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Indiana Cancer Pain and Depression (INCPAD) Trial Design of a Telecare Management Intervention for Cancer-Related Symptoms and Baseline Characteristics of Study Participants

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Abstract

Objective—Pain and depression are two of the most prevalent and treatable cancer-related symptoms, each present in at least 20-30% of oncology patients. Both symptoms, however, are frequently either unrecognized and/or undertreated. The objective is to describe a telecare management intervention delivered by a nurse-psychiatrist team that is designed to improve recognition and treatment of pain and depression. The enrolled sample is also described.

Method—The Indiana Cancer Pain and Depression (INCPAD) study is an NCI-sponsored randomized clinical trial. A total of 405 patients with cancer-related pain and/or clinically significant depression from 16 urban or rural oncology practices throughout Indiana have been enrolled and randomized to either the intervention or a usual care control group. Intervention patients receive centralized telecare management coupled with automated home-based symptom monitoring. Outcomes will be assessed at 1, 3, 6 and 12 months by research assistants blinded to treatment arm.

Results—Of 4465 patients screened, 2185 (49%) endorsed symptoms of pain or depression. Of screen-positive patients, about one-third were ineligible (most commonly due to pain or depression not meeting severity thresholds, or pain that is not cancer-related). Of the 405 patients enrolled, 32% have depression only, 24% pain only, and 44% both depression and pain. At baseline, participants report an average of 16.8 days out of the past 4 weeks in which they were confined to bed or had to reduce their usual activities by ≥ 50% due to pain or depression. Also, 176 (44%) report being unable to work due to health reasons.

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Conclusions—When completed, the INCPAD trial will test whether centralized telecare management coupled with automated home-based symptom monitoring improves outcomes in cancer patients with depression and/or pain. Findings will be important for both oncologists and mental health clinicians confronted with oncology patients' depression or pain.

Keywords

cancer; pain; depression; antidepressants; analgesics; telemedicine; care management

1. Introduction

1.1. Pain and Depression in Cancer

Pain and depression are two of the most common, treatable symptoms in cancer patients yet often remain undetected and/or inadequately treated. Pain is present in 14-100% of cancer patients, depending upon the setting, and the prevalence of major depressive disorder is 10-25%, with a similar range for clinically depressive symptoms.[1-4] The impact of these symptoms on functional status and quality of life is considerable.[5-10] Depression is frequently underdiagnosed in cancer patients,[11-13] and up to half of cancer patients depressed at baseline remain depressed at one-year follow-up.[1] Likewise, cancer pain often is undertreated.[1,14,15]

1.2. Barriers to Optimal Management

Four common barriers to effective treatment of symptoms in both primary and specialty care are underdetection of bothersome symptoms, inadequate initial treatment, failure to monitor adherence and response, and failure to adjust therapy in non-responding patients.[16] This is well-established for depression as well as pain and other symptoms.[17-25] These four barriers are also among the most common and “action-able” in oncology.[26-30] In primary care, much has been written about the concept of “competing demands” in time-limited visits.[31,32] Clearly, this pertains to oncology practice as well where the time required for evaluation and treatment of the primary cancer competes with time left over for associated symptoms like pain and depression. Understandably, the nuances of antidepressants and various pain regimens as well as subsequent symptom monitoring may be outweighed by the requisite attention to chemotherapy, tumor response, hematological nadirs, and other complexities of cancer treatment.

1.3. Potential Benefits of Care Management

Multi-component systems interventions consistently improve depression outcomes, whereas single component interventions, such as depression screening or provider education, are insufficient by themselves.[17,18,33,34] Indeed, the U.S. Preventive Services Task Force recommends depression screening only if there are adequate systems in place to support depression treatment and monitoring.[35] A review of 28 randomized multi-component effectiveness trials for treatment of depression in primary care demonstrated a median absolute increase of 18.4% in the proportion of patients achieving a 50% improvement.[36] Disease management programs have also proven beneficial for diabetes, heart failure, asthma, and other chronic medical disorders.[37] However, the effectiveness of collaborative care and/or disease management programs for pain has not been established, and the generalizability of studies largely conducted in primary care to the more specialized setting of oncology practices is not known.

1.4. Role of Telemedicine

Numerous clinical trials have established the effectiveness of telephone care management and telepsychiatry for depression treatment in primary care patients across a variety of settings, ranging from large organized health care systems to more rural settings.[38-42] Indeed, the benefits compared to usual care may even be greater in rural settings.[43] Preliminary data in cancer trials also suggest the potential effectiveness of telemedicine for pain management. [44].

Although simple telephone-based screening for depression in oncology practices has proven acceptable,[45] telecare management of depressed cancer patients has not been studied. Promising studies in cancer patients with depression, pain, and/or fatigue by Given et al[44, 46,47] differ from our trial in that: (a) their interventions were psychoeducational rather than pharmacological (which affects generalizability since medications are more commonly the initial approach for pain and depression in oncology practices); (b) the number of required nursing contacts (9 to 10) was higher, and half were in-person visits; and (c) some of the outcomes were of marginal significance due to a much smaller sample size.

1.5. Conceptual Model in INCPAD: Three-Component Model (TCM)

Figure 1 illustrates the Three-Component Model (TCM) developed for the treatment of depression in medical settings[48] and empirically validated in a dissemination depression trial involving 60 primary care practices.[49,50] TCM is based on relationships between three types of providers collaborating through complementary roles in overcoming barriers to optimal disease management. The three ***providers*** are the patient's primary provider, a nurse care manager, and a specialty consultant. In the INCPAD trial, this comprises the oncology practice (often consisting of an intra-practice oncologist-nurse partnership), a Depression-Pain Care Manager (DPCM), and a psychiatrist with special expertise in pain management. The ***relationships*** are illustrated in Figure 1, reflecting the central role of the DPCM as the key liaison between the patient, oncology practice, and psychiatrist. The four cardinal ***barriers*** addressed by the TCM model are failures in symptom detection (in this case, pain and depression), treatment initiation, monitoring of symptom response as well as adherence to and adverse effects of treatment, and adjustment of therapy in patients not responding to or intolerant of initial treatment. The primary ***roles*** are as follows: (a) the oncology practitioners – either physician or nurse – detect bothersome symptoms (e.g., pain and depression screening complemented by spontaneous patient reporting and provider inquiry); (b) the DPCM care manager recommends treatment for symptoms in accordance with evidence-based guidelines, and monitors response and adherence; and (c) the psychiatrist supervises the DPCM and advises on complex or nonresponding cases. The oncologist implements treatment recommendations and the psychiatrist becomes directly involved in the management of difficult cases (telephone or in-person patient consultation).

2. Methods

2.1. Overall Design

Following an eligibility interview and ascertainment of informed consent, patients are randomized to the TCM intervention arm or the usual care control arm. The intervention consists of automated home-based symptom monitoring coupled with centralized telephonic care management. Outcome assessments are conducted at baseline, 1, 3, 6, and 12 months by interviewers blinded to treatment arm. The two primary outcomes are depression severity (assessed by the SCL-20) and pain severity/interference (assessed by the Brief Pain Inventory). Secondary outcomes include health-related quality of life, treatment satisfaction, and costs.

2.2. Recruitment

2.2.1. Identifying and Enrolling Study Participants—The enrollment period was from March 2006 through August 2008. Patients presenting for oncology clinic visits completed a 4-item depression and pain screener, consisting of the PHQ-2 depression scale and the SF-36 bodily pain scale, both of which are well-validated measures for assessing depression and pain severity.[51,52] Patients who presented to the clinic multiple times during the study enrollment period were eligible to be screened on more than one occasion if at least 4 weeks had elapsed since the last time they were screened.

Patients who screened positive for pain (at least moderate pain severity or pain interference) [52,53] or for depression (PHQ-2 score ≥2) [51] and documented a willingness to be contacted received a telephone call to undergo an eligibility interview. If the patient was eligible, the study was described in detail and audiotaped telephone-based informed consent and HIPAA release was obtained from those who desired to participate. Then the baseline interview was conducted after which the subject was randomized to the intervention or usual care group. For intervention patients the initial telephone care manager contact was scheduled. Informed consent and HIPPA forms were mailed to the subject, signed, and returned in a pre-addressed, stamped envelope.

2.2.2. Eligibility—*Depression* had to be of at least moderate severity, defined as a PHQ-9 score of 10 or greater with either depressed mood and/or anhedonia being endorsed.[54-56] In previous studies, > 90% of patients fulfilling this PHQ-9 criterion had major depression and/or dysthymia, and the remaining patients had clinically significant depression with substantial functional impairment.[54,57] Patients who are on antidepressants but yet meet the entry criterion for clinical depression (PHQ-9 ≥ 10) are still eligible since they remain depressed despite antidepressant therapy. We have used this approach in multiple prior effectiveness trials of depression in medical populations.[49,58-60]

Pain had to be: (a) at least moderate in severity, defined as a Brief Pain Inventory score of 5 or greater;[14,61-63] (b) persistent despite having tried at least one different analgesic medication; (c) cancer-related. The rationale for eligibility criterion b (i.e., persistent pain despite analgesic use) is that numerous over-the-counter analgesic medications containing acetaminophen or various types of NSAIDs are widely available. Most patients experiencing pain will have already tried (either on their own or following their physician's advice) at least one simple analgesic which, if it ameliorates the pain, will obviate the need for more intensive analgesic management. Cancer-related is defined as pain occurring in the region of the primary tumor or cancer metastases and/or occurring after the onset of cancer treatment. Excluded were pre-existing pain conditions unrelated to cancer (e.g., migraine or tension headache, arthritis, back disorders, bursitis/tendonitis, injuries, fibromyalgia). Patients are asked: “Does your doctor (or you) feel that any of this pain is related to your cancer?” Patients are eligible if they respond “probably”, “possibly”, or “don't know”. Only patients who report that all of their pain symptoms are definitely due to a condition other than cancer are excluded. This patient report was not independently validated by chart review or oncologist verification.

Also excluded were individuals who: (a) did not speak English; (b) had moderately severe cognitive impairment as defined by a validated 6-item cognitive screener[64]; (c) had schizophrenia or other psychosis; (d) had a disability claim currently being adjudicated for pain; (e) had depression directly precipitated by a cancer therapy for which depression is a well-known side effect (e.g., interferon, corticosteroids) and in whom short treatment duration and tolerable depression severity justify withholding antidepressant therapy; (f) were pregnant; or (g) were in hospice care.

2.2.3. Randomization—After providing informed consent and completing the baseline assessment, participants were randomized by a computer program to either the intervention or usual care group. Randomization was stratified by symptom type (pain only, depression only, or both pain and depression), and was conducted in randomly varying block sizes.

2.2.4. Participation and Practice Compensation—Participants receive $25 for the baseline telephone-based research interview and for each of the four follow-up assessments. The oncology practice receives $85 per patient enrolled to compensate for the time involved in screening patients and in providing medical record information for participants enrolled in the study.

2.2.5. Participant Enrollment and Baseline Characteristics—Figure 2 summarizes the participant flow in INCPAD. Of 4465 screeners received, nearly half screened positive for depression and/or pain on the 4-item screener administered in the oncology clinics. Of the 1851 unique patients who screened positive, about a third were ineligible (most commonly because their pain or depression did not reach the severity threshold), a third had an indeterminate eligibility status either because they refused to complete an eligibility interview or could not be contacted, and a third were eligible. Of the 616 subjects determined to be eligible, about two-thirds consented to enroll in the study and were randomized to either the intervention or the control group. Reasons for refusal in the 568 patients for whom this information was available (asked of patients who either refused the eligibility interview or refused after being determined eligible) is summarized in Table 1.

Of the 405 participants enrolled, randomization resulted in intervention (n = 202) and control (n = 203) groups balanced in terms of baseline characteristics (Table 2). The sample includes 131 (32%) participants with depression only, 96 (24%) with pain only, and 178 (44%) with both depression and pain. Enrolled participants have a mean age of 58.8 years, 68% are women, and 20% are minority (principally African-American). The type of cancer is breast in 118 (29%) of the participants, lung in 81 (20%), gastrointestinal in 70 (17%), lymphoma or hematological in 53 (13%), genitourinary in 41 (10%), and other in 42 (10%). The average SCL-20 depression score in the 309 depressed participants is 1.64 (on 0-4 scale), and the average BPI severity score in the 274 participants with pain is 5.2 (on 0-10 scale), representing at least moderate levels of symptom severity. Also, 283 (92%) of the 309 patients enrolled for depression had major depression, dysthymia, or both. Thus, although a symptom severity cutpoint (PHQ-9 $\geq$ 10) rather than diagnostic interview was used to determine study eligibility for depression, the vast majority of subjects enrolled for depression had a depressive disorder diagnosis for which antidepressant therapy can be considered evidence-based.

Symptom-specific disability is high, with participants reporting an average of 16.8 days out of the past 28 (i.e., 60% of their days in the past 4 weeks) in which they were either confined to bed (5.6 days) or had to reduce their usual activities by 50% (11.2 days) due to pain or depression. Moreover, 176 (43%) report being unable to work due to health-related reasons. The mean SF-12 Physical Component Summary score of 32.7 substantiates the rather severe degree of impairment, as does the mean SF-36 Vitality score (28.3) and mean General Health Perceptions score (28.2).

2.3. Data Collection Protocol

Table 3 outlines the data collection protocol, including the variables that are measured and how and when they are assessed. The baseline, 3 and 12 month interviews take approximately 45 minutes; the 6 month interview about 35 minutes; and the 1 month interview about 20 minutes. All assessments are administered by telephone interview and conducted by a research assistant blinded to study group.

Depression diagnoses are established with the Patient Health Questionnaire, which with several added questions, categorizes individuals into 3 DSM-IV diagnostic subgroups: major depression, dysthymia, and other depression.[54] Depression severity is assessed, as a primary outcome, with the SCL-20,[57,65,66]

Pain is assessed primarily with the Brief Pain Inventory (BPI) which rates the *severity* of pain on 4 items (current, worst, least, and average pain in past week), and the *interference* in 7 areas (mood, physical activity, work, social activity, relations with others, sleep, enjoyment of life).[14,67,68] The SF-36 Bodily Pain scale,[69] provides a secondary measure of pain.

Clinical response is assessed with a 7-point Global Rating of Change with the options being worse, the same, or a little, somewhat, moderately, a lot, or completely better.[60] Health-related quality of life is assessed with the SF-12 Physical Component Summary (PCS) and Mental Component Summary (MCS) scores [70], as well the SF-36 [71,72] mental health scale, vitality scale, and a single general health perceptions item that has shown to predict long-term health outcomes.[73] Functional status, an important aspect of health-related quality of life, is further assessed with the 3-item Sheehan Disability Scale and a single-item overall quality of life measure[74,75] In addition, disability days are assessed as the number of days during the preceding 4 weeks in which the patient was either in bed or had to reduce his or her work or usual activities by ≥ 50%.[76,77]

Anxiety is assessed by the GAD-7[78,79], a 3-item version of the Social Phobia Inventory [80], the 5-item PHQ panic module [81], and a single PTSD screening question. Physical symptom type and severity are assessed with twelve symptoms from the PHQ-15[82] plus 10 more from the Memorial Symptom Assessment Scale and the MD Anderson Symptom Inventory.[83]

A treatment survey inquires about treatments received for pain and depression at both baseline and follow-up. An economic evaluation consists of 38 items derived from: (a) the IMPACT trial[75] which in turn used items from prior trials[84-86] to measure patient time costs, employment, nonmarket productivity (e.g., caregiving and volunteer work), receipt of informal care, living arrangements, income and household wealth; and (b) the Cornell Services Index, a detailed assessment of health care used during the prior 3 or 6 months.[50,75] Finally, pain and depression-specific treatment satisfaction is assessed.[60], as well as satisfaction with the INCPAD intervention.

2.4. Details of Treatment

2.4.1. Depression-Pain Care Managers (DPCMs) and Supervising Physicians—

Telephone care management is delivered by two nurse Depression-Pain Care Managers (DPCMs) who are trained in assessing symptom response with standardized pain and depression scales; in evaluating medication adherence; in providing brief pain and depression-specific patient education; and in making treatment adjustments according to evidence-based depression and cancer pain treatment guidelines. The DPCMs meet weekly for 1-2 hour supervisory sessions with one or both supervising physicians to review all new cases as well as patients previously enrolled for whom management may need to be modified. Also, one of the physicians is available at all times to discuss any management issues that arise between the weekly case meetings. The DPCMs have bachelors of science in nursing degrees with specialized training in oncology and are provided with approximately 12 hours of training to familiarize them with the symptom monitoring scales, medication algorithms, and automated symptom monitoring reports unique to the INCPAD trial. These skills are refined and reinforced in the weekly case management sessions with the supervising physicians. The two supervising physicians include a board-certified psychiatrist (DT) with a certificate of added qualification in addiction psychiatry whose clinical practice focuses on psych-oncology and

palliative care, and a board-certified general internist (KK) with research experience in depression, pain, and somatic symptoms.

2.4.2. Automated Symptom Monitoring and Telephonic Care Management— Participants in the intervention arm undergo automated symptom monitoring either by telephone or internet, depending upon their preferences. Participants can receive scheduled (automated) calls from the system (outbound); they can initiate calls themselves to the system if this is more convenient (inbound); or, if they have a personal computer, they can enter a secure website to complete their surveys. There is a tapering schedule of automated symptom monitoring: twice a week for the first 3 weeks, then weekly during weeks 4 through 11, twice a month during months 3 through 6, and once a month during months 7 through 12. However, in subjects who undergo treatment changes during a later phase of the study, more frequent automated monitoring can be reinstituted.

The 21-item measure includes 8 BPI items, the PHQ-9 depression scale, and a single item each on adherence, side effects, global improvement, and whether or not the patient would like to be contacted by the DPCM. Those not completing their scheduled assessment are contacted by the DPCM to complete the symptom measures.

All participants receive an initial call (week 0) to assess symptom severity and initiate treatment, and a follow-up call at 1-2 weeks to assess symptom severity, adherence, and adverse effects. Participants with depression receive two additional DPCM follow-up calls in the first 12 weeks of treatment in accordance with the National Committee on Quality Assurance HEDIS guidelines. Participants with pain have follow-up DPCM telephone contacts guided by initial symptom response and automated symptom monitoring. In addition to these *scheduled* DPCM phone contacts, *triggered* DPCM phone calls occur when automated monitoring indicates inadequate symptom improvement, suicidal ideation, nonadherence to medication, side effects, or a patient request to be contacted.

Substituting telephone contact for in-clinic assessment, treatment and monitoring of depression has proven effective in numerous clinical trials in primary care,[38,39,42], patients referred to mental health [41], and a recent trial in cancer-related depression,[13] Automated symptom monitoring should conserve DPCM time, minimize the number of times the DPCM and patient are playing “telephone tag”, and allow patients to complete symptom monitoring at a time convenient to them.

2.4.3. Antidepressant Management—The INCPAD antidepressant algorithm is informed by two recent trials: the landmark multi-center STAR*D trial, and our own SCAMP trial.[60,87] In STAR*D, no specific antidepressant or combination proved superior; instead the key to improving remission rates was regular depressive symptom monitoring coupled with dosage escalations or medication or other treatment changes.

Table 4 outlines the general prioritization of antidepressant selection and indications in special circumstances. Notably, all drugs listed in Table 4 are available as generic medications. An SSRI is the first choice because of wide usage, low cost, and well-established efficacy, safety and tolerability.[57,88] Since individual SSRI antidepressants are similar in both efficacy and tolerability,[57,89] the particular SSRI selected is based upon other factors including patient history (i.e., experience with prior antidepressants in terms of response, intolerance, etc.); medical comorbidity (e.g., demonstrated safety of sertraline and citalopram in cardiovascular disease[90,91]); other medications (e.g., citalopram and sertraline have the least effect on cytochrome P450 enzymes that metabolize other drugs), drug benefits and copayments, comorbid anxiety, and other factors.

Clinical response is assessed at 3 weeks and, if there is not a partial response (i.e., a 5 point drop in PHQ-9[55,92]), a *dose increase* occurs as shown in Table 4. If a partial response is not attained by 6 weeks, the antidepressant may be switched. The ultimate goal is remission (PHQ-9 score < 5) or, failing this, a PHQ-9 score < 10 with a 50% decline from baseline score. Further details of rules and timepoints for medication and dose adjustments are published elsewhere.[60] While Table 4 outlines a rational sequence of drug selection, INCPAD is not testing any particular antidepressant but, instead, optimal medication management that is both effective and tolerated in an individual patient. Since fewer than half of patients started on a given antidepressant will achieve remission with the first drug, this pragmatic, patient-specific approach approximates real-world *in vivo* depression management rather than an inflexible *in vitro* testing of a single drug.[87,93]

Of note, some depressed patients (up to 30% in some effectiveness trials) may prefer not to be treated with antidepressants and opt instead for either nonpharmacological treatments (e.g., psychotherapy) or "watchful waiting". In INCPAD, such patients will be encouraged to discuss alternative treatment options, including mental health referral, with their oncologist.

2.4.4. Analgesic Management—The DPCM assesses what pain treatments have been tried by the patient and whether an adequate treatment trial has been completed. If inadequate dosage, scheduling, or adherence has been a problem, the DPCM may recommend a brief trial of the current analgesic with appropriate dosing and scheduling. The "analgesic ladder" used in INCPAD (Table 5), is adapted from the National Comprehensive Cancer Network Cancer Pain Clinical Practice Guidelines.[94], with some simplification based upon the American Pain Society, World Health Organization, and American Medical Association pain management guidelines.[26,95,96] The treatment goal is to obtain at least a 30% reduction in the BPI interference score and, ideally, a score of 3 or less. The Appendix summarizes some key principles of pain management for INCPAD.

2.4.5. Comorbid Pain and Depression—The DPCM typically treats the pain for 4 weeks, and reassesses both pain and depression response. For patients who continue to meet the severity threshold for depression (PHQ-9 ≥ 10) after 4 weeks of pain treatment, the intervention for depression is initiated. Patients with more severe depression at baseline (PHQ-9 scores ≥ 15) will be considered for initial antidepressant therapy rather than wait for a 4 week trial of the pain intervention.[54,55] Also, any patient with suicidal ideation is immediately evaluated using an evidence-based algorithm from our previous trials.[57,59,60] Finally, some patients may develop pain and depression *sequentially* rather than simultaneously, i.e., they will enroll in the study with pain or depression only but subsequently develop the other symptom. In this case, the DPCM will treat the emergent depression or pain according to the same treatment guidelines, consistent with the dual-symptom focus of our intervention. For primary hypothesis testing, the enrollment symptom remains the primary outcome, but the development during 12-month follow-up of incident pain and/or depression and their response to treatment will be examined as secondary outcomes.

2.4.6. Usual Care Arm—Patients randomized to usual care are informed of their depressive and pain symptoms and their screening results are provided to their oncologist. Other than this initial step, there are no further attempts by study personnel to influence depression or pain management unless a psychiatric emergency arises (e.g., suicidal ideation is detected on a baseline or follow-up outcome assessment interview). While randomization by patient means oncologists have both intervention and control patients in their practices, numerous primary care effectiveness trials of depression care have shown there is little spillover of the intervention to usual care patients in the absence of the care management, symptom monitoring and treatment adjustment that occurs with enhanced care of varying types.[17,18,59,65,66,97-99]

Whatever minor spillover occurs results in a conservative estimate of the intervention's effectiveness.

2.5. Statistical Analysis

2.5.1. Sample Size Estimates—The target sample size was based on power analysis for our two primary outcomes, depression and pain. The measures (SCL-20 and BPI) provide both categorical and continuous data. For categorical data, a reduction of ≥ 50% in depression severity and ≥ 30% in pain severity are accepted thresholds for clinically significant improvement in depression and pain trials, respectively.[100,101] With a two-sided alpha of 0.05, we will have *at least* 80% power to detect a 20% group difference in improvement rates if we maintain a sample size of 97 in each of the treatment groups. For continuous data, to detect a moderate TCM treatment effect size of 0.4 SD on either the SCL-20 depression score or BPI pain score, INCPAD would need 100 patients per group. By enrolling 125 patients per group with pain (250 total), and 125 patients per group with depression (250 total), we have a 25% cushion in the sample size to test our co-primary hypotheses that TCM is effective for both pain and depression. Preliminary work suggested that approximately a quarter of patients had pain only, a third had depression only and 40-45% had both depression and pain. Thus, to enroll 250 patients with pain and 250 patients with depression, INCPAD requires a sample size of 385.

2.5.2. Primary Analyses—The principal outcomes will be depression (SCL-20) and pain (BPI) severity at the end of the acute (3 months) and maintenance (12 months) phases of treatment. We will conduct an intent-to-treat analysis, i.e., all participants are included in the analysis according to the group to which they are assigned. For participants with missing outcome data, we will use last observation carried forward (LOCF) and multiple imputation (MI) strategies in order to use all randomized participants in the 3- and 12-month analyses. We will fit mixed-effects regression models for repeatedly measured continuous variables or mixed-effects logistic regression models for dichotomous variables using baseline and follow-up data. The random effects portion of these models provides the structure needed to account for clustering or potential lack of independence that may exist between observations for the same practice, although we found that clustering had a minimal effect in a prior community-based depression trial in which practices were the unit of randomization [49]. Since patients are the unit of randomization in INCPAD, each practice will have both intervention and control patients which will help control for factors unique to a particular practice as well as differences between practices. In these models, we will treat time as a categorical variable and examine the fixed effects for time, intervention group, and their interactions.

2.5.3. Secondary Analyses—Analytic techniques will be similar to those described under primary analyses, with the dependent variable in separate models being secondary outcomes that are both clinically important as well as potentially modifiable by the intervention. These include health-related quality of life (e.g., SF-36 scales), disability days, anxiety, satisfaction with treatment; and other outcomes in Table 3. For these secondary outcomes, the p-values will be adjusted for multiplicity using the Sidak method:[57,102] where: adjusted p-value = $1 - (1 - \text{unadjusted p-value})^{\#\ \text{tests}}$.

2.6. Cost Analysis

Costing—The economic analysis will be similar to that used by Rost et al in analyzing the cost-effectiveness of a depression care management program in primary care[103] which in turn is based upon economic analyses in several previous depression care management trials.[40,97,104-106] While these trials focused solely on the impact of depressive symptoms, we will focus on the impact of both pain and depressive symptoms. We will do a cost accounting [107] of the TCM intervention to estimate the cost from the perspective of both the provider

and society (patient + provider). Incremental provider costs are defined as the difference between TCM and usual care in actual program and outpatient treatment costs. Incremental societal costs are defined as the difference between TCM and usual care in actual program costs, outpatient costs, and costs to the patient (e.g., time, transportation).

Program costs include staff time costs (salary plus fringe benefits) derived from care manager logs for patient screening, preparation for and delivery of TCM care, post-session record keeping and review, care manager/oncology practice communication; supervising psychiatrist time, and overhead. *Outpatient costs* for oncology and other clinic visits, emergency room visits, and pain and psychotropic medication will be estimated from patient-reported utilization at each wave, reflecting that participants are insured by multiple different payers. Outpatient and emergency room visit costs will be estimated using current Medicare payment rates. For the cost estimate, psychotropic and pain medication costs will be priced at the lowest average generic wholesale price per medication dosage reported in the current Red Book of Prescription Drugs. *Patient time costs* will be estimated from patient reports of travel times to and from the clinic plus waiting time. For employed patients, time costs are calculated using self-reported wage rates. For unemployed patients, we will substitute current year average wage rates by gender and education as a proxy of patient time costs. Also, caregiver time costs will be estimated from patient report. *Transportation costs* will be calculated from patient reported round-trip miles to and from the location of services. Finally, we will also estimate inpatient days and costs from patient-reported utilization at each wave. However, as with cost analyses of other outpatient programs,[105,108,109] we may not be able to include inpatient costs because hospitalization may affect only a small percent of patients which, coupled with high inpatient costs, makes estimates of between-group differences imprecise.

Cost-Effectiveness Analysis—The TCM intervention's impact on *depression or pain impairment-free days* will be evaluated using two methods from previous trials. The first method asks patients to estimate the number of days over the past 4 weeks that their depressive or pain symptoms kept them in bed all/most of the day or caused them to cut down on things they usually do for one half day or more.[103,110] The second derives depression- or pain-free days from the patient's SCL-20 [40,97,104] or BPI scores. We will run separate analyses for each method of estimating depression or pain impairment-free days. In each analysis, we will estimate the intervention's impact on generic QALYs using the SF-12, adapted from similar analyses using the full SF-36.[111-113] Two types of cost-effectiveness ratio will be estimated: 1) Incremental Cost per symptom-free day; and, 2) Cost per QALY gained. The numerator in each CE ratio is the incremental difference in cost between TCM and usual care. One denominator will be the incremental difference in the number of symptom-free days and the other will be the difference in QALYs between TCM and usual care.

3. Summary

INCPAD has been successful in enrolling 405 cancer patients from 16 urban and rural oncology clinics, the majority of which are community-based. Many eligible patients did not enroll because of lack of interest, poor health due to their cancer or other comorbid medical illnesses, feeling too well or too busy, problems with a telephone-based intervention, or family factors. Barriers to enrollment in cancer symptom research have been recently reviewed.[114]

In summary, the Indiana Cancer Pain and Depression (INCPAD) trial has a number of strengths, including: (1) an intervention aimed at improving the care of two of the most prevalent and burdensome cancer-related symptoms, i.e., pain and depression; (2) a focus on 4 of the most common barriers to optimal symptom management, namely underdetection, inadequate initial treatment, failure to regularly monitor adherence and symptom response, and failure to adjust treatment in patients not responding to or intolerant of initial therapy; (3) a

TCM conceptual model which has been empirically validated and draws on the respective skills of the primary oncologist, a nurse care manager, and a supervising pain-psychiatrist; (4) a unique partnership between an academic unit with special expertise in depression and pain effectiveness trials and a statewide network of community-based oncology clinics located in rural as well as urban areas; (5) a sufficiently large sample (n = 405) to test the effectiveness of TCM for both depression and pain; (6) an innovative use of technology that couples automated home-based symptom monitoring with centralized care management to cover multiple geographically-dispersed oncology practices in a manner that is at once patient-friendly as well as provider-efficient; (8) an explicit decision to include a broad rather than narrow spectrum of cancer patients, such that the study findings will be maximally generalizable and pragmatic.

Should TCM prove effective for pain and depression, there are several exciting directions that might be pursued. One would be to add additional symptoms (e.g., fatigue, nausea) to the nurse care manager's portfolio, moving beyond a care management model that too often has focused on a single disease to a “pluripotential” symptom care manager. A second possibility would be to determine if automated symptom monitoring could be linked with systems enhancements at the “local” level of the individual practice (provider training, decision support, patient activation, etc.) to provide an alternative model for using home-based symptom monitoring to improve outcomes.

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Appendix

Appendix. General Principles of Pain Management in INCPAD

- The appropriate dose is the dose that relieves the patient's pain throughout its dosing interval without causing unmanageable side effects
- In some patients, immediate-release opioids alone are desirable, such as initial dose-finding (e.g., first 48 hours) in opioid-naïve patients or rapidly changing pain (e.g., acute worsening after treatments or procedures).
- Calculate increase based upon total opioid dose (around the clock/scheduled and as needed) taken in the previous 24 hours
- When increasing dose of opioid or changing to new opioid
  - Better to be conservative (“undershoot”) on fixed dose increases and use liberal dosing of rescue opioid for breakthrough pain
  - Better to make first dose changes in the morning to monitor for oversedation
- Increase both around the clock and as needed doses. The rapidity of dose escalation should be related to the severity of symptoms
- Allow immediate-release rescue doses of 10-20% of 24-hr oral dose (mg) every 2 hr PRN
- Increase dose of sustained release opioid
  - If patient persistently needs doses of as needed (rescue) opioids
  - When dose of around the clock opioids fails to relieve pain

- When analgesic dose or medication is changed, ask patient to do an automated symptom report within 1-2 days to determine if pain control has improved
- Switch from fixed-combination opioids to single-entity opioids when acetaminophen dose exceeds 4000 mg per day
- Constipation is the most common adverse effect of opioids. The majority of patients should be advised on some bowel regimen (increased fluids, bulking agent such as psyllium, and in many cases a stool softener/laxative (Colace, Senakot-S, etc.)
- If side effects are unmanageable and pain score < 4, consider downward dose titration by approximately 25% and reevaluate.
- Transdermal opioids (fentanyl) may have a role for patients with: (a) swallowing or other GI problems limiting oral intake; (b) poor compliance; (c) side effects from other opioids, especially constipation or pruritis.
- Rectal formulations available for morphine (5, 10, 20, 30 mg) and hydromorphine (3 mg)

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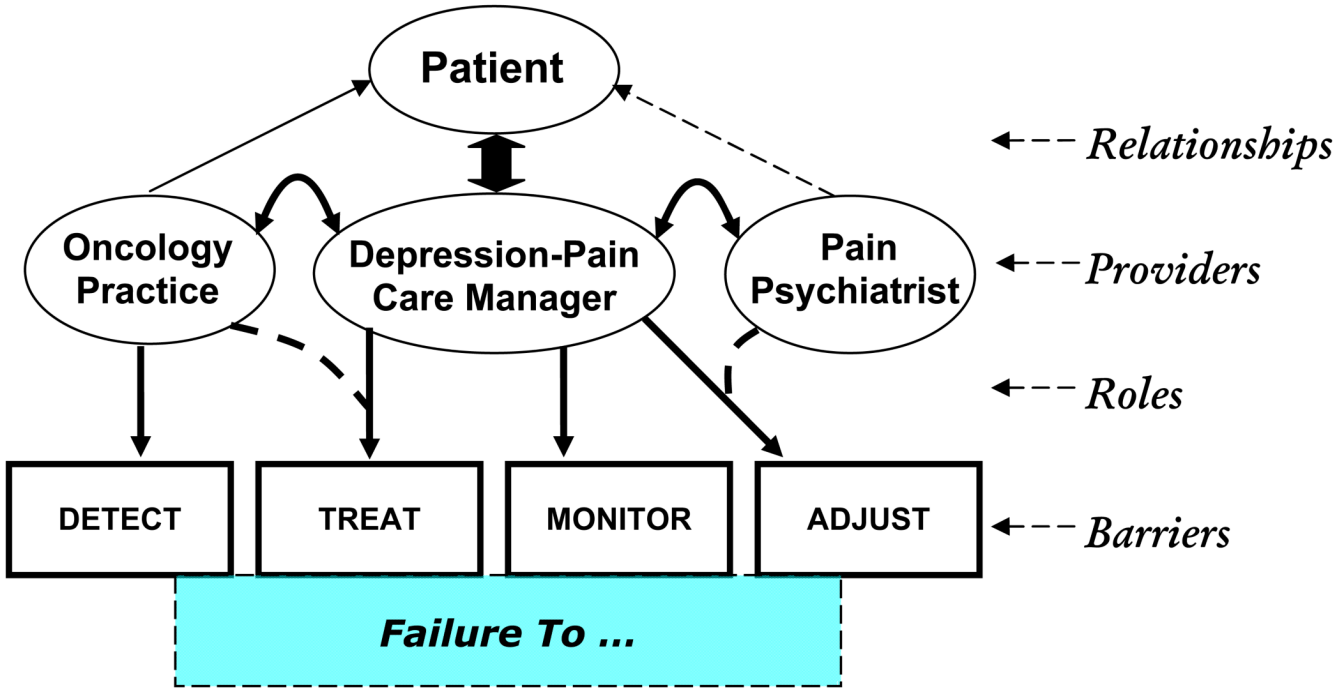

Figure 1.
Conceptual Model underlying INCPAD Trial.

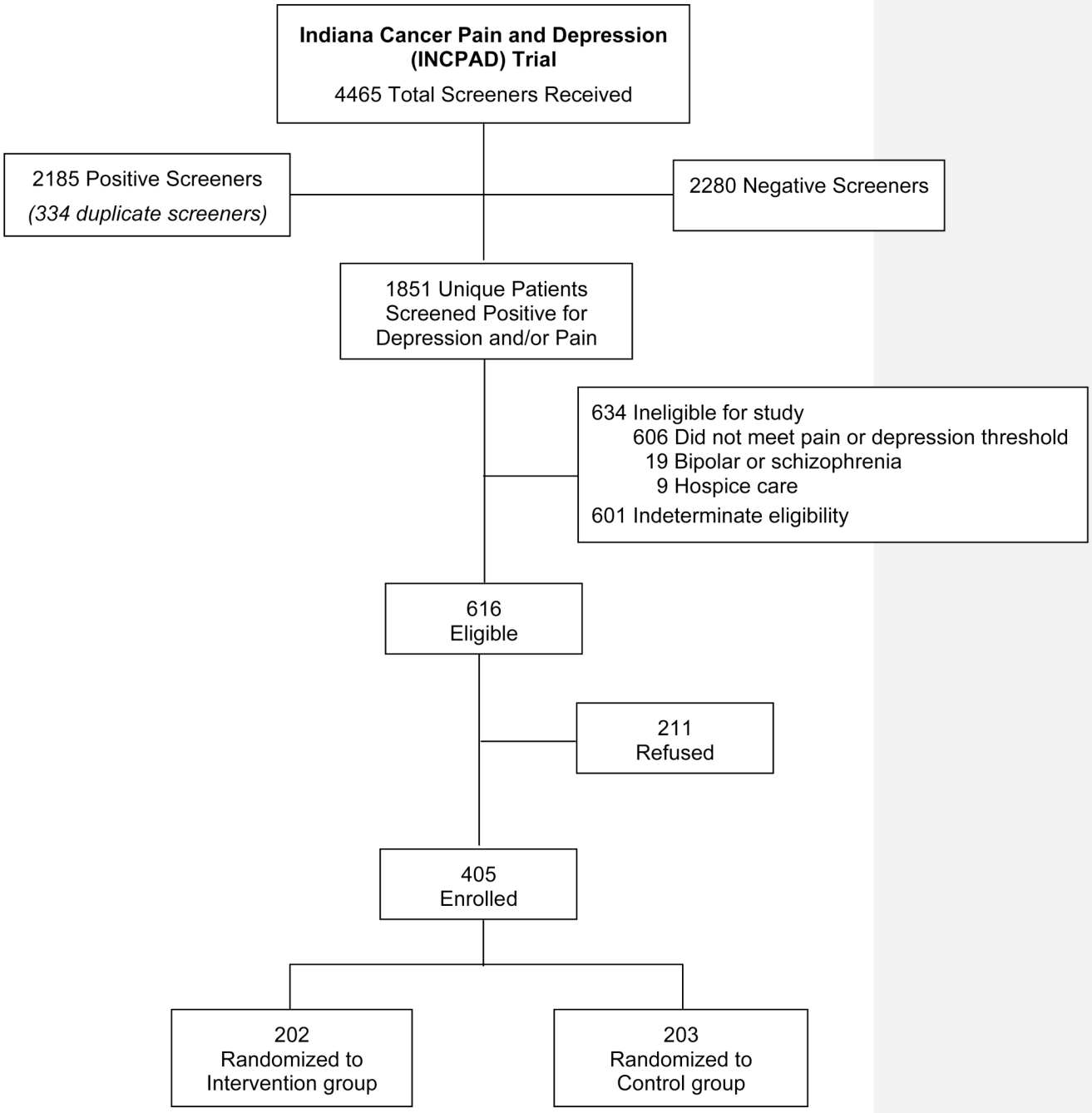

Figure 2.
Participant Flow Diagram in INCPAD Trial

Table 1

Reasons for Refusal to Participate in INCPAD Trial

Reason for refusing enrollment	N	(%)
Not interested (including hung up when called)	142	25.0
Refused at screening	82	14.4
Too sick from cancer (not feeling well enough to participate)	69	12.1
Other medical conditions (including difficulty hearing)	37	6.5
Too busy	31	5.5
Condition improved; feeling better; things going well	25	4.4
Cannot communicate by phone: difficulty speaking, spoke another language, or had only cell phone, did want to tell business over phone	22	3.9
Doesn't like study: questions, using the phone, or study too long	20	3.5
No need for study (getting help outside; performs other activities)	20	3.5
Terminal prognosis	13	2.3
Family issues (e.g., taking care of family members; death in family)	12	2.1
No significant pain	12	2.1
No cancer currently or cancer in remission	12	2.1
Moving or traveling	8	1.4
Outside influences: declined due to family, financial reasons, or felt pressure by clinic staff	6	1.4
Miscellaneous	57	10.0
Total	568	100.0

Table 2

Baseline Characteristics of the 405 Subjects Enrolled in INCPAD Trial *

Baseline Characteristic	Intervention Group (N=202)	Usual Care Group (N=203)
Mean (SD) age, yr	58.7 (11.0)	59.0 (10.6)
Women, n (%)	128 (63)	147 (72)
Race, n (%)		
White	159 (79)	163 (80)
Black	40 (20)	33 (16)
Other	3 (2)	7 (3)
Education, n (%)		
Less than High school	45 (22)	42 (21)
High school	83 (41)	77 (38)
Some college or trade school	55 (27)	53 (26)
College graduate	19 (9)	31 (15)
Married, n (%)	105 (52)	87 (43)
Employment status, n (%)		
Employed	36 (18)	45 (22)
Unable to work due to health reasons or disability	90 (45)	86 (42)
Retired	62 (31)	55 (27)
Other	13 (6)	17 (8)
Comfortable level of income, n (%)	46 (23)	54 (27)
Symptom group, n (%)		
Depression only	65 (32)	66 (33)
Pain only	48 (24)	48 (24)
Depression and pain	89 (44)	89 (44)
Type of cancer, n (%)		
Breast	55 (27)	63 (31)
Lung	42 (21)	39 (19)
Gastrointestinal	40 (20)	30 (15)
Lymphoma and hematological	22 (11)	31 (15)
Genitourinary	17 (8)	24 (12)
Other	26 (13)	16 (8)
Mean (SD) no. of medical diseases	2.0 (1.6)	2.2 (1.6)
Mean (SD) scale scores		
BPI pain severity (score range, 0-10)	4.30 (2.36)	4.23 (2.35)
SCL-20 depression (score range, 0-4)	1.43 (0.71)	1.46 (0.71)
Mean SF functional status (score range, 0 to 100)		
General health perceptions	28.3 (29.6)	28.1 (27.5)
Vitality	28.1 (19.1)	28.4 (19.3)
Mental health	56.8 (21.7)	55.0 (21.7)
Bodily pain	38.3 (22.6)	37.4 (21.9)
Physical component summary	32.3 (8.6)	33.0 (9.1)
Mental component summary	40.8 (12.8)	40.1 (12.2)

Baseline Characteristic	Intervention Group (N=202)	Usual Care Group (N=203)
Mean Sheehan Disability Index (score range, 0 to 10)	5.44 (2.84)	5.44 (2.88)
Mean overall quality of life (score range, 0 to 10)	5.74 (2.28)	5.51 (2.27)
Mean disability days in past 4 weeks		
Bed days	5.6 (7.3)	5.7 (8.1)
Days activities reduced by ≥ 50% (excluding bed days)	11.3 (8.9)	11.1 (9.1)
Currently being seen by a mental health professional, n (%)	18 (9)	26(13)
Currently being seen in a pain clinic, n (%)	12 (6)	9 (4)

* There are no significant differences between the intervention and usual care groups except marginally significant differences for gender (p=0.0512) and marital status (p=0.0527)

Table 3

INCPAD Outcome Assessment: Measures and Schedule of Administration

Domain	No	Measure	Items	Alpha*	Schedule				
					0 mo	1 mo	3 mo	6 mo	12 mo
Demographics	1	age, race, sex, education, marital, job status, income	7	n/a	X				
Medical comorbidity	2	Checklist of 8 conditions	8	n/a	X				
Depression diagnoses	3	Patient Health Questionnaire	11	n/a	X		X		X
Depression severity	4	SCL-20 depression scale	20	0.89	X	X	X	X	X
Pain severity	5	Brief Pain Inventory †							
		• BPI severity (4 items)	13	0.79	X	X	X	X	X
		• BPI interference (7 items)		0.89					
	6	SF-36 Bodily Pain scale	2	0.73	X	X	X	X	X
Clinical response	7	Global Rating of Change for pain and depression	2	n/a		X	X	X	X
Health-related quality of life (HRQL)	8	SF-12 for Component scores:							
		• Physical (PCS)	18	0.84					
		• Mental (MCS)		0.84					
		plus additional SF items for			X		X		X
		• Mental Health subscale,		0.82					
		• Vitality subscale		0.75					
		• General Health item		n/a					
	9	Sheehan disability scale	3	0.82	X	X	X	X	X

Domain	No	Measure	Items	Alpha*	Schedule				
					0 mo	1 mo	3 mo	6 mo	12 mo
Disability days	10	Pain and depression-specific disability days, past 4 weeks	6	n/a	X	X	X	X	X
Anxiety disorder screener †	11	• Mini-SPIN (3 items) • PHQ panic scale (5 items) • PTSD (1 item)	9	0.79 0.94 n/a	X				
Anxiety severity	12	GAD-7	7	0.86	X	X	X	X	X
Physical symptoms	13	PHQ somatic scale, plus selected MMAS/MDASI items	22	0.76	X	X	X	X	X
Baseline treatments	14	Pain/depression treatments	12	n/a	X				
Baseline health care use	15	Clinic, emergency, hospital	5	n/z					
Follow-up treatments	16	Pain/depression treatments in past 6 months	12	n/a				X	X
Economic evaluation	17	Work status (8 items) and health care use (30 items)	38	n/a			X	X	X
Treatment satisfaction	18	Pain and depression-specific	6	n/a			X		X
Intervention satisfaction‡	19	Automated symptom monitoring and care management	11	n/a					X

*Cronbach's coefficient alpha for internal reliability of the scale. n/a = not applicable since not a scale.

†There are several other items in these measures which do not constitute a scale score.

‡Asked only intervention group.

Table 4

Antidepressant Selection and Dosing Details for INCPAD

Step	Indications	Class	Drug	Dose (in mg)	
				Initial	Increases
1	Standard SSRI	SSRI	Fluoxetine	20	30, 40
1	If drug interactions a concern or CV disease	SSRI	Citalopram	20	30, 40
1	Similar to citalopram	SSRI	Sertraline	50	100, 150
1	Similar to citalopram	SSRI	Escitalopram	10	20, 30
2	Obesity; sexual side effects	Other	Bupropion	200	300, 400
2	Need to gain weight; insomnia	Other	Mirtazepine	15	30, 45
2	Refractory pain; hot flashes	SNRI	Venlafaxine	75	150, 225
3	Refractory pain	TCA	Nortriptyline	25	50, 75
4	Partial response to monotherapy	*	Combination		

* Buproprion is the first priority drug to add as the second antidepressant in combination therapy (most commonly with an SSRI), followed by mirtazapine and nortriptyline.

Table 5

Analgesic Ladder for Cancer Pain (INCPAD Trial)

Step	Drug (Generic)	Drug (Brand)	Initial Dose	Titration	Frequency	Maximum (24 hrs)	Side Effects / Comments
1	Acetaminophen	Tylenol	500 mg	1000	TID-QID	4000	Liver
1	Ibuprofen	Motrin, Advil	400 mg	600, 800	TID-QID	2400-3200	GI upset or bleeding
1	Naproxen	Naprosyn, Alleve	250 mg	500, 750	BID-TID	1500	GI upset or bleeding
Immediate-Release Opioids							**See separate table below**
2	Hydrocodone *	Norco, Vicodin	5-10 mg	10, 20	QID	Variable	325 acet in Norco; 500 Vicodin
3	Oxycodone *	Percocet (acet.)	5 mg	10, 20	QID	Variable	OxyFast is fast-acting form
3	Morphine, IR		15 mg	30	Q 2-4 hr	Variable	Nausea > other opioids
4	Hydromorphone	Dilaudid	2-4 mg	4, 8	QID	Variable	Good for breakthrough pain
4	Fentanyl oral	Actiq (200,400)	100 uq	200,300,400	Variable	800 uq	Fast-acting (5-10 minutes)
Sustained-Release Opioids							**See separate table below**
3	Morphine, SR	MS-Contin, Oramorph SR	15 mg	30	BID	Variable	Nausea > other opioids
3	Fentanyl patch	Duragesic	25-50 ug	50,75,100	Q 2-3 days	Variable	Fewer side effects
3	Oxycodone, SR	Oxycontin	10 mg	10	BID	Variable	Expensive
3	Methadone		5 mg	10,15	BID-TID	Variable	Cheaper, sedation
Adjuncts							
Adj	Gabapentin	Neurontin	100 mg	200,300,400	TID	3600	Neuropathic pain
Adj	Pregabalin	Lyrica	150 mg	300, 450	BID	450	Neuropathic pain
Adj	Nortriptyline		25 mg	50, 75, 100	QD	150	Neuropathic pain