Findings	Conclusions and Limitations
Gaynes BN. Does a coexisting anxiety disorder predict persistence of depressive illness in primary care patients with major depression? Gen Hosp Psychiatry. 1999. 21: 158-167.[30]	Prospective cohort study (12 months) 85 primary care patients (18 to 64 years of age) who screened positive for depression No intervention	The risk of depression at month 12 (persistent depression) was 44% higher in patients with comorbid anxiety. There was no difference in baseline depression severity.	**Conclusions**: Suggests that depression and comorbid anxiety are associated with worse treatment outcomes. **Limitations**: Small sample size, did not capture treatment for all patients.
Lecrubier Y. Panic and depression: a worldwide primary care perspective. Int Clin Psychopharm. 1998. 13 (suppl 4): S7-S11.[61]	Cross-sectional study with follow-up at 3 and 12 months (3-12 months) 5,447 primary care patients (15 to 65 years of age) No intervention	Comorbid panic disorder and depression was associated with greater depressive severity at baseline and more disability days than those with either disorder alone. Similar results were seen for patients with depression and panic attacks not reaching criteria for panic disorder.	**Conclusions:** Suggests that depression and comorbid panic disorder and panic attacks are associated with greater depressive severity and disability than either alone. **Limitations:** Results appear to be based on cross sectional data only; however, there was a low response rate at month 12 (62%).
Lin EH. Relapse of depression in primary care rate and clinical predictors. Arch Fam Med. 1998. 7: 443-449. [59]	Prospective cohort study (19 months) 251 primary care patients (18 to 80 years of age) with major depression Antidepressant medication	Significantly more patients who relapsed had a history of GAD/panic disorder; anxiety was not a significant predictor of relapse in the logistic regression model (the 2 main predictors were persistence of depressive symptoms and a history of ≥2 depressive episodes or chronic mood symptoms for 2 years).	**Conclusions**: Provides some evidence that anxiety (GAD/panic) is associated with relapse. **Limitations**: Small sample size, no details about medication.

First Author, Title, Citation	Study Design (duration), Population, Intervention	Findings	Conclusions and Limitations
Brown C. Phenomenology and severity of major depression and comorbid lifetime anxiety disorders in primary medical care practice. Anxiety. 1996. 2: 210-218.[62]	Prospective, randomized controlled study (Follow-up undefined) 276 primary care patients (age range undefined) with major depression IPT vs. nortriptyline vs. usual care	Panic disorder was associated with greater depressive severity in patients with MDD (with or without GAD). Psychosocial functioning was also impaired in patients with MDD and panic disorder vs. MDD alone. Depressed patients with panic disorder differed from depressed patients with or without GAD in somatic symptoms, functional impairment, suicidality, and mood disturbance but not on cognitive symptoms or depression.	**Conclusions**: Suggests that depression and comorbid anxiety, and panic in particular, are associated with greater depression severity and greater impairment in a number of different domains. **Limitations**: Small sample size; studied treatments which may not be as commonly used in primary care as SSRIs.
Brown C. Treatment outcomes for primary care patients with major depression and lifetime anxiety disorders. Am J Psychiatry. 1996. 153 (10): 1293-1300.[55]	Prospective, randomized, longitudinal, controlled study (8 months) 157 primary care patients (18-64 years of age) with major depression IPT vs. nortriptyline	Both treatments were effective for the treatment of depression. Lifetime panic disorder was associated with longer time to recovery and lack of response to treatment.	**Conclusions**: Suggests that depression and comorbid anxiety, and panic in particular, are associated with worse treatment outcomes. **Limitations**: Small sample size; studied treatments which may not be as commonly used in primary care as SSRIs.
Katon W. The predictors of persistence of depression in primary care. Journal of Affective Disorders. 1994. 31:81-90.[65]	Prospective cohort study (4 months) 164 depressed primary care patients (18 to 75 years of age) Not Applicable (NA)	Symptoms of panic disorder were not a predictor of persistent depression.	**Conclusions:** Suggests that symptoms of panic disorder may not be associated with depression treatment outcomes. **Limitations**: Small sample size, panic disorder determined using screening questions; the model did not control for treatment.

First Author, Title, Citation	Study Design (duration), Population, Intervention	Findings	Conclusions and Limitations
Zung WWK. The comorbidity of anxiety and depression in general medical patients: a longitudinal study. J Clin Psych. 1990. 61 (supp 6): 77-80.	Prospective, cohort study (12 months) 112 depressed males in a general medical practice (age range not presented) NA	Depressed patients who improved (as measured by the Zung Self-Rating Depression Scale) had a decrease in their anxiety symptoms (as measured by the Zung Self-Rating Anxiety Scale). Depressed patients who had a worsening of depressive symptoms also experienced a worsening of anxiety symptoms.	**Conclusions:** Suggests that improvement in anxiety symptoms accompanies improvement in depressive symptoms. **Limitations:** While follow-up continued for 12 months, it is unclear what time point is used for the calculation of the change scores for depression and anxiety.

The Overlap of Depression and Anxiety

There is some symptom overlap in depression and anxiety

Whether depression and anxiety are distinct disorders or clinical variants of the same disorder has been debated for more than 30 years. While the early literature (1970s and 1980s) supported depression and anxiety as separate entities, some of the more recent literature suggests that anxiety and depression should be considered together because of the significant comorbidity of both disorders.[73] However, the recent psychiatric literature also suggests that there are symptoms specific to each disorder, lending credence to diagnostic separation between the two disorders.[74] Anxiety disorders tend to precede depressive disorders, which lends support to the conditions as separate disorders rather than an epiphenomenon.[75]

A recent review of the genetic epidemiology literature related to the comorbidity of anxiety and depression revealed 23 twin studies and 12 family studies.[75] Middeldorp et al. concluded that anxiety disorders and major depressive disorder are distinct entities rather than "alternative phases of one disorder."[75] The comorbidity between anxiety disorders and depression is explained in part by overlapping genetic etiological factors.

The Treatment of Depression and Anxiety

SSRIs and Serotonin Norepinephrine Reuptake Inhibitors (SNRIs) are indicated for the treatment of both depression and anxiety

There are a number of SSRIs indicated for the treatment of depression including fluoxetine, paroxetine, sertraline, fluvoxamine maleate, citalopram, and escitalopram oxalate, many of which are also indicated for the treatment of anxiety disorders (Table 3). For

patients who have depression with comorbid anxiety, some clinicians suggest that treatment should begin with monotherapy using either an SSRI or SNRI such as duloxetine or venlafaxine as these agents are effective in the treatment of both disorders.[76] In addition, the use of a single agent can minimize adverse effects that may be associated with dual therapy.[76]

Table 3. Approved indications for SSRIs/SNRIs*

SSRI/SNRI	Depression	Panic Disorder	SAD	OCD	GAD	PTSD
Citalopram [77]	√					
Escitalopram [78]	√				√	
Fluoxetine [79]	√	√		√		
Fluvoxamine [80]	√			√		
Paroxetine [81]	√	√	√	√	√	√
Sertraline [82]	√	√	√	√		√
Venlafaxine [83]	√		√		√	
Duloxetine [84]	√				√	
* SAD=seasonal affective disorder, OCD=obsessive compulsive disorder, GAD=generalized anxiety disorder, PTSD=posttraumatic stress disorder						

SSRIs are commonly prescribed by PCPs

Approximately 65% of antidepressant prescriptions in primary care are for SSRIs SSRIs.[7] Other newer antidepressants (bupropion, mirtazapine, nefazadone, and venlafaxine) accounted for only 17% of antidepressant prescriptions.[7] Many of the SSRIs and SNRIs are indicated for the treatment of both depression and anxiety (including panic disorder for fluoxetine, paroxetine, and sertraline, see Table 3). Given the Food and Drug Administration (FDA) approved indications for the SSRIs, along with the prevalence of SSRI use in primary care, it is important to understand the effect of depression and comorbid panic disorder in primary care patients treated with SSRIs.[7]

Depression and Comorbid Pain

Comorbid pain symptoms are common in depressed patients

More than 50% of depressed patients experience comorbid pain including, but not limited to, headache, back pain, chest pain, gastrointestinal discomfort, and other body aches[10, 11, 85, 86] and the prevalence of pain is unrelated to the study setting (primary vs. specialty care).[10] While some suggest that physical symptoms should be considered as an important part of depression and there are many symptoms of depression and pain that overlap (insomnia, fatigue, psychomotor agitation/retardation, etc.), the DSM-IV criteria for a depressive episode includes only a few somatic symptoms (e.g., fatigue, sleep disturbances).[87] In fact, depression may often go unrecognized when it presents mainly as physical symptoms.[88] There is evidence that depression is a risk factor for pain and that pain leads to development of depression.[87]

Comorbid pain is associated with poor depression outcomes

Data from the Epidemiologic Catchement Area Study,[89] the Canadian general population,[90] and a random sample of health maintenance organization members in Michigan[91] support an association between depression and abdominal pain, chronic back pain, or migraine, respectively. However, a Swedish-based population study found no association between lifetime migraine and depression in women aged 40-74 years of age.[92] Additional epidemiologic evidence has demonstrated that the presence of pain complaints (e.g., abdominal pain, headache pain, back pain, chest pain, and facial pain) are associated with more depression severity[93, 94] as well as the duration[95] and course[94] of the depressive episode.

Clinical trials have demonstrated that patients who experienced improvements in pain also experienced higher depression remission rates[96] and that pain is associated with longer time to remission of recurrent depression.[97] In an inpatient study of depression and pain, depressed nonresponders reported greater pain levels at baseline and at 10 days of follow-up.[98] Furthermore, almost all depressed patients with residual symptoms after partial remission also had mild to moderate physical symptoms.[99] However, another clinical trial of late-life depression did not find any association of pain with time to depression response or with suicidality.[100]

Primary care patients with depression and comorbid pain can be difficult to treat

While population-based surveys have demonstrated that baseline pain is associated with greater depression severity, few studies have evaluated the effect of pain on depression treatment outcomes in primary care settings.[10] Longitudinal evidence

support that pain improvement is associated with a reduction in depressive symptoms and that patients without improvement in pain are less likely to experience remission.[101-103]

The effects of baseline pain and changes in pain were also evaluated in ARTIST, the same dataset that was used for the current project. The ARTIST study is described in more detail in Chapter 3. Bair and colleagues reported that pain severity was associated with baseline depression severity and that having pain at baseline was a predictor of depression treatment response at 3 months of treatment.[104] Pain symptoms decreased during the first month of treatment and then remained fairly constant from month 1 to month 9.[105] Patients who experienced depression remission or partial response at months 1 and 3 had significantly greater improvement in their pain symptoms than nonresponders. The difference in pain improvement was similar for patients experiencing remission and partial response. It is important to note that the analyses did not control for anxiety symptoms, and did not take treatment dose, duration, or changes to medication into account.

Limitations of the available longitudinal studies of depression and comorbid pain

There are several limitations to the available evidence. Only two longitudinal studies focused on pain in depressed patients (as opposed to depression in patients with pain).[104, 105] Two additional studies focused on the presence of depression in patients seeking treatment for pain in a primary care setting.[101, 103] Table 4 presents each longitudinal, primary care study along with a summary of the study design and the author's conclusions.

Table 4. Longitudinal studies of depression and pain in primary care

First Author, Title, Citation	Study Design (duration), Population, Intervention	Key Findings	Conclusions and Limitations
Bair MJ. Impact of pain on depression treatment response in primary care. Psychosom Med. 2004. 66 (1): 17-22.[104]	Prospective, randomized, clinical trial (ARTIST) (9 months) 573 clinically depressed patients (≥18 years of age) Paroxetine, sertraline, fluoxetine	69% of depressed patients had baseline pain. ORs for poor depression response at month 3 were 1.5 (mild pain), 2.0 (moderate pain), and 4.1 (severe pain) (all compared to no pain).	**Conclusions**: Suggests that pain symptoms are common in depressed patients; severity of pain is associated with depression treatment response after 3 months of treatment. **Limitations**: Only evaluated depression treatment outcomes after 3 months of treatment; analyses did not control for the presence of anxiety.
Greco T. The outcome of physical symptoms with treatment of depression. J Gen Intern Med. 2004. 19 (8): 813-818.[105]	Prospective, randomized, clinical trial (ARTIST) (9 months) 573 clinically depressed patients (≥18 years of age) Paroxetine, sertraline, fluoxetine	Pain symptoms decreased during the first month of treatment and then remained fairly constant through month 9. Patients who experienced partial depression response and remission had greater improvement in pain than patients who were nonresponders.	**Conclusions**: Suggests that pain symptoms are common and tend to improve in the first month of treatment with an SSRI. **Limitations**: Only evaluated the effect of depression treatment outcomes on pain symptoms at months 1 and 3; analyses did not control for the presence of anxiety.
Von Korff M. The relationship between pain and depression. Br J Psychiatry. 1996. 30: 101-108.[102]	Review of epidemiologic studies (population based and primary care) Unknown study design, results from poster by Cherkin et al., which is summarized, in this review article. No Intervention.	Depression scores appear to decrease as pain improves; depression scores appear to be lower in patients without pain compared to those with pain.	**Conclusions**: Suggests an association between chronic pain and depression. **Limitations**: This is a review article of studies of depression and pain. The studies focus on depression levels among patients with pain rather than pain among patients with depression.

First Author, Title, Citation	Study Design (duration), Population, Intervention	Key Findings	Conclusions and Limitations
Von Korff M. Back pain in primary care: outcomes at 1 year. Spine. 1993. 18: 855-862.[101]	Prospective cohort study of patients in the Group Health Cooperative of Puget Sound Health Maintenance Organization (12 months) 1128 primary care patients who sought treatment for back pain (18 to 75 years of age) No Intervention	Patients with a higher pain level at baseline tended to have a higher level of depression. Back pain outcome also appeared to be associated with depression level at follow-up, i.e., patients with back pain improvement had lower depression levels at follow-up.	**Conclusions**: Suggests that improvement in pain is associated with improvement in depression. **Limitations**: The focus was on depression levels among patients with back pain rather than on pain levels in depressed patients.
Von Korff M. Grading the severity of chronic pain. Pain. 1992. 50: 133-149.[103]	Prospective, longitudinal study of patients in the Group Health Cooperative of Puget Sound Health Maintenance Organization (12 months) 2389 patients with back pain headache, or temporomandibular disorder No Intervention.	Chronic pain grade was significantly associated with depression both at baseline and 1-year follow-up.	**Conclusions**: Suggests an association between chronic pain and depression. **Limitations**: The focus was on depression levels among patients with pain (back pain, headache, or TMD disorder) rather than on pain levels in depressed patients.

Depression, Anxiety, and Pain

There is overlap of Depression, Anxiety, and Pain

There is sparse evidence of an association between depression, anxiety, and pain (e.g., migraine).[106-108] The association of anxiety and pain appears to be independent of other comorbid mental disorders including depression.[109, 110] Furthermore, the relationship between anxiety[111] and chronic pain (e.g., arthritis, migraine) or panic[111, 112] and chronic pain may be even stronger than the relationship between depression and chronic pain. [111, 112] In a large cross-sectional study (n=5,808) of primary care patients with MDD, the prevalence of panic disorder was significantly higher in patients with MDD and chronic disabling pain than other respondents.[113] By contrast, a large Swedish study found no association between lifetime migraine and panic disorder in women aged 40 to 74 years of age.[92]

Limitations of the available longitudinal evidence on depression, panic, and pain

Overall, few studies are available which explore depression, panic, and pain despite the strong link between depression and panic or depression and pain, and the perhaps even stronger link between panic and pain. Furthermore, the available evidence is limited to cross sectional studies. Therefore, the proposed study will provide important information on how comorbid panic and pain symptoms affect depression treatment outcomes in a primary care population.

CHAPTER III

A RANDOMIZED TRIAL INVESTIGATING SSRI TREATMENT (ARTIST)

The current study used data from ARTIST. This section focuses on ARTIST, including the study design, study population, and information about the rating scales used. It also provides information about prior research that utilized the ARTIST dataset (including the original publication).

Overview of Study Design

ARTIST was a 9-month randomized, open-label, effectiveness clinical trial comparing three SSRIs: fluoxetine, paroxetine, or sertraline (n=573) in primary care using patients from two primary care research networks.[2] The first primary care research network was a not-for-profit voluntary organization of more than 10,000 family practitioners, internists, and pediatricians throughout the country [The Primary Care Network (n=51 study practitioners)]. The second primary care network was an academic site management organization within the Duke University Health System made up of over 150 family physicians, internists, and pediatricians who participate in clinical outcomes trials [The Duke Primary Care Research Consortium (n=26 study practitioners)].

Study Population

The ARTIST study population included patients aged 18 years and over who were visiting network primary care doctors between April and November 1999; the visits were not required to be depression related. If the patient was diagnosed with depression and the PCP deemed him/her appropriate for SSRI treatment, further enrollment criteria were assessed including access to a telephone. Exclusion criteria included: being actively suicidal; current treatment or treatment within the past two months with an SSRI; taking a non-SSRI antidepressant either for depression or for a non-depressive disorder; active substance abuse; pregnant or breastfeeding; cognitive impairments (e.g., dementia or psychosis); inability to read, speak, or write English; or a terminal illness. At the start of the trial, patients were randomly assigned to open-label treatment with one of three SSRIs (sertraline, paroxetine, fluoxetine).

A total of 601 patients provided informed consent and were randomized, 573 completed the baseline assessments, and 455 patients (79%) completed 9 months of treatment. The pre-baseline dropouts were similar to the patients who remained in the study except they had slightly less severe depression.[2]

Rating Scales

Depression measures included the PHQ-9, the SCL-20, and the Primary Care Evaluation of Mental Disorders (PRIME-MD) depression module.

In the original ARTIST study, the SCL-20 was one of the scales used to measure depression treatment outcome at each visit (baseline and months 1, 3, 6, and 9).[114] The SCL-20 is a modified subscale of the Hopkins Symptom Checklist and Brief Symptom

Inventory and has been shown to detect differences in severity among treatment groups in primary care trials.[115-117] The SCL-20 is made up of 20 questions about how distressed ("not at all", "a little bit", "moderately", "quite a bit", or "extremely") patients were by various symptoms during the past 4 weeks. The items are scored from 0 to 4 and averaged to provide an overall severity from 0 to 4, with a score of 4 indicating more severe depression.[118] The scale has been used in many primary care studies and has been shown to have similar responsiveness to the Hamilton Depression Rating Scale and the Inventory of Depressive Symptomatology.

Other psychological measures included the three anxiety screening questions from the BPHQ, the PHQ-15, and the Short Form-36 (SF-36) bodily pain subscale (BPS). SSRI compliance, current antidepressants, reasons for antidepressant change, and adverse effects were assessed at each of the post-baseline visits. The schedule of visits for selected study measurements relevant to the proposed analyses is provided in Table 5.

Table 5. Schedule of visits and measures for the ARTIST study through month 6

Measure	Baseline	Month 1	Month 3	Month 6
Demographics	X			
Medications		X	X	X
SCL-20	X	X	X	X
3 anxiety questions from BPHQ	X		X	
SF-36 BPS	X		X	
PHQ-15 pain scale	X	X	X	X

In addition to measures of depression, pain, and anxiety, ARTIST also captured a number of other covariates, including demographic and other clinical characteristics,

psychosocial measures, social function, work function, health-related quality of life, medication use, and healthcare utilization (Table 6).

Table 6. Covariates captured in ARTIST

Demographics and Clinical Characteristics
Age
Race
Sex
Alcohol Use/Problems with alcohol
Psychological Measures
Positive well-being scale from the RAND Medical Outcomes Study (MOS) questionnaire
Hopefulness scale from the Health Outcomes Study Questionnaire
Somatization severity scale from the PHQ
Disposition (self-esteem) scale from the Health and Daily Living Form
Social Function
SF-36 social functioning scale
Quality of Social Interaction scale
Quality of Close Relationships Scale
Work Function
Work Limitations Questionnaire
Questions about work effectiveness and impaired work functioning
Health-related Quality of Life
SF-36 physical functioning scale
SF-36 role-physical scale
SF-36 bodily pain scale
SF-36 general health perceptions
SF-36 vitality scale
Medical Outcomes Study (MOS) concentration and memory scale
MOS sleep scale
MOS sexual functioning scale
Medication Use
SSRI randomized
Prior Use of Antidepressants
SSRI compliance
Current antidepressant use
Changes in antidepressant use
Adverse effects
Healthcare Utilization
Clinic, emergency department, and hospital use (including visits to a mental health professional)

ARTIST Results

Overall, the three SSRIs (fluoxetine, paroxetine, sertraline) were similar in all measures including improvement of depression as measured by the MCS score.[2] At month 9, mean change from baseline in MCS scores were +15.8 for paroxetine-treated patients, +15.1 for fluoxetine treated patients, and +17.4 for sertraline-treated patients. The three treatment groups were also similar in mean change from baseline in SCL-20 score: -0.82 for paroxetine-treated patients, -0.85 for fluoxetine treated patients, and -0.99 for sertraline-treated patients. Rates of depression recovery (defined by an MCS score greater than or equal to 40) at Month 9 were 81%, 77%, and 84% for paroxetine, fluoxetine, and sertraline patients, respectively. When recovery was defined as an SCL-20 score of 1.0 or less at Month 9, 69%, 67%, and 74% of patients, respectively, experienced recovery. The treatment groups were also similar in the numbers and types of adverse effects reported.

Response, partial response, and nonresponse in ARTIST

Corey-Lisle et al. evaluated response, partial response, and nonresponse after 6 months of treatment.[119] Using the reliable change index (RCI) to define a clinically meaningful response, SCL-20 change scores were not clinically meaningful unless the change was greater than or less than 12.3.[119] Remission was defined as meeting the RCI criteria and having a score of 6 or less on the SCL-20 and partial response was defined as meeting the RCI criteria and experiencing a >50% change from baseline in SCL-20 score. Patients were considered non-responders if they did not meet the minimum RCI criteria.

At month 6, using the criteria above, 109 patients (22.6%) were responders, 152 were partial responders (31.5%) and 221 were nonresponders (45.9%). Nonresponders were older than responders and partial responders; patients who responded were less likely to have double depression or suicidal ideation than partial responders or nonresponders. Age, diagnosis, worse physical functioning, and lower energy level were all predictors of response. Anxiety symptoms (symptoms of panic disorder and GAD) were not evaluated as potential predictors of nonresponse.

Baseline pain and depression outcomes in ARTIST

As described briefly above (Background and Significance), Bair et al. evaluated the effect of pain at baseline, defined using both the SF-36 BPS and the PHQ-15 pain scale, on depression outcomes.[104] Pain was categorized (none, mild, moderate, severe) using both the SF-36 and the PHQ-15. Severity of pain, as measured by the SF-36 pain intensity items, was associated with baseline depression severity. Patients with severe pain had higher SCL-20 scores than patients with moderate or mild pain (1.91 vs. 1.76 and 1.61, respectively) while patients with no pain had the lowest SCL-20 scores (1.48). Pain severity, as measured by both the SF-36 and the PHQ-15, was a predictor of depression outcomes in both the logistic regression model where depression was measured as a dichotomous outcome and in the linear regression model where depression outcomes was defined as a continuous variable (change from baseline at month 3 in SCL-20 score). Both the logistic and linear regression models controlled for age, gender, race, SSRI, clinic site, treating physician, non-pain somatic symptoms, and baseline SCL-20 depression score; the strongest predictor was baseline depression severity.

Prevalence of physical symptoms and the outcome of physical symptoms in ARTIST

Greco et al. evaluated the prevalence of physical symptoms as well as the effect of physical symptoms on health related quality of life and the outcome of physical symptoms over 9 months of treatment.[105] Between 30-50% of patients reported one or more of the 14 pain symptoms at baseline with 10-20% of patients reporting that the pain symptoms were severe. Only a small percentage (<15%) of patients reported new physical symptoms, i.e., physical symptoms that were not present at baseline but began during the study. The prevalence of pain symptoms decreased during the first month of treatment and then remained fairly constant from Month 1 to Month 9.

Patients who experienced depression remission (an SCL-20 score <0.5 after 3 months of antidepressant treatment) or partial response (>50% improvement in SCL-20 score with a final score >0.5) experienced greater improvements in pain symptoms than nonresponders (patients who had neither an SCL-20 improvement of greater than 50% nor an SCL-20 score less than 0.5) at Months 1 and 3 ($p<0.001$). There was no difference in pain improvement between patients who achieved depression remission or partial response. This study did not include an analysis of the effect of panic symptoms as a potential confounder or effect measure modification (EMM), but this was not the primary focus of their study.

The current study expanded on this research by evaluating how baseline pain and early improvement in pain affect depression outcomes during the maintenance phase of treatment (month 6). Additionally, we explored whether panic was a confounder or EMM of the relationship between pain and depression outcomes. Examining outcomes at

month 6 is important since this is a critical time for depression relapse, and adverse prognostic factors such as pain may be particularly salient in predicting relapse.

CHAPTER IV

STUDY OVERVIEW

This section describes the study design and study population of the current study.

Study Population

The study population consisted of subjects who participated in ARTIST (described in detail in Chapter 3).

Of the 573 patients randomized to treatment, 569 had information about baseline panic symptoms. Over one-third (35%) of the 569 patients reported baseline panic symptoms (n=199) and 12% reported persistent panic symptoms (n=67)(Table 7). Almost all (99%) of the randomized patients had baseline pain information (n=572) and more than three quarters (79%) had pain symptoms (mild, moderate, or severe) (Table 7).

Table 7. Prevalence of baseline panic, persistent panic, and pain

	n (%)
Panic	
Baseline panic	
No	370 (65%)
Yes	199 (35%)
Missing	4 (<1%)
Persistent panic	
No	428 (75%)
Yes	67 (12%)
Missing	78 (14%)
Pain	
PHQ-15 Pain	
None	114 (20%)
Mild	190 (33%)
Moderate	165 (29%)
Severe	103 (18%)
Missing	1 (<1%)
SF-36 Pain	
None	114 (20%)
Mild	190 (33%)
Moderate	165 (29%)
Severe	103 (18%)
Missing	1 (<1%)

Study Measures

We used the SCL-20, to measure depression, the three anxiety screening questions from the BPHQ to measure symptoms of panic disorder and GAD, and both the PHQ-15 pain subscale and the SF-36 BPS to measure pain. The schedule of visits and study measurements relevant to the proposed analyses are provided in Table 5.

Measurement of Outcome: Depression Treatment Response

For the proposed study, the outcome was depression treatment response, defined as a categorical variable (remission, partial response, and nonresponse) using the SCL-

20.[114] Remission was defined as an SCL-20 score ≤ 0.5; partial response was defined as ≥ 50% improvement in SCL-20 score but not to a level of ≤ 0.5. Nonresponse was defined as patients who do not meet either of these criteria. Nonresponse was the referent level for all analyses. The SCL-20 is described in greater detail in Chapter 3.

Measurement of Exposure: Symptoms of Panic Disorder (Specific Aim 1)

One of the exposures of interest was symptoms of panic disorder (measured at baseline and month 3), based on the single panic question from a three-question anxiety screening instrument:

"During the past month, have you often been bothered by…

1. nerves or feeling anxious or on edge
2. worrying about a lot of different things
3. **have you had an anxiety attack (suddenly feeling fear or panic)?"**[120]

For the proposed analyses, participants who answered "yes" to this panic question (question 3 above) at baseline were considered to have symptoms of panic disorder.

This question has demonstrated good sensitivity and specificity in a population of non-depressed patients attending a clinic where the prevalence of current panic disorder was 8.8%. In this study, the sensitivity and specificity (and associated 95% confidence intervals) were 93% (81%-99%) and 78% (74%-82%), respectively.[121] Analyzing data from the 1000 primary care patients evaluated in the original PRIME-MD[32] study where the prevalence of current panic disorder was 3.6%, we found similar operating characteristics for the panic question. With the PCP's diagnosis (which uses a structured DSM-IV based interview in the PRIME-MD Clinician Evaluation Guide) as the reference

standard, the sensitivity and specificity of the panic question were 100% and 91%, respectively. With the mental health professional's independent diagnosis (using the telephone-based SCID) as the reference standard, the sensitivity and specificity of the panic question were 86% and 92%, respectively.

Measurement of Exposure: Symptoms of Pain (Specific Aim 2)

Pain was measured using the PHQ-15 at baseline and months 1, 3, and 6 and the SF-36 at baseline and month 3.[122] We focused primarily on the PHQ-15.

Pain, the second exposure of interest, was measured using the pain subscale of the PHQ-15[122] at baseline and months 1, 3, and 6. The PHQ-15 evaluates 15 different physical symptoms including 5 specific pain symptoms (headache, back pain, limb or joint pain, abdominal pain, and chest pain) with each pain item scored from 0 ("not bothered at all") to 2 ("bothered a lot"). Scores on the five specific pain items are summed to form a composite pain score (0 to 10) with higher scores indicating more pain. A score of 0-2 indicates no pain, 3-4 indicates mild pain, 5-6 indicates moderate pain, and 7-10 indicates severe pain.[104] The validity of the PHQ-15 has been demonstrated in general internal medicine and family practice clinics as well as obstetrics-gynecology clinics.[122]

The SF-36 bodily pain subscale includes two items, which address pain severity and pain interference; the overall score ranges from 0 to 100 (with 100 indicating best health status). The SF-BP is a validated tool that is commonly used in psychiatric research.[123] For the current analysis, we focused on the single pain severity question. For the purposes of this analysis, pain was categorized as follows: "none" or "very mild" = none, "mild" = mild, "moderate" = moderate, and "severe" or "very severe" = severe pain.

For the proposed analyses, we considered pain as a dichotomous variable (none/mild, moderate/severe) and a categorical variable (none, mild, moderate, or severe pain).

Measurement of Exposure: Improvement in Pain (Specific Aim 3)

Early pain improvement was defined as ≥ 3 point change from baseline to month 1 in the PHQ-15 pain score.[122] A 3-point change was used because it reflects the mean change from baseline to endpoint for patients treated with extended-release venlafaxine in anxious and/or depressed patients with multisomatoform disorder.[124] Furthermore, a 3-point improvement in pain is approximately equal to a change in pain level when pain is categorized as none, mild, moderate, or severe using the PHQ-15 pain subscale. To explore how sensitive the results were to our choice of pain change cut-off, we explored the final regression model with pain improvement defined as ≥ 2-point change in pain score.

Covariates of Interest

As described in Chapter 3, ARTIST captured demographic and other clinical characteristics, psychological measures, social function, work function, health-related quality of life, medication use, and healthcare utilization.

For the current study, we considered age (measured at baseline), race (baseline), sex (baseline), SSRI randomized (baseline), prior use of an antidepressant (baseline), alcohol use (baseline), and problems with alcohol (baseline, months 1, 3, and 6) as potential confounders or effect measure modifiers (EMM).

Comprehensive antidepressant information was captured (both the name of the medication and its dosing), including changes made to the treatment over the course of the study. We evaluated adequacy of antidepressant treatment in two ways. First, treatment was defined as adequate (treatment at month 6 above the usual recommended minimum dose [Table 8]) or inadequate (no treatment or treatment at month 6 below the minimum usual recommended dose) based on treatment at the month 6 visit only. We also explored adequate treatment over the initial 6 months of the study. Adequate treatment over 6 months was defined as treatment at each visit above the usual recommended dose range with no gaps in treatment greater than 2 weeks whereas inadequate treatment over 6 months was defined as treatment at any visit below the recommended dose range or intermittent treatment (gaps in treatment greater than 2 weeks).

Table 8. Minimum usual antidepressant dose[125]

Generic Name (Trade Name)	Minimum Usual Daily Dose
Amitriptyline (Elavil®)	150mg
Bupropion (Wellbutrin®)	300mg
Citalopram (Celexa®)	20mg
Fluoxetine (Prozac®)	20mg
Mirtazapine (Remeron ®)	15mg
Nefazadone (Serzone®)	300mg
Paroxetine (Paxil®)	20mg
Sertraline (Zoloft®)	50mg
Trazadone (Desyrel®)	300mg
Venlafaxine (Effexor®)	125mg

Abbreviations: milligrams (mg)

Because treatment of pain may affect our results, we also explored prior treatment with pain medications. The pain medications reported at baseline included: non-steroidal anti-inflammatory drugs (ibuprofen, naproxen, Piroxicam®, Celebrex®, Vioxx®,

Voltaren®, Lodine®, Relafen®, Daypro®), Tylenol®, aspirin, migraine/tension headache medications (Midrin®, Imitrex®), arthritis medications (Enbrel®), and other pain medications and muscle relaxants (including Ultram®, Vicodin®, Percocet®, Robaxin®, Valium®, Flexeril®, Skelaxin®, Soma®, Lortab®, Oxycontin®, MS Contin®, Fioricet®, Tylenol #3 with Codeine® and Tylox®). No information about pain medication over the course of the study was available.

Additionally, symptoms of panic disorder was considered a potential confounder or EMM for specific aims 2 and 3. We also controlled for baseline pain severity (measured as a continuous covariate) for specific aim 3, because we were exploring improvement in pain based on a change score (baseline to month 1).

All models included baseline depression severity.

Data Acquisition

Permission to use the ARTIST data was obtained from Dr. Ralph Swindle, Senior Research Scientist in Outcomes Research at Eli Lilly and Company and Dr. Kurt Kroenke, Research Scientist at The Regenstrief Institute and Professor of Medicine at Indiana University School of Medicine.

CHAPTER V

DATA ANALYSIS METHODS

Data Transformations and Basic Analysis Methods

To ensure accurate characterization of the relationships, we began with exploratory analysis and univariate descriptive analysis before progressing to multivariate analysis. All analyses were completed using SAS version 9.1 (SAS Institute, Cary, NC).

Because the continuous variables appeared to be normally distributed and linear in the logit, no transformations were applied nor were any continuous variables recoded into indicator variables to meet the assumptions of statistical tests applied to the data.

Common Analysis Approach to Specific Aims 1, 2, and 3

Definition of Depression Treatment Response

As described above, the primary outcome of interest for all analyses was depression treatment response (remission, partial response, nonresponse). Remission was defined as an SCL-20 score ≤ 0.5; partial response was defined as $\geq 50\%$ improvement in SCL-20 score but not to a level of ≤ 0.5. Nonresponse was defined as patients who do not meet either of these criteria.

A new variable was created for the three level outcome, depression treatment response, from the original ARTIST variable (Table 9)

Table 9. Variable coding (depression outcome)

Name	Variable Description	Variable type	Coding
DEPRESS	Outcome: Remission from depression	Categorical	0=no remission 1=partial response 2=remission

Analyses to Address Specific Aim 1

Specific Aim #1: To determine the effect of panic symptoms on the outcomes for treatment of depression at month 6. ***Hypothesis:*** Depressed patients with panic symptoms will have worse outcomes than depressed patients without panic symptoms.

Variable Recoding

To address specific Aim #1, we created a new variable for the main exposures of interest, symptoms of panic disorder at baseline and persistent panic (panic at baseline and month 3) (Table 10).

Table 10. Variable coding (panic)

Name	Variable Description	Variable type	Coding
PANIC_0	Exposure: self-reported panic symptoms at baseline	Binary	0=no 1=yes
PER_PANIC	Exposure: self-reported panic symptoms at baseline *and* month 3	Binary	0=no 1=yes

Statistical Analysis

Exploratory Analysis

First, we examined the univariate distribution of both the outcome (depression treatment response at month 6) and the exposure (panic symptoms). This included the percentage in each category (including missing values). We also examined the distributions of each of the categorical covariates (including the frequency distribution and missingness) and the univariate distributions (including normality distribution, skew, kurtosis, outliers, and missingness) for each of the continuous covariates.

If there was more than 5% missing for any variable (outcome, exposure, or covariate) we examined whether the missingness was associated with the other variables (outcome, exposure, or covariates, as appropriate). For categorical covariates, we calculated an odds ratio (OR) that explores the level of missingness at each level of the other variable; a strong association of the missingness was defined as an OR ≥ 3.0 or ≤ 0.3. For continuous covariates, we examined whether the missingness was associated with continuous covariates by exploring the mean, standard deviation, minimum, and maximum at each level of missingness (missing vs. not missing). This information was used to determine if the missingness was missing at random, missing completely at random, or not missing at random.

Effect Measure Modification

To determine whether there was EMM, we constructed a multinomial logistic regression model that included the exposure, the potential EMM, and the interaction term and we assessed the interaction term for confounding (see below). To assess

EMM, we compared the ORs and likelihood scores for the full model (the model with the interaction term) and the reduced model (the model without the interaction term). Covariates with a significant likelihood ratio test ($P < 0.20$) with an adequate sample size to explore an interaction (>10 in each cell) were considered EMMs.

Confounding

First, we examined whether each of the potential confounders (i.e., covariates that are not strong EMM) was correlated with the main exposure (baseline or persistent panic symptoms). To assess confounding in all of the regression models we used a change in estimate approach. A covariate was considered a confounder if the adjusted estimate was greater than 10% different from the unadjusted estimate.

Because we had a three level outcome, a covariate was considered a confounder if the adjusted estimate was greater than 10% different from the unadjusted estimate in either comparison (remission vs. nonresponse or partial response vs. nonresponse).

Logistic Regression Modeling

As the outcome of interest, depression treatment response, was a three level categorical variable (remission, partial response, nonresponse), we used multinomial logistic regression.

Model 1

We used multinomial logistic regression (model 1) to explore the effect of baseline and persistent panic symptoms on depression treatment outcomes at month 6.

Model 1: Logit (DEPRESS) = $\beta_0 + \beta_1 * \text{PANIC} + \beta_2 * \text{SCL-20}_{\text{baseline}} + \text{error}$

Where panic is baseline panic or persistent panic depending on the analysis.

For this model (model 1), we explored the following covariates:

- Age (baseline)
- Race (baseline)
- Sex (baseline)
- SSRI randomized (baseline)
- Use of antidepressants prior to current diagnosis (baseline)
- Problems with alcohol (baseline)
- Adequacy of antidepressant treatment (over 6 months of treatment and at the 6 month visit)

Model building strategy - Model 1

The model-building strategy was backward elimination, which allowed us to look at the effect of each covariate in the presence of the other variables. The model-building steps were:

1. All potential effect measure modifiers were evaluated by running a model with the main exposure, the potential effect measure modifier, and the interaction term in SAS (proc logistic, glogit link) and using a likelihood ratio test (see above).
2. A full model (including the main exposure, all possible covariate confounders, and the interaction terms, if any) was run in SAS (proc logistic, glogit link).
3. All covariates (including the main exposure of interest) and interaction terms (see step 1 above) were assessed for confounding using a change-in-estimate approach.
    a. The OR for the main exposure, adjusting for all covariates (including interaction terms) was calculated from the full model (OR_{full}).

b. The covariate that was least likely to change the relationship between the exposure and the outcome was identified by determining which covariate has the highest p-value in the full model.

c. The covariate with the highest p-value was removed and an OR for the relationship between the exposure and the outcome was calculated ($OR_{reduced}$).

d. The two ORs were compared using the following formula:

$\ln|OR_{full}/OR_{reduced}|$

within each strata of the effect measure modifier if any interaction term were retained (see step 1 above).

e. Steps b-d were repeated for each covariate in the model, building on the prior steps (i.e., the retention/removal of variables).

f. The final model included all retained variables.

Missing Data

The effect of missing data was explored using last observation carried forward and multiple imputation analyses. For the last observation carried forward analysis, the last observed SCL-20 score was carried forward and used to create the outcome variable (depression outcome defined as remission, partial response, or nonresponse). For the multiple imputation analysis, we imputed missing values for the month 6 SCL-20 score. The imputation algorithm included age, race, gender, problems with alcohol, alcohol use, SCL-20 score (months 1, 3, and 6), adequacy of depression treatment, and type of depression. After imputation of the SCL-20 score at month 6 using SAS PROC MI, we created the outcome variable (depression treatment

outcome at month 6 defined as remission, partial response, and nonresponse) and used SAS PROC LOGISTIC and SAS PROC MIANALYZE to generate the multinomial logistic regression parameter estimates and associated standard errors.

Sensitivity Analysis

Because one of the main exposures of interest, symptoms of panic disorder, was self-reported using a 3-item anxiety-screening instrument rather than a clinical diagnosis, there is possibility that panic disorder was misclassified. Even though panic disorder was classified as a dichotomous variable and the expected direction of bias is towards the null, there have been instances where this assumption is incorrect. Despite the fact that the bias might be toward the null, i.e., conservative, this is still an incorrect inference. We used a probabilistic sensitivity analysis that allowed us to quantify, in addition to random error, the magnitude and direction of systematic error.

Probabilistic sensitivity analysis uses Monte Carlo techniques to simulate, based on a range of postulated sensitivity and specificity estimates, what would have been the observed data had misclassification not occurred. The technique is described in detail by Fox and Lash [Int J Epid] and a SAS macro was developed by Lash and Fink that is available on the web.[126, 127] We used this macro to assess the effect of varying the sensitivity and specificity of the three anxiety questions, with specific focus on the panic question. The macro provided a median estimate of the measure of association along with three 95% confidence intervals, an interval for: random error only, systematic error only, and one that accounts for both random and systematic error.

The range of sensitivity and specificity explored was determined using published data about the sensitivity/specificity of the panic question.[121, 128] We varied both the sensitivity and the specificity of the panic question from a low of 60% to a high of 100%.

We specified a trapezoidal density function, which is described by Fox et al. as "the simplest realistic density function" which is specified by four points: the lower and upper bounds and the lower and upper modes.[127] Between the upper and lower modes the density is flat and equal to the modes; "this flat region is the zone of indifference." The minimum was set to 60%, mode 1 to 75%, mode 2 to 90%, and the max to 100%.

Analyses to Address Specific Aim 2

Specific Aim #2: To determine the effect of baseline pain symptoms on depression treatment outcomes at month 6. Hypothesis 2: Depressed patients with baseline pain symptoms will have worse outcomes than depressed patients without baseline pain symptoms.

To address specific Aim #2, we created new variables for pain symptoms at baseline (Table 11).

Table 11. Variable coding (pain)

Name	Variable Description	Variable type	Coding
Pain_sev_0	Self-reported pain at baseline	Categorical	0=no pain 1=mild pain 2=moderate pain 3=severe pain
Any_Pain_0	Self reported pain at baseline	Binary	0=no/mild pain 1=moderate/severe pain

The analyses began with the dichotomous pain variable, which allowed us to evaluate depression treatment outcomes for patients with moderate/severe pain vs.

no/mild pain. We also explored the interaction between pain and panic. Because there was no interaction of pain and panic, we explored the effect of baseline pain on depression treatment outcomes using the 4-level categorical variable.

Statistical Analysis

Exploratory Analysis

As in specific aim 1, we examined the univariate distribution of the outcome (depression treatment response at month 6) and the exposure (baseline pain symptoms), the distributions of each of the categorical covariates, and the univariate distributions for each of the continuous covariates.

As described in Specific Aim 1, if there was more than 5% missing for any variable (outcome, exposure, or covariate) we examined whether the missingness was associated with the other variables (outcome, exposure, or covariates, as appropriate). For categorical covariates, we examined odds ratios; for continuous covariates, we explored the mean, standard deviation, minimum, and maximum at each level of missingness (missing vs. not missing).

Effect Measure Modification and Confounding

EMM and Confounding was assessed using the methods described for Specific Aim 1.

Logistic Regression Modeling

As in Specific Aim 1, the outcome of interest, depression treatment response was a three level categorical variable (remission, partial response, nonresponse); therefore, we used multinomial logistic regression.

Model 2

We used multinomial logistic regression model (model 2) to explore the effect of baseline pain on depression treatment outcomes at month 6.

Model 2: Logit (DEPRESS) = $\beta_0 + \beta_1 * PAIN + \beta_2 * SCL\text{-}20_{baseline} + error$

For this model, we explored the following covariates:

- Age (baseline)
- Race (baseline)
- Sex (baseline)
- SSRI randomized (baseline)
- Use of antidepressants prior to current diagnosis (baseline)
- Problems with alcohol (baseline)
- Symptoms of panic (baseline)
- Adequacy of antidepressant treatment
- Concomitant pain medication (baseline)

Model building strategy - Model 2

The model-building strategy was backward elimination, which allowed us to look at the effect of each covariate in the presence of the other variables. The model-building steps were the same as described for Specific Aim 1.

Missing Data

As described for Specific Aim 1, we first used a complete case analysis, followed by a LOCF analysis, and an analysis using multiple imputation.

Sensitivity Analysis

If panic was retained in the model (after assessment of confounding and EMM), we conducted a probabilistic sensitivity analysis (described in detail in for Specific Aim 1).

Analyses to Address Specific Aim 3

Specific Aim 3: To determine the effect of early improvement in pain (baseline to month 1) on depression treatment outcomes at months 1 and 6. Hypothesis 3: Depressed patients without early improvement in pain will have worse outcomes at months 1 and 6 than depressed patients with early improvement in pain.

To address specific Aim #3, we created new variables for the improvement of pain (early pain improvement). This variable was created by taking the difference in the pain score (measured as a continuous variable) from baseline to month 1 (Table 12). If a patient had at least a three point improvement in pain score they were deemed to have early pain improvement. All analyses were repeated using a 2-point change in pain score.

Table 12. Variable coding (early pain improvement)

Name	**Variable Description**	**Variable type**	**Coding**
Early_improve3	Exposure: early improvement in pain (improvement from baseline to month 1)	Categorical	1= ≥ 3 point change 0= < 3 point change
Early_improve2	Exposure: early improvement in pain (improvement from baseline to month 1)	Categorical	1= ≥ 2 point change 0= < 2 point change

Statistical Analysis

Exploratory Analysis

As in specific aim 1, we examined the univariate distribution of the outcome (depression treatment response at month 6) and the exposure (early pain improvement), the distributions of each of the categorical covariates, and the univariate distributions for each of the continuous covariates.

If there was more than 5% missing for any variable (outcome, exposure, or covariate) we examined whether the missingness was associated with the other variables (outcome, exposure, or covariates, as appropriate) (described in detail for specific aim 1). For categorical covariates, we examined odds ratios; for continuous covariates, we explored the mean, standard deviation, minimum, and maximum at each level of missingness (missing vs. not missing) for continuous covariates.

Effect Measure Modification and Confounding

EMM and Confounding was assessed using the methods described for Specific Aim 1.

Logistic Regression Modeling

As in Specific Aim 1, the outcome of interest, depression treatment response, was a three level categorical variable (remission, partial response, nonresponse) we used multinomial logistic regression.

Model 3

We used multinomial logistic regression model (model 3) to explore the effect of early pain improvement on depression treatment outcomes.

Model 3:

Logit (DEPRESS) =

$\beta_0 + \beta_1$*EARLY PAIN IMPROVE + β_2*SCL-$20_{baseline}$ + β_3*PHQ-$15_{baseline}$ + error

For this model, we explored the following covariates:

- Age (baseline)
- Race (baseline)
- Sex (baseline)
- SSRI randomized (baseline)
- Use of antidepressants prior to current diagnosis (baseline)
- Problems with alcohol (baseline)
- Symptoms of panic (baseline)
- Adequacy of antidepressant treatment
- Concomitant pain medication (baseline)

Model building strategy - Model 3

The model-building strategy was backward elimination, which allows us to look at the effect of each covariate in the presence of the other variables. The model-building steps were the same as described for Specific Aim 1.

Missing Data

As described for Specific Aim 1, we first used a complete case analysis, followed by a LOCF analysis, and an analysis using multiple imputation.

Statistical Power

Approximately 30% of patients treated for depression with an SSRI in primary care achieve remission of symptoms after initial treatment with an SSRI.[129] In ARTIST, 22% of patients experienced remission at month 6; we estimated that patients without panic/pain and those with improvement in pain would have a higher rate of remission (40%). Given the literature and the results from ARTIST, we examined the power of this study to detect a range of plausible ORs for depression remission. We are only presenting the power calculations for remission vs. nonresponse; because fewer patients were expected to achieve remission as compared to partial response, the remission analyses will have less power than the partial response analyses.

We had the following power for a two-sided alpha=0.05 for each "exposure" (panic/pain, early improvement in pain): 1) given 385 participants with complete data available for analysis and a 34% prevalence of **baseline panic** symptoms at baseline, we had approximately 80% power to detect an OR = 0.70 for the effect of panic symptoms on remission from depression; 2) given 365 participants with complete data available for analysis and a 12% prevalence of **persistent panic**, we had 80% power to detect an OR = 0.56 for the effect of persistent panic symptoms on remission from depression; 3) given 336 participants with complete data available for analysis and a 80% prevalence of **pain** symptoms at baseline, we had 80% power to detect an OR = 0.73 for the effect of pain symptoms on remission from depression; 4) given 482 participants with complete data available for analysis and a 27% prevalence of **early pain improvement**, we had 80% power to detect an OR = 1.44

for the effect of early improvement in pain symptoms on remission from depression at month 6. Adjustment for confounding will diminish statistical power somewhat; however, preliminary results suggest that the covariates are relatively balanced between the exposure groups. Missing data will also diminish statistical power somewhat.

CHAPTER VI

DEPRESSION AND COMORBID PANIC IN PRIMARY CARE PATIENTS

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Abstract

Background: Comorbid panic symptoms may complicate depression treatment. However, most research focuses on specialty care, and the evidence in primary care is mixed.

Methods: We analyzed data from A Randomized Trial Investigating Selective Serotonin Reuptake Inhibitor (SSRI) Treatment, a longitudinal effectiveness study comparing 3 SSRIs for the treatment of depression in primary care (n=573). Depression at month 6 was measured using the Symptom Checklist-20; remission was defined as a score ≤ 0.5; partial response was defined as $\geq 50\%$ improvement but not to a level of ≤ 0.5. Nonresponse, the referent level for all analyses, was defined as patients who do not meet either of these criteria. Panic symptoms (yes/no) were measured using a screening question.

Results: Rates of remission vs. nonresponse [OR=1.06 (95% confidence interval 0.67, 1.67)] or partial response vs. nonresponse [OR=0.92 (95% CI 0.54, 1.57)] were similar among patients with baseline panic symptoms, adjusting for baseline depression severity. Patients with persistent panic symptoms were less likely to experience remission (OR=0.38, 95% CI 0.18, 0.81) or partial response (0.66, 95% CI 0.33, 1.33). Results were similar using complete case, last observation carried forward, and multiple imputation methods, and were robust to varying the sensitivity and specificity of the panic screening question.

Conclusion: Panic symptoms that persist are associated with worse depression outcomes in the maintenance phase. Consequently, improvement in panic symptoms may be important for improved depression outcomes and primary care physicians should be attuned to the presence of panic symptoms when making treatment decisions.

Introduction

Depression is a common and debilitating illness that is often treated in a primary care setting.[4, 5] Though depression seen in primary care is often thought to be less severe,[24-26] a direct comparison of the two treatment settings revealed that severity of depression was similar among patients treated in primary vs. specialty care.[27, 28] Regardless of treatment setting, the goal of depression treatment is remission, or absence of depressive symptoms. However, a large "real world" antidepressant effectiveness trial demonstrated that only about 30% of patients experience remission, with similar remission rates for primary vs. specialty care.[1] With remission as the goal of depression treatment, understanding the factors that may influence treatment outcomes, such as comorbid panic symptoms, is critical.

Like depression, anxiety symptoms and anxiety disorders [e.g., generalized anxiety disorder (GAD), obsessive-compulsive disorder (OCD), panic disorder, posttraumatic stress disorder (PTSD), and social anxiety disorder (SAD)] are common in the primary care setting.[130] Furthermore, comorbid anxiety symptoms and anxiety disorders are common in depressed patients. In the National Comorbidity Survey (NCS) and NCS-Replication almost 60% of patients with lifetime major depressive disorder (MDD) had a comorbid anxiety disorder with even more patients experiencing comorbid anxiety symptoms.[13] In the STAR*D study, which compared depression outcomes in primary and specialty care, depression with comorbid anxiety was significantly more common in primary vs. specialty care, even after adjusting for baseline depression severity.[14, 15] The most common anxiety disorders in primary care are GAD and SAD,[29, 30] although many depressed patients treated in primary care suffer from comorbid panic disorder. Panic disorder is associated with severe disability and work impairment in

patients treated in primary care, even when controlling for the presence of physical and depressive illness.[131]

In a primary care setting, comorbid panic attacks and panic disorder are associated with more severe depressive illness and greater disability.[61, 64] Similarly, some studies have found that a lifetime history of panic disorder is associated with more severe depression,[62] greater impairment,[62] and poorer treatment response.[55, 62, 63] However, other studies have not confirmed this, finding instead that the presence of comorbid panic does not affect treatment outcomes[64], persistence of depression, [65] or quality of life.[132] In light of the mixed evidence, the high prevalence of comorbid anxiety in depressed patients, and the clinical importance of panic disorder, it is important to understand how comorbid panic affects depression outcomes, particularly in primary care patients. Thus, our research question was: for depressed primary care patients, do baseline panic symptoms or persistent panic symptoms affect treatment outcomes at 6 months?

Methods

Design and Setting

ARTIST (A Randomized Trial Investigating SSRI Treatment) was a 9-month randomized, open-label, effectiveness trial comparing three selective serotonin reuptake inhibitors (SSRIs) using patients from two primary care research networks.[2] The first primary care research network was a not-for-profit voluntary organization of more than 10,000 family practitioners, internists, and pediatricians [The Primary Care Network (n=51 study practitioners)]. The second primary care network was an academic site management organization within the Duke University Health System made up of over 150 family

physicians, internists, and pediatricians who participate in clinical outcomes trials [The Duke Primary Care Research Consortium (n=26 study practitioners)].

Study Population

The ARTIST study population included patients aged 18 years and over who were visiting network primary care doctors between April and November 1999; the visits were not required to be depression related. Patients were eligible if they received their primary care from a participating physician, were over 18 years of age, had a depression diagnosis that was deemed appropriate for SSRI treatment, and had access to a telephone. Exclusion criteria included: suicidal ideation; SSRI treatment currently or within the past 2 months; current non-SSRI antidepressant use either for depression (any dose level) or for a non-depressive disorder (at more than low doses, e.g. >50mg of amitriptyline or its equivalent); active substance abuse; pregnancy or breastfeeding; cognitive impairments (e.g., dementia or psychosis); inability to read, speak, or write English; or a terminal illness. At the start of the trial, patients were randomly assigned to open-label treatment with one of three SSRIs (fluoxetine, paroxetine, sertraline).

Study Measures

Outcome

Outcomes were assessed using a Computer Assisted Telephone Interview (CATI) at baseline, and months 1, 3, 6, and 9.[2] Presence of depression was assessed using the Primary Care Evaluation of Mental Disorders (PRIME-MD) depression module.[128] The PRIME-MD is a screening instrument designed for use in a primary care setting for the diagnosis of specific mental disorders using criteria from the Diagnostic and Statistical Manual III – Revised (DSM-III-R) and DSM-IV.[128] Depression severity was assessed

using the Symptom Checklist-20 (SCL-20), a modified subscale of the Hopkins Symptom Checklist and Brief Symptom Inventory, which has been shown to detect differences in severity among treatment groups in primary care trials.[115-117] The SCL-20 is scored from 0 to 4, with a higher score indicating more severe depression. Our primary outcome was depression response at the month 6 visit, categorized as remission, partial response, and nonresponse. Remission was defined as an SCL-20 score ≤ 0.5; partial response was defined as $\geq 50\%$ improvement in SCL-20 score but not to a level of ≤ 0.5. Nonresponse was defined as patients who do not meet either the remission or partial response criteria.

Exposure

Symptoms of panic disorder (yes/no) were assessed at baseline and month 3 using one question from the PRIME-MD ["During the past 4 weeks, have you had an anxiety attack (suddenly feeling fear or panic)?"][120] This question has demonstrated good sensitivity and specificity in a population of non-depressed patients attending a clinic where the prevalence of current panic disorder was 8.8%. In this setting, the sensitivity and specificity (and associated 95% confidence intervals) were 93% (81%-99%) and 78% (74%-82%), respectively.[121] Analyzing data from the 1000 primary care patients evaluated in the original PRIME-MD[32] study where the prevalence of current panic disorder was 3.6%, we found similar operating characteristics for the panic question. With the PCP's diagnosis (which uses a structured DSM-IV based interview in the PRIME-MD Clinician Evaluation Guide) as the reference standard, the sensitivity and specificity of the panic question were 100% and 91%, respectively. With the mental health professional's independent diagnosis (using the telephone-based SCID) as the

reference standard, the sensitivity and specificity of the panic question were 86% and 92%, respectively.

Additional Demographic and Clinical Characteristics

ARTIST captured demographic and additional clinical characteristics (e.g., prior treatment for depression, alcohol use), psychological measures, social functioning, work functioning, health-related quality of life, medication use, and healthcare utilization. Of particular interest in the current study are demographic characteristics (age, race, sex.) and clinical characteristics [type of depression, initial SSRI (paroxetine, sertraline, fluoxetine), prior use of antidepressants, baseline problems with alcohol, baseline depression severity, and symptoms of GAD]. For the purposes of this analysis, race/ethnicity was defined as white vs. other.

Comprehensive antidepressant information was captured (both the name of the medication and its dosing), including changes made to the treatment over the course of the study. We evaluated adequacy of antidepressant treatment in two ways. First, treatment was defined as adequate (treatment at month 6 within the usual recommended dose range [Table 1]) or inadequate (no treatment or treatment at month 6 below the minimum usual recommended dose) based on treatment at the month 6 visit only. We also explored adequate treatment over the initial 6 months of the study. Adequate treatment over 6 months was defined as treatment at each visit within the usual recommended dose range with no gaps in treatment greater than 2 weeks whereas inadequate treatment over 6 months was defined as treatment at any visit below the recommended dose range (Table 1) or intermittent treatment (gaps in treatment greater than 2 weeks).

Statistical Analysis

We used multinomial logistic regression to assess the effects of panic symptoms on depression outcomes at month 6 where outcome was defined as remission, partial response, or nonresponse; nonresponse was the referent for all analyses. The final models were constructed using a manual backward elimination change in estimate procedure, allowing us to explore the effects of each covariate in the presence of the other covariates. The final models included the exposure of interest as well as any covariates that changed the odds ratio (OR) by greater than 10% for either comparison (remission vs. nonresponse; partial response vs. nonresponse). To assess effect measure modification, we compared the ORs and likelihood scores for the full model (the model with the interaction term) and the reduced model (the model without the interaction term). Covariates with a significant likelihood ratio test ($P < 0.20$) with an adequate sample size to explore an interaction (>10 in each cell) were considered effect measure modifiers. Baseline depression severity was included as a covariate in all regression models. Initial analyses included only those patients with complete data (complete case analysis).

The effect of missing data was explored using last observation carried forward and multiple imputation analyses. For the last observation carried forward analysis, the last observed SCL-20 score was carried forward and used to create the outcome variable (depression outcome defined as remission, partial response, or nonresponse). For the multiple imputation analysis, we imputed missing values for the month 6 SCL-20 score. The imputation algorithm included age, race, gender, problems with alcohol, alcohol use, SCL-20 score (months 1, 3, and 6), adequacy of depression treatment, and type of

depression. After imputation of the SCL-20 score at month 6 using SAS PROC MI, we created the outcome variable (depression treatment outcome at month 6 defined as remission, partial response, and nonresponse) and used SAS PROC LOGISTIC and SAS PROC MIANALYZE to generate the multinomial logistic regression parameter estimates and associated standard errors.

All analyses (including the sensitivity analysis described in greater detail below) were run in SAS version 9.1.3 (SAS Institute, Cary, NC).

Sensitivity Analysis

Because the exposure of interest, symptoms of panic disorder, was self-reported using a single dichotomous question from a 3-item anxiety-screening instrument rather than from a clinical diagnosis, there is a possibility that panic disorder was misclassified. Although the expected direction of bias is towards the null, there may be instances where this assumption is incorrect leading to an inaccurate inference. Therefore, we used a probabilistic sensitivity analysis that allowed us to quantify, in addition to random error, the magnitude and direction of potential systematic error for each logistic regression model (remission vs. nonresponse and partial response vs. nonresponse).

Probabilistic sensitivity analysis uses Monte Carlo techniques to simulate, based on a range of postulated sensitivity and specificity estimates, what the observed data would have been had misclassification not occurred. The technique is described in detail by Fox and Lash [Int J Epid] and a SAS macro was developed by Lash and Fink.[126, 127] The macro provides a median estimate of the measure of association along with three 95% confidence intervals: random error only, systematic error only, and one that accounts for both random and systematic error.

The range of sensitivity and specificity for the sensitivity analysis was determined using published[121] data (as well as previously unpublished data from the original PRIME-MD study analyzed for the current paper[128]) regarding the sensitivity/specificity of the panic question, along with evaluation of plausible values. We varied both the sensitivity and the specificity of the panic question from a minimum of 60% to a high of 100% (mode 1: 75%, mode 2: 90%).

Results

A total of 601 patients provided informed consent and were randomized to treatment, 573 completed the baseline assessments and 482 (84%) completed assessment at 6 months (Figure 1). The mean age was 46 years; most patients were women (79%) and white (84%). Of the 573 patients randomized to treatment, 569 had information about baseline panic symptoms and 35% of those patients reported baseline panic symptoms (n=199, Table 2); 12% of patients reported panic symptoms at both the baseline and month 3 visits.

Several baseline and other clinical characteristics differed between patients with and without panic at baseline. Patients with baseline symptoms of panic disorder were younger [43.1 years (SD=14.2) vs. 47.7 (SD=16.5)], had greater baseline SCL-20 depression severity [1.94 (SD=0.67) vs. 1.51 (SD=0.72)], and were less likely to have a diagnosis of minor depression. They were more likely to have: a diagnosis of double depression (major depression with dysthymia), prior antidepressant treatment, and suicidal ideation in the past 2 weeks. More patients with baseline panic symptoms received adequate treatment over the initial 6 months of treatment (77.4% vs. 67.3 %) and at the month 6 visit (81.2% vs. 72.0%).

Baseline Panic Symptoms

The unadjusted ORs revealed no difference in either remission or partial response compared with nonresponse after 6 months of treatment (Table 3). With adjustment for baseline depression severity, baseline panic was not associated with depression treatment outcomes at month 6 (remission vs. nonresponse OR=1.06, 95% CI 0.67, 1.67; partial response vs. nonresponse OR=0.92, 95% CI 0.54, 1.57) (Table 4). Results were similar in the LOCF and MI analyses. The results of the SA are similar; however, there is a loss of precision in the SA analysis compared to the CC, LOCF, and MI analyses.

Persistent Panic Symptoms

Though baseline panic was not associated with worse depression outcomes, patients with persistent panic symptoms (panic symptoms at both baseline and month 3) were less likely to experience remission at month 6 in the bivariate analysis (OR=0.28, 95% CI 0.14, 0.60, Table 5). Similar results were seen in the multivariate model which adjusted for baseline depression severity (OR=0.38, 95% CI 0.18, 0.81, Table 6). There is a weaker relationship in the partial response vs. nonresponse comparison (OR=0.66, 95% CI 0.33, 1.33), suggesting an incremental response. Results were similar for the CC, LOCF, and MI analyses. Results were similar in the SA, though there was evidence of a slightly stronger association between persistent panic and depression remission (OR=0.15, 95% CI 0.02, 0.54); the results are less precise in the SA vs. the CC, LOCF, and MI analyses.

Subgroup Analysis

Two additional subgroup analyses were conducted. The first subgroup analysis included only those patients with a diagnosis of major depression. ARTIST included patients who the primary care physician had deemed sufficiently depressed to warrant treatment with

an SSRI, but there was no entry criterion for depression diagnosis. Though the majority of patients in the ARTIST study had a diagnosis of major depression with or without dysthymia (73%), the study population also included patients with other depression diagnoses such as minor depression. Because the severity of depression could affect our results, we evaluated the effect of baseline panic (n=351) and persistent panic (n=330) symptoms in those patients with major depression. Among patients with MDD and baseline panic, results were similar to those seen in the overall study population; the odds of remission vs. nonresponse was 0.85 (95% CI 0.51, 1.44) and the odds of partial response vs. nonresponse was 0.85 (95% CI 0.50, 1.47) in the CC analysis. For persistent panic, the results in the subset with MDD were also similar to those seen in the overall population [remission vs. nonresponse OR=0.38 (95% CI 0.17, 0.83); partial response vs. nonresponse, OR=0.61 (95%CI 0.30, 1.22)]. Results were similar using LOCF, MI, and SA (results not shown).

The second subgroup analysis included only those patients with baseline GAD symptoms, which were reported by 95% of the study sample. As expected, results in this subgroup were similar to those seen with the full study sample (results not shown).

Discussion

Although baseline panic symptoms did not affect depression outcomes at 6 months, patients with persistent panic symptoms (panic symptoms at baseline and month 3) were much less likely to achieve remission at month 6. The adverse effect of persistent panic symptoms on partial response is less than the effect on remission, consistent with an incremental or graded response. Though our study included a heterogeneous group of depressed patients with a variety of depression diagnoses (double depression, major

depression, minor depression, dysthymia etc.), results were similar in the subgroup of patients with major depression (with or without dysthymia).

Similar to our results, prior research of depression and comorbid panic has consistently shown that baseline panic symptoms are associated with greater baseline depression severity.[61, 62, 64, 65] However, research has been inconclusive with respect to the effect of baseline panic on depression treatment outcomes. Some prior research in primary care settings has demonstrated that the presence of a lifetime or current history of panic attacks or panic disorder is associated with worse depression outcomes including longer time to recovery,[55, 61-63] other studies suggest that panic disorder is not a significant predictor of depression outcomes.[64, 65] However, like the current study, these studies, which failed to demonstrate an association based the presence of panic disorder on screening questions, rather than a clinical diagnosis, which may account for the varied results.

To assess how misclassification of panic symptoms due to the use of the panic screening question would affect our results, we conducted a probabilistic sensitivity analysis. The single panic screening question has demonstrated excellent sensitivity and specificity in non-depressed primary care samples, both in a published study[121] and in our secondary analysis of data from the original PRIME-MD study.[128] While the current analyses demonstrated some variability in the results of the sensitivity analysis compared to the CC, LOCF, and MI analyses, including a loss of precision in the estimates, overall, the results are robust to varying sensitivity and specificity within a large range of plausible values.

It is also important to consider how the use of a screening question may effect our definition of persistent panic symptoms. Because we used a screening question to assess panic symptoms, persistent panic may result in poorer depression outcomes because it

represents more severe or unremitting panic symptoms, or it may simply be a better indicator of the presence of panic disorder than baseline panic symptoms alone. Despite the use of a screening question, our results appear to be consistent with the finding by Davidson and colleagues that early resolution of anxiety symptoms (defined by psychic anxiety on the Hamilton rating scale for depression) may be a predictor of depression remission. Moreover, our study conducted in primary care complements that by Davidson et al in which patients were treated in a specialty care setting.[133]

There was some evidence of differential treatment patterns by baseline panic symptoms in our study. Patients with baseline panic were more likely to report adequate doses of antidepressant treatment over 6 months of treatment and at the 6-month visit. There are two possible explanations for the differential treatment patterns observed in this study. Because patients with baseline panic had more severe depressive symptoms at baseline and over the 6 months of treatment (results not shown) physicians may have treated these patients more aggressively. Alternatively, physicians may have identified the comorbid panic symptoms, which in turn prompted more aggressive treatment. If anything, this differential treatment might make our findings regarding the adverse impact of persistent panic symptoms on depression outcomes a conservative estimate.

Though we found no important effect of treatment adequacy in our regression analyses, this may a result of the limitations of our classification of adequate treatment. Our definitions of adequacy of antidepressant treatment (treatment at month 6 at doses within the usual recommended dose range or treatment over the course of 6 months within the usual recommended dose range) are relatively simple classifications that incorporate doses at the low end of the effective range. However, there is evidence that lower antidepressant doses

are commonly used in a primary care setting,[134, 135] and antidepressant dosing in the ARTIST study was primarily in the lower end of the usual recommended dose range.[125] This limited our ability to explore a more comprehensive definition of adequate treatment or to explore a relationship between dose and antidepressant response.

Finally, it is also important to consider how loss-to-follow-up would affect our results. Over the initial 6 months of this longitudinal study, 16% of patients missed the 6-month visit or were lost to follow-up. We would expect that the more severe patients would be more likely to be lost to follow-up, which would likely lead to a weaker effect among those who remained in the study. However, patients who were lost to follow-up were similar to patients who remained in the study in terms of baseline depressive severity, and results were similar when we imputed 6-month outcomes for those with missing data.

In conclusion, our study demonstrates that the presence of comorbid panic symptoms may negatively affect depression outcomes, particularly when panic symptoms persist despite antidepressant therapy, regardless of whether they meet the DSM criteria for panic attacks and panic disorder. Therefore, it may be important to consider the presence of panic symptoms, both at baseline and over the course of depression treatment, when making treatment decisions in a primary care setting. Future research should explore how improvements in panic symptoms affect depression outcomes, and should rely on clinical diagnoses or validated scales that provide information on the severity of the panic symptoms.

Table 13 (MS1 Table 1). Usual minimum antidepressant dose

Generic Name (Trade Name)	Minimum Usual Daily Dose
Amitriptyline (Elavil®)	150mg
Bupropion (Wellbutrin®)	300mg
Citalopram (Celexa®)	20mg
Fluoxetine (Prozac®)	20mg
Mirtazapine (Remeron ®)	15mg
Nefazadone (Serzone®)	300mg
Paroxetine (Paxil®)	20mg
Sertraline (Zoloft®)	50mg
Trazadone (Desyrel®)	300mg
Venlafaxine (Effexor®)	125mg

Table 14 (MS1 Table 2). Baseline characteristics by baseline panic symptoms

Characteristic	Panic Symptoms (*n*=199) %	No Panic Symptoms (*n*=370) %
Gender		
Female	81.9	77.6
Male	18.1	22.4
Race		
White	82.4	84.3
Other	17.6	15.7
Depressive disorder diagnosis		
Double Depression	52.7	44.5
Major Depression without dysthymia	37.2	34.8
Dysthymia only	4.8	9.0
Minor depression	5.3	11.6
Past history of depression treatment		
Yes	40.2	28.6
No	59.8	71.4
Suicidal ideation in the past week		
Yes	18.6	8.1
No	81.4	91.6
Don't know	0	0.3
Any alcohol use in the past month		
Yes	42.7	46.2
No	57.3	53.8
Any problems with alcohol in the past month		
Yes	19.6	15.9
No	80.4	84.1
Randomized Treatment		
Fluoxetine hydrochloride	33.2	34.1
Paroxetine	32.7	33.2
Sertraline hydrochloride	34.2	32.7
Treatment classification at month 6		
Adequate	81.2	72.0
Inadequate	18.8	28.0
Treatment classification over 6 months		
Adequate	77.4	67.3
Inadequate	22.6	32.7

Table 15 (MS1 Table 3). Treatment response at month 6 by baseline panic symptoms*

Depression Outcome at Month 6	Panic (n=161)	No Panic (n=317)	Unadjusted OR (95% CI)
Remission	54 (33.5)	129 (40.7)	0.79 (0.51, 1.21)
Partial Response	37 (23.0)	56 (56.3)	1.25 (0.75, 2.07)
Nonresponse	70 (43.5)	132 (41.6)	1.

* Overall X^2 baseline panic symptoms by response was not significant (X^2=6.53, degrees of freedom=2, p=0.3)

Table 16 (MS1 Table 4). Association between baseline panic symptoms and depression outcome in primary care patients

Analysis	Adjusted OR (95% CI) *
Complete Case (n=478)	
Remission	1.06 (0.67, 1.67)
Partial Response	0.92 (0.54, 1.57)
Nonresponse	1.
Last Observation Carried Forward (n=569)	
Remission	0.93 (0.61, 1.40)
Partial Response	0.79 (0.48, 1.31)
Nonresponse	1.
Multiple Imputation (n=573)	
Remission	0.99 (0.64, 1.54)
Partial Response	0.90 (0.54, 1.54)
Nonresponse	1.
Sensitivity Analysis (n=454)	
Remission	0.72 (0.16, 1.36)
Partial Response	1.30 (0.59, 4.88)
Nonresponse	1.

*adjusted for baseline depression severity.

Table 17 (MS1 Table 5). Treatment response at month 6 by persistent panic symptoms*

Depression Outcome at Month 6	Yes (n=59) n (%)	No (n=397) n (%)	Unadjusted OR (95% CI)
Remission	10 (17.0)	163 (41.1)	0.28 (0.14, 0.60)
Partial Response	15 (25.4)	76 (19.1)	0.92 (0.47, 1.79)
Nonresponse	34 (57.6)	158 (39.8)	1.

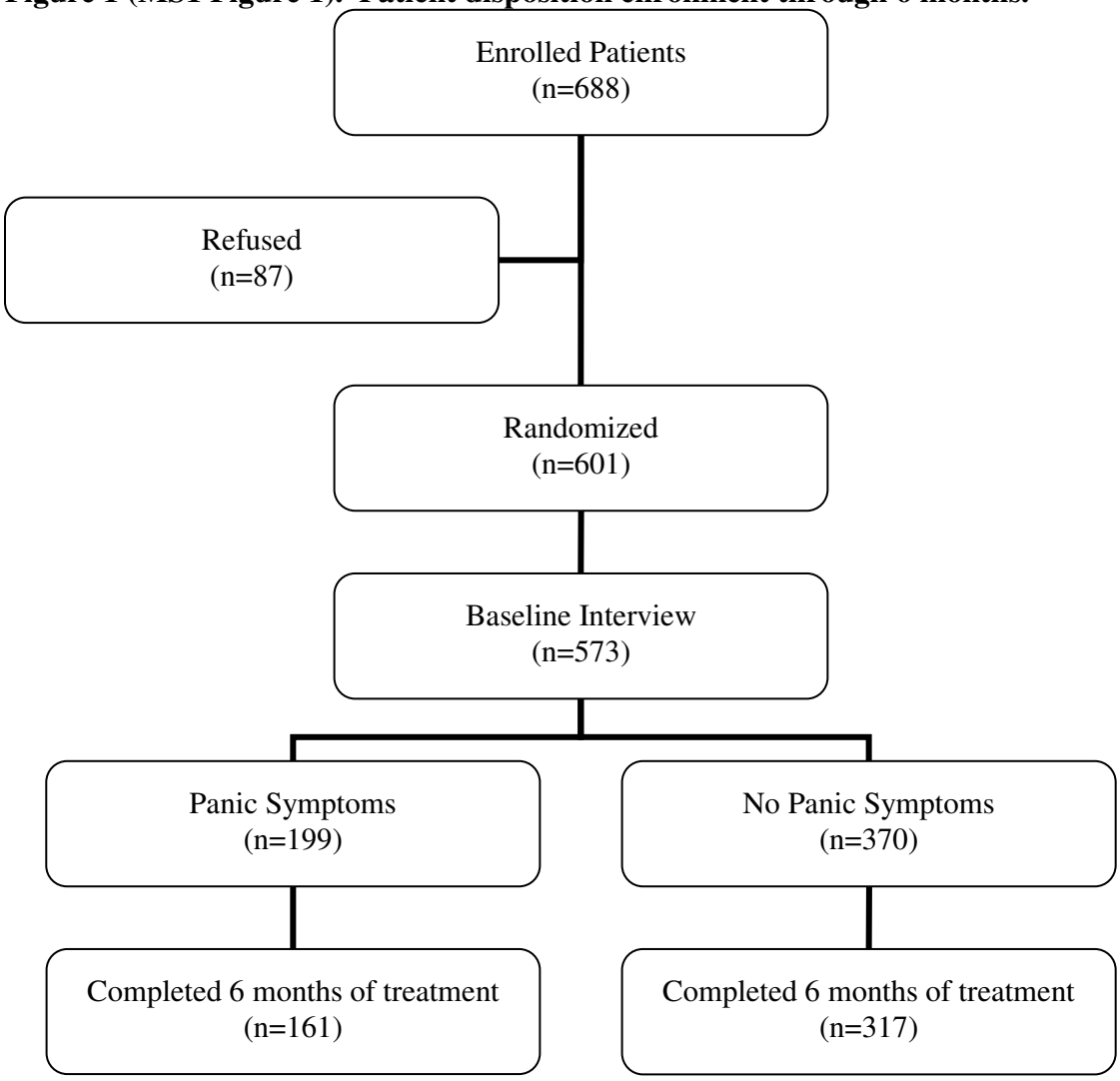
* Overall X^2 persistent panic symptoms by response was significant (X^2=12.76, degrees of freedom = 2, $p < 0.01$)

Table 18 (MS1 Table 6). Association between persistent panic symptoms and depression outcome in primary care patients

Analysis	Adjusted OR (95% CI) *
Complete Case (n=456)	
Remission	0.38 (0.18, 0.81)
Partial Response	0.66 (0.33, 1.33)
Nonresponse	1.0
Last Observation Carried Forward (n=495)	
Remission	0.36 (0.18, 0.73)
Partial Response	0.64 (0.33, 1.24)
Nonresponse	1.0
Multiple Imputation (n=573)	
Remission	0.32 (0.16, 0.67)
Partial Response	0.63 (0.32, 1.23)
Nonresponse	1.0
Sensitivity Analysis (n=456)	
Remission	0.15 (0.02, 0.54)
Partial Response	0.65 (0.16, 1.80)
Nonresponse	1.0

*adjusted for baseline depression severity.

Figure 1 (MS1 Figure 1). Patient disposition enrollment through 6 months.



CHAPTER VII

THE ADVERSE EFFECTS OF COMORBID PAIN ON DEPRESSION OUTCOMES IN PRIMARY CARE PATIENTS: RESULTS FROM THE ARTIST TRIAL

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Abstract

Objective: To explore the effect of pain symptoms and improvements in pain on depression outcomes at month 6 in depressed primary care patients.

Methods: We analyzed data from A Randomized Trial Investigating Selective Serotonin Reuptake Inhibitor (SSRI) Treatment (ARTIST), a randomized longitudinal effectiveness study comparing three SSRIs for the treatment of depression in a primary care setting (n=573). Depression outcome at month 6, defined as remission, partial response, and nonresponse using the Symptom Checklist-20, was the primary outcome.

Results: 80% of patients reported pain symptoms (defined using the PHQ-15 pain subscale) at baseline; 27% of patients with baseline pain reported improvement of at least 3-points on the PHQ-15 pain subscale from baseline to month 1. Compared to patients with no pain at baseline, those with severe pain were less likely to achieve remission (OR=0.11, 95%CI 0.05-0.25) and partial response (OR=0.24, 95%CI 0.10-0.59) vs. nonresponse. Patients with moderate pain were less likely to achieve remission vs. nonresponse (OR=0.25, 95% CI 0.13-0.48). Patients with early improvement in pain were more likely to achieve remission (OR=1.90, 95% CI 1.03-3.49) and slightly more likely to achieve partial response (OR=1.24, 95% CI 0.63-2.43). The ORs increased slightly using a 2-point cut-off for early pain improvement. Accounting for missing data with last observation carried forward or multiple imputation yielded similar results.

Conclusion: Pain symptoms are present in the majority of depressed primary care patients beginning antidepressant therapy. Pain symptoms are associated with worse depression outcomes, while improvement in pain is associated with significantly better depression outcomes. Attention to comorbid pain may be important in enhancing depression care.

Introduction

More than half of depressed patients experience comorbid pain, including but not limited to headache, back pain, chest pain, gastrointestinal discomfort, and other body aches.[10, 11, 85, 86] Most primary care patients with depression present with somatic rather than psychological complaints[136], and pain accounts for more than half of all somatic complaints.[137] While some suggest that physical symptoms should be considered as an important part of depression[87], the DSM-IV criteria for a depressive episode comprise only a few somatic symptoms, among which pain is not included.[16] In fact, depression may often go unrecognized when it presents with primarily somatic complaints.[88] Not only do depression and pain frequently co-occur, they have reciprocal adverse effects on quality of life, disability, and health care use.[10]

Depression may be a risk factor for pain.[87] Conversely, pain also may lead to development of depression.[87] However, the efficacy of antidepressants in the treatment of pain is limited. The tricyclic antidepressants have demonstrated efficacy in treating certain pain conditions.[138, 139] Duloxetine, approved by the FDA in 2001, is effective for major depression, generalized anxiety disorder, and diabetic peripheral neuropathic pain.[84] In contrast, the selective serotonin reuptake inhibitors (SSRIs) have uncertain efficacy in pain or in coexisting depression and pain.[139, 140] However, a recent meta-analysis and systematic review of eight trials comparing duloxetine and paroxetine found insufficient evidence to support the choice of one antidepressant over the other for the treatment of pain accompanying depression.[141]

Although baseline pain appears to be associated with greater depression severity in specialty care settings and in the general population[89-95], the effect of pain in depression

treatment outcomes in primary care settings have not been evaluated in depth.[10, 101-105, 142, 143] Primary care patients with depression and pain have worse depression outcomes.[142, 143] and quality of life[113] than those without comorbid pain. Furthermore, pain improvement is associated with a reduction in depressive symptoms and patients without improvement in pain are less likely to experience remission.[101-103]

In A Randomized Trial Investigating SSRI Treatment (ARTIST), a primary care effectiveness study, pain severity was associated with baseline depression severity and baseline pain was a significant predictor of depression response at 3 months.[104] Pain symptoms decreased during the first month of treatment and then remained fairly constant through month 9.[105] Patients who experienced depression remission or partial response at months 1 and 3 had significantly greater improvement in their pain symptoms than nonresponders, and pain improvement was similar for patients experiencing remission and partial response. However, these analyses did not explore confounding by panic symptoms or adequacy of antidepressant treatment.

In this report, our aim is to expand on the prior analyses of the ARTIST data by exploring: 1) the effect of baseline pain on depression treatment outcomes at month 6, and 2) the effect of early pain improvement on depression treatment outcomes at month 6. Examining outcomes at month 6 is important since this is a critical period for depression relapse, and adverse prognostic factors such as pain may be particularly salient in predicting relapse.

Methods

The ARTIST study methods, design, and population are described in detail elsewhere [2] and are summarized here.

Design and Setting

ARTIST was a 9-month randomized, open-label, effectiveness trial comparing three SSRI antidepressants.[2] Patients were enrolled from two primary care research networks: The Primary Care Network (n=51 study practitioners) and the primary care network from the Duke University Health System (n=26 study practitioners).

Study Population

Patients 18 years of age and older were eligible for inclusion in the ARTIST trial if they visited a network primary care doctor between April and November 1999; the visits were not required to be depression related. A depression diagnosis that was deemed appropriate for SSRI treatment and access to a telephone were also inclusion criteria. Patients were excluded if they were: actively suicidal; currently receiving treatment or had received treatment within the past 2 months with an SSRI; or currently taking a non-SSRI antidepressant either for depression (any dose level) or for a non-depressive disorder (at more than low doses, e.g. >50mg of amitriptyline or its equivalent); active substance abuse; pregnancy or breastfeeding; cognitive impairments (e.g., dementia or psychosis). Additional exclusion criteria include an inability to read, speak, or write English, or a terminal illness.

Eligible patients were randomized to open-label treatment with one of three SSRIs (fluoxetine, paroxetine, sertraline) at the start of the study.

Study Measures

Outcome

A Computer Assisted Telephone Interview (CATI) was used to assess outcomes at each study visit (baseline, and months 1, 3, 6, and 9). Depression measures included the Primary Care Evaluation of Mental Disorders (PRIME-MD) depression module, which was used to assess the presence of depression,[128] and the Symptom Checklist-20 (SCL-20), which was used to assess depression severity. The SCL-20 (range 0-4, with lower scores indicating better health) has been shown to detect differences in severity among treatment groups in primary care trials.[115-117] In the current study, depression outcome was categorized as remission (SCL-20 score ≤ 0.5), partial response ($\geq 50\%$ improvement in SCL-20 score but not to a level of ≤ 0.5), and nonresponse (patients who do not meet either the remission or partial response criteria).

Exposure

Pain was measured using the Patient Health Questionnaire-15 (PHQ-15) at baseline and months 1, 3, and 6 and the Short Form-36 (SF-36) at baseline and month 3.[122] We focused primarily on the PHQ-15.

The PHQ-15 evaluates 15 different physical symptoms including 5 specific pain symptoms (headache, back pain, limb or joint pain, abdominal pain, and chest pain) with each pain item scored from 0 ("not bothered at all") to 2 ("bothered a lot"). Scores on the five specific pain items are summed to form a composite pain score (0 to 10) with higher scores indicating more pain. For the current analysis, the PHQ-15 pain subscale was categorized into pain severity classes where scores of 0-2 indicates no pain, 3-4 indicates mild pain, 5-6 indicates moderate pain, and 7-10 indicates severe pain.[104] The validity of the

PHQ-15 has been demonstrated in general internal medicine and family practice clinics as well as obstetrics-gynecology clinics.[122] It has also proven responsive to change in treatment trials of patients with pain and other somatic symptoms.[2, 144]

The SF-36 bodily pain subscale includes two items, which address pain severity and pain interference; the overall score ranges from 0 to 100 (with 100 indicating best health status). The SF-BP is a validated tool that is commonly used in psychiatric research.[123] For the current analysis, we focused on the single pain severity question. For the purposes of this analysis, pain was categorized as follows: "none" or "very mild" = none, "mild" = mild, "moderate" = moderate, and "severe" or "very severe" = severe pain.

Early pain improvement was defined as ≥ 3 point change from baseline to month 1 in the PHQ-15 pain score. A 3-point change was used because it reflects the mean change from baseline to endpoint for patients treated with extended-release venlafaxine in anxious and/or depressed patients with multisomatoform disorder.[124] Furthermore, a 3-point improvement in pain is approximately equal to a change in pain level when pain is categorized as none, mild, moderate, or severe using the PHQ-15 pain subscale. To explore how sensitive the results were to our choice of pain change cut-off, we explored pain improvement defined as ≥ 2-point change in pain score in the final regression model.

Additional Demographic and Clinical Characteristics

The original ARTIST study captured demographic and additional clinical characteristics (e.g., prior treatment for depression, alcohol use, etc.), psychological measures, social function, work function, health-related quality of life, medication use, and healthcare utilization. For the current analysis, the following covariates were of particular interest: age, race (white vs. other), sex, type of depression, initial SSRI

randomized, prior use of antidepressants, baseline problems with alcohol, baseline depression severity, symptoms of panic, and adequacy of antidepressant treatment. Adequacy of antidepressant treatment was explored in two ways. Adequate treatment was defined using both dosing at the 6 month visit (treatment at month 6 above the minimum usual recommended dose, Table 1) and dosing over the course of the 6 months of study (treatment at each visit above the usual minimum recommended dose at each visit with no gaps in treatment greater than 2 weeks).

Because treatment of pain may affect our results, we also explored prior treatment with pain medications. The pain medications reported at baseline included: non-steroidal anti-inflammatory drugs (ibuprofen, naproxen, Piroxicam®, Celebrex®, Vioxx®, Voltaren®, Lodine®, Relafen®, Daypro®), Tylenol®, aspirin, migraine/tension headache medications (Midrin®, Imitrex®), arthritis medications (Enbrel®), and other pain medications and muscle relaxants (including Ultram®, Vicodin®, Percocet®, Robaxin®, Valium®, Flexeril®, Skelaxin®, Soma®, Lortab®, Oxycontin®, MS Contin®, Fioricet®, Tylenol #3 with Codeine® and Tylox®).

Statistical Analysis

The final multinomial logistic regression models were built using manual backward elimination change in estimate procedure, allowing us to explore the effects of each covariate in the presence of the other covariates. The final models included the exposure of interest as well as any covariates that changed the odds ratio (OR) by greater than 10% for either comparison (remission vs. nonresponse; partial response vs. nonresponse). EMM was assessed using the likelihood ratio test; any covariate with a significant likelihood ratio test ($P < 0.20$) where there was adequate sample size to

explore an interaction (>10 in each cell) was deemed an EMM. Baseline depression severity was included as a covariate in all regression models evaluating the effect of baseline pain on depression outcomes. Both baseline depression severity and baseline pain severity were included as covariates in the regression models evaluating the effect of pain improvement on depression outcomes. Initial analyses included only those patients with complete data (complete case analysis).

Last observation carried forward and multiple imputation were used to assess the affect of missing data. The last observed SCL-20 score was carried forward and used to create the outcome variable (depression outcome defined as remission, partial response, or nonresponse) in the last observation carried forward analysis. The imputation algorithm included age, race, gender, problems with alcohol, alcohol use, baseline panic symptoms, baseline pain severity, SCL-20 score (months 1, 3, and 6), adequacy of depression treatment, and type of depression. We used the imputed values to create the outcome variable, remission, partial response, or nonresponse at month 6. SAS PROC LOGISTIC and SAS PROC MIANALYZE were used to generate the multinomial logistic regression parameter estimates and associated standard errors.

All analyses were run in SAS version 9.1.3 (SAS Institute, Cary, NC).

Results

Of the 573 patients who completed the baseline assessments, 458 (80%) reported some level of pain: 190 (33%) reported mild pain, 165 (29%) reported moderate pain, and 103 (18%) reported severe pain (Figure 1). Most subjects (n=482, 84%) completed 6 months

of treatment: of these treatment completers, 94 (19%) had no pain, 164 (34%) had mild pain, 137 (28%) had moderate pain, and 87 (18%) had severe pain.

Several baseline and other clinical characteristics differed between patients with and without pain at baseline (Table 2). Patients with baseline pain (mild, moderate, or severe pain) were younger [mild: 44.9 years (SD=15.7), moderate: 45.6 years (SD=15.6), and severe: 45.0 (SD=14.5) vs. no baseline pain: 49.0 (SD=17.1), respectively] and had greater depression severity at baseline as measured by the SCL-20 [mild: 1.55 (SD=0.68), moderate: 1.77 (SD=0.68), and severe: 2.03 (SD=0.68) vs. no baseline pain: 1.34 (SD=0.78), respectively]. Patients with baseline pain were also more likely to have a diagnosis of double depression (depression with dysthymia) compared to patients with no pain at baseline. Compared to patients with no pain at baseline, those with moderate or severe pain were more likely to be female, have suicidal ideation in the past month, and have baseline panic symptoms, and were less likely to have a diagnosis of dysthymia only. Patients with moderate pain were also more likely to have a prior history of depression treatment.

Baseline Pain

Patients with moderate or severe baseline pain were much less likely to achieve remission at month 6 while patients with mild pain at baseline were only slightly less likely to achieve remission at month 6 compared to patients with no baseline pain (Table 3). A similar pattern of results was seen in the partial response vs. nonresponse comparison though the effect is weaker.

In the multivariable analysis, adjusting for baseline depression severity and age, patients with severe pain as defined by the PHQ-15 pain subscale were much less likely to achieve remission (OR=0.11, 95% CI 0.05, 0.25) and partial response (OR=0.24, 95% CI

0.10, 0.59) vs. nonresponse at month 6 (Table 4). Similarly, patients with moderate pain were much less likely to achieve remission (OR=0.25, 95% CI 0.13, 0.48) and were slightly less likely to achieve partial response (OR=0.65, 95% CI 0.30, 1.42) at month 6. Mild baseline pain had a smaller effect on remission (OR=0.72, 95% CI 0.39, 1.32). Overall, the results suggest an incremental effect of baseline pain on depression outcomes, as well as an incremental effect by depression outcome (remission vs. partial response). Results were consistent using the LOCF and MI analyses (results not shown).

The results varied somewhat when we used the single SF-36 pain severity question to assess baseline pain symptoms (Table 4). The remission vs. nonresponse comparison was similar in magnitude to that seen when the PHQ-15 pain subscale is used to classify pain severity, though the effect of severe pain was much weaker for partial response vs. nonresponse at month 6 (OR=0.75, 95% CI 0.32, 1.73). The magnitude of the effect (remission vs. nonresponse) seen in patients with mild pain is much stronger when we define pain using the SF-36 pain severity question (OR=0.46, 95% CI 0.26, 0.81). Results were consistent using the LOCF and MI analyses (results not shown).

Pain Improvement

Of the 458 patients reporting any pain at baseline, 387 remained in the study and completed the 6-month visit and had information about both pain and depression, and 100 of the 387 patients (25.8%) experienced early pain improvement, defined as ≥ 3-point change in pain severity as measured by the PHQ-15 pain subscale from baseline to month 1. There was no association of early pain improvement and depression outcome in the crude analysis (Table 5). In the multivariate analysis, adjusting for age, baseline depression severity (baseline SCL-20 score), and baseline pain severity, early pain improvement was associated

with better depression outcomes, particularly remission, at month 6 (remission vs. nonresponse OR=1.90, 95% CI 1.03, 3.49) (Table 6). Results were similar in the LOCF and MI analyses.

The multinomial regression model was repeated with early pain improvement defined as ≥ 2-point improvement in pain as measured by the PHQ-15 pain subscale from baseline to month 1 (Table 6). Overall, using the 2-point cut-off, there was a slightly stronger association between pain improvement and depression outcomes: those with early pain improvement were much more likely to achieve remission vs. nonresponse (OR=2.97, 95% CI 1.73, 5.12). Results were similar for the partial response vs. nonresponse comparison using both the 2- and 3-point cut-off. Compared to the 3-point cut-off, the ORs are larger using the 2-point cut-off suggesting a strong association between early pain improvement and depression outcomes even when using a less conservative definition of early pain improvement.

Discussion

Our results demonstrate that depression outcomes after 6 months of treatment are worse in patients with comorbid pain at baseline, which is consistent with prior studies conducted in a primary care setting.[93, 104, 142, 143, 145] Furthermore, our results extend the analyses previously conducted in the ARTIST dataset,[104] which evaluated the effect of baseline pain on depression and other health-related quality of life outcomes after 3 months of treatment using ARTIST, a primary care study of the effectiveness of SSRI treatment. Consistent with these results, we found an incremental effect with increasing pain severity. Additionally, we found the effect varied according to depression outcome, with a stronger effect seen in the remission vs. nonresponse comparison compared to the partial response vs.

nonresponse comparison. With a few exceptions, the results were consistent whether we defined baseline pain using the PHQ-15 pain scale or the SF-36 pain severity question. The differences between the results using the PHQ-15 pain subscale and the SF-36 likely arise because the categorization of pain is slightly different depending on the scale used to classify baseline pain severity. There was a reduction in sample size, particularly for the comparison of partial response vs. nonresponse among patients with severe pain vs. no pain, which likely led to the change in the OR and the increase in imprecision of the estimates.

Though the presence of pain negatively affects depression outcomes, [93, 104, 142, 143, 145] and can limit the effectiveness of depression interventions,[142] improvement in pain is associated with improved depression outcomes.[93, 105, 143] In the ARTIST study, remitters and partial responders had significantly greater changes in pain symptoms (measured using the PHQ-15 pain subscale) at both months 1 and 3.[105] Most improvement in pain symptoms occurred during the first month of treatment. Thus, we expanded these prior analyses by exploring how baseline pain and early improvement in pain affect depression outcomes at 6 months.

We found that, among patients with any pain at baseline, early improvement of pain was associated with better depression outcomes at month 6, with an incremental effect according to depression outcome (remission and partial response). The association between early pain improvement and improved depression outcomes, particularly depression remission, was observed using both a 2- and 3-point cut-off for early pain improvement. In fact, a stronger relationship was observed between early pain improvement and remission using the less conservative 2-point cut-off, suggesting that even small improvements in pain result in significantly better depression outcomes. As with the analyses of baseline pain,

there was evidence of an incremental effect, with a stronger effect observed for remission vs. nonresponse comparison and a weaker effect seen for partial response vs. nonresponse comparison.

While most improvement in pain symptoms occurred in the first month after the initiation of treatment, and our definition of pain improvement is based on this first month of treatment, it is unclear whether the pain improvement was a consequence of depression improvement or was due instead to a direct effect on antidepressants on pain symptoms. However, analyses in the ARTIST study have found a different time-course of results for pain and depressive symptoms, suggesting that physical symptoms are at least in part a separate entity from the depressive symptoms.[105] We had insufficient sample size to explore how residual pain symptoms, or pain symptoms that persist despite antidepressant treatment, effect depression outcomes.

Differences between patients with and without baseline pain were observed in a number of demographic and clinical characteristics. Our results are consistent with a cross-sectional study of patients seen in the Kaiser Permanente network, which found that panic disorder was more common in patients with MDD and chronic disabling pain.[113] We likewise found that panic symptoms were significantly more common in patients with moderate or severe baseline pain vs. no baseline pain. However, the presence of panic was similar among patients with pain improvement compared to patients without pain improvement.

It is important to note the limitations of our definitions of adequacy of antidepressant treatment. Our definitions of adequacy of antidepressant treatment are relatively simple classifications that incorporated doses at the low end of the effective range. However, lower doses are commonly used in a primary care setting[134, 135] and the dosing in the ARTIST

study was primarily at the lower end of the recommended dose range (results not shown). Unfortunately, this limited our ability to explore a more comprehensive definition of adequate treatment or to explore a relationship between dose and antidepressant response.

Furthermore, any concomitant pain medication used during the study could have reduced pain scores, which in turn may have improved depression outcomes. While we had information about baseline medications, including prescription and over the counter pain medications, we did not have information about the use of pain medications over the course of the study. Therefore, we were unable to adjust for pain medication use over the course of the study, and future studies should seek to incorporate both baseline pain medications and medication use over the course of treatment.

An additional limitation is the heterogeneity of the depressed population in ARTIST population. ARTIST included patients who had a depression diagnosis that was deemed appropriate for SSRI treatment. Therefore, subjects in ARTIST had a variety of depression diagnoses, including double depression (major depression with dysthymia), dysthymia, and minor depression. We would expect that the inclusion of less severe depressive diagnoses would dilute the effect, leading to a weaker relationship between pain and depression outcome. However, results were similar in the subgroup of patients with MDD (results not shown).

In this 9-month longitudinal study, 16% of patients missed the 6-month visit or were lost to follow-up by month 6. However, these patients were similar to patients who remained in the study in terms of baseline depressive severity, and results were similar when we imputed 6-month outcomes for those with missing data.

Despite these limitations, our study demonstrates that comorbid pain symptoms negatively affect depression outcomes and early improvements in pain result in better depression outcomes. Given that only about 30% of depressed patients experience remission, [1] the average visit to a PCP lasts only about 15 minutes[8, 9, 19, 146] and diagnosis and treatment for depression must compete with other demands,[20-23] it is critical that PCPs understand what factors are contributing to poor depression outcomes. Our results suggest that identification of comorbid pain at the onset of depression treatment, as well as follow-up of those pain symptoms to resolution, may enhance depression outcomes in primary care. Further research is warranted which prospectively explores the comparative effectiveness of currently approved antidepressants for the treatment of depression and comorbid pain. In addition, the added value of pain-specific management strategies (e.g., optimized analgesic therapy, behavioral interventions) in patients with comorbid pain should be examined.

Table 19 (MS2 Table 1). Minimum usual antidepressant dose

Generic Name (Trade Name)	Minimum Usual Daily Dose
Amitriptyline (Elavil®)	150mg
Bupropion (Wellbutrin®)	300mg
Citalopram (Celexa®)	20mg
Fluoxetine (Prozac®)	20mg
Mirtazapine (Remeron ®)	15mg
Nefazadone (Serzone®)	300mg
Paroxetine (Paxil®)	20mg
Sertraline (Zoloft®)	50mg
Trazadone (Desyrel®)	300mg
Venlafaxine (Effexor®)	125mg

Table 20 (MS2 Table 2). Baseline demographic and clinical characteristics of patients by baseline pain severity (PHQ-15 pain subscale)

Characteristic	No Pain (n=115) %	Mild (n=190) %	Moderate (n=165) %	Severe (n=103) %
Female	68.7	77.9	82.4	87.4
Race				
White	86.1	82.6	85.4	80.6
Other	13.9	17.4	14.6	19.4
Panic	20.9	28.4	40.0	53.4
Depressive disorder diagnosis				
Double Depression	25.2	37.4	50.3	53.4
Major Depression (no dysthymia)	27.8	33.2	29.7	35.0
Dysthymia only	11.3	7.4	4.8	1.9
Minor depression	12.2	8.4	8.5	2.9
Other	23.5	13.7	6.7	6.8
Past history of depression treatment	25.2	29.5	41.2	32.0
Any alcohol use in the past month	45.2	49.0	57.0	59.2
Any problems with alcohol in the past month	16.5	19.5	12.7	20.4
Any suicidal ideation in past month	7.0	7.9	15.8	18.5
Baseline treatment with pain medication	14.8	10.0	19.4	20.4
Randomized Treatment				
Fluoxetine hydrochloride	40.0	31.1	32.7	33.0
Paroxetine	29.6	32.1	37.6	31.1
Sertraline hydrochloride	30.4	36.8	29.7	35.9
Treatment classification at month 6				
Adequate	59.1	62.1	68.5	66.0
Inadequate	22.6	25.3	15.8	22.3
Missing	18.3	12.6	15.8	11.7
Treatment classification over 6 months				
Adequate	55.6	58.9	63.6	60.2
Inadequate	26.1	27.4	20.0	27.2
Missing	18.3	13.7	16.4	12.6

Table 21 (MS2 Table 3). Depression response at month 6 by baseline pain symptoms*

	Baseline Pain Severity, n (%)				Unadjusted OR (95% CI)		
Depression Outcome	**No Pain (n=94)**	**Mild (n=164)**	**Moderate (n=137)**	**Severe (n=87)**	**Mild vs. No Pain**	**Moderate vs. No Pain**	**Severe vs. No Pain**
Remission	53 (56)	85 (52)	34 (25)	13 (15)	0.77 (0.43, 1.39)	0.24 (0.13, 0.45)	0.10 (0.05, 0.22)
Partial Response	16 (17)	27 (16)	36 (26)	15 (17)	0.81 (0.37, 1.77)	0.84 (0.40, 1.77)	0.40 (0.17, 0.93)
Nonresponse	25 (27)	52 (32)	67 (49)	59 (68)	1.0	1.0	1.0

* Overall X^2 baseline pain by depression response was significant (X^2=63.95, degrees of freedom=9, p<0.0001)

Table 22 (MS2 Table 4). Adjusted* OR (95% CI) for the association between baseline pain symptoms (measured using the PHQ-15 pain subscale and the SF-36 pain severity question) and depression outcome in primary care patients (complete case analysis)

	Adjusted* OR (95% CI)	
	PHQ-15 pain subscale	**SF-36 pain severity**
Severe Pain		
Remission	0.11 (0.05, 0.25)	0.11 (0.05, 0.27)
Partial Response	0.24 (0.10, 0.59)	0.75 (0.32, 1.73)
Nonresponse	1.0	1.0
Moderate Pain		
Remission	0.25 (0.13, 0.48)	0.33 (0.19, 0.58)
Partial Response	0.65 (0.30, 1.42)	0.70 (0.33, 1.45)
Nonresponse	1.0	1.0
Mild Pain		
Remission	0.72 (0.39, 1.32)	0.46 (0.26, 0.81)
Partial Response	0.67 (0.30, 1.52)	1.08 (0.51, 2.30)
Nonresponse	1.0	1.0

*PHQ adjusted for baseline depression severity and age; SF-36 adjusted for baseline depression severity, adequacy of antidepressant over 6 months, and baseline pain medication.

Table 23 (MS2 Table 5). Depression response at month 6 by early pain improvement *

Depression Outcome	Early Pain Improvement (n=100) n (%)	No Early Pain Improvement (n=287) n (%)	Unadjusted OR (95% CI)
Remission	35 (35)	97 (33.8)	1.09 (0.65, 1.83)
Partial Response	21 (21)	57 (19.9)	1.11 (0.61, 2.04)
Nonresponse	44 (44)	133 (46.3)	1.0

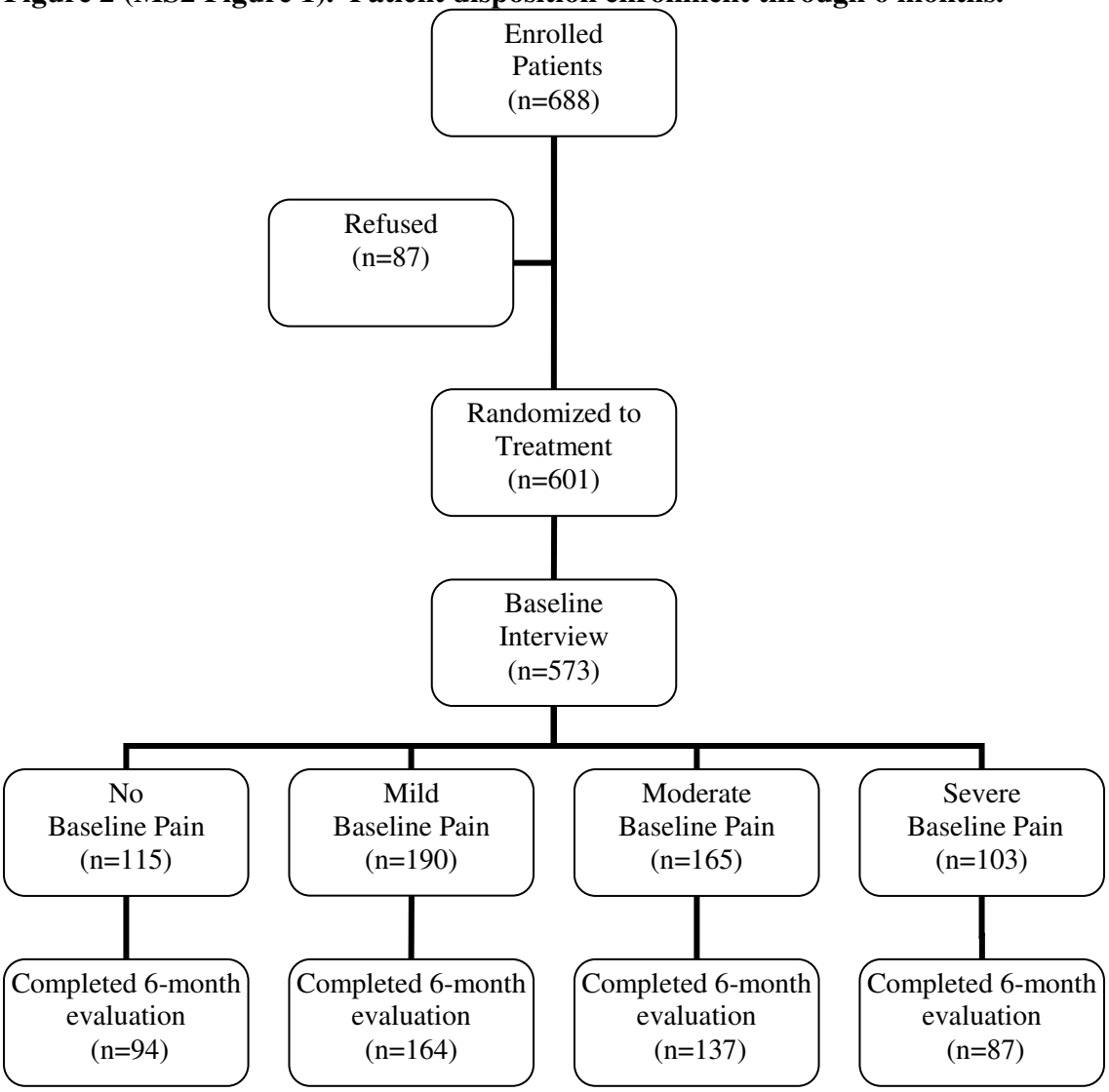
* Overall X^2 for pain improvement by response was not significant (X^2=0.17, degrees of freedom=2, p=0.92)

Table 24 (MS2 Table 6). Adjusted* OR (95% CIs) for the association between early pain improvement and depression outcome at month 6 in primary care patients (complete case analysis)

	Adjusted* OR (95% CI)	
	3-point improvement	**2-point improvement**
Remission	1.90 (1.03, 3.49)	2.97 (1.73, 5.12)
Partial Response	1.24 (0.63, 2.43)	1.34 (0.74, 2.44)
Nonresponse	1.0	1.0

*adjusted for baseline depression severity, baseline pain severity, and age.

Figure 2 (MS2 Figure 1). Patient disposition enrollment through 6 months.



CHAPTER VIII

DISCUSSION

Summary of Findings

This dissertation examined the association of two common comorbid conditions, panic and pain symptoms, with depression outcomes in a depressed primary care population. The research had three primary goals. First, we explored the association of baseline and persistent panic symptoms on depression outcomes after 6 months of treatment (manuscript 1). Second, we explored the association of baseline pain symptoms on depression outcomes after 6 months of treatment (manuscript 2). Third, we explored how early improvement in pain symptoms affected depression outcomes after 6 months of treatment (manuscript 2).

Baseline Panic and Persistent Panic

In the first portion of this dissertation, we found that baseline panic symptoms were not associated with worse depression outcomes at month 6 (remission vs. nonresponse and partial response vs. nonresponse, subsequently referred to as "both regression models"). However, persistent panic was associated with worse depression outcomes. Furthermore, there was evidence of an incremental response, with a stronger association with remission vs. nonresponse and a weaker association with partial response vs. nonresponse. Adjustment for demographic and other clinical covariates had a minimal effect. Results were similar using complete case analysis, last observation carried forward, and multiple imputation analysis.

Furthermore, the results of the sensitivity analysis demonstrate that our results are robust to varying the sensitivity and specificity across a wide range of values.

Baseline Pain and Early Improvements in Pain

Our second manuscript aimed to explore how baseline pain symptoms and improvements in pain affect depression outcomes at 6 months in primary care patients. We found that baseline pain was associated with worse depression outcomes at month 6, and there was evidence of an incremental effect with increasing pain severity. Additionally, there was evidence of an incremental effect with a stronger association in the remission vs. nonresponse comparison than in the partial response vs. nonresponse comparison. The results were consistent across different measures of pain (the PHQ-15 pain subscale and the SF-36 pain severity question).

Additionally, we explored the effect of early pain improvement (pain improvement from baseline to month 1) on depression treatment outcomes at month 6. Among patients with any pain at baseline, early improvement of pain was associated with better depression outcomes at month 6. Furthermore, early pain improvement was associated with higher odds of depression remission using both a 2- and 3-point cut-off to define early pain improvement. In fact, a stronger relationship was observed between early pain improvement and depression outcome using the less conservative 2-point cut-off, suggesting that even small improvements in pain result in significantly better depression outcomes.

In both pain analyses, adjustment for demographic and other clinical covariates had a minimal effect, with the exception of age.

Interpretation

Baseline and Persistent Panic

Though the presence of baseline panic can negatively affect depression outcomes in both primary[55, 63-65] and specialty[38, 42, 43, 45, 47-54] care settings, we did not observe an association between baseline panic symptoms and depression outcomes. However, our analysis, like prior analyses which have failed to demonstrate an association, [64, 65] relied on the use of a screening question to assess panic symptoms rather than a clinical diagnosis or a more comprehensive measure of panic severity. To address this potential misclassification of our panic variable, we conducted a probabilistic sensitivity analysis. The results were comparable to the complete case, last observation carried forward, and multiple imputation analyses, suggesting that our results are robust despite the use of a screening question.

Although we did not find an association between baseline panic symptoms and depression outcomes (remission or partial response) at month 6, we did find a strong association of persistent panic with depression outcome, particularly remission. By requiring patients to have panic at baseline and at 3 months of follow-up, our definition of persistent panic may be associated with worse depression outcomes because it represents more severe or unremitting panic symptoms. Alternatively, it may be a better indicator of the presence of panic disorder than baseline panic symptoms alone. To our knowledge, this is the first analysis of the longitudinal effects of panic on depression treatment outcomes in a primary care setting.

Despite the use of a screening question for panic, our results are informative because we have identified that panic symptoms, regardless of whether they met DSM-IV criteria for panic attacks or disorder, can negatively affect depression outcomes when they persist despite antidepressant treatment. This is particularly important because many of the

antidepressants, including the SSRIs, are also indicated for the treatment of panic disorder. Furthermore, the magnitude of the effect for persistent panic symptoms suggests that the presence of panic symptoms alone is enough to affect depression outcomes; it follows that the effect of panic disorder or panic attacks would result in an even greater effect.

Baseline Pain and Early Improvements in Pain

Our results demonstrate that depression outcomes after 6 months of treatment are worse in patients with comorbid pain at baseline, which is consistent with prior studies conducted in a primary care setting.[93, 104, 142, 143, 145] Furthermore, our results extend the analyses previously conducted in the ARTIST dataset,[104] which evaluated the effect of baseline pain on depression and other health-related quality of life outcomes after 3 months of treatment using ARTIST, a primary care study of the effectiveness of SSRI treatment. Consistent with these results, we found an incremental effect with increasing pain severity. Additionally, we found an incremental effect according to depression outcome, with a stronger effect seen in the remission vs. nonresponse comparison compared to the partial response vs. nonresponse comparison.

Though the presence of pain negatively affects depression outcomes, [93, 104, 142, 143, 145] and can limit the effectiveness of depression interventions,[142] improvement in pain is associated with improved depression outcomes.[93, 105, 143] Consistent with prior research,[104] we found that, among patients with any pain at baseline, early improvement of pain was associated with better depression outcomes at month 6, with an incremental effect according to depression outcome (remission and partial response). Our analyses extend the previous findings by exploring depression outcomes in the maintenance phase of treatment and by exploring what the how baseline pain and early improvement in pain (pain improvement

from baseline to month 1) affect depression outcomes at 6 months. Examining outcomes at month 6 is important since this is a critical time period for depression relapse, and adverse prognostic factors such as pain may be particularly salient in predicting relapse.

Public Health Significance

Why is it important to understand the affect of panic and pain symptoms on depression outcomes in primary care patients? Depression is common, affecting approximately 121 million people worldwide[3] and most of the research on depression has been conducted in specialty care settings. While the goal for depression treatment is remission, a large "real world" antidepressant effectiveness trial demonstrated that only about 30% of patients experienced remission regardless of treatment setting (primary vs. specialty care).[1] In order to effectively treat depressed patients, it is vital to understand what leads to 70% of patients failing to meet remission, the goal of antidepressant treatment.

Depression is often treated in a primary care setting: approximately 10% of all visits are depression-related,[5] nearly half the outpatient care for depression occurs in primary care settings,[4] and the number of antidepressant visits is similar for primary and specialty care.[6] Furthermore, the average visit to a PCP lasts only about 15 minutes[8, 9, 19, 146] and diagnosis and treatment for depression must compete with other demands.[20-23] Given the time constraints and that most depression research has been conducted in specialty care settings, it is critical that PCPs understand the factors contributing to poor depression outcomes.

Finally, both comorbid anxiety and pain symptoms are common in depressed patients, occurring in approximately 65% (anxiety) to 80% (pain) of depressed patients. Although other anxiety disorders may more commonly co-occur with depression, such as GAD and SAD, panic disorder is associated with severe disability and work impairment in patients

treated in primary care, even when the presence physical and depressive illness is controlled for.[131]

Finally, both panic and pain symptoms are treatable. Because an improvement in these comorbid conditions leads to improved depression outcomes, it follows that a treatment strategy that focuses not only on depressive symptoms but also on these common comorbid conditions is warranted.

Recommendations for Future Research

The results of this research suggest that the presence of both panic and pain symptoms are important to consider when treating depressed primary care patients. To date, little is known about the effect of improvements in panic or pain on depression outcomes in primary care patients. While our study sought to explore panic and pain improvements, there were some inherent limitations in the data.

Panic was measured using a screening question, rather than a clinical diagnosis. Though we were able to demonstrate that even symptoms of panic disorder negatively affect depression outcomes when they persist despite antidepressant treatment, we are unable to explore the effects of DSM-IV panic disorder or panic attacks. Additionally, as we only had a dichotomous measure of panic, we were unable to fully explore how changes in panic affect depression outcomes. However, our results suggest that panic that does not improve may be crucial to the improvement in depression. Therefore, future research should explore not only baseline panic symptoms or panic disorder, but also the severity of panic symptoms, and changes in panic over the course of treatment.

Our study demonstrated that the presence of baseline pain negatively affected depression outcomes and early pain improvement (both measured using the PHQ-15 pain subscale) led to significantly better depression outcomes. The validity of the PHQ-15 has been demonstrated in general internal medicine and family practice clinics as well as obstetrics-gynecology clinics[122] and it has also proven responsive to change in treatment trials of patients with pain and other somatic symptoms.[2, 144] However, no research has explored the minimal clinically meaningful difference in pain score using this scale. To define pain improvement, we used a 3-point change because it reflects the mean change from baseline to endpoint for patients treated with extended-release venlafaxine in anxious and/or depressed patients with multisomatoform disorder.[124] Furthermore, a 3-point improvement in pain is approximately equal to a change in pain level when pain is categorized as none, mild, moderate, or severe using the PHQ-15 pain subscale. Additionally, we re-analyzed the data using a 2-point cut-off to examine how sensitive our results were to our choice of cut-point. While our results demonstrated that even changes in pain of as little as 2 points significantly affect depression outcomes, definitions of clinically meaningfully differences on this validated scale should be explored and applied to future research.

Finally, while we did not find any evidence of confounding by adequacy of antidepressant treatment, our study was limited by relatively simple classifications of adequate antidepressant treatment that incorporated doses at the low end of the effective range. Although the minimum dose was low, there is evidence that lower antidepressant doses are commonly used in a primary care setting,[134, 135] and antidepressant dosing in the ARTIST study was primarily in the lower end of the usual recommended dose range. This limited our ability to explore a more comprehensive definition of adequate treatment or to

explore a relationship between dose and antidepressant response. However, future studies should incorporate comprehensive measures of treatment in order to assess the effect of treatment on depression outcomes, particularly among patients with other comorbid conditions, as adequacy of antidepressant dosing, particularly in populations where patients are treated with a greater range of doses, may affect treatment outcomes.

Finally, although we sought to examine comorbid panic and pain symptoms, we were unable to control for concurrent treatment of comorbid panic and pain symptoms. The added value of pain-specific management strategies (e.g., optimized analgesic therapy, behavioral interventions) in patients with comorbid pain should be examined, as should anxiety-specific management strategies (e.g., optimized antidepressant or anxiolytic therapy, behavioral management) in patients with comorbid panic.

APPENDICES

APPENDIX A. ETHICAL REVIEW AND INFORMED CONSENT

Ethical Review

This study was reviewed by the Institutional Review Board (IRB) of The University of North Carolina at Chapel Hill (Determination that Research or Research-Like Activity does not require IRB Approval). Because the study used de-identified data (with out access to key of identifiers) from the ARTIST study, the IRB determined that this activity does not constitute human subjects research as defined under federal regulations, and therefore did not require IRB approval.

Informed Consent

Informed consent was not required for the current study; the original consent form for ARTIST covers secondary analysis of the data. Data for the study were obtained already coded with an identification number and participant names were not be obtained.

APPENDIX B. RESULTS OF EARLY PAIN IMPROVEMENT ON DEPRESSION OUTCOMES AT MONTH 1

Because manuscript 2 provided a more informative analysis of early pain improvement on depression outcomes by focusing on results at Month 6 rather than at Month 1, we did not include results from Month 1 analysis in either the dissertation or the manuscripts. Results were similar at Month 1, though there is evidence of a stronger association and there is a substantial loss of precision.

Of the 458 patients reporting any pain at baseline, 436 remained in the study and completed the 1-month visit and 117 of these patients (27%) experienced early pain improvement, defined as ≥3-point change in pain severity as measured by the PHQ-15 pain subscale from baseline to month 1. In the bivariate analysis, early pain improvement was associated with better depression outcomes at Month 1, mainly for remission but also for partial response (Table 25). There was no association of early pain improvement and partial response in the crude analysis.

Similar to the bivariate analysis, the multivariate analysis indicated that early pain improvement was associated with better depression outcomes at Month 1, adjusting for age, baseline depression severity (baseline SCL-20 score), and baseline pain severity (Table 26). However, the association was stronger at month 1 than it was at month 6, and there was a loss of precision. Results were similar in the last observation carried forward and multiple imputation analyses.

The multinomial regression model was repeated with early pain improvement defined as ≥ 2-point improvement in pain as measured by the PHQ-15 pain subscale from baseline to month 1 (Table 26). Overall, using the 2-point cut-off, there was a slightly stronger

association between pain improvement and depression outcomes, with early pain improvement were much more likely to achieve remission vs. nonresponse and more likely to achieve partial response vs. nonresponse. Compared to the 3-point cut-off, the ORs are larger using the 2-point cut-off suggesting a strong association between early pain improvement and depression outcomes even when a less conservative definition of early pain improvement is utilized.

Overall, the results at Month 1 are consistent with the results at Month 6 and support our overall conclusions. Additionally, they support that early improvement in pain is associated with depression response as early as Month 1.

Table 25 (Appendix B, Table 1). Depression response at month 1 by early pain improvement *

Depression Outcome	Early Pain Improvement (n=117) n (%)	No Early Pain Improvement (n=319) n (%)	Unadjusted OR (95% CI)
Remission	28 (24)	50 (16)	1.73 (1.01, 2.95)
Partial Response	19 (16)	53 (17)	1.11 (0.61, 1.99)
Nonresponse	70 (60)	216 (68)	1.0

* Overall X^2 for pain improvement by depression outcome was not significant ($X^2 = 0.17$, degrees of freedom=2, p=0.92)

Table 26 (Appendix B, Table 2). Adjusted* OR And 95% CI for the association between early pain improvement and depression outcome at month 1 (complete case analysis)

Depression Outcome	Adjusted * OR (95% CI)	
	3-point improvement	2-point improvement
Remission	3.20 (1.66, 6.16)	4.08 (2.21, 7.54)
Partial Response	1.09 (0.57, 2.10)	1.81 (1.02, 3.23)
Nonresponse	1.0	1.0

* adjusted for baseline depression severity, baseline pain severity, and age.

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