NSAIDs are associated with Lower Depression Scores in Patients with Osteoarthritis

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ABSTRACT

BACKGROUND:

Studies have demonstrated the success of augmentation of anti-depressant therapy with nonsteroidal anti-inflammatory drug (NSAID) in decreasing depressive symptoms, however little is known about the benefit of NSAID therapy on depressive symptoms.

METHODS:

This study pooled data from five post-approval trials, each trial a six-week, multicenter, randomized, double-blinded, placebo-controlled, active-comparator, parallel-group study in subjects with active osteoarthritis. Subjects were randomized to placebo group, Ibuprofen 800mg TID or Naproxen 500mg BID group, or Celebrex 200mg daily group. Apart from different ethnicities enrolled, these trials had identical study designs. Depression was assessed using the patient health questionnaire-9 (PHQ-9). Outcome measured were 1) change in PHQ-9 score after six weeks of NSAID therapy and 2) change in classification of depression with a PHQ-9 score ≥10 as a marker of depression.

RESULTS:

1497 patients were included. Median PHQ-9 score was similar in all three groups at baseline and after 6 weeks of treatment. Multivariable regression analysis demonstrated a detectable effect in lowering PHQ-9 score in the Ibuprofen or Naproxen group (-0.31) and Celebrex group (-0.61) (p=0.0390). With respect to the change in classification of
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depression, logistic regression analysis demonstrated a trend towards significant
treatment effect of all NSAIDs compared with placebo.

CONCLUSION:

Our analysis of pooled data from five post-approval trials show that NSAID usage
demonstrates a trend towards reduction of depression symptoms in patients with
osteoarthritis based upon PHQ-9 scores. Future clinical trials should investigate this
association with maximum dosage of drugs, increased treatment duration, and
monitoring of social and environmental changes.
INTRODUCTION

Osteoarthritis and depression are debilitating comorbidities that lead to functional decline if inappropriately treated. Osteoarthritis results from articular cartilage failure induced by a complex interplay of genetic, metabolic, biochemical, and biomechanical factors with secondary components of inflammation. This process involves interactive degradation, and repair processes of cartilage, bone, and synovium. Depression is a heterogeneous disorder that can manifest with symptoms at psychological, behavioral, and physiological levels. The magnitude of the problem, the delayed onset of action of antidepressants, adverse drug effects, and non-compliance with current drugs call for the development of effective management and preventive approaches to reduce the burden and morbidity associated with this illness.

Recent studies indicate that depression is two to three times more prevalent in patients with osteoarthritis. However, a significant proportion of patients with osteoarthritis are not receiving appropriate treatment, suggesting a care gap. The current target of drug therapy in depression is based upon the mechanism of a deficiency of serotonergic and noradrenergic neurotransmitters in the central nervous system. A recent hypothesis has emerged attributing aspects of depression to chronic systemic inflammation. Cytokines such as interleukin (IL)-1, IL-6 and tumor necrosis factor-α have been implicated in the response to stress and illness, also leading to depression and cognitive deficits in genetically susceptible hosts. Under normal homeostasis, the cortisol release response of the body to stress modulates this cytokine
NSAIDs are associated with lower Depression Scores in Patients with Osteoarthritis. With sustained stress and inflammation, the feedback modulation of cytokines by cortisol becomes ineffective leading to hypothalamus-pituitary-axis (HPA) overactivity. This elevated cortisol and cytokine levels lead to disordered tryptophan metabolism and 5-hydroxy-tryptamine (serotonin) production, and thus a predilection for clinical depression.

This association between cytokine release and prostaglandin synthesis in depression has led to the exploration of benefits of anti-inflammatory agents in depression. Nonsteroidal anti-inflammatory drugs (NSAID) inhibit COX and impair the cascade of enzymatic reactions that transform arachidonic acid to prostaglandins, prostacyclins, and thromboxanes. Selective COX-2 inhibitors such as celecoxib (Celebrex™) possess anti-inflammatory and analgesic properties while offering the benefit of gastrointestinal protection compared to traditional NSAIDs. Recent studies have demonstrated benefit of NSAIDs as augmentation therapy, shown to reduce depressive symptom in those taking concurrent antidepressant therapy. However, the benefit of NSAID therapy in affecting depression in patients with osteoarthritis has not been studied. We performed a pooled analysis of five trials that examined NSAIDS (Ibuprofen, Naproxen, and Celebrex) usage in patients with established osteoarthritis. Subjects underwent screening for the presence or absence of depression which was repeated following 6 weeks of NSAID therapy. We hypothesized that NSAID usage in patients with osteoarthritis would show a trend towards a decrease in depressive symptoms.

METHODS
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Pooled data was included from five trials with identical protocols conducted by Pfizer Pharmaceuticals Inc., each of which was for a six-week period, multicenter, randomized, double-blind, placebo-controlled, active-comparator, parallel-group study in subjects with osteoarthritis. The original data from these trials conducted in 2001-2003 have never been published (Figure 1, Supplement 1).

In each trial eligible subjects were randomized to one of three regimens: placebo group, Ibuprofen 800mg TID or Naproxen 500mg BID group, or Celebrex 200 mg daily group, in a 1:2:2 ratio. Apart from different ethnicities enrolled, these trials had identical study designs. Details are provided in supplementary materials.

Subjects were eligible for study participation if at least 40 years of age and diagnosed with active and symptomatic osteoarthritis with a Functional Capacity Classification of I-III, including subjects in a flare state. Subjects taking NSAIDs or analgesic therapy were required to discontinue medications at least 48 hours prior to the baseline assessments.

All subjects were screened for major depression with the standard patient health questionnaire-9 (PHQ-9) scale at baseline. PHQ-9 score is a survey of functional impairment over the previous 2 weeks. Areas assessed in this survey include each of the DSM-IV criteria for depression including interest or pleasure in daily activities, mood, sleep disturbance, eating habits, self-reflection/guilt, concentration, speech patterns, suicidal ideation, and overall severity of symptoms affecting function, rated on a scale of intensity of 0 (“not at all”) – 3 (“nearly every day”). The diagnosis of major depression has been validated at a PHQ-9 sum ≥ 10 with a sensitivity of 88% and a specificity of 88%.
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Patients were not eligible for participation in enrollment if age under 18 years or greater than 50 years, past history of coronary artery disease, concurrent musculoskeletal disorders requiring NSAID therapy, pregnancy, current and past substance abuse, medical conditions leading to symptoms of depression including history of untreated or uncontrolled hypothyroidism, syphilis, HIV, and current glucocorticoid therapy. Further exclusion in those with psychiatric comorbidities such as major depressive disorder or currently taking anti-depressant therapy such as selective serotonin reuptake inhibitor (SSRI), selective norepinephrine reuptake inhibitor, and tricyclic antidepressants, as well those with bipolar disorder, schizophrenia, anxiety disorders, and DSM-IV axis II traits such as personality disorders (cluster A, B, and C).

Patients were assessed at 4 visits: Screening, Baseline, Week 2, and Week 6 (or early termination). The screening visit occurred within 1 to 14 days prior to the administration of the first dose of study medication. Between Screening and Baseline, subjects discontinued use of any NSAID and/or analgesic therapy. Acetaminophen (up to 2 grams/day) was permitted as rescue analgesia for the treatment of arthritis symptoms during the pre-treatment screening period. Subjects were to discontinue use of acetaminophen at least 24 hours prior to the Baseline arthritis assessments.

At screening, subjects had an abbreviated physical examination, underwent clinical laboratory testing, and if trial participant was a female of childbearing potential, she received a urine pregnancy test. An evaluation of arthritis consisting of both subject and physician assessments was performed, and subjects completed a PHQ-9 and a Complementary and Alternative Medicines Questionnaire. Eligible subjects returned for the Baseline visit. Study medication and the American Pain Society Pain Measure diary
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At the Week 6 visit each subject completed PHQ-9 survey, arthritis assessments, and study medication was collected. In addition, concomitant medication and adverse event information was recorded. Patients with a PHQ-9 score ≥ 10 were diagnosed with persistent major depressive disorder. Changes in PHQ-9 score were recorded.

Outcome Measures

The outcome measured was a change in PHQ-9 score at week 6 (or early termination). Additional outcome was a change in classification of depression with a PHQ-9 score ≥ 10 as a marker for depression. Further outcome measures included measurement of Visual Analog Scale (VAS), Patient’s and Physician’s Global Assessments of Arthritis, and change in Western Ontario and McMaster Universities (WOMAC) Osteoarthritis index.

Statistical Analysis:

Statistical analysis was conducted in R version 2.14.028. An intent-to-treat approach was used with respect to the treatment group assignments. Patients taking anti-depressants at baseline were excluded. Since the amount of missing data was low, a complete case analysis was performed for the regression models.

There is a known strong association between the 24-item WOMAC scale and VAS pain scale. The WOMAC scale is a more standardized and representative
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interpretation of osteoarthritis than the VAS pain score and thus was used in our model.

The Week 6 PHQ-9 data was analyzed by multiple linear regression. In addition to the treatment variable, the model was adjusted for age, sex, body mass index (BMI), diabetes mellitus, baseline PHQ and the difference in WOMAC between Baseline and Week 6. An interaction between Baseline PHQ and WOMAC difference was also considered. The possibility of non-linear associations of baseline PHQ and WOMAC difference with the Week 6 PHQ were fit using restricted cubic splines with three knots. The number of knots specifies the degree of smoothness with fewer knots resulting in more smoothing. Since the associations appeared to change gradually, three knots was deemed sufficient. The interaction between Baseline PHQ and WOMAC difference was estimated between the splines as well.

The presence of a diagnosis of depression at Week 6 was analyzed by multivariate regression analysis. The same adjusting variables as were used in the multiple regression model were used in the logistic regression model with the exception that non-linear associations were not evident, nor were any interactions considered.

P-values < 0.05 indicate statistically significant associations. However, all variables were retained in the models, irrespective of statistical significance to reduce potential bias and overfitting. Model overfitting was assessed by bootstrapping and examining various model indexes (e.g. $R^2$ for linear regression, SommersD$_{xy}$ for logistic regression, among others). This method revealed no excessive overfitting. The residuals from the multiple regression model were examined and revealed mild non-normality.
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The multivariable regression was adjusted for age, gender, BMI, diabetes mellitus, baseline PHQ-9, and WOMAC that yielded this significant p-value. Prior to choosing the best fit model, a decision to adjust for age, gender, and BMI was made. This decision was based on previous studies that have demonstrated age, gender, and BMI are strongly associated with depression in osteoarthritis. Prior to model selection, the decision to adjust for diabetes mellitus was based upon the relationship between metabolic syndrome and osteoarthritis. The WOMAC and PHQ-9 Baseline scores were also adjusted for in this best fit model selection.

RESULTS

1497 patients were included in this analysis. Baseline demographics including race and ethnicity, co-morbidities, vital signs, and medications taken at screening were similar between all three groups (Table 1, Table 2). No significant increase in systolic or diastolic blood pressure and heart rate were observed between Baseline and Week 6 in the placebo and treatment groups. The WOMAC and VAS pain sum differences were reduced in all three groups at Week 6 (Table 2).

PHQ-9 Score at Week 6 of NSAID treatment

In this study, change in PHQ-9 score over six weeks with NSAID treatment was assessed. Treatment was divided into three groups, Placebo, Ibuprofen/Naproxen, and Celebrex groups (Table 3). Median PHQ-9 score was similar in all three groups at Baseline and Week 6 (Table 4). Multivariable regression analysis demonstrated a detectable difference in PHQ-9 score dependent on treatment groups,
NSAIDs are associated with lower Depression Scores in Patients with Osteoarthritis. Ibuprofen/Naproxen (-0.31) or Celebrex treatment (-0.61) (p=0.0390) compared to placebo (Table 4).

Figure 2 shows the interaction between the PHQ-9 at Week 6 with WOMAC difference score (WOMAC at Week 6 – WOMAC at Baseline) and PHQ-9 baseline. The interaction fit increases with PHQ-9 at Week 6 and increased WOMAC difference and increased Baseline PHQ-9, therefore as PHQ-9 increases, the greater effect baseline PHQ-9 and WOMAC difference (Figure 2).

The occurrence of depression as defined by a PHQ-9 score ≥ 10 was also assessed. After six weeks of treatment, 9% of subjects in the Ibuprofen or Naproxen group and 9% of the Celebrex group compared to 14% of the Placebo group were classified as depressed with a PHQ-9 score ≥ 10 (Table 3). Logistic regression analysis showed a trend towards significant treatment effect for the NSAIDs treatment groups compared to Placebo (p=0.087).

DISCUSSION

Our study has shown through new analysis of pooled data from five post-approval trials that NSAID usage demonstrates a trend towards reduction of depression symptoms in patients with osteoarthritis based upon PHQ-9 scores. Our data supports the findings of previous studies that assessed the effects of NSAIDs on depression. A multicenter prospective study including 2228 patients with osteoarthritis treated with 25mg daily of rofecoxib resulted in a 12% absolute reduction in comorbid depressive symptoms\textsuperscript{25}. A prospective study of 40 patients suffering from an acute depressive episode revealed SSRI reboxetine combined with Celebrex significantly improved
NSAIDs are associated with lower Depression Scores in Patients with Osteoarthritis. A simultaneous study of depressed patients whom had not responded to at least 4 weeks of SSRI treatment found that adding 160mg daily of aspirin to this regimen resulted in a response rate of 52.4%. This response rate was comparable to classic augmentation strategies such as lithium or triiodothyronine supplementation.

Several aspects of the trial design may have potentially reduced the treatment effect observed. Patients in the Ibuprofen or Naproxen group received maximum effective dose at 800mg TID and 500mg BID respectively. The Celebrex group received only 200 mg daily compared to previous studies that demonstrated therapeutic benefit with a dose of 400 mg daily. This lower dose may have potentially underestimated the prospective benefit of Celebrex on depressive symptoms. The length of observation was only six weeks without continuous observation; measurements only upon study commencement and termination. Six weeks of therapy in both NSAID groups demonstrated a treatment effect, and longer follow-up may demonstrate even greater therapeutic benefit with progressive decrease in PHQ-9 depression scores. The baseline demographics of this study did not take into account social and economic factors. Generalizability of these results is limited as potential confounders are still unknown which may precipitate depression or mood changes in all groups. It is also likely that symptomatic osteoarthritis may have limited patient function, which was improved by NSAID usage. This may have also resulted in an improvement in PHQ-9 scores, which are markers of functional impairment.

The results of our study are intriguing, as after six weeks of therapy with NSAIDs there was a significant trend towards reduction in PHQ-9 scores, and a trend towards
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change in classification of depression based upon PHQ-9 scores. The results of this study suggest a prospective reduction in the development of depressive symptoms in this high-risk population of patients with osteoarthritis. This has important implications from an epidemiologic and public policy standpoint because of the high costs associated with the management of depressive disorders. Our exploratory study supports the putative connection between depression and inflammation, however based upon our results we do not recommend routine population-based screening for depression and prophylactic NSAID use in those at high risk for the development of depression. Our study does confirm the importance of NSAID therapy in osteoarthritis as the benefit is likely to be beyond anti-inflammatory properties acting only on synovial cartilage. Future large, randomized clinical trials should investigate the benefits of NSAIDs on depression in osteoarthritis with dosages that have maximal anti-inflammatory effects, study period greater than six-week duration used in these clinical trials, and with monitoring of covariates such as social and environmental changes.
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Reference List

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**Figure 1:** Selection criteria for population used this study

**Figure 2:** Joint relationship of Baseline PHQ and WOMAC difference on Week 6 PHQ depression scale. Adjusted to reference groups = Ibuprofen or Naproxen, mean Age = 61, Body Mass Index = 29.47, reference Gender = Female, Diabetes diagnosis = No as reference. PHQ = Patient Health Questionnaire, WOMAC = Western Ontario and McMaster Universities