CRITICALLY APPRAISED TOPIC

FOCUSED CLINICAL QUESTION

In an adult patient (18 – 65 years of age) with chronic musculoskeletal pain, is yoga more effective than pharmaceutical intervention at reducing pain?

AUTHOR

Prepared by	Molly Rose Miller	**Date**	December 3, 2016
Email address	molly_miller@med.unc.edu		

CLINICAL SCENARIO

The patient is a 55-year-old female with chronic low back pain (regularly 5/10) who has been taking pain medication (opioid analgesic) for the past 5 years. She fears she is addicted and her doctor is recommending surgery. She recommends that patient exhaust options before surgery.

Musculoskeletal conditions such as low back pain (LBP), osteoarthritis (OA), rheumatoid arthritis (RA), fibromyalgia and others can cause chronic debilitating pain.[1] Though prevalence rates vary, together these conditions are the leading causes of chronic pain and disability in the developed world,[1] and result in diminished physical function leading to disability and decreased quality of life.[2]

Opioid analgesic medication is a common form of pain treatment for those with chronic pain, including musculoskeletal non-oncologic pain; however, reports of up to 50% of those taking these medications do not have adequate relief of pain.[2] There are also high rates of adverse effects associated with these drugs, including addiction.[2]

Complementary and alternative medicine (CAM), such as yoga, has been shown to be a safe intervention for those with musculoskeletal conditions and is typically used as an adjunct to traditional forms of medicine such as physical therapy and pharmaceuticals.[1] Therefore, yoga should be further investigated as a viable evidence-based intervention for the treatment of chronic musculoskeletal pain.

SUMMARY OF SEARCH

[Best evidence appraised and key findings]

- Searches from 3 electronic databases identified 10 relevant articles which included all systematic reviews, with or without meta-analyses, consisting of all controlled trials (randomized and/or non-randomized). There were no articles directly comparing yoga with pharmaceutical interventions for pain relief. However, three high quality studies most pertinent to this clinical question include 2 regarding the effects of yoga and 1 regarding the effects of opioids on chronic musculoskeletal pain.
- Yoga significantly improves pain outcomes in OA, RA and LBP, especially when compared with passive interventions. Meta-analyses show that there is a moderate treatment effect of yoga for pain for both mild-to-moderate and moderate-to-severe LBP, and for other musculoskeletal conditions (RA, OA).
- The opioid analgesic, tapentadol, significantly reduces pain intensity when compared with placebo and oxycodone controls; however, this is only minimally clinically meaningful. Though both cause adverse effects, tapentadol has less risk of withdrawal/discontinuation of treatment that oxycodone.

CLINICAL BOTTOM LINE

Despite lack of evidence directly comparing yoga and pharmaceutical interventions for the treatment of chronic musculoskeletal pain, it can be inferred from the current evidence that while yoga and opioid analgesics both potentially significantly reduce pain outcomes, yoga is a safer intervention with less overall adverse effects and consequent discontinuation. Yoga is particularly beneficial to patients who are female with moderate-to-severe LBP, such as the patient described above, especially when compared with standard or usual care. However, yoga does not seem to be significantly better than active interventions such as physical therapy at reducing pain. Therefore, a physical therapist could incorporate yoga into a plan of care for this specific patient with chronic musculoskeletal pain in order to significantly reduce pain intensity and subsequently avoid back surgery as well as potentially reduce pain medication usage.

This critically appraised topic has been individually prepared as part of a course requirement and has been peer-reviewed by one other independent course instructor

SEARCH STRATEGY

Terms used to guide the search strategy			
Patient/Client Group	**I**ntervention	**C**omparison	**O**utcome(s)
Chronic pain Chronic pain [MeSH Terms]	Yoga Yoga therapy	Pain medication Pharmacological Pharmaceutical Opioid analgesics	Pain

Final search strategy: PubMed

#1	Search ("chronic pain") OR "chronic pain"[MeSH Terms]	29947
#2	Search ((yoga) OR yoga[MeSH Terms]) OR "yoga therapy"	3682
#3	Search yoga[MeSH Major Topic]	1494
#4	Search (pharmacological OR pharmaceutical)	3690429
#5	Search (medication OR intervention OR management)	3283579
#6	Search (opioid OR opiate OR analgesi*)	143697
#7	Search pain[MeSH Major Topic]	213909
#8	Search (#6 AND #7)	24421
#9	Search (#4 AND #5)	609250
#10	Search (#9 OR #8)	630821
#11	Search (#1 AND #10)	4566
#12	Search (#1 AND #2)	73
#13	Search (#1 AND #3)	20
#14	Search (#2 AND #10)	84
#15	Search (#2 AND #11)	**9**

Note: Of the 9 studies, there were 5 that were eligible; however, they were non-analytical research designs and evaluated other interventions in addition to yoga. Of the 84 studies found on yoga for chronic pain management, there were 5 eligible studies, all of which were RCTs or SRs with or without MAs.

Databases and Sites Searched	**Number of results**	**Limits applied, revised number of results (if applicable)**
PubMed	**9**	**5 eligible**
PEDro	**72**	**N/A**
Cochrane Library	**29**	**4** (Keywords only) → **3 eligible**
CINAHL	**2**	**444** (without yoga, only in academic journals, English) → (NOT "cancer pain") → 375 (NOT constipation) → 357 (NOT "neuropathic pain") → 310 **9 eligible studies** **15** (without pharmaceuticals) **5 eligible studies**

INCLUSION and EXCLUSION CRITERIA

Exclusion Criteria
• Abstracts, conference lectures, magazine or news articles • Not published in English

Inclusion Criteria
• Studied adults with chronic pain (pain duration greater than 3 months) • Measured reduction of pain at discharge • Measured direct effect of yoga intervention • Studied adults who were not taking pain medication at the time of yoga intervention

RESULTS OF SEARCH

Summary of articles retrieved that met inclusion and exclusion criteria

Author (Year)	Study quality score	Level of Evidence	Study design
Santos (2015)[2]	**11/11 AMSTAR**	**Level 1a**	**Systematic Review & Meta-Analysis of RCTs**
Büssing (2012)[3]	**11/11 AMSTAR**	**Level 1a**	**Meta-Analysis of Randomized and Non-Randomized Controlled Trials**
Ward (2013)[1]	**8/11 AMSTAR**	**Level 1a**	**Systematic Review & Meta-Analysis of RCTs**
Cramer (2012)[4]	**10/11 AMSTAR**	**Level 1a**	**Systematic Review & Meta-Analysis of RCTs**
Kalso (2004)[5]	**9/11 AMSTAR**	**Level 1a**	**Systematic review of Double-Blind RCTs**
Chung (2013)[6]	**8/11 AMSTAR**	**Level 1a**	**Systematic Review & Meta-Analysis of Double-Blind RCTs**
Abdel Shaheed (2016)[7]	**8/11 AMSTAR**	**Level 1a**	**Systematic Review of RCTs**
Kuijpers (2010)[8]	**7/11 AMSTAR**	**Level 1a**	**Systematic Review & Meta-Analysis of RCTs**
Crow (2015)[9]	**6/11 AMSTAR**	**Level 1a**	**Systematic Review of RCTs**
McCaffrey & Park (2012)[10]	**5/11 AMSTAR**	**Level 1a**	**Systematic Review of RCTs and Non-Randomized Trials**

BEST EVIDENCE

The following 3 studies were identified as the 'best' evidence and selected for critical appraisal. Reasons for selecting these studies were:

- **Büssing et al. (2011)** examines 16 controlled trials (4 were non-randomized controlled studies) investigating the effects of yoga on pain intensity or pain-associated disability. This is the second highest evidence I could find examining multiple chronic pain conditions (not just low back pain), including RA and carpal tunnel syndrome. Meta-analyses were performed on multiple subgroups of data.
- **Ward et al. (2013)** examines 17 RCTs investigating the effect of yoga on chronic pain as well as functional ability and psychosocial outcomes. The majority of RCTs focus on musculoskeletal disorders such as low back pain, osteoarthritis, rheumatoid arthritis, kyphosis or fibromyalgia, which most closely align with the primary PICO question.
- **Santos et al. (2014)** examines the effect of the opioid medication, Tapentadol, on reduction of pain in adults with chronic musculoskeletal disorders, including low back pain and knee osteoarthritis. According to its AMSTAR score, it is a very high quality systematic review and meta-analysis.

SUMMARY OF BEST EVIDENCE

(1) Description and appraisal of Effects of Yoga Interventions on Pain and Pain-Associated Disability: A Meta-Analysis by Arndt Büssing, Thomas Ostermann, Rainer Lüdtke and Andreas Michalsen (2012)

Aim/Objective of the Study/Systematic Review:

The objective of this study was to examine the effects of yoga intervention on pain symptoms and pain-related disability through a meta-analysis of the literature in patients with various chronic pain conditions.

Study Design

[e.g., systematic review, cohort, randomised controlled trial, qualitative study, grounded theory. Includes information about study characteristics such as blinding and allocation concealment. When were outcomes measured, if relevant]

Note: For systematic review, use headings 'search strategy', 'selection criteria', 'methods' etc. For qualitative studies, identify data collection/analyses methods.

Meta-analysis

Search Strategy: Büssing et al. searched several databases (PubMed/Medline, EMBASE, CAMbase) using the words "yoga * pain" for articles until January, 2010. They did not limit their search by type of pain condition, language, year, status or design. They searched the grey literature, as well as references from pertinent articles and authors.

Selection Criteria:

Inclusion criteria: Studies were included that were either randomized or nonrandomized controlled clinical trials that examined the effect of yoga on pain. The studies had to assess pain in terms of either intensity/frequency of symptoms or disability as a result of pain.

Exclusion criteria: Studies were excluded if they were case reports or series, theoretical reflections or expert statements. Studies were excluded if they did not have a control group and if the intervention group focused on mindfulness or stress reduction programs; the authors wanted to focus solely on yoga as an intervention, not other interventions that also happen to include yoga.

Study designs: A total of 16 studies met inclusion criteria: all had prospective design.

- 5 randomized studies with single-blinding (high quality)
- 7 randomized studies without blinding (moderate quality)
- 4 nonrandomized studies (low quality)

Methods:

Data extraction: Two independent authors of the review narrowed down the articles based on selection criteria and extracted data separately with the use of the Jadad score to assess methodological quality of the studies. The Cochrane Handbook for Systematic Reviews of Interventions, version 5.0.1 was used to assess allocation concealment as well as quality.

Statistical Analysis: All data from each study was converted to standardized outcomes (standardized mean differences, standard errors, and weighted mean differences) to compare clinical findings. The authors performed subgroup analyses of pain using the VAS scores from several studies, as well as other subgroup analyses of both pain and disability, including duration of interventions, and methodological quality (based on Jadad and Cochrane Guideline scores). A random-effects meta-analysis was used to assess treatment effects. Heterogeneity was calculated using X^2 tests and I^2 coefficients and the Egger's test for funnel plot asymmetry was used to assess publication bias. Heterogeneity was also assessed for several subgroup analyses.

Setting

[e.g., locations such as hospital, community; rural; metropolitan; country]

The type of setting for yoga intervention for each study was not summarized; the authors did not specify whether the settings were congruous across studies. It can be assumed that patients participating in yoga must be relatively cognitively sound and physically active; therefore, settings were likely outpatient clinics rather than hospital or inpatient settings. The study took place in Germany, as all four authors work in medicine there.

Participants

[N, diagnosis, eligibility criteria, how recruited, type of sample (e.g., purposive, random), key demographics such as mean age, gender, duration of illness/disease, and if groups in an RCT were comparable at baseline on key demographic variables; number of dropouts if relevant, number available for follow-up]

Note: This is not a list of the inclusion and exclusion criteria. This is a description of the actual sample that participated in the study. You can find this descriptive information in the text and tables in the article.

A total of 16 studies were included in the meta-analysis; all were controlled clinical trials (either randomized or non-randomized) and investigated the effect of yoga on pain-related outcomes. In total, 1,007 participants were involved across all 16 studies and the majority of participants were younger than 50 years of age.

For the two pain-related outcomes, 12 of 16 studies assessed pain symptoms while 12 studies also studied pain-induced disability. Of the several pain conditions, back pain was most commonly examined in 6 studies, followed by 2 studies examining rheumatoid arthritis and 2 studies examining headaches or migraines. The remaining 6 studies investigated outcomes for various other conditions (some non-musculoskeletal) including muscle soreness, carpal tunnel syndrome, labour pain, hemo-dialysis, irritable bowel syndrome, and pain from consistent PC computer use.

Intervention Investigated

[Provide details of methods, who provided treatment, when and where, how many hours of treatment provided]

Control

Control groups utilized physical activity (5 studies), lecture or educational sessions (4 studies), routine care and conversation (1 study) or anti-inflammatory drugs (1 study) or a combination. The remaining studies (7) utilized a waiting-list design and 1 study did not specify control group intervention.

Experimental

The duration of intervention varied across studies; 4 studies involved short-term treatment (0-4 weeks), 7 used intermediate (6-10 weeks) and 5 used long-term (12 – 24 weeks) yoga intervention. Frequency of yoga was not stated for any of the included studies. Various yoga styles were used as interventions with Hatha yoga being most commonly investigated in 5 studies, followed by Iyengar yoga in 4 studies; the remaining studies involved Viniyoga, LAYT, Raj or did not specify type of style.

Outcome Measures

(Primary and Secondary)

[Give details of each measure, maximum possible score and range for each measure, administered by whom, where]

This meta-analysis utilized data from several outcome measures either investigating pain symptoms (intensity/frequency) or pain-related disability. Below is a list of outcome measures used for each:

Pain Symptoms:

- VAS (Visual Analogue Scale)
- MPQ (McGill Pain Questionnaire)
- PPI (Present Pain Index)
- CMDQ (Cornell Musculoskeletal Discomfort Questionnaire)

Pain-related Disability:

- ODI (Oswestry Disability Index)
- FDI (Functional Disability Inventory)
- RDS (Roland Disability Scale)
- PDI (Pain Disability Index)
- SRT (Sit-and-Reach Test)
- CMDQ (Cornell Musculoskeletal Discomfort Questionnaire)
- HAQ (Health Assessment Questionnaire)
- MCQ (Maternal Comfort Questionnaire)

For all outcome measures, a standardized mean difference (SMD) was calculated and authors determined that an SMD of less than 0 indicates that yoga is superior to control group intervention at reducing pain and disability. Furthermore, they concluded that SMDs < -.5 mean that yoga is "putatively clinically relevant" or assumed to make a difference, while SMDS < -.8 are considered to mean that yoga has a large effect on pain-related outcomes. Any effect size between -.5 and -.8 was deemed a moderate treatment effect.

Main Findings

[Provide summary of mean scores/mean differences/treatment effect, 95% confidence intervals and p-values etc., where provided; you may calculate your own values if necessary/applicable]

All studies had outcome measures with SMDs less than 0, favouring yoga intervention over control group interventions; however not all studies in the meta-analysis had statistically significant results. For the two constructs, pain and pain-related disability, effect sizes from each study were pooled together to create an overall treatment effect for each construct. Overall treatment effect and heterogeneity were calculated using a random effects meta-analysis. There was a 95% confidence interval with $p<.05$.

For the primary meta-analyses, the main findings showed a moderate effect of yoga for both pain and pain-related disability. The effect size for pain was -0.74, while the effect size for disability was -.79, which is very close to being a large effect. Heterogeneity of pain studies was moderate (44%), while heterogeneity of disability studies was relatively high (54%).

1) **PRIMARY Meta-Analyses**
   PAIN: Overall treatment effect: -0.74 [-0.97, -0.52], $p<.0001$, $I^2 = 44\%$ → MODERATE
   DISABILITY: Overall treatment effect: -0.79 [-1.02, -0.56], $p<.0001$, $I^2 = 54\%$ → MODERATE

2) **SECONDARY Meta-Analyses**

For both pain and disability, there were sensitivity (subgroup) analyses for duration of treatment, methodologic quality, control group types and randomized controlled trials only. Listed below are the overall treatment effects from yoga for each of these subgroups, with only LARGE effect sizes noted. One of the subsets for pain included studies that used the Visual Analogue Scale as an outcome measure; the researchers rescaled the VAS based on the weighted mean differences instead of standardized mean differences and found that were was an overall WMD of -12mm. The authors did not state whether this WMD was a large, moderate or small treatment effect. For studies assessed as high quality on the Jadad scale, as well as randomized controlled trials, there was a larger effect size for pain, -0.88 and -0.82 respectively, than studies of lower methodological quality or non-randomized. For studies utilizing a passive wait list control group, there was larger treatment effect for yoga (-0.85) than studies utilizing active methods of intervention for the control (-0.62). There was also a larger treatment effect for studies with healthy subjects (i.e. labour pain, PC user, muscle soreness), with a large effect size of -1.14, than studies with subjects with chronic pain (-0.69) or other pain conditions (-0.54).

a) **Subgroup Meta-Analyses for Pain**
   VAS: Overall effect size: -12 mm [-17, -7], $p<.001$, $I^2=19\%$
   HIGH JADAD SCORE: -0.88 [-1.55, -.21], $I^2=87\%$ → **LARGE**
   RCTs: -0.82 [-1.20, -.53], $I^2=54\%$ → LARGE
   WAITING LIST DESIGN: -0.85 [-1.22, -.48], $I^2=65\%$ → **LARGE**
   HEALTHY SUBJECTS: -1.14 [-1.36, -.91], $I^2=0\%$ → **LARGE**

b) **Subgroup Meta-Analyses for Disability**
   DURATION: SHORT: -1.14 [-1.50, -.79], $I^2=0\%$ → **LARGE**
   HEALTHY SUBJECTS: -0.88 [-1.28, -.47], $I^2=57\%$ → **LARGE**

c) **Other Important Subgroup Meta-Analyses**
   PAIN CONDITION: For both pain and disability outcomes, studies focusing on chronic conditions (such as LBP or RA) had higher treatment effects from yoga than those focusing on other pain conditions. The treatment effect of yoga for chronic pain symptoms compared with other pain symptoms was -0.69 > -0.54, while the treatment effect of yoga for chronic pain disability versus other pain-related disability was -0.76 > -0.73.

   DURATION: There was not much difference in the effect sizes between short (-.75), intermediate (-.69), and long-term (-70) yoga for pain symptoms; however, for pain-related disability, shorter duration yoga had a large treatment effect (-1.14) compared to intermediate (-.78) and longer duration (-.64) programs.

   QUALITY: For studies evaluating pain symptoms, there was a large treatment effect (-.88) for higher quality studies (high Jadad score) compared with studies of intermediate (-.73) and low (-.69) quality studies. Likewise, for studies evaluating pain-related disability, high, intermediate and low quality studies had similar effect sizes, -.75, -.56, and -.72, respectively.

   CONTROL GROUP: For studies evaluating pain symptoms, there was a large effect size for those with a passive waiting list control design (-.85), then other active control groups (-.62).

Original Authors' Conclusions

The findings of this meta-analysis show that there is a moderate effect of yoga on pain and pain-related disability (as well as mood). Subgroup meta-analyses suggest that short-term duration yoga interventions are more effective than longer duration programs. The authors conclude that yoga is a safe and useful intervention for various types of pain-causing diseases.

Critical Appraisal

Validity

[Identify the strengths and limitations of the study, including potential sources of bias. Comment on the overall methodological quality (including the score) as you determined from your assessment of the article. Comment on anything you believe was missing in the paper.]

Strengths

The AMSTAR Checklist was used to assess the quality of this meta-analysis, which received a score of 11/11. The factors used to compile this score are some of the strengths of this study. To break down this score, the authors had an 'a priori' design and had two different authors select studies and extract data to reduce confirmation bias as well as chance of error. They used several databases as well as other search strategies, and they included a search of the gray literature by asking experts, further reducing selection bias.

The authors provided a description of each of the 16 studies in table format; excluded studies were referenced with reasoning. Methodological quality was evaluated by the Jadad scale. Out of 16 total studies, there were 5 studies that received a score of 4/5 on the Jadad scale, 3 total studies that received a 3/5, 4 studies with a 2/5, 2 studies with a 1/5 and 2 studies with a 0/5, with a score of 4 indicating high quality. In summary, a little more than 30% (5:16) of studies were of high quality in this meta-analysis. The authors considered study quality when discussing conclusions; the subgroup meta-analysis of methodologic quality found no significant differences between high, moderate and low quality studies although there was a trend for larger effect sizes in higher quality studies.

The authors calculated heterogeneity for each of the meta-analyses to assess consistency or precision of the data, and they also completed a funnel plot analysis to assess publication bias. There was not significant asymmetry shown from the graph, meaning there is little chance of publication bias. The authors were not biased by funding sources as there was none; therefore, there was no conflict of interest reported.

Missing Data

When evaluating the subset of studies using the VAS as an outcome measure, the authors found a weighted mean difference (WMD) of -12mm, but they did not report whether this was a small, moderate or large treatment effect. They stated that they used published mean changes for the VAS to calculate the WMD, but these were not included. Published MCIDs would clarify the effect size for clinical purposes.

Cochrane guidelines for were used to assess allocation concealment and ranked as adequate (telephone randomization or using consecutively numbered sealed, opaque envelops), inadequate (alternate days, odd/even date of birth, hospital number) or uncertain. The authors stated that allocation concealment was assessed and gave a system for classification (A = adequate, B = uncertain, C = inadequate); however, this information is missing from the tables and not discussed any further in relation to the findings, or risk of bias.

In addition to allocation concealment, authors report that data was extracted for general study design, treatment concealment and blinding, gender of participants, or adherence/compliance to therapy including number of dropouts/attrition rates. There was no additional figures or tables to refer to for this data.

Limitations

There were several various styles of yoga being assessed with over 5 different styles across all 16 studies. They also mention that there might be discrepancies in the qualification and expertise of the yoga teachers across studies. Therefore, it is unclear what components of yoga maximize the treatment effect. There was also a large variety of control groups (over 6 different types), which included both active and passive interventions, decreasing the homogeneity.

Pain conditions varied, some of which do not fall within the PT scope of practice. There were 3 of the 16 studies included in the meta-analysis that evaluated the effect of yoga on labour pain, hemo-dialysis, and irritable bowel syndrome, which may have elicited different pain pathways or responses than chronic pain.

While the overall quality of this systematic review was high based on the AMSTAR score, several of the studies had poor methodological quality. There were 4 nonrandomized studies, with 2 studies receiving a score of 0 on the Jadad score. Overall, there were small sample sizes, with an average of 63 participants, diminishing the overall power, and the majority of participants were young adults. More importantly, there were several studies with 95% confidence intervals that included the null line of 0, meaning the results are not statistically significant. There were 2 of these studies evaluating pain and 5 of these studies evaluating pain-related disability.

Interpretation of Results

[This is YOUR interpretation of the results taking into consideration the strengths and limitations as you discussed above. Please comment on clinical significance of effect size / study findings. Describe in your own words what the results mean.]

The primary results of this meta-analysis suggest that yoga should be considered as a possible treatment for pain, as it is shown to have a moderate effect on pain symptoms and disability related to various painful conditions, compared with other active and passive control interventions.

Secondary meta-analyses provide additional information regarding quality, duration, control groups, subject type and pain conditions. For both pain and disability constructs, methodological quality does not seem to make that much difference in treatment effects. There is also not much difference in treatment effects for varying duration of yoga interventions. However, shorter duration yoga programs have a large treatment effect on pain-related disability. Clinically, it cannot be absolutely assumed that shorter programs are more effective, however, because the authors do not mention the drop-out rates or loss of enthusiasm for yoga intervention over time which could be contributing to a decreased effect.

It makes sense that studies with waitlist control groups have larger treatment effects because the subjects are passive compared to other active intervention controls. Some of the control groups may be irrelevant, since it is unclear whether the mechanism of intervention for active treatments can truly be compared (i.e. educational handouts versus physical activity). Interestingly, yoga had larger treatment effects for healthy subjects for both pain symptoms and disability; however, there were greater effect sizes for chronic pain conditions than other pain-related impairments, which include healthy subjects. Therefore, it is difficult to tell if yoga is more effective for chronic pain or for pain conditions in healthy subjects. From the data, I would posit that the conditions in healthy subjects, which included muscle soreness, PC user, and labour pain, are more easily treated. Also, chronic pain conditions, like RA or low back pain, may respond more favourably than other pain conditions such as IBS, headaches, or hemo-dialysis because of their musculoskeletal nature.

Heterogeneity was relatively high for both primary outcome measures, meaning that different yoga types may impact pain conditions differently. Small sample sizes decrease the power of the results, meaning there is a higher probability that the authors may have made a Type II error. The external validity is diminished due to the majority of subjects being younger, meaning these results cannot be applied to older adults or the elderly, which are populations with a higher prevalence of pain conditions.

While yoga was favoured over control groups for all of the included studies, given this summary, it is difficult to definitively say that yoga should be incorporated into physical therapy treatment. However, the results suggest that healthy subjects or those with chronic pain may respond more favourably to a shorter duration yoga intervention than other active interventions.

(2) Description and appraisal of: Yoga for Functional Ability, Pain and Psychosocial Outcomes in Musculoskeletal Conditions: A Systematic Review and Meta-Analysis by Leslie Ward BSc, PGDipSci, Simon Stebbings MB BS, MMed Sc, FRCP, FRACP, Daniel Cherkin PhD and G David Baxter PhD, MBA (2013)

Aim/Objective of the Study/Systematic Review:

The objective of the systematic review was to investigate the effects of yoga on functional outcomes, pain and psychosocial outcomes in patients with musculoskeletal conditions (MSCs).

Study Design

[e.g., systematic review, cohort, randomised controlled trial, qualitative study, grounded theory. Includes information about study characteristics such as blinding and allocation concealment. When were outcomes measured, if relevant] Note: For systematic review, use headings 'search strategy', 'selection criteria', 'methods' etc. For qualitative studies, identify data collection/analyses methods.

Systematic Review

Search Strategy: Ward et al. searched a total of 20 databases relevant to MSCs and complementary and alternative medicine (CAM) (i.e. CINAHL, International Journal of Yoga Therapy) from inception to December 31, 2011. Key words identified using MeSH, Thesaurus and subject headings included 'yoga', 'musculoskeletal', and 'random', which were combined with 'back pain' and 'arthritis' using strategies specific to each database with advice from (medical) librarians. Authors also conducted hand searches of journals, reference lists and relevant reviews (from 2000). Dissertations and theses were included.

Selection Criteria: Two independent reviewers assessed each article with respect to inclusion criteria; a third independent reviewer settled discrepancies.

Inclusion criteria:
1) Yoga was primary intervention
2) Study population had clinical diagnosis of musculoskeletal condition (MSC)
3) Participants 18+ years of age
4) RCT study design
5) Published in peer-reviewed journal
6) Available as full text

Study Designs: A total of 17 articles met inclusion criteria; 8 of these were included in meta-analysis (see Participants section for information on study characteristics)

Methods: Articles were critiqued by two independent reviewers with disagreements resolved with consensus; one article excluded from quality assessment due to lack of data.

Methodological Quality: PEDro and 19-item van Tulder scales were used to assess methodological quality; a score of 50% on each was required for the article to be considered of good quality.

Risk of Bias Assessment: Cochrane Collaboration tool (7 domains) was used to assess risk of bias; articles were rated as having low risk of bias if greater than or equal to 4 domains were rated as low, while articles with greater than or equal to 4 domains with high ratings were considered as having high risk of bias.

Data Extraction: Demographics, study characteristics, outcome measures and statistics were compiled and double checked by an independent third person. Data from outcome measures was grouped according to category (function, pain and psychosocial).

Meta-Analyses

Study selection: 8 of 17 studies were included in the meta-analysis due to their high quality rating on the van Tulder scale. Meta-analyses were conducted on pain and functional outcomes, not psychosocial outcomes due to limited number of studies evaluating this construct. There was a meta-analysis conducted for the effects of yoga on pain outcomes and a meta-analysis conducted for functional outcomes.

Statistical Analysis: Published, unadjusted continuous data was converted to standardized mean differences (SMDs) with standard deviations using Review Manager 5 (RevMan5) software to standardize results from multiple outcome measures. Heterogeneity was calculated using a random-effects model and analysed according to *a priori* level of $I^2 > 50\%$. To accurately compare sample sizes across studies, sample size of yoga groups was halved in studies containing three treatment groups.

Setting [e.g., locations such as hospital, community; rural; metropolitan; country]

All but two studies were conducted in outpatient settings, which were conducted residentially. Majority of studies conducted at one site; two studies conducted at multiple sites. Research locations included the USA, India and the UK. This review did not further describe location or setting of intervention.

Participants

[N, diagnosis, eligibility criteria, how recruited, type of sample (e.g., purposive, random), key demographics such as mean age, gender, duration of illness/disease, and if groups in an RCT were comparable at baseline on key demographic variables; number of dropouts if relevant, number available for follow-up]

Note: This is not a list of the inclusion and exclusion criteria. This is a description of the actual sample that participated in the study. You can find this descriptive information in the text and tables in the article.

There was a total of 17 studies included in the systematic review with 8 of those studies included in the meta-analysis. One of the 17 studies (Jacobs, 2004) provided baseline data only; therefore, was not included in assessments. All of these studies were full text, randomized controlled trials (RCTs) published between 1994 and 2011. Fifteen of these had a two-arm RCT design investigating yoga intervention versus one control intervention while the remaining two studies (Sherman, 2005, 2011) utilized a three-arm design examining two different controls each compared with yoga intervention.

In terms of methodological quality rated by the 19-item van Tulder scale, 12 of the 17 studies were rated as good quality (scored above 50%), while 4 studies were rated as poor quality (scored below 50%). Ranges of PEDro and van Tulder scales were 1-9 (out of 10) and 2-16 (out of 19), respectively, and there was a good correlation between the two scales.

In total, 1626 participants were involved across all 17 studies, all above the age of 18. Sample sizes ranged from 12 – 313 and ages ranged from 23 – 90. The majority of total participants (72%) were female. One study (Greendale, 2009) examined older adults (average age 76) while one study examined females exclusively due to disease prevalence (Carson, 2010). Another study specifically investigated ethnic minorities (83% of participants) (Saper, 2009).

MSCs included low back pain (LBP), osteoarthritis (OA), rheumatoid arthritis (RA), fibromyalgia (FM), and kyphosis. The majority of studies (12 of 17) assessed outcomes related to LBP, while 2 studies assessed OA, 1 study assessed RA, 1 study assessed FM and 1 study assessed kyphosis. The average duration for clinically diagnosed LBP ranged from ten to 15 years, and 12 years for fibromyalgia, which were the only ones reported. According to participants' baseline scores, overall severity of pain and function was mild-to-moderate. Only two studies reported moderate-to-severe MSC pain associated with LBP and OA and three studies did not provide sufficient data to determine severity.

Intervention Investigated

[Provide details of methods, who provided treatment, when and where, how many hours of treatment provided]

Control

Control groups involved either passive or active interventions compared with yoga intervention. Passive interventions included usual/standard medical care (or wait list) (8 studies), education (i.e. self-care book) (4 studies), and social environment (1 study). Active interventions included therapeutic exercise (2 studies), physical therapy exercise (2 studies), and conventional stretching (1 study). One study did not report control group intervention; authors deemed as passive to be conservative.

Experimental

Yoga styles included Hatha, Iyengar, Viniyoga, Integrated Yoga Therapy (IYT), Yoga of Awareness and integrated approach to yoga therapy (IAYT). All 6 of these styles incorporate physical yoga postures, breathing, relaxation or meditation. The duration of intervention varied from 1-24 weeks; the frequency varied from 1-7 times per week and the length of sessions varied from 40 – 120 minutes each. Across all studies, the total amount of yoga intervention ranged from 8 – 72 hours. Several studies (10 of 17) incorporated recommended home yoga practice which they facilitated through written handouts, yoga mat and props, and audio-visual aids. Frequency of encouraged home practice varied as well as reported adherence to home practice. Authors provided further details regarding average number of minutes of home practice to which participants were encouraged and adhered.

Outcome Measures (Primary and Secondary)

[Give details of each measure, maximum possible score and range for each measure, administered by whom, where]

There were several outcome measures measuring pain, function and psychosocial outcomes; many of these outcomes were valid and reliable measures that have been recommended for the MSC population. However, for the purpose of this clinically appraised topic, only the outcomes measuring the construct of pain will be the focus of this summary and are listed below.

Pain Outcomes:

- SDPIS (Simple Descriptive Pain Intensity Scale) – RA (Bhandari, 2009)
- VAS Pain (Visual Analogue Scale) – OA, LBP (Garfinkel, 1994; Jacobs, 2004; Williams, 2009)
- Numeric Pain Scale – LBP (Saper, 2009; Sherman, 2005)
- Bothersomeness – LBP (Sherman, 2005, 2011)

Of the 17 total studies, 7 studies specifically investigated the effects of yoga on pain symptoms. Studies investigating the effects of yoga on LBP, OA and RA used pain as a primary outcome measure; studies investigating the effects of yoga on fibromyalgia or kyphosis used primarily functional outcomes. The most commonly used pain outcome measures were the VAS and the Numeric pain scale, used in three and two studies, respectively. Among all baseline data, levels of pain ranged from 4.2 – 7.1 on a scale of 1-10 using the VAS or Numeric pain scale. Two studies (Bhandari, 2009 & Garfinkel, 1994) did not include baseline pain levels. Authors did not describe the outcome measure of "bothersomeness"; upon further review of the individual study, this is described as a single question of symptom bothersomeness on a scale from 0 – 10. The authors did not describe the specific reliability or validity of these pain measures.

Meta-Analysis

There were four studies included in a meta-analysis of pain outcomes and their SMDs were pooled to compare treatment effects between yoga and control intervention groups. SMDs less than 0 indicated that yoga intervention was more effective than controls. Authors determined *a priori* SMD < -0.50 means medium effect size and SMD < -0.80 means a large effect size with potential for meaningful clinical relevance.

Main Findings

[Provide summary of mean scores/mean differences/treatment effect, 95% confidence intervals and p-values etc., where provided; you may calculate your own values if necessary/applicable]

Systematic Review

Of the 17 studies, only 14 studies had sufficient data to provide analysis of comparison between yoga and control interventions. Authors did not specifically state why the three excluded studies were insufficient. Among all three constructs (pain, function and psychosocial), there was significant effects of yoga compared with controls with a *p*-value >0.05. For the purpose of this CAP, main findings of the effects of yoga on pain outcomes will be the focus.

Pain Outcomes: There were 7 total studies in which pain was a primary outcome; these studies excluded those investigating kyphosis or fibromyalgia, meaning that only pain associated with LBP, OA and RA was assessed. The authors discussed the results of 6 of these studies in regards to scores on the pain outcome measures as discussed in the previous section. One of the studies (Jacobs, 2004) was excluded for further assessment because it provided baseline data only.

There was a significant reduction in pain for all three yoga groups (OA, RA, LBP) compared with passive controls. There were significant reductions in pain levels at 12 weeks for mild, moderate, and severe LBP compared with passive controls. More importantly, this statistically significant result was clinically meaningful for participants in the yoga group with moderate-to-severe LBP who averaged a 2.3-point reduction in pain levels compared with passive controls, who averaged a 0.4-point reduction. For RA and OA, pain levels improved significantly as well with yoga when compared with passive intervention.

Yoga vs. Passive Control Interventions

- For mild-to-moderate LBP, yoga resulted in a significant reduction in pain levels at 12 and 24 weeks
- For moderate-to-severe LBP, yoga results in a significant reduction in pain levels at 12 weeks
    - *Clinically significant:* average 2.3 (yoga) versus 0.4 (passive) point reduction on a 10-pt scale
- For OA (of the hands), yoga resulted in a significant reduction in pain levels at 8 weeks
- For RA, yoga resulted in a significant reduction in pain after 40 days

Yoga vs. Active Control Interventions

- For mild-to-moderate LBP, yoga did NOT result in a significant reduction in pain levels at 12 weeks

Meta-Analysis

Eight total studies were of high enough quality to include in meta-analyses. Studies investigating OA, RA, and kyphosis were of too poor quality to include; therefore, only studies investigating outcomes related to LBP and fibromyalgia were analysed. To reiterate, due to the limited number of studies investigating psychosocial outcomes, only pain and function were statistically analysed. For the purpose of this CAP, only pain outcomes will be further discussed.

Pain Outcomes: There were 4 total studies in which pain was a primary outcome. Two of these studies (Saper, 2009, Williams, 2009) included only passive interventions (standard medical care, waitlist/usual care) while two of these studies (Sherman, 2005, 2011) included both active (therapeutic exercise, conventional stretching) and passive interventions (self-care book).

A random effects model was used analysing standardized mean differences with 95% CI to calculate standardized treatment effects. For the meta-analysis of pain outcomes, there was an overall moderate treatment effect of yoga (-0.61) compared with controls. Both active control interventions had CIs that included 0; when excluded, there was a strong treatment effect of yoga (-0.84) compared to passive controls.

- Overall treatment effect: -0.61 [-0.97, -0.26], $p < 0.0007$, $I^2 = 63\%$ → **MODERATE**
- Passive controls treatment effect: -0.84 [-1.24, -0.44], $p < 0.0001$ → **STRONG**

Original Authors' Conclusions [Paraphrase as required. If providing a direct quote, add page number]

Authors conclude from this systematic review that yoga has a clinically meaningful effect on pain functional, and psychosocial outcomes in various musculoskeletal conditions (LBP, OA, RA, fibromyalgia, kyphosis). The findings of the meta-analysis suggest a moderate treatment effect of yoga for pain and function outcomes. Specifically, yoga is significantly more effective than passive interventions when compared with active interventions. Authors conclude that yoga is a safe intervention to be used for patients with MSCs.

Critical Appraisal

Validity

[Identify the strengths and limitations of the study, including potential sources of bias. Comment on the overall methodological quality (including the score) as you determined from your assessment of the article. Comment on anything you believe was missing in the paper.]

Strengths

To assess methodologic quality, the AMSTAR checklist was used; this systematic review and meta-analysis received a score of 8/11. This high score reflects the strengths of this review and will be used as a guide.

AMSTAR: Questions 1,7, and 8: Positive scores on these specific questions suggest strong methodological rigor. The authors determined *a priori* inclusion criteria for quality using the PEDro and van Tulder scales, which have been previously used to rate musculoskeletal interventions. In addition to rating the articles themselves, authors cross-checked their scores with those in the PEDro database. PEDro scores ranged from 1-9 out of 10, while van Tulder scores ranged from 2-16 out of 19. When compared to the PEDro database, there were some discrepancies, as the authors determined that self-assessed outcome measures should be deemed unblended. The authors corresponded with PEDro about this discrepancy and their response supported the authors' conclusions. These efforts demonstrate that the authors showed initiative in pursuing the most accurate data regarding study quality, lessening the risk for researcher bias.

AMSTAR: Questions 2 & 3: Receiving points for these questions suggests this article has low publication and research bias. Two independent reviewers assessed articles for selection, methodological quality, and risk of bias, with disagreements settled by consensus or a third reviewer. The search impressively involved twenty relevant electronic databases, and included dissertations and theses, hand searches, and reference lists. The authors used pilot-tested searches specific to each to each database which a senior faculty medical librarian developed, suggesting their search was likely very comprehensive and standardized. The authors made concerted efforts to obtain articles with relevant abstracts from authors, publishers, and journals that were difficult to obtain; furthermore, the authors inquired about additional publications from authors of dissertations and theses.

AMSTAR: Questions 5 & 6: The authors provided detailed tables about the study characteristics and intervention parameters of each included study, as well as the one excluded study (Jacobs, 2004). Data for each study was comprehensive and included information on participants (number, age), specific control interventions, primary time points, outcome measures, attrition and compliance rates for yoga as well as adverse events. Intervention characteristics included type of yoga, duration and frequency of yoga sessions and home practice, as well as details regarding how yoga was administered at home (through audio-visual guides). Sharing this information not only provides transparency for more conclusive analysis when comparing studies, but also provides detail necessary for reproducibility.

AMSTAR Question 9: The authors also set *a priori* I^2 of greater than 50% to indicate heterogeneity; a random effects model was used due to the presence of heterogeneity among studies. To account for this variance, authors decided to divide the total number of participants in three-arm studies to more accurately compare with the sample size of control groups in two-arm studies. This advice was corroborated by the Australasian Cochrane Centre; again, this shows the initiative authors chose to take to most accurately represent and analyse data. To pool the findings, authors used standardized mean differences to compare the data across studies. They determined a priori levels of treatment effects regarding SMDs from the meta-analysis and mentioned that a medium effect size (SMD < -0.50) indicates "potential clinical relevance" which is helpful for determining external validity.

Methodological Quality: In summary, the overall quality of this systematic review was relatively high and several of the studies (12 out of 16 rated) had good methodological quality, increasing the internal validity.

Missing Data

Missing data among the 17 studies included missing baseline data (Jacobs, 2004), lack of statistical analyses (Bhandari and Singh, 2009) and lack of statistical power (Cox, 2010). However, the authors explicitly stated and considered this missing data when conducting analyses. Due to the high variability in types of passive and active controls, easily comparing these components with the various yoga styles requires more detail. For instance, "usual care" and "standard medical care" passive controls are not explicitly described by the authors; it is unclear what the standard of care is for chronic musculoskeletal conditions. For the purposes of the CAP, it would be helpful to know if this included pharmaceutical interventions in order to more accurately compare active yoga interventions with opioid analgesics for pain reduction in this population.

AMSTAR Question 2: Specifically regarding duplicate data extraction, authors state that "data…were independently extracted…and checked by an independent assessor." (pg. 205) Both study selection and methodologic quality/risk of bias assessments were conducted by two independent reviewers and this was clearly stated; therefore, it is curious as to why it was not explicitly stated that data extraction was performed by two independent reviewers.

AMSTAR Questions 3 & 4: Regarding comprehensive literature searches, there is no mention of whether language was used as exclusion criteria. This is relevant as it appears that research locations took place in India. However, there was not much disclosure of the location or setting of interventions either, so assumptions have to be made by the reader. Additional pertinent information that could have been included were details about the nature of yoga instruction; for instance, whether the instructor certifications were consistent across studies.

In Table 1, the characteristics are listed for each study, including the outcome measures; however, some of the outcome measures are unclear and not further described by the authors. For instance, authors made a blanket statement regarding pain outcomes: "assessment was mainly conducted using generic visual analogue scales or numerical rating scales" (pg. 211) It can be inferred that the VAS and Pain numeric scales are being referred too; however, the outcome titled "bothersomeness" was not described. Upon further investigation into the individual study, this scale is a numeric rating scale, which would have been helpful to know for this analysis. The authors state that the reduction in pain for LBP was "clinically significant" due to a greater average point decrease in the yoga group than the waitlist control. However, there is no reference or description of how they determined that this is clinically relevant. It would have been helpful if authors had included minimal clinically important differences (MCIDs) for the pain scales to validate this statement. Furthermore, the authors did not describe the specific reliability or validity of any of the outcome measures, stating simply that all outcome measures were "predominantly reliable and valid questionnaires." Due to the large variety of outcome measures used for each construct, more details would be pertinent to the internal and external validity of this systematic review and meta-analysis.

AMSTAR Question 11: While the authors acknowledged contributors and declared no conflict of interest, there is no mention of funding sources or support for either the systematic review or included studies.

Limitations

AMSTAR Questions 4 & 10: Despite the thoroughness of their search strategies, the authors limited their inclusion criteria to published, full text, RCTs only. Regarding the status of publication, authors excluded grey literature, unpublished literature and articles of varying study designs which may have increased the risk for publication bias. Furthermore, they did not assess publication bias with a funnel plot or other statistical tests, as well as failed to mention appropriate reasons why they chose not to use these tests. In their discussion, they did not mention heterogeneity specifically, but they did acknowledge that there may have been "incomplete retrieval" of potentially relevant articles.

AMSTAR Questions 2 & 3: The authors acknowledge that there is a skewed distribution of studies focusing on musculoskeletal LBP over the other MSCs included in this review. This bias could be due to the prevalence of conditions, the rate at which conditions are researched, or the likelihood of specific populations using yoga. The authors state that people with LBP are 4x more likely to use CAM (complementary and alternative medicine) treatments, such as yoga, then those with fibromyalgia or arthritis. The authors state that excluding studies other than RCTs increased the bias toward LBP conditions.

Risk of Bias: There were only 3 total studies that were deemed to have low risk of bias based on pre-determined criteria from the seven-domain Cochrane Collaboration tool. The seven domains include random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias. Authors state that the studies with high risk of bias tended to have inadequate random sequence generation, allocation concealment, blinding and unclear reporting of outcomes and other potential sources of bias. The three studies with low risk of bias typically followed a published protocol and had low attrition bias. For the purpose of this CAP, there was only one study with low risk of bias with a primary pain outcome (Sherman, 2011). Therefore, with high risk of bias, internal validity is decreased overall.

Adherence, Attrition & Adverse events: Authors considered that 80% adherence rates and above were deemed acceptable; however, only 4 studies reported acceptable percentages. The authors conclude that there were relatively high levels of adherence compared with recommended dosages for home practice; however, there was low adherence to yoga intervention sessions led by an instructor.

While there were studies that did not report or unclearly reported adherence, the range of reported percentages was from 14 – 91%, suggesting high levels of inconsistency among yoga interventions. There was even more discrepancy in adherence to home practice, ranging from 52 minutes per week to 30 minutes, 4 days per week, which was at high risk for bias due to self-report High variability in adherence indicates that research has failed to determine appropriate dosages of yoga; low adherence rates suggest that results will not be clinically meaningful.

Attrition rates ranged from 0 – 50% in yoga intervention groups and 0 – 55% in control groups. Due to the high variability in sample size (12 – 313), it is difficult to make inferences regarding high attrition rates. High attrition rates could indicate lower statistical power, decreased internal and external validity, and potential adverse events. Adverse events can also potentially partially explain attrition or adherence rates. Among all participants, there was a range of 0 – 17% who reported adverse effects, with increased LBP being the most common. When investigating this further, there was a reported herniated disc in 1 participant in one of the studies investigating pain outcomes (Sherman, 2011). The studies with the highest percentages of increased LBP also had the greatest number of participants, which could suggest that with higher statistical power, this adverse effect is more likely. Adherence and attrition are extremely important to determining whether yoga interventions were effective. Authors suggest that perceived barriers to adherence as well as yoga and CAM therapies should be investigated for future studies.

Interpretation of Results

[This is YOUR interpretation of the results taking into consideration the strengths and limitations as you discussed above. Please comment on clinical significance of effect size / study findings. Describe in your own words what the results mean.]

The primary results of this systematic review indicate that yoga should be considered as a safe and effective treatment for chronic musculoskeletal conditions as it has been shown to significantly reduce pain levels in participants with OA, RA and LBP. This meta-analysis suggests that yoga can have a moderate treatment effect of yoga for pain outcomes, and effect sizes were more pronounced when compared with passive versus active interventions.

While there was a statistically significant reduction in pain levels, the question remains whether this reduction is clinically meaningful. Authors only reported one clinically meaningful result which was for moderate-to-severe LBP at 12 weeks. However, when compared to active interventions, this same cohort did not experience significant reductions in pain at all. There is so much variability in the control groups that it is difficult to assess the reasoning behind these findings. The passive controls included standard medical care, usual care, self-care book and waitlist control, compared with active controls of therapeutic exercise and conventional stretching. In addition to variability with control groups, there is a large variety in yoga styles, frequencies, durations, and recommendations for home practice. While the yoga styles were based upon similar principles and included yoga postures, breathing, relaxation and meditation, it is unclear which component of yoga was primarily responsible reduction of pain. The time point for studies investigating pain outcomes was 12 weeks for LBP; however, there were significant reductions in pain for OA and RA before this time point, suggesting that the necessary dosage may be dependent upon the individual musculoskeletal condition. It is unclear whether improvements in pain levels for mild-to-moderate LBP, OA of the hands or RA were clinically meaningful, as no MCID was reported. Furthermore, there was only one included study each for both OA and RA, making general conclusions about pain relief uncertain. Due to the high percentage of female participants (72%), the question remains whether this treatment effect would be consistent across genders.

In summary, the variability in both intervention and control groups regarding type, dosage and time points, the lack of variability of participants' gender, and the lack of clinically meaningful references makes it difficult to definitively assume that yoga interventions can impact pain outcomes for the chronic pain population regardless of musculoskeletal condition.

(3) Description and appraisal of: Tapentadol for chronic musculoskeletal pain in adults by Joao Santos, Joana Alarcao, Filipa Fareleira, Antonio Vaz-Carneiro, Joao Costa (2015)

Aim/Objective of the Study/Systematic Review:

The purpose of this study was to investigate the efficacy of a relatively new opioid analgesic called tapentadol (extended release) on reducing moderate-to-severe chronic musculoskeletal pain (duration greater than three months). The study also aimed to examine the safety and tolerability of this drug via analysis of associated adverse events, quality of life, functional status and health/well-being.

Study Design

[e.g., systematic review, cohort, randomised controlled trial, qualitative study, grounded theory. Includes information about study characteristics such as blinding and allocation concealment. When were outcomes measured, if relevant]

Note: For systematic review, use headings 'search strategy', 'selection criteria', 'methods' etc. For qualitative studies, identify data collection/analyses methods.

Systematic Review

Search Methods: Santos et al. searched several databases (Central; The Cochrane Library, Medline, Embase, Web of Science) from inception until March 17, 2014. The authors screened reference lists and trial registries to account for unpublished and ongoing trials, regardless of language. Common key words searched among all databases included "tapentad*", and "drug therapy" as well as other common opioid medication names. Authors contacted drug manufacturers as necessary.

Selection Criteria: Note: Regarding tapentadol dosage, authors considered data from extended release (ER) tapentadol versus immediate release due to the chronicity of musculoskeletal pain. Approved dosages range from 100 to 500 mg per day according to the Food and Drug Administration (FDA) and European Medicines Agency (EMA).

Inclusion Criteria: Inclusion criteria were studies that were either published or unpublished RCTs (could be parallel or cross-over) that compared either tapentadol with placebo, tapentadol with other strong opioids, or both. Included studies investigated tapentadol extended release (ER) within a dosage range of 100 – 500 mg per day.

Exclusion Criteria: Studies were excluded if they were uncontrolled trials, non-randomized studies, cost-effectiveness studies, pooled analysis and review articles. Studies were excluded if they investigated immediate release tapentadol or acute types of pain (post-operative, neuropathic, etc.).

Methods: Two independent authors reviewed all abstracts and full reports to meet inclusion criteria and settled disputes by consensus or with third author.

Study Designs: A total of 4 studies met inclusion/exclusion criteria and were included in qualitative analysis.

- **Afilalo (2010):** Randomized double-blind parallel-arm, multicentre, phase III study including both active and placebo-controls
- **Afilalo (2013):** Randomized double-blind parallel-arm, phase III trial including both active and placebo-controls; not fully published at time of data collection
- **Buynak (2010):** Randomized double-blind parallel-arm, multicentre, phase III study including both active and placebo-controls
- **Wild (2010):** Randomized, open-label, parallel-arm, phase III long-term safety trial

Data extraction: Two review authors extracted data, double checked each other and used a third author for discrepancy. Data extracted from eligible studies included publication details, participant population details, interventions, outcome measures, analgesic results, quality of life scores, participant preferences, withdrawals, quality assessment criteria.

Risk of Bias Assessment: Two authors independently assessed study quality and risk of bias using the Cochrane 'Risk of bias' assessment tool, as well as definitions from three separate sources regarding assessments of systematic reviews. Authors deemed studies to be high quality if they had low risk of bias and low quality of they were rated as having high risk of bias according to the tool. Additionally, studies were rated high quality if they had adequate allocation concealment and low quality if they had poor or unclear allocation concealment.

Meta-Analysis

Two meta-analyses were performed for placebo controls and active controls. Despite plans to conduct further subgroup analyses, there was limited data available. Therefore, there were only three subgroup analyses performed, one for tapentadol versus placebo and two for tapentadol versus active controls. Aetiology of chronic pain conditions was analysed for both placebo and active control groups and study quality was also a subgroup assessed for active control groups.

Statistical Analysis: Authors used mean differences of continuous data (i.e. pain scores) to compare treatment groups using the inverse variance method. For dichotomous data, relative risk ratios (RR) were calculated to compare tapentadol versus active and placebo-controls. Using odds ratios calculated by the Mantel-Haenszel test to adjust for prevalence, authors used data from the meta-analyses (baseline risk of adverse events) to calculate the number needed to treat (or harm) (NNTH/NNTB). Meta-analyses calculated 95% confidence intervals for all summary statistics. Review Manager 5 was used to calculate overall treatment effects.

Heterogeneity: Authors evaluated presence of heterogeneity as $I^2 > 50\%$; they used a random effects meta-analysis with absence of heterogeneity and fixed-effects meta-analysis with presence of heterogeneity. When heterogeneity was present, authors further investigated with other analyses such as using a post-hoc analysis for data with varying lengths of follow-up.

Setting

[e.g., locations such as hospital, community; rural; metropolitan; country]

The setting or location of intervention was not summarized by the authors. It can be assumed that participants taking analgesic medications for at least three months for musculoskeletal pain are outpatient; it is likely that opioid medication was dispensed through a controlled outpatient setting. Authors do not describe the geographic location of medicine dispersal.

Participants

[N, diagnosis, eligibility criteria, how recruited, type of sample (e.g., purposive, random), key demographics such as mean age, gender, duration of illness/disease, and if groups in an RCT were comparable at baseline on key demographic variables; number of dropouts if relevant, number available for follow-up]

Note: This is not a list of the inclusion and exclusion criteria. This is a description of the actual sample that participated in the study. You can find this descriptive information in the text and tables in the article.

A total of 4 RCTs were included in the systematic review and meta-analysis involving 4094 total participants. All participants were at least 18 years of age, with one study requiring men and women to be greater than 40 years of age, due to higher prevalence of knee OA in older adults (Alfilalo 2010). Of the total number of participants, 1876 were treated with tapentadol, 1226 were treated with the active control (oxycodone) and 992 were treated with placebo.

Three studies were double-blinded studies with both active and placebo controls while one study was an open-label trial with an active control, meaning both participants and researchers know which drug is being administered. The open-label trial compared tapentadol extended release (ER) with oxycodone controlled release (ER) for long-term safety. While the open-label trial's aim was to evaluate safety as a primary outcome, the remaining three studies aimed to evaluate efficacy as their primary outcome. The dosage range of tapentadol ER was the same for all included studies (200 – 500 mg/day) as well as the dosage range for oxycodone controlled release (CR), (40 – 100 mg/day) which was the active-control for all trials. The follow-up period for investigation of treatment effects was 12 weeks for the three RCTs and 52 weeks for the open-label trial.

All participants experienced moderate-to-severe chronic musculoskeletal pain, which chronic pain being defined as occurring for at least three months. Moderate and severe pain were differentiated by pain outcome measures. Of the four studies included in this SR/MA, two of them investigated knee osteoarthritis, one of them investigated chronic low back pain and the last one investigated participants with both conditions.

Two of the four total studies were considered to have low risk of bias (Afilalo 2010, Buynak 2010), while two were considered to have high risk of bias (Afilalo 2013, Wild 2010). Risk of bias was assessed using the Cochrane tool and authors included their results from the Cochrane tool for each study, along with supporting evidence for their individual claims for all seven domains (See pg. 20 – 28, Characteristics of Included Studies Table). Afilalo (2010) and Buynak (2010) were deemed to have low risk of bias due to having adequate random sequence generation, allocation concealment, and blinding of participants, personnel and outcomes, as well as having good selective reporting. For both, there was unclear risk of bias from attrition due to the fact that data from participants who discontinued early was unavailable. Wild (2010) was an open-label study and therefore, had a high risk of bias and Afilalo (2013) was deemed to have high risk of bias due to unclear risk of selection bias due to inadequate allocation concealment as well as concerns about outcomes utilized. However, the authors did not explicitly state these concerns.

Authors assessed study quality based on risk of bias assessment. Study quality was also based upon adequate allocation concealment. Therefore, the two studies that had low risk of bias according to the Cochrane tool (Afilalo, 2010 & Buynak, 2010) were deemed high quality studies. The two studies that had high risk of bias according to the Cochrane tool (Afilalo 2013 & Wild 2010) were deemed to be low quality studies.

Intervention Investigated

[Provide details of methods, who provided treatment, when and where, how many hours of treatment provided]

Control

Placebo control: ineffectual medication that is intended to imitate an active treatment; participants are blinded to receiving active or placebo controls in the three RCTs.

Active control: oxycodone controlled release (CR) within the dosing range of 40 – 100 mg/day, which is a strong opioid analgesic medication. Opioids are a well-established pharmacological intervention that used to treat chronic pain that is moderate-to-severe and can be either oncological or non-oncological in nature. The primary action of these drugs is to act upon μ-opioid receptors in the central nervous system as an agonist. All four studies utilized active controls with oxycodone CR versus tapentadol ER.

Experimental

Tapentadol: extended release (ER) within the dosing range of 200 – 500 mg/day; relatively new opioid analgesic medication that is considered to be "weak" compared to strong opioids, like oxycodone. This weakness is due to its lower binding affinity for μ-opioid receptors. In addition to acting upon these receptors in the CNS, Tapentadol also facilitates re-uptake of the neurotransmitter noradrenaline. Due to adverse effects such as constipation, nausea and vomiting associated with μ-opioid agonists, tapentadol is considered to have potentially lower incidence of adverse side effects compared with those drugs that do not have this synergistic effect.

Outcome Measures (Primary and Secondary)

[Give details of each measure, maximum possible score and range for each measure, administered by whom, where]

Primary Outcomes

The two primary outcomes were efficacy and safety. Efficacy was measured in the three RCT studies and safety was measured in the open-label study. Efficacy of both the tapentadol and the active control drug, oxycodone, were measured by both change in pain intensity scores and the rate of responders. Safety was measured by the rate of withdrawal of participants as a result of adverse effects. For the purpose of this CAP, efficacy, or pain reduction, will be the primary focus.

- *Pain Intensity*: NRS (Numerical Rating Scale) – 11-point scale – (All four included studies)
- *Responder's Rate*: 50% pain relief from responder analysis – (Alfilalo 2010, Buynak 2010)

The authors determined the following classification system for rating severity of pain from the NRS, which was utilized in all four studies.

- *Moderate Pain*: NRS (Numerical Rating Scale) – 11-point scale: 4 – 6 (inclusive)
- *Severe Pain*: NRS (Numerical Rating Scale) – 11-point scale: >7

Secondary Outcomes

While this review discussed results of subgroup analyses of other outcomes such as quality of life, as measured by functional health status and well-being outcomes, the focus of this CAP concerns the effectiveness of opioids to reduce pain; therefore, secondary measures that relate to efficacy will be discussed. These include the withdrawals rate, which is the number of participants with discontinuation of drug treatments due to lack of efficacy, and the prevalence of adverse effects or serious adverse events, which contribute to withdrawals rate and should be considered when evaluating the clinical implications of this CAP.

- Withdrawals rate – (All four included studies)
- Adverse effects (global, serious and most frequently reported)
    - PAC-SYM (Patient Assessment of Constipation Symptoms) – (Alfilalo 2013)
    - Incidence of nausea, vomiting, dry mouth, somnolence, dizziness, fatigue, diarrhoea, headache and pruritus – (Alfilalo 2010 & 2013, Buynak 2010)
- PGIC (Patient Global Impression of Change) – (Alfilalo 2010 & 2013, Buynak 2010)
- Brief Pain Inventory – (Buynak, 2010)
- Functional health status, well-being and QOL
    - SF-36 – (Alfilalo 2013)
    - EQ-5D – (Alfilalo 2013)
    - WOMAC – (Alfilalo 2010 & 2013)
- Sleep characteristics – (Alfilalo 2010 & 2013, Buynak 2010)

Main Findings

[Provide summary of mean scores/mean differences/treatment effect, 95% confidence intervals and p-values etc., where provided; you may calculate your own values if necessary/applicable]

The primary outcomes of efficacy and safety are described below as well as secondary outcomes of withdrawal rates and adverse effects. For the purpose of this CAP, other secondary outcomes related to quality of life, sleep, and patient global impression of change were excluded due to irrelevance.

Efficacy: Tapentadol vs. Placebo

When comparing tapentadol with placebo, participants taking tapentadol experienced an overall significant reduction in pain intensity, measured by the 11-point NRS, from baseline to 12 weeks. This was calculated from mean differences using a random effects model with a 95% CI. There was moderate heterogeneity between the three studies (Afilalo, 2010, 2013 & Buynak, 2010). However, one of the studies (Afilalo, 2013) had a confidence interval that included the null line, meaning the change in pain intensity was not significant. There was a significantly higher responder rate (at least 50% pain reduction) for tapentadol than placebo. This was calculated using risk ratios and a fixed effects model with a 95% CI. There was 0% heterogeneity between the two studies, suggesting perfect consistency between outcomes of the two studies analysed. The number needed to treat for an additional beneficial outcome was 16, which is low compared with the total number of participants who received the tapentadol (1876).

- Change in pain intensity: -0.56 [-0.92, -0.20], I^2 = 65%
- Responder Rate: 1.36 [1.13, 1.64], I^2 = 0%

Efficacy: Tapentadol vs. Oxycodone

When comparing tapentadol ER with oxycodone CR, tapentadol was associated with a greater decrease in pain intensity at week 12, as measured by the 11-point Numeric Rating Scale for pain. However, there was no significant difference in rate of responders between the two active interventions.

- Change in pain intensity: -0.24 [-0.43, -0.05], I^2 = 14%
- Responder Rate: 1.46 [0.92, 2.32], I^2 = 82%

Safety: Withdrawals due to Adverse Effects

When compared to placebo, tapentadol was associated with greater risk of withdrawal or discontinuation in general than the placebo group. Tapentadol was associated with greater risk of withdrawal due to adverse effects than placebo. Among all causes for discontinuation, 27% of withdrawals were due to adverse effects. There was no difference between tapentadol and placebo in the risk of serious adverse effects, suggesting that the risk for adverse effects in opioids is low overall.

Tapentadol vs. Placebo

- Risk of Withdrawal due to Adverse Effects: RR: 2.68 [2.05, 3.52], I^2 = 0%
- Risk of Overall Withdrawal: RR: 1.09 [0.90, 1.32], I^2 = 73%
- Risk of Adverse Effects: RR: 1.25 [1.16, 1.35], I^2 = 0%
- Risk of Serious Adverse Effects: 1.01 [0.47, 2.16], I^2 = 21%

It is relevant to note the findings of subgroup analyses comparing tapentadol and oxycodone regarding safety and tolerability as it relates to adverse effects and withdrawals. There was an overall higher risk of withdrawal or discontinuation in general in the oxycodone group when compared to the tapentadol group. Tapentadol was deemed "safer" due to having lower risk of withdrawal from adverse effects than oxycodone at 12 weeks. Reasons for withdrawal in the tapentadol group included loss to follow-up and lack of efficacy, while reasons for withdrawal in the oxycodone group included adverse effects (49%), withdrawal by participant (24%), lack of efficacy (8%), drug non-compliance (6%), and loss to follow-up (5%).

Tapentadol was associated with lower risk of adverse effects including constipation, nausea, vomiting, dizziness, and pruritus. However, there was no difference between tapentadol and oxycodone in terms of risk for diarrhoea, fatigue, insomnia, somnolence and headache. There was no significant difference between the two opioids in terms of risk for serious adverse effects. There was a greater risk of having dry mouth with tapentadol vs. oxycodone.

Tapentadol vs. Oxycodone:

- Risk of Overall Withdrawal: RR: 0.76 [0.70, 0.83], I^2 = 41%
- Risk of Withdrawal due to adverse effects: RR: 0.05 [0.42, 0.60], I^2 = 44%
- Risk of Adverse Effects: RR: 0.91 [0.85, 0.96], I^2 = 57%
- Risk of Serious Adverse Effects: RR: 0.57 [0.24, 1.33], I^2 = 64%

Heterogeneity

There was moderate to high heterogeneity for both efficacy and safety outcomes between groups as shown by the I^2 among the results listed above. There was low heterogeneity between participants with knee OA, which were the majority of subjects within two RCTs.

Original Authors' Conclusions

[Paraphrase as required. If providing a direct quote, add page number]

The findings of this study indicate that tapentadol ER was associated with greater reduction in pain intensity compared with placebo or active control groups (oxycodone CR). Additionally, tapentadol ER is associated with greater safety (withdrawal rate due to adverse effects) and tolerability than oxycodone CR. For those with moderate-to-severe chronic musculoskeletal pain, there is a relatively small clinical benefit from tapentadol ER for reduction of pain.

Authors provided a plain language summary that reported moderate quality evidence for tapentadol effectiveness in reducing pain by 50% in 3 out of 10 people, while only 2 out of 10 people responded to oxycodone and placebo controls. The authors conclude that opioids in general do not provide large clinical benefits and more research needs to be done to figure out which musculoskeletal condition would be most affected by opioid analgesic medication.

Critical Appraisal

Validity

[Identify the strengths and limitations of the study, including potential sources of bias. Comment on the overall methodological quality (including the score) as you determined from your assessment of the article. Comment on anything you believe was missing in the paper.]

Strengths

The AMSTAR checklist was used to assess methodological quality of this systematic review and meta-analysis, which received a perfect score of 11/11. This score, among other reasons, indicates high internal validity and suggests that this study provides high quality evidence and for the efficacy and safety of tapentadol versus placebo and oxycodone. However, there a few limitations which decrease the external validity and clinical meaningfulness of the main findings.

Regarding the AMSTAR checklist, this review established research objectives and inclusion criteria a priori as well as for effect sizes and heterogeneity. There was duplicate study selection and data extraction by two independent authors with discrepancies solved by consensus or a third review author. A comprehensive literature search was performed using several electronic databases, with key words stated clearly, and supplemental search strategies were used to screen articles from multiple sources. The authors searched for unpublished and ongoing trials as well, meaning the status of publication was not used as inclusion criteria. For all four studies, authors included demographic data, inclusion and exclusion criteria, interventions, primary and secondary outcomes, as well as notes about the funding and contributions. They also included the titles of excluded studies in addition to reasons for why they were excluded. This was a true strength of this review because the data was well organized and details from each study could be referenced for further comprehension of results.

Authors established a priori methods for determining quality of included studies, which was based on the results from the Cochrane "risk of bias" tool. For all seven domains, authors included their judgment of risk as well as provided quotes supporting their judgments for each component. Regarding the Cochrane Risk of Bias assessment, all studies have adequate random sequence generation, indicating low risk of selection bias. All but one study, which was unclear, had adequate allocation concealment, suggesting low risk of selection bias among three studies. Three studies were double blinded, (one was open-label) and therefore the risk of performance and research bias were decreased. There was also blinding of outcome assessments in these three RCT studies, suggesting low risk of detection bias. There was adequate selective reporting in all four studies, including one study which included all outcomes despite it being unpublished, suggesting decreasing reporting bias. When forming conclusions, authors mentioned overall quality of evidence and gave specific reasons for how components of each study related to quality may influence clinical significance.

Another important strength of this review is the large sample size of each study, increasing the overall power. The authors used appropriate random and fixed effects model for studies with heterogeneity and without heterogeneity, respectively. The authors attempted to evaluate publication bias by comparing data from other published reported outcomes and similar study protocols. They indicated that they did not use a funnel plot analysis for publication bias due to there being fewer than 10 included studies.

Missing Data

Authors attempted to retrieve baseline data for primary outcomes from drug manufacturers for an intention-to-treat (ITT) analysis; however, requests were denied. This baseline data could have provided information about participants who experienced zero pain relief who had discontinued treatment, which would have increased accuracy and validity of results. Originally, authors planned to use a baseline-observation-carried-forward (BOCF) imputation method to include all data from participants regardless of withdrawal but due to the denial of information, authors had to use a last-observation-carried forward (LOCF) imputation method for primary efficacy outcomes.

There were two studies that did not report/publish responder rates (Afilalo 2013 and Wild 2010), which decreases the ability to analyse accurate efficacy of each drug. There was also limited data available to perform originally planned subgroup analyses for both placebo and active controls. For primary pain outcomes, there was no discussion of differences between types of musculoskeletal conditions including knee OA and LBP, which would have been helpful details for answering the clinical question. This was due to limited data regarding each chronic musculoskeletal condition and therefore subgroup analysis of this construct was not possible. Authors also planned to investigate differences in pain intensity (moderate vs. severe) but could not due to limited available data.

Limitations

Heterogeneity: Heterogeneity was moderate to high (65%) for the primary efficacy outcome (change in pain intensity from baseline to 12 weeks), which is the focus of this CAP. From subgroup meta-analyses (not discussed in this review) and other sensitivity analyses, heterogeneity was only partially explained. The low number of studies could contribute to relatively high statistical heterogeneity for some of the primary results. There is a small number of included studies in this review despite the large overall sample size (over 4,000). Authors state that this could be due to the fact that tapentadol is a relatively new drug (approved by the FDA in 2011). Having high heterogeneity suggests that the inclusion of additional studies may have impacted effect sizes for primary outcomes.

Risk of Bias: There were only two of four studies considered to be high quality due to low risk of bias. The open-label study (Wild 2010) had high risk of performance and detection bias, while Afilalo (2013) had unclear allocation concealment. Furthermore, despite their efforts, authors could not obtain data for all outcomes, including baseline data for an intention-to-treat analysis (forcing them to use LOCF method rather than BOCF imputation method). This could increase risk for high attrition bias due to incomplete outcome data, and potentially impact accuracy of effect sizes. While authors could not feasibly analyse publication bias, they concluded that there was no evidence according to previously published protocols. However, one study was never published, and data from this particular study indicates slightly worse primary outcomes, suggesting possibility of publication bias from this included study.

Conflicts of Interest: the drug manufacturer funded all included studies, suggesting possible conflicts of interest for each. This is especially important to note due to the absence of baseline data and other types of data which was unpublished because there could be even higher risk of researcher bias. The authors of the systematic review state that no direct or indirect payment was made for this review; however, the research centre where it was conducted receives annual funds from pharmaceutical companies including the specific company that develop tapentadol. This must be taken into consideration when evaluating results.

Interpretation of Results

[This is YOUR interpretation of the results taking into consideration the strengths and limitations as you discussed above. Please comment on clinical significance of effect size / study findings. Describe in your own words what the results mean.]

Authors conducted a highly rigorous systematic review and meta-analysis with high methodological quality; however, evidence from the four included studies was moderate. Taking into account the relatively high heterogeneity, risk of bias, missing data, high withdrawals rates due to adverse effects, and moderate effect sizes it can be concluded from these results that tapentadol is minimally effective at reducing pain in chronic musculoskeletal conditions (specifically knee OA and LBP).

While the effect sizes were moderate for primary efficacy outcomes for tapentadol, the clinical significance is small (0.56-point reduction in pain intensity after 12 weeks). Additionally, there are multiple reasons why the effect sizes shown may be overestimated, suggesting an even lower treatment effect of tapentadol for chronic pain. First, the inability to conduct imputation using BOCF (baseline-observation-carried-forward) method due to data access restrictions could have resulted in overestimated effect sizes, as this data included those who withdrew due to lack of efficacy. This is especially important to consider for these studies due to the already high withdrawal rates, which could have affected accuracy of treatment effects. There were high withdrawal rates due to adverse effects (27% for tapentadol, 49% for oxycodone) in all four studies. To put it plainly, 1 in 6 people taking tapentadol experience adverse effects, reflecting the high incidence of adverse effects for opioid medication. When considering the time period for follow up for three of the studies (12 weeks), it is relatively short compared to the duration of consumption for most people with chronic pain. The pre-requisite for participant inclusion was having chronic pain for greater than 3 months for all four studies; however, the average duration of chronic pain was not included. Therefore, the duration for the study of 12 weeks may not be reflective of the average duration in which people experience chronic musculoskeletal pain. Given this short-term follow-up, high withdrawals rates from adverse effects seem even more salient, suggesting that withdrawals rate could be even higher with long-term follow-up.

Because the only musculoskeletal conditions investigated were knee OA and LBP, it cannot be assumed that efficacy of tapentadol is the same for other conditions such as rheumatoid arthritis and fibromyalgia. Due to lack of sufficient data, authors were not able to determine if effect sizes varied between those with moderate and those with chronic pain.

EVIDENCE SYNTHESIS AND IMPLICATIONS

Evidence Synthesis: Three systematic reviews and meta-analyses provide moderate evidence for comparing the effects of yoga and pharmaceuticals (opioid analgesics) on chronic pain caused by musculoskeletal conditions. Despite there being no studies directly comparing them, inferences from their main findings suggest that yoga may be an adequate alternative or supplement to pharmaceutical intervention for this population. Yoga results in fewer and less serious adverse effects than opioids and results in greater reduction in pain when comparing effect sizes: 2.3-point average reduction vs. 0.56 points on a 10-pt scale. The main findings from Büssing et al. (2011) and Ward et al. (2013) indicate there is a moderate treatment effect of yoga on pain outcomes. Both studies showed significant reductions in pain from various musculoskeletal conditions when compared with both active and passive interventions. Main findings regarding effectiveness of tapentadol from Santos (2015) show significant reductions in pain intensity when compared with placebo and oxycodone. They found that tapentadol was safer and more tolerable than oxycodone; however, clinical meaningfulness regarding tapentadol efficacy is questionable. Females with chronic LBP will be more likely to respond to yoga intervention, as these demographics were highly prevalent among all included studies. It cannot be assumed that treatment effects are necessarily similar or significant for patients with RA or OA due to small number of included studies. Despite high variability in control groups, it can be inferred from results that yoga is recommended over passive interventions but should not be a replacement for active interventions.

Major Limitations: For each study, there were weaknesses that affected both their internal and external validity. There was moderate heterogeneity overall and high heterogeneity for primary outcomes for Büssing (2011). While 12 of 17 studies included in Ward (2013) were of good quality, on 3 had low risk of bias. In Santos (2015), due to imputation method and high withdrawal rates due to adverse effects, there was likely overestimation of treatment effects.

Implications for Clinical Practice: In 2015, the U.S. Dept. of Health and Human Services publically announced there is an opioid epidemic that is "unprecedented".[11] With more than 650,000 prescriptions dispensed and 3,900 new people abusing opioids in an average day, as well as more drug overdose deaths in 2014 than ever before, it is imperative to research effective alternative treatments for chronic pain.[11] According to the neuromatrix theory, pain is an output of multiple networks in the brain, rather than solely input from sensation, that can be affected by stress, behaviour, genetics and perception.[12] Psychosocial factors, therefore, influence one's experience of chronic pain; this could explain why opioids do not produce very large treatment effects, as they only address a single mechanism. Therefore, evaluating pain outcomes alone may not be comprehensive without including psychosocial influences, quality of life and functional disability. Both Büssing (2011) and Ward (2013) also investigated yoga's effects on psychosocial outcomes and pain-related disability, but that would be another CAT. When speaking with a physical therapist who regularly incorporates yogic principles into her patient care, she suggested *pranayama* (control of breathing), and reported anecdotal success using a technique called *chandrabhedana*, or alternate nostril breathing (ANB), for chronic pain patients. In fact, there is evidence showing that individuals with no prior yoga experience who practiced controlled breathing techniques (either ANB or paced breathing) for 30 minutes had an immediate increase in autonomic cardiac regulation, which is associated with the body's response to stress.[13]

Application to Clinical Case: Regarding the female patient with moderate chronic LBP, evidence from these three studies can be used to guide treatment intervention from a physical therapist, as the data from the two yoga studies were heavily weighted toward LBP and there were clinically meaningful reductions in pain for those with moderate LBP at 12 weeks.[1] Plan of care would likely last for 12 weeks to see intended results, as this was also the time for long-term follow-up in Büssing et al. (2011) and was half the time among included studies from Ward et al. (2013) which ranged from 1 to 24 weeks. For specific yoga intervention, Hatha style yoga would be recommended as it was the most prevalent among included studies. The reported data was highly variable for dosage (frequency and duration) of yoga sessions; therefore, it would make most sense to match the dosage to a typical physical therapy schedule. Due to the association between pain and stress,[12] psychosocial factors related to her pain (increased stress, traumatic MOI, decreased QOL) should be assessed to more thoroughly understand sources (besides tissue damage) which may be perpetuating the chronic pain cycle. She could be taught controlled breathing techniques as part of her yogic practice to improve autonomic regulation and ultimately improve her body's ability to cope with stress. To track progress, the patient's pain rating (either by NPRS or VAS) should be assessed at baseline and discharge.

Future Research: Most importantly, further research must directly compare yoga and pharmaceutical interventions for the treatment of chronic musculoskeletal pain, as there is no current evidence as of yet. To further investigate the effect of yoga, the limitations from Büssing et al. (2011) and Ward et al. (2013) lend suggestions for needed evidence. Due to high variability in yoga styles for both studies, as well as the varying components of yoga (postures, breathing, relaxation), research needs to delineate which styles and/or components are most effective for musculoskeletal chronic pain. Similarly, dosage and adherence rates were variable across studies, suggesting the need for research examining the minimal dosage to achieve treatment effects, reasons for discontinuation or non-compliance, as well as the feasibility of participants to realistically comply with instruction or home practice in a clinical setting. Suggestions for research on opioid analgesic effects on chronic pain involve the inclusion of more types of musculoskeletal conditions (i.e. RA). Analyses comparing treatment effects for severity of chronic pain could also be clinically useful. Santos et al. (2013) states that longer duration studies are needed to obtain more accurate results; however, due to the high withdrawal rate, it is questionable whether this would be feasible.

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