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# The Effects of Curcumin in Decreasing Pain in Patients with Osteoarthritis

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# The Effects of Curcumin in Decreasing Pain in Patients with Osteoarthritis

## **Abstract**

**Background:** Osteoarthritis (OA) is a common degenerative joint disorder that affects millions of people worldwide. It occurs when the cartilage or cushion between joints breaks down from “wear and tear” causing inflammation and symptoms such as pain, stiffness and swelling that can lead to chronic disability and functional impairment. The most common conventional treatment is non-steroidal anti-inflammatory drugs (NSAIDs), but there are significant risks associated with their use. Recent studies have demonstrated curcumin, an extract of turmeric, to be just as safe and effective as ibuprofen in the reduction of pain and functional improvement but with fewer side effects. This review focuses on the efficacy and safety of curcumin compared with NSAIDs in the symptomatic treatment of osteoarthritis pain.

**Methods:** An exhaustive search of available medical literature was performed using MEDLINE-Ovid, MEDLINE-PubMed, ClinicalKey, Web of Science, Google Scholar, and UpToDate. Keywords used included: curcumin, turmeric, osteoarthritis, arthritis, pain, inflammation, and NSAIDs. Relevant articles were assessed for quality using GRADE.

**Results:** Three studies meeting inclusion criteria were used for this systematic review. In all three studies, the use of curcumin significantly decreased pain severity in patients with osteoarthritis, with symptoms improving within 4-6 weeks. Curcumin also decreased gastrointestinal adverse effects in all three studies. In two of the studies, patients taking curcumin reported an improved quality of life and decreased need of additional treatments. Curcumin also improved WOMAC scores in two of the studies.

**Conclusion:** These studies give fair evidence for the use of curcumin as an effective and safe therapy for decreasing pain severity in patients with osteoarthritis. Curcumin can be used alternatively to or concomitantly with NSAIDs. Therefore, curcumin therapy could be implemented in clinical practice for the treatment of osteoarthritis. Further research using randomized trials with a larger population size and longer length of study needs to be conducted in order to determine the long-term efficacy of curcumin.

**Keywords:** curcumin, turmeric, osteoarthritis, arthritis, pain, inflammation and NSAIDS.

## **Degree Type**

Capstone Project

## **Degree Name**

Master of Science in Physician Assistant Studies

## **Keywords**

curcumin, tumeric, osteoarthritis, arthritis, pain, inflammation, NSAIDS

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**The Effects of Curcumin in Decreasing Pain in Patients with Osteoarthritis**



**Andrea Nesteby & Lisa Ha**

*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 12, 2017*

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

## **Biographies**

Lisa Ha is a native of San Jose, California and received her Bachelor of Arts in Psychology and a Biology minor from University of Hawai'i at Manoa. After graduation, she became a competitive boxer and within 4 years became a nationally ranked athlete and world champion. Her passion for the sport led her to become a personal trainer, where she fell in love with helping others to achieve their best health through exercise and nutrition. Her curiosity and fascination with medicine and its integral role in healing the human body lead her to further her career as a Physician Assistant. She hopes to continue to help others achieve optimal health with the integration of science and medicine.

Andrea Nesteby was born in Guilin, China, but grew up in Barrow, Alaska. She received her Bachelor of Science in Biology from the University of Alaska Fairbanks. After completion of her undergraduate degree, she took a year off to enjoy the things she loves: traveling, ice-climbing, and skiing. She worked as an EMT and CNA in Alaska prior to starting her Physician Assistant studies. She has a passion for working with underserved populations and plans on working in rural Alaska when finished with PA school.

## **Abstract**

**Background:** Osteoarthritis (OA) is a common degenerative joint disorder that affects millions of people worldwide. It occurs when the cartilage or cushion between joints breaks down from “wear and tear” causing inflammation and symptoms such as pain, stiffness and swelling that can lead to chronic disability and functional impairment. The most common conventional treatment is non-steroidal anti-inflammatory drugs (NSAIDs), but there are significant risks associated with their use. Recent studies have demonstrated curcumin, an extract of turmeric, to be just as safe and effective as ibuprofen in the reduction of pain and functional improvement but with fewer side effects. This review focuses on the efficacy and safety of curcumin compared with NSAIDs in the symptomatic treatment of osteoarthritis pain.

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**Keywords:** curcumin, turmeric, osteoarthritis, arthritis, pain, inflammation and NSAIDS.

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## **Table of Contents**

Biography

Abstract

Acknowledgements

Table of Contents

List of Tables

List of Figures

List of Abbreviations

List of Appendices

BACKGROUND

METHODS

RESULTS

DISCUSSION

CONCLUSION

References

Table I. Characteristics of Reviewed Studies

Table II. Summary of Findings

## **List of Tables**

Table 1: Quality Assessment of Reviewed Articles

## **List of Abbreviations**

|        |   |
|--------|---|
| OA     | Osteoarthritis  |
| NSAIDs | Non-steroidal anti-inflammatory drugs                             |
| GRADE  | Grading of Recommendations, Assessment, Development and Education |
| WOMAC  | Western Ontario and McMaster Universities Osteoarthritis Index    |
| vs     | versus  |
| AE     | adverse effects   |
| GI     | gastrointestinal  |

## **The Effects of Curcumin in Decreasing Pain in Patients with Osteoarthritis**

### **BACKGROUND**

Osteoarthritis (OA) is the most common degenerative joint disorder and a leading cause of chronic disability and functional impairment in the United States.<sup>1</sup> It is a prevalent articulate disease that affects more than 27 million adults, making OA the fourth most global cause of disability in women and eighth most important in men.<sup>2</sup>

There are more than 100 different forms of arthritis most often affecting joints in the knees, hips, hands, and spine. Inflammation results from the breakdown of cartilage and fluid inside the joints causing severe pain. The severity of pain varies from person to person. Twenty-five percent of adults suffering with arthritis state that it causes severe pain (7 or higher on a 0 to 10 point scale).<sup>3</sup> Pain can range from mild to immobilizing, negatively affecting the quality of life of individuals suffering from OA and also increasing their risk of morbidity and mortality.<sup>2</sup> Non-steroidal anti-inflammatory drugs (NSAIDs) is the most common conventional pharmacologic treatment used for addressing pain associated with OA.<sup>4</sup> However, some patients are unable to use NSAIDs due to their adverse effects on the gastrointestinal (GI) system and increased risk for cardiovascular disease.

For individuals who suffer from OA pain and cannot tolerate NSAIDs or for those who prefer a more natural approach to treatment, they can consider using Turmeric.<sup>2</sup> Turmeric is a member of the ginger family (*Zingiberaceae*), an ancient herb native to Southern Asia. The primary active constituent of turmeric is curcumin (*syn. Curcumin domestica*). It gives turmeric its' vibrant yellow-orange color and sharp flavor, making it

one of the principle spices used in oriental food and curry dishes. Curcumin has been used in holistic medicine for its' anti-inflammatory, antioxidant, and antimicrobial properties. It has a long history of use in Ayurvedic, herbal, and traditional Chinese medicine.<sup>5</sup> According to the New York University Langone Medical Center, 400-600 milligrams of curcumin taken 3 times per day is needed to see therapeutic benefits.<sup>6</sup> Because curcumin exists in less than 5% in turmeric spice, a significant amount needs to be consumed in order to potentially improve health.<sup>7</sup> Curcumin supplements have been proven to provide therapeutic levels and can be used at 2000 mg/day for up to 6 weeks or a higher dose up to 8000 mg/day for 3 months without any serious adverse events.<sup>2,8</sup>

Compared to NSAIDs, curcumin has notable advantages in the treatment of inflammatory conditions such as osteoarthritis.<sup>2</sup> Curcumin selectively inhibits the activity of cyclooxygenase (COX-2), reducing the prostaglandins which contribute to inflammation by promoting vasodilation and increasing vascular permeability. Curcumin also inhibits the production of inflammatory cytokines such as interferon interleukins, tumor necrosis factor, nitric oxide synthase enzymes, and activation of NF-kB.<sup>1</sup> The role of curcumin in modulating the inflammatory process and all of these substances provides a more natural and therapeutic treatment for OA as long as it is as effective as NSAIDs in managing pain.<sup>2</sup> This review focuses on the efficacy and safety of curcumin compared with NSAIDs in the symptomatic treatment of osteoarthritis pain.

## **METHODS**

An exhaustive search of available medical literature was performed using MEDLIN-Ovid, MEDLINE-PubMed, ClinicalKey, Web of Science, Google Scholar, and

UpToDate. Keywords used included: curcumin, turmeric, osteoarthritis, arthritis, pain, inflammation, and NSAIDS. The search was narrowed to include English language articles and human trials only. The bibliographies of the articles were further searched for relevant sources. Relevant articles were assessed for quality using Grading of Recommendations, Assessment, Development and Education (GRADE).<sup>9</sup>

## **RESULTS**

Three studies meeting inclusion criteria were used for this systematic review. One of the studies was an observational study<sup>10</sup> and two were controlled studies.<sup>2,11</sup> See Table I for quality assessment of each article using GRADE criteria.

### **Kuptniratisaikul et al (*Curcuma domestica* extracts compared with ibuprofen)**

In this double-blind randomized control study,<sup>2</sup> 367 patients with primary knee osteoarthritis age  $\geq$  50 years from July 2010 to March 2012 were included. The randomization number was generated by computerized method and allocated 185 patients to receive 1200 mg/day of ibuprofen and 182 patients to receive 1500 mg/day of *C. domestica* extracts. For blinding both patients and assessors, medications were manufactured to be identical capsules in appearance. Treatment codes were kept from the pharmacist who was not involved in the study. Patients were instructed to take two capsules after meals 3 times a day for 4 weeks. Outcomes were evaluated at week 2 and week 4 by the same assessor at each site. The inclusion criteria were primary knee OA according to the American Rheumatism Association criteria who had a numerical rating scale of knee pain of 5 out of 10 and age  $\geq$  to 50 years. Patients who had abnormal liver

function or renal function, history of peptic ulcer, allergy to curcumin or ibuprofen, or were unable to walk were excluded.<sup>2</sup>

After being recruited, participants received a knee X-ray, which indicated the severity (II–IV grading) according to Kellgren–Lawrence criteria. The outcomes were measured using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). The WOMAC scores were composed of 3 subscales: pain, stiffness, and function. Each scale ranged from 0 to 10; higher scores represented more pain, more stiffness, or worse knee functions. A 6-minute walk distance was also compared between groups at week 4. For safety concerns, the adverse effects were recorded if patients experienced new symptoms during the study. Compliance of treatment was determined at each visit by the pill count. Lastly, global assessment and satisfaction of each patient was evaluated at the end of the study.<sup>2</sup>

This study was designed as a noninferiority trial with the assumption that there was a significant difference of  $\pm 0.5$  points in the WOMAC pain score after treatment. To compare the WOMAC mean scores and the 6-minute walk distance between groups, analysis of covariance and the unpaired *t*-test for noninferiority and equality were used. Chi-square test was used to analyze the AEs, satisfaction levels, and compliance of drug intake was measured using the *t*-test for equality.<sup>2</sup>

Baseline characteristics of participants were the same between groups with the mean age of 60 years, approximately 90% female, and a body mass index of 26 kg/m<sup>2</sup>. Nearly 60% of participants had unilateral knee pain. At baseline, both groups had WOMAC scores greater than 5 out of 10. The 6-minute walk distance was 304 meters

and 310 meters in the ibuprofen and *C. domestica* extracts groups, respectively. The numbers of knee X-rays with grading classified by Kellgren–Lawrence criteria were 138 (86.8%) versus (vs) 150 (87.7%) in the ibuprofen and *C. domestica* extracts groups, respectively, same in both groups.<sup>2</sup>

The changes over time of *C. domestica* and ibuprofen were measured at week 0, 4, and 6 using the WOMAC index. A within-group comparison showed decreased WOMAC scores in both groups (P-value < 0.001), which meant significant improvement from baseline. However, a between-group comparison showed no difference in WOMAC total score (P-value 0.326), WOMAC pain (P-value 0.531), or WOMAC function (P-value 0.278). In addition, the 6-minute walk distance at week 4 was approximately 350 meters with no difference between groups (mean difference and 95% CI were 7.18 meters and -7.01 to 21.38 meters).<sup>2</sup>

During the study, common AEs included dyspepsia, abdominal pain/distension, nausea, loose stool, and pitting edema. The number of participants that developed AEs during the study was not different between the two groups (P value 0.222). Symptoms of loose stool was higher in the *C. domestica* extracts group than in the ibuprofen group but with no significant difference (P-value 0.330). For the numbers of events that occurred, the rate of abdominal pain/distension was significantly lower in the *C. domestica* extracts group than in the ibuprofen group (P-value 0.046).<sup>2</sup>

There was no difference between groups in drug compliance (P-value 0.202) including the patient's global assessment and satisfaction that was measured between groups at week 4 (P-value 0.665 and P-value 0.707, respectively). Overall, about 97% of

participants were satisfied with the treatment and two-thirds rated themselves as improved in a global assessment.<sup>2</sup>

A total of 160 patients in the ibuprofen and 171 in the *C. domestica* extract groups completed the study. The reasons for being lost to follow up included withdrawal, inconvenience, participants unable to be contacted, and adverse effects (seven patients in the ibuprofen and one patient in the *C. domestica* group).<sup>2</sup>

### **Appelboom et al (Flexofytol Study)**

An observational study<sup>10</sup> was performed in 2013 with the help of general physicians in evaluating the potential benefits of Flexofytol (which contains curcumin extract as its main active ingredient) on joint function, pain severity, flexibility, and quality of life of their patients. There were 110 general practitioners from Belgium who participated in the study and followed 820 patients treated with Flexofytol for a 6-month duration. Physicians were asked to report the effects of Flexofytol, including: number of joints affected, pain intensity (0 = no pain to 10 = intolerable pain), joint flexibility (0 = bad to 10 = excellent), and quality of life (visual scale of 0 = bad to 10 = excellent). Global evaluation of the efficacy of treatment according to the patient, use of concomitant treatments, undesirable effects and patients' desire to continue or discontinue the treatment was also measured.<sup>10</sup>

In total, 820 patients suffering from OA (36.7% men) with a mean age of 64.2 +/- 12.4 years were followed and evaluated by their physicians after 6 weeks, 3 months, and 6 months of treatment. There were 739 patients who were using 2 capsules two times daily and 81 patients took 2 capsules three times daily to improve joint function. Of the

total patients, 563 of them reported suffering unilateral joint pain, mainly knee and the lower back, and 67 patients suffered from at least 3 locations. Before starting Flexofytol, most patients (85%) were treated with NSAIDs, analgesic agents (64.7%) and/or chondroprotective agents (13.4%). Global evaluation of efficacy of treatment, use of concomitant treatment, AEs, and patient's desire to continue or discontinue treatment were also ascertained. The General Linear Model Method was used to analyze pain, mobility, and quality of life, and differences were considered statistically significant at  $p < 0.05$ .<sup>10</sup>

Improvements were reported within the first 6 weeks of Flexofytol treatment. Most patients reported a decrease in pain (6.9 to 3.2,  $p < 0.0001$ ), a significant increase in flexibility (4.2 to 6.7,  $p < 0.001$ ), better quality of life (4.7 to 6.9,  $p < 0.0001$ ) and a reduction in the amount of concomitant therapies used ( $p < 0.001$ ). Gastrointestinal side effects such as diarrhea were reported by 3.6% of patients at 6 weeks, 2.5% at 3 months, and 1.3% at 6 months. Global assessments provided by patients confirmed 77.1% were satisfied with Flexofytol at 6 weeks and 79% were still satisfied at 6 months. At 6 months, 41.7% of patients wished to continue using Flexofytol, 10.8% responded negatively, and 47.5% had no opinion for continuing for a longer period.<sup>10</sup>

### **Belcaro et al (Meriva Study)**

In an 8-month study,<sup>11</sup> researchers evaluated the efficacy and safety of Meriva, a curcumin-phosphatidylcholine phytosome complex. The study involved 100 patients with symptomatic osteoarthritis. The inclusion criteria included patients who with grade 1 or 2

knee osteoarthritis (one or both knees) following the American Rheumatism Association grading scale and diagnosed via X-ray. The exclusion criteria included patients with “cardiovascular disease requiring drug treatment, diabetes, body mass index >25, severe metabolic disorders, surgery or arthroscopy within 3 months prior to inclusion, any oncological condition, or severe bone or joint deformation or condition making the patient unable to walk...pregnancy, breast feeding, and planned conception.”

Participants were required to perform a treadmill-walking test and be able to fill out a WOMAC questionnaire.<sup>11</sup>

Patients were either given NSAIDs alone (control group), or a combination of NSAIDs and curcumin (treatment group). Patients in the treatment group were given two 500 mg tablets daily, one after breakfast and one after dinner, for a total of 1000 mg a day. Results were recorded at enrollment and at 8 months.<sup>11</sup>

Five patients in the treatment group and six in the control group left the study early for non-medical reasons including moving and work problems.<sup>11</sup>

The Kanofsky Performance Scale was used to measure functional impairment. Lower scores corresponded with greater functional impairment. Functional ability improved significantly in the treatment group from 73.3 at enrollment to 92.2 at 8 months, with no significant improvement in the control group.<sup>11</sup>

The WOMAC questionnaire was used to evaluate symptoms using a score range for pain (0-20), stiffness (0-8), and physical function (0-68). Higher scores corresponded with greater pain, stiffness, and physical function. All WOMAC scores showed significant improvement at 8 months in the treatment group compared to the control

group ( $p < 0.05$ ). Pain dropped significantly in the treatment group from 16.6 (at enrollment) to 7.3 (at 8 months), compared to 16 to 15.2 in the control group. Stiffness also reduced significantly from 7.4 to 3.2 in the treatment group compared to 6.6 to 6.7 in the control group. The total WOMAC score in the treatment group decreased significantly from 80.6 to 33.3 compared to the control group, which slightly decreased from 77.8 to 68.8.<sup>11</sup>

The treadmill test was used to evaluate physical performance. A speed of 3 km/h with an inclination of 10% was used, and the total distance achieved by patients was documented at enrollment and 8 months. Patients taking Meriva were able to achieve a significantly greater total distance on the treadmill test at the end of the study (increased from 77.3 meters at enrollment to 344.4 meters at 8 months) compared to the control group (increased from 82.3 meters to 156 meters). This corresponds to a 345% (3.87 times greater) improvement in the treatment group at 8 months compared to an 89% increase in the control group.<sup>11</sup>

There was a 63% decrease in the use of NSAIDs or other painkillers in the treatment group compared to a 12% decrease in the control group. Meriva patients had a 49% decrease in management costs compared to 3% in controls.<sup>11</sup>

## **DISCUSSION**

Osteoarthritis is a chronic disabling disease requiring lifelong treatment. NSAIDs are currently the standard of care used to treat the symptoms associated with OA. Considering the gastrointestinal and cardiovascular adverse effects caused by the use of NSAIDs, a more natural option for treatment of osteoarthritis should be sought. This

evidence suggests that curcumin can be used as an alternative or in addition to NSAIDs for decreasing pain in patients with osteoarthritis.<sup>2,10,11</sup> These studies have also shown that curcumin can improve physical function, flexibility, and quality of life. The studies have shown that curcumin can be effective at as early as 4-6 weeks of treatment for decreasing pain.<sup>2,10,11</sup> Evidence from the three studies used in this review confirm the safety and analgesic efficacy of curcumin as a natural therapeutic option for patients with osteoarthritis.

In addition to the health benefits of curcumin, evidence shows the use of curcumin to be cost effective. In the study by Belcaro et al,<sup>11</sup> individuals taking Meriva had a 49% decrease in management costs compared to 3% in the control group. Patients with OA require lifelong treatment, therefore decreasing management costs can lessen their financial burden. The study also showed a 63% decrease in the use of NSAIDs or other painkillers in the treatment group compared to a 12% decrease in the control group. In the study by Kuptniratsaikul et al,<sup>2</sup> there were no significant differences in results (non-inferiority test) between ibuprofen and *C. domestica* for the WOMAC scores and 6-minute walk test. This suggests that *C. domestica* extracts are as efficacious as ibuprofen in pain reduction and functional improvement, with *C.domestica* extracts showing a better safety profile than ibuprofen in terms of abdominal pain and distension.

The study conducted by Appelboom et al<sup>10</sup> showed anti-inflammatory effects of Flexofytol within 6 weeks of treatment, showing a decrease in inflammatory mediators at 6 months: interleukin 1B, interleukin 6, the ligand of CD40, and decrease in blood sedimentation rate. Flexofytol is a new curcumin formulation that can be used to combat

the low oral bioavailability of curcumin. Flexofytol has a polyphenol structure that makes it 1350 times more assimilable than native curcumin powder, allowing it to penetrate tissues more easily and remain relatively stable in the intestines. A dose of 42 mg of Flexofytol is equivalent to 57 g of native curcumin or 1 kg of curcuma powder. While the analgesic effects of Flexofytol were observed in all joints, it was most noticeably in the knee and hip joints. The study<sup>10</sup> reported high patient satisfaction and a decrease in concomitant therapies after six months of therapy with Flexofytol.

The three studies used in this review have all shown that curcumin has an analgesic effect on osteoarthritic joints; however, there are some limitations. In the study by Belcaro et al,<sup>11</sup> the study did not directly compare Meriva against NSAIDs in a head-to-head comparison. The study was only 8 months, which may make it difficult to determine the long-term efficacy of Meriva. The mean age of the participants was 44, which is relatively young. Another thing worth noting is that Meriva has low bioavailability; however, studies have suggested that consuming pepper or piperidine with the curcumin tablets can help increase the oral bioavailability of curcumin.<sup>2</sup> The study conducted by Kuptniratsaikul et al<sup>2</sup> consisted of participants who were all Thai females. In the study, researchers had to adjust the max daily ibuprofen levels to a lower dose of 1200 mg/day from the normal 1800 mg/day because Thai individuals have a lower mean body weight compared to Caucasians. One of the limitations of the study by Appelboom et al<sup>10</sup> is that it lacks a control group.

Based on the results of these three studies, the use of curcumin as an analgesic is supported in patients with osteoarthritis. However, the length of these studies did not

exceed 8 months, therefore, further research with a longer length of study should be conducted in order to determine the long-term efficacy and potential adverse side effects of curcumin. Only one of the studies that was reviewed directly compared curcumin to NSAIDs. More research directly comparing the efficacy and safety of curcumin to NSAIDs is needed to confirm if curcumin can be used as a replacement for NSAIDs in decreasing pain severity in patients with osteoarthritis. Research evaluating the efficacy of curcumin at different doses and determining the maximum dose of efficacy should also be conducted, as this may be beneficial for health care providers who are treating patients with different severity levels.

## **CONCLUSION**

Curcumin is an effective and safe natural option for decreasing pain severity and improving quality of life in patients with osteoarthritis. Curcumin can be used as an alternative to NSAIDs or concomitantly across the lifespan. Curcumin therapy should be implemented in clinical practice for the treatment of osteoarthritis. Further research using randomized trials with a larger population size and longer length of study needs to be conducted in order to determine the long-term efficacy of Curcumin. Moreover, research investigating the direct comparison of Meriva to NSAIDs would be of value in determining the efficacy of Meriva, and whether it can be used as an alternative to NSAIDs.

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Table

| Table 1: Quality Assessment of Reviewed Articles                      |               |                      |              |               |                      |                  |                  |          |
|---|---------------|----------------------|--------------|---------------|----------------------|------------------|------------------|----------|
| Study   | Design        | Downgrade Criteria   |              |               |                      |                  | Upgrade Criteria | Quality  |
|   |               | Limitations          | Indirectness | Inconsistency | Imprecision          | Publication bias |                  |          |
| Kuptniratsaikul et al   | RCT           | Not Serious          | Not Serious  | Not Serious   | Not Serious          | Unlikely         | None             | High     |
| Appelboom et al   | Observational | Serious <sup>a</sup> | Not Serious  | Not Serious   | Not Serious          | Unlikely         | None             | Very Low |
| Belcaro et al   | Observational | Not Serious          | Not Serious  | Not Serious   | Serious <sup>b</sup> | Unlikely         | None             | Very Low |
| <sup>a</sup> Lacked a control group<br><sup>b</sup> Small sample size |               |                      |              |               |                      |                  |                  |          |