Efficacy of Oral Enzyme Combination vs. Diclofenac in the Management of Large Joint Osteoarthritis: A Systematic Review

Scott T. Hall

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Efficacy of Oral Enzyme Combination vs. Diclofenac in the Management of Large Joint Osteoarthritis: A Systematic Review

Abstract

Background: Osteoarthritis is the most common joint disorder in the world today and affects over 27 million individuals in the US. The standard treatment of osteoarthritis is the use of NSAIDs, which come with a list of potentially serious side effects, the most common being GI perforation and bleeding. Bromelain, a proteolytic enzyme that is found in the stem of the pineapple plant may be an effective alternative to typical NSAID therapy with a lower risk profile. Bromelain is currently sold as a combination with other enzymes such as rutin and trypsin. The purpose of this review is to evaluate the efficacy of oral enzyme combinations to the potent NSAID diclofenac in the management of osteoarthritis.

Method: An extensive literature search was done using CINHAL, Medline, Evidence-Based Medicine Reviews Multifile, and Web of Science. The search included the terms Bromelain, Arthritis and Non-Steroidal Anti-inflammatory agents.

Results: Five randomized control trials met the inclusion criteria. Each study was very similar with respect to study design and results. Primary outcomes were pain and function measured most often with the Lequesne Index, the VAS or a variation of the two. Each of the 5 studies showed that the oral enzyme combination was as effective as diclofenac in the treatment of osteoarthritis with regards to the primary outcome.

Conclusion: This review showed that Oral enzyme therapy is as effective as diclofenac in the treatment of osteoarthritis and can be recommended to patients because of its efficacy and low risk-to-benefit ratio.
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Efficacy of Oral Enzyme Combination vs. Diclofenac in the Management of Large Joint Osteoarthritis: A Systematic Review

Scott Tryon Hall

A Clinical Graduate Project Submitted to the Faculty of the

School of Physician Assistant Studies

Pacific University

Hillsboro, OR

For the Masters of Science Degree, August 11, 2012

Faculty Advisor: Mark Pedemonte, MD

Clinical Graduate Project Coordinator: Annjanette Sommers, PA-C, MS
Biography

Scott Hall grew up in Grand Junction, CO. where he graduated from Fruita Monument High school in 2001. Upon graduation he left for Brazil where he spent his time learning Portuguese and doing service work. Upon return from Brazil, Scott started his undergraduate studies at Mesa State College where he studied exercise physiology. While completing his undergraduate, he worked full time as a surgical assistant in oral surgery before being accepted to Pacific University School of PA studies class of 2012.
Abstract

**Background:** Osteoarthritis is the most common joint disorder in the world today and affects over 27 million individuals in the US. The standard treatment of osteoarthritis is the use of NSAIDs, which come with a list of potentially serious side effects, the most common being GI perforation and bleeding. Bromelain, a proteolytic enzyme that is found in the stem of the pineapple plant may be an effective alternative to typical NSAID therapy with a lower risk profile. Bromelain is currently sold as a combination with other enzymes such as rutin and trypsin. The purpose of this review is to evaluate the efficacy of oral enzyme combinations to the potent NSAID diclofenac in the management of osteoarthritis.

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**Keywords:** Bromelain, Arthritis, and Non-Steroidal Anti-inflammatory agents
Acknowledgements

To my wife Lauren: I can’t begin to tell you how much you mean to me and how much I love you. Your support and selflessness throughout this journey has been amazing to me and can’t express how grateful I am to you for that. Your hard work, your sacrifice, all the dinners you ate alone while I was studying, all the months we spent apart, you put up with a lot and never complained. I know it has been hard on both of us but your support made it so much easier. We have surely had our highs and also some of our very lows these past couple of years but I am glad I have had you to go through it with. This chapter is now over and we are beginning a new one. I can’t wait for the adventures we will have together and I am glad I have to go through it with. I LOVE YOU!

To My Mom and Dad: Thank you for your love and support and thank you for teaching me from a young age the value of hard work and dedication. I may not have always listened at the time but I came around. I am the man I am today because of you two.

To the PA faculty: Thank you for your endless support, hard work, dedication, and desire to teach that we may be the best PA’s we can be.

To the Class of 2012: Well look at that…We Made It! Congratulations! All the hard work, the dedication, the long nights of studying till our heads almost pop off, all the long hours in the ER or surgery or perhaps a clinic somewhere, all the miles we put on our cars or traveled in a plane, all the time away from our family and friends. It has all paid off and we have reached this goal. Congratulations and best of luck to all of you in your future endeavors.
# Table of Contents

Biography .................................................................................................................. 2  
Abstract .................................................................................................................. 3  
Acknowledgements .................................................................................................. 4  
Table of Contents .................................................................................................... 5  
List of Tables ........................................................................................................... 6  
List of Abbreviations................................................................................................... 6  
List of Appendices..................................................................................................... 6  
Background ............................................................................................................. 7  
Method ..................................................................................................................... 8  
Results ..................................................................................................................... 9  
Discussion ............................................................................................................... 15  
Conclusion ............................................................................................................. 18  
References ............................................................................................................. 19  
Tables ..................................................................................................................... 21  
Appendix ................................................................................................................. 23
List of Tables

Table I: Characteristics of Reviewed Studies (GRADE)
Table II: Summary of Finding

List of Abbreviations

AE……………………………………………………………...………Adverse Effects
ANCOVA……………………………………………………..Analysis of Co-variance
b.i.d…………………………………………………………………….Two times a day
CI…………………………………………………………….…….Confidence Interval
DC………………………………………………………….………………..Diclofenac
ITT……………………………………………...…………………….Intention-to-treat
LI……………………………………………….………………………Lequesne Index
NSAID………………………………………...Non-Steroidal Anti-inflammatory Drug
OA………………………………………………………………...………Osteoarthritis
OE……………………………………………………………...………….Oral Enzyme
RCT……………………………………………………….....Randomized Control Trial
t.i.d……………………………………………………………………Three times a day
VAS…………………………………………………………..……..Visual analog scale
VRS……………………………………………………………..……Visual rating scale
WOMAC………………………...Western Onterio and McMasters Osteoarthritis index

List of Appendices

Appendix A……………………………………………………...Lequesne Index Questionnaire
BACKGROUND

Osteoarthritis (OA) is the most common joint disorder in the world and is one of the most frequent causes of pain and loss of function in adults. Radiologic evidence of OA occurs in most people by age 65 and in 80% of those 75 and older. In the US it is the second most common cause of work disability in men over 50 years of age.\(^1\) The Rate of OA in the US has increased from 21 million in 1995 to over 27 million in 2008.\(^2,3\)

Standard treatment of OA is the use of a class of medications called non-steroidal anti-inflammatory drugs, also known as NSAIDs. NSAIDs are symptom modifying drugs and do not modify the disease itself. However, the prolonged use of NSAIDs is often associated with the increased risk of gastric and duodenal ulcers and upper gastrointestinal perforation and bleeding.\(^4\) There is also a risk of acute renal failure as well as an increase in cardiac risk, such as heart attack or stroke, associated with long term and high dose use of NSAIDs.

Bromelain, a proteolytic enzyme derived from the stem of the pineapple plant, may be an effective alternative to NSAIDs as the standard of care in the treatment of OA. Bromelain is found most commonly in combination with other enzymes. Phloenzym\(^\text{TM}\) contains 90mg bromelain, 48mg trypsin and 100mg rutin. Wobenzyme\(^\text{TM}\) contains 45mg bromelain, papain, trypsin, chymotrypsin, pancreatin, lipase and amylase. Proteolytic enzymes such as trypsin and bromelain have shown in vivo and in vitro to have anti-inflammatory, anti-edematous, antithrombotic and fibrinolytic effects.\(^5\) Enzymes have been shown to be much better tolerated when compared to NSAIDS and do not have the
These oral enzymes have also proven to be non-toxic, mutagenic or tetratogenic in previous animal studies.\textsuperscript{7,8}

Diclofenac sodium is a prescription strength NSAID and is among the more potent NSAIDs used in acute and chronic pain. Diclofenac is also one of the most commonly prescribed NSAIDs in the treatment of OA. As compared to ketorolac, diclofenac is shown to have a better tolerance profile and lower risk of gastrointestinal effects such as bleeding peptic ulcers.\textsuperscript{9}

Because of the high prevalence of OA and the risks associated with the standard use of NSAIDs, it is important to consider alternative treatments. The objective of this review is to evaluate the efficacy of oral enzyme combination in the management of large joint osteoarthritis as compared to traditional NSAIDs, in this case diclofenac.

**METHODS**

**Search Strategy**

An extensive literature search was done using the following databases accessed through Pacific University Library: CINHAL, Medline, Evidence-Based Medicine Reviews Multifile (EBMRM), and Web of Science (WOS). The search included the following search terms: Bromelain, Arthritis, and Non-Steroidal Anti-inflammatory agents. These terms were used individually and in combination. These articles were then screened by reviewing the titles and abstracts. The articles were then reviewed for quality and validity using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) scale. (See table I.)
RESULTS

A comprehensive literature search of four databases using the specified search strategy, resulted in 78 total articles of which 5 met the inclusion criteria and were relevant to the clinical question of, the efficacy of oral enzyme therapy as compared to NSAIDs in the treatment of osteoarthritis. All five articles included in this review were double-blinded randomized control trials comparing Phlogenzm™ to diclofenac. (See Table I.)

**Klein et al 2000**

In 2000, Klein et al\(^\text{10}\) preformed a randomized, double-blinded prospective study to address the short-term efficacy of an oral enzyme preparation compared to Diclofenac in patients suffering from painful osteoarthritis of the knee. The trial included 73 patients, who were randomized to receive 3 weeks of the oral-enzyme Phlogenzym, which contains bromelain, trypsin, and rutin, or the NSAID diclofenac. Patients were eligible for the study if they presented with symptomatic gonarthrosis and radiological evidence of joint space narrowing and a Lequesne index score (LI), which measures pain and function, of \(\geq 10\) at baseline. (See appendix A.) Exclusion criteria included other anti-rheumatic treatment within 2 weeks of the study, pregnancy or lactation, oral anticoagulants, systemic or intra-articular corticosteroids within 2 months of study, and cardiovascular, gastrointestinal, hepatic, hematological or renal diseases. No other treatment was allowed during the 3 weeks of this trial.\(^\text{10}\)

The 73 enrollees were randomized to two groups, Diclofenac (\(n=37\)) or Phlogenzym (\(n=36\)). The double-dummy method was used by giving placebo tablets to each group in the dose regimen of the other.\(^\text{10}\)
Efficacy was evaluated primarily using the Lequesne index at baseline, 3 weeks and at 7 weeks without breaking code. The visual analogue scale (VAS) was also used to document pain at rest, pain on movement, and restricted movement. The mean score of the LI for the enzyme group decreased from 13.56 at baseline to 3.10 at the end of 3 weeks to 2.05 at the end of 7 weeks from baseline. The mean score of the LI for the diclofenac group decreased from 14.04 at baseline to 3.50 at 3 weeks to 2.24 at the end of 7 weeks. The lower bound of the 95% CI of the Mann-Whitney estimator was at all intervals above 0.44 which is the limit for equivalence. In the enzyme group the VAS sum score of pain was markedly reduced after 1 week of treatment (mean sum score 16.9 at baseline to 6.93, a 59% improvement from baseline) and continued to decrease to 2.12 after 3 weeks and to 1.01 at 7 weeks. Similar results were noted in the diclofenac group: mean sum score 17.42 at baseline decreased to 60.2% at week 1 (numerical mean sum score at week 1 was not included in text or in the table, only percentage was given in text), 2.24 at week 3 and 0.99 at week 7. Only one patient from the enzyme group withdrew because of adverse effects, a headache that was “probably not drug related.” There were 3 patients who withdrew from the diclofenac group due to adverse effects, sinus bradycardia, which was likely not drug related, duodenal ulcer and nausea, which were possibly drug related.\textsuperscript{10}

\textbf{Klein et al 2006}

In 2006, Klein et al\textsuperscript{11} put out a study addressing the efficacy of an oral enzyme vs. diclofenac in the management of osteoarthritis (OA) of the hip. The study was a randomized, double-blinded, parallel group trial, which lasted for 6 weeks of treatment. A
total of ninety patients were included in this study and randomized into two groups, one group to receive the oral enzyme Phlogenzym (n=45) and the other to receive diclofenac (n=45). Inclusion criteria for the study were: patients over 20 years of age, radiological or CT evidence of OA, WOMAC visual rating scale (VRS) subscale pain $\geq 20$ out of a possible 50, Lequesne Index of $\geq 10$. Excluded from the study were patients with a current medical or arthritic disease or abnormal laboratory results that could potentially confound the results. Also excluded were patients who received steroid or hyaluronic acid injections within 2 months of the study or systemic steroids within 4 weeks of the study. The enzyme group received Phlogenzym three times a day (t.i.d.), diclofenac was administered twice a day (b.i.d.), and each group also received a placebo following the double dummy technique.11

Primary efficacy was measured using the Lequesne index and the WOMAC index (Western Ontario McMasters Osteoarthritis index). A total of 88 subjects were part of the intent-to-treat analysis (ITT), 72 patients were analyzed for per protocol. The WOMAC total index at baseline was between 68 and 194 and was $121.6 \pm 22.5$ on average $\pm$ SD. The Lequesne index varied between 10.0 and 14.0 and baseline and was $11.44 \pm 1.24$ on average $\pm$ SD. In the ITT analysis, non-inferiority of the oral enzyme was shown as compared to diclofenac with regard to the O’Brien Global sum from baseline to endpoint in the 4 primary endpoints of pain, stiffness, function and Lequesne index, with a p-value of 0.0025. Individual p-values were given for each of the individual scales: WOMAC pain (p=0.0033), WOMAC stiffness (p=0.0061), WOMAC function (p=0.0039) and Lequesne index (p=0.0008). The per protocol analysis set showed an even clearer
tendency in favor of oral enzymes with a treatment difference of 1.05+-0.79 and a 95% confidence limit of -2.63/0.53.

A total of 46 patients, 23 in each group, had at least one adverse side effect. In the enzyme group 11 (24.4%) were classified as “possibly drug related.” In the diclofenac group 13 (28.9%) were “possibly drug related.” GI disorders were the most common adverse events. Dropout was 6/45 (13.3%) in the DC group and 5/45 (11.1%) in the enzyme group.  

Akhtar et al

In 2004, Akhtar et al published a double blind, prospective, randomized study on oral enzyme combination vs. diclofenac in the treatment of osteoarthritis of the knee. The study included a total of 103 patients that were treated for a total of 6 weeks at two study centers. The main inclusion criteria were symptomatic OA of the knee confirmed by radiology and LI of >= 10. Patients were excluded if they had been treated for OA within 2 weeks of baseline, had rheumatoid arthritis or had received systemic or intra-articular steroids within 2 months of baseline. Patient evaluations were done at baseline, 2, 4, and 6 weeks. Primary efficacy criteria were the Lequesne index and complaint index, which includes pain at rest, pain with movement and restricted function. Each of the 3 domains was rated on a visual analog scale (VAS) ranging from 0 (best) to 10 (worst) with a total possible score of 30.

The ITT population included 98 patients (enzyme 46/diclofenac 52). A total of 56 patients (enzyme 24/diclofenac 32) were evaluated in the per protocol population. A total of 20 patients (10 in each group) discontinued the study early. In the ITT population the mean LI decreased from 13.0 to 9.4 (26.3%) in the enzyme group, and from 12.5 to 9.4
Non-inferiority was measured using the Mann-Whitney estimator. The analysis was performed as one-sided sets with 97.5% CIs. Non-inferiority was considered to be proven if the lower bound of the CI was greater than MW=0.36. Non-inferiority of the oral enzyme in the ITT population was demonstrated (MW=0.5305; CI-LB=0.4171) at 6 weeks. Also at 6 weeks, the mean complaint index from the sum of all three domains, decrease from 4.9 to 3.5 (30.2%) in the enzyme group and from 4.9 to 3.6 (26.6%) in the diclofenac group. Again non-inferiority of the oral enzyme was demonstrated (MW=0.5434; CI-LB=0.4296).

Singer et al

In 2001, Singer et al⁶ published a double-blind randomized study that compared the efficacy of Phlogenzm™ to diclofenac in the treatment of OA of the knee. Patients were included in the study if they had symptomatic OA with evidence of joint space narrowing on radiography as well as a LI of >= 10. This study included 63 patients randomized to two groups, oral enzyme (OE) n=31 and DC n=32. The double dummy technique was applied in this study. The study duration was 3 weeks with a follow up at 7 weeks from baseline. Examinations were made at weeks 1, 2, 3 and 7. Efficacy was measured using the LI and the VAS and all patients were evaluated in the intent-to-treat analysis. In the enzyme group using the LI, 29/31 patients showed improvement and 2-showed deterioration. In the diclofenac group using the LI, 28/32 showed improvements, one showed no change and 3-showed deterioration. The mean value of the LI decreased from 15.48 to 9.81 in the OE group after 7 weeks. The mean value of the LI decreased from 15.81 to 10.83 after 7 weeks in the DC group. In the statistical evaluation, the lower band 95% CI of the Mann-Whitney estimator was above 0.44 at all times which is the
limit for equivalence. The reported tolerance for the enzyme group was 18 AE in 15 patients, which included flatulence, nausea, allergic exanthema and epigastric pain. In the DC group 20 AE were reported in 16 patients, which included retrosternal pain, pressure and pain over stomach, epigastric pain, nausea and ulcus ventriculi.  

**Tilwe et al**

In 2001, Tilwe et al\textsuperscript{13} published a single-blinded randomized open trial comparing the efficacy of Phlogenzym\textsuperscript{TM} to diclofenac in the treatment of osteoarthritis of the knee. Patients were included if they had active arthritis of the knee and radiologic evidence of joint space narrowing. Patients were excluded from the study if they had recently received anti-rheumatic therapy, suspected bacterial infection of the knee joint, existing pregnancy or lactation. A total of 50 patients were included in the study, 25 were randomized to each group. Patients in the study group received 3 tablets of Phlogenzym b.i.d. for the first week and then 2 tablets b.i.d. for the second week. Patients in the control group received 50mg diclofenac b.i.d. for all three weeks of the study. Patients were examined at baseline, 3 weeks (end of study), and at 7 weeks from baseline, by evaluators who were different from those dispensing the medication. Pain was subjectively assessed by rating pain at rest or on movement as none, mild, moderate or severe and improvement was noted as severe to moderate, moderate to mild and so on. Joint tenderness was also assessed in a similar fashion.\textsuperscript{13}

Eighteen patients in the oral enzyme (OE) group vs. 10 in the diclofenac group had reduction in joint tenderness at the end of the study (p=0.05). In the OE group 12 showed reduction in pain at rest and 17 showed reduction in pain on movement as compared to 9 and 15 in the diclofenac group, respectively. Neither group suffered
dropout or loss to follow up. Statistical analysis showed no significant difference in
efficacy between the two groups.  

DISCUSSION

It is known that osteoarthritis has a high prevalence across the US and the world
and physicians are continuing to reach to NSAIDs as first line symptom control for these
patients. As previously mentioned NSAIDs do not come without risk, GI risk being the
most common. Wouldn’t it be beneficial if there were a drug that could reduce pain and
improve mobility as effectively as NSAIDs without the associated risks?

Although oral enzyme therapy has proven to be better tolerated and have fewer
AE as compared to NSAIDs and although some of the studies in this review make
mention of the tolerance and AE of the oral enzyme, that was not the outcome to be
considered in this review. The purpose of this review was only to show the effectiveness
of OE therapy when compared to NSAIDs. Studies addressing the long term AE of oral
enzyme therapy should be investigated to more accurately address tolerance and risk.

This systematic review, which included 5 studies addressing the effectiveness of
oral enzyme therapy compared to diclofenac in the management of large joint
osteoarthritis, shows that Phlognezym™ is as effective as diclofenac in the treatment of
osteoarthritis.

All 5 studies included in this review were very similar in study design and results
were consistent across all studies in regards to diclofenac vs. oral enzymes. (Tables I &
II) However, there were found to be some variation and limitations among them that
should be noted.
Four of the 5 studies\textsuperscript{6,10,11,12} were double-blinded randomized control trials (RCT) that used a double-dummy technique in the administration of the medications. The Tilwe et al\textsuperscript{13} study was an open randomized single-blinded study and did not use the double-dummy technique in the administration of the medications. All 5 studies used the same study drug and the same drug for control, which is an important consistency among the studies.

Three of the five studies\textsuperscript{6,11,12} followed the intention-to-treat (ITT) analysis (table 2). The Klein et al\textsuperscript{11} 2006 study was the only study to use the ANCOVA (analysis of co-variants) as part of their statistical methods. Prognostic balance between the study group and the control group was not shown in the Klein et al\textsuperscript{10} 2000 study. This could have an impact on results if the groups were not similar at the start and end of the study. Each study however, was similar with respect to the inclusion and exclusion criteria of the patients.

Patient important outcomes that should be considered are, pain, function, activities of daily living, and AE. The Lequesne index accounts for the first three of these outcomes. Three of the 5 studies\textsuperscript{6,10,12} used the Lequesne index (LI) exclusively as their measure of the primary outcome. The Lequesne index is a questionnaire that includes three categories: Pain and discomfort, Maximum distance walked, and Activities of daily living. Each category can score a potential 8 points for a total potential score of 24. (See Appendix A.) Outcomes were also measured using the visual analog scale (VAS), sometimes referred to as the complaint index, which rated pain at rest, pain with movement, and restricted function. Each category was rated on a scale of 0-10 for a total potential score of 30. The Klein et al\textsuperscript{11} 2006 study used the Lequesne index along with a
similar scale called the WOMAC, which evaluated pain, joint stiffness, and function. It
did not report the mean LI as a numerical value but as a p-value only (p=0.0008) making
comparison all but impossible. The Tilwe et al\textsuperscript{13} study did not use the Lequesne index or
the VAS but used a much more subjective 4 point rating scale, measuring pain at rest and
pain with movement with the patient rating each as none, slight, moderate or severe. It is
unclear how points were assigned to this scale, whether or not it was a 0-3 scale or a 1-4
scale. The subjective nature of this measurement is concerning because of the potential
for bias which affects the validity of the results.

All 5 studies included in this review had very small sample sizes, the largest being
103 total patients (table 2). This was one of the reasons of a downgrade on the GRADE
scale. Only one study (Singer et al) did not recognize the role Mucos Pharma or Pacific
Pharmaceutical in the study. This presents possible bias within the studies, which could
have an impact on the validity of the results. Another questionable area is the author’s
assessment of which AE were drug related, not drug related or “possibly drug related”
with no apparent attempt to explain these classifications. In the studies which reported
AE\textsuperscript{6,10,11,12} it was not stated whether or not the investigators reporting the side effects
were blinded also, adding in potential bias if they were in fact not blinded. While some of
the outcomes were not of primary interest in this review, the fact that bias could well be
an issue has implications for the studies as a whole beyond the specific outcomes because
bias anywhere in a study suggests bias everywhere.

The similarities mentioned across studies helps support the validity of their result
and helps make the overall conclusion that oral the enzyme combination is as effective as
diclofenac in the treatment of OA. Based on the overall grade of these studies, which is
moderate, further research is likely to have improve our confidence in the effect and may change the effect. A larger sample size and a multicenter approach would yield greater precision. Allocation concealment and further steps in blinding would also increase the validity of such a study and support the clinical application of oral enzyme therapy.

**CONCLUSION**

In conclusion, the main focus of this review was on the efficacy of oral enzyme therapy as compared to diclofenac. Primary outcomes were in large part measured using either the Lequesne index or the VAS, or some sort of variation of the two. These measurements mainly focused on the pain and function of the patient. The efficacy of the oral enzyme was shown to be statistically equivalent to diclofenac in all outcomes measured across all 5 studies. Although the over all grade of the studies was moderate, which means further studies would likely be of benefit in our confidence of the effect but not is not likely to change the effect, a recommendation could be made to use oral enzyme therapy in patients suffering from OA. This recommendation would be justified because of the nature of the oral enzyme and its low risk to benefit ratio. This therapy could be especially beneficial in patients that may already be suffering from AE from NSAIDs or that can no longer take NSAIDs due to AE.

Other patient important outcomes that would be of benefit to know would be addressed by long-term studies that show whether or not there is a delay in time to hip or knee replacement with the use of OE therapy. A long-term study looking at the harm of diclofenac vs OE would also be of benefit, showing what the harm would be of not using OE.
References


Table I. Characteristics of Reviewed Studies

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<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Findings</th>
<th>Starting Grade</th>
<th>Decrease Grade</th>
<th>Grade of Evidence</th>
<th>Overall Grade Of Evidence</th>
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\(a\) failure to report prognostic balance  
\(b\) no use of double-dummy technique  
\(c\) small sample size
### Table II. Summary of Findings

<table>
<thead>
<tr>
<th>Study</th>
<th>Length of study in weeks</th>
<th>Dosing schedule</th>
<th>Lequesne Index (LI) (Mean)</th>
<th>VAS</th>
<th>WOMAC</th>
<th>Mann-Whitney</th>
<th>ITT Analysis</th>
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<td>Akhtar et al¹²</td>
<td>6</td>
<td>tid</td>
<td>50mg bid</td>
<td>13.0 to 9.4</td>
<td>12.5 to 9.4</td>
<td>4.9 to 3.5</td>
<td>4.9 to 3.6</td>
</tr>
<tr>
<td>Klein et al¹⁰ (2000)</td>
<td>3</td>
<td>2 tabs tid</td>
<td>50mg tid wk 1 then 50mg bid</td>
<td>13.56 to 3.10</td>
<td>14.04 to 3.50</td>
<td>16.90 to 2.12 @ 3 weeks</td>
<td>17.42 to 2.24</td>
</tr>
<tr>
<td>Singer et al⁶</td>
<td>3</td>
<td>2 tabs tid</td>
<td>50mg tid wk 1 then 50mg bid</td>
<td>15.48 to 10.97</td>
<td>15.81 to 10.83</td>
<td>12.37 to 5.51</td>
<td>11.05 to 5.36</td>
</tr>
<tr>
<td>Klein et al¹¹ (2006)</td>
<td>6</td>
<td>2 tabs tid</td>
<td>50mg bid</td>
<td>P=0.0008</td>
<td>NA</td>
<td>P=0.0025</td>
<td>No</td>
</tr>
<tr>
<td>Tilwe et al¹³</td>
<td>3</td>
<td>3 tabs bid</td>
<td>50mg bid</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>No</td>
</tr>
</tbody>
</table>


APPENDIX A

Lequesne Index\textsuperscript{14}

I. Pain or discomfort

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Finding</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain or discomfort during nocturnal bedrest</td>
<td>None</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Only on movement or in certain positions</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Without movement</td>
<td>2</td>
</tr>
<tr>
<td>Duration of morning stiffness or pain after getting up</td>
<td>None</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Less than 15 min</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>$\geq 15$ min</td>
<td>2</td>
</tr>
<tr>
<td>Remaining standing for 30 minutes increases pain</td>
<td>No</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>1</td>
</tr>
<tr>
<td>Pain on walking</td>
<td>None</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Only after walking some distance</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Early after standing</td>
<td>2</td>
</tr>
<tr>
<td>Pain or discomfort in sitting position for 2 hours</td>
<td>No</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>1</td>
</tr>
</tbody>
</table>
II. Maximum distance walked

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Finding</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum Distance Walked</td>
<td>Unlimited</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>&gt; 1 kilometer but limited</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>About 1 kilometer (about 15 minutes)</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>About 500-900 meters (about 8-15 minutes)</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>From 300-500 meters</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>From 100-300 meters</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>&lt; 100 meters</td>
<td>6</td>
</tr>
<tr>
<td>Waking aid required</td>
<td>None</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>1 walking stick or crutch</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>2 waking sticks or crutches</td>
<td>2</td>
</tr>
</tbody>
</table>

III. Activities of daily living

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Finding</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Can you put on socks by bending forward?</td>
<td>Easily</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>With mild difficulty</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>With moderate difficulty</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>With marked difficulty</td>
<td>1.5</td>
</tr>
<tr>
<td></td>
<td>Impossible</td>
<td>2</td>
</tr>
<tr>
<td>Can you pick up an object from the floor?</td>
<td>Easily</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>With mild difficulty</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>With moderate difficulty</td>
<td>1</td>
</tr>
<tr>
<td>------------------------</td>
<td>--------------------------</td>
<td>----</td>
</tr>
<tr>
<td></td>
<td>With marked difficulty</td>
<td>1.5</td>
</tr>
<tr>
<td></td>
<td>Impossible</td>
<td>2</td>
</tr>
<tr>
<td><strong>Can you go up and down a flight of stairs?</strong></td>
<td>Easily</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>With mild difficulty</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>With moderate difficulty</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>With marked difficulty</td>
<td>1.5</td>
</tr>
<tr>
<td></td>
<td>Impossible</td>
<td>2</td>
</tr>
<tr>
<td><strong>Can you get into and out of a car?</strong></td>
<td>Easily</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>With mild difficulty</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>With moderate difficulty</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>With marked difficulty</td>
<td>1.5</td>
</tr>
<tr>
<td></td>
<td>Impossible</td>
<td>2</td>
</tr>
</tbody>
</table>

**Lequesne Index of severity**

<table>
<thead>
<tr>
<th>INDEX SCORE</th>
<th>HANDICAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>None</td>
</tr>
<tr>
<td>1-4</td>
<td>Mild</td>
</tr>
<tr>
<td>5-7</td>
<td>Moderate</td>
</tr>
<tr>
<td>8-10</td>
<td>Severe</td>
</tr>
<tr>
<td>11-13</td>
<td>Very Severe</td>
</tr>
<tr>
<td>&gt;= 14</td>
<td>Extremely Severe</td>
</tr>
</tbody>
</table>