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Vitamin D for the treatment of chronic painful conditions in adults (Review)

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[Intervention Review]

Vitamin D for the treatment of chronic painful conditions in adults

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ABSTRACT

Background

This review is an update of a previously published review in the Cochrane Database of Systematic Reviews (Issue 1, 2010) on 'Vitamin D for the treatment of chronic painful conditions in adults'.

Vitamin D is produced in the skin after exposure to sunlight and can be obtained through food. Vitamin D deficiency has been linked with a range of conditions, including chronic pain. Observational and circumstantial evidence suggests that there may be a role for vitamin D deficiency in the aetiology of chronic painful conditions.

Objectives

To assess the efficacy and safety of vitamin D supplementation in chronic painful conditions when tested against placebo or against active comparators.

Search methods

For this update, we searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, and EMBASE to February 2015. This was supplemented by searching the reference lists of retrieved articles, reviews in the field, and online trial registries.

Selection criteria

We included studies if they were randomised double-blind trials of vitamin D supplementation compared with placebo or with active comparators for the treatment of chronic painful conditions in adults.

Data collection and analysis

Two review authors independently selected the studies for inclusion, assessed methodological quality, and extracted data. We did not undertake pooled analysis due to the heterogeneity of the data. Primary outcomes of interest were pain responder outcomes, and secondary outcomes were treatment group average pain outcomes and adverse events.

Main results

We included six new studies (517 participants) in this review update, bringing the total of included studies to 10 (811 participants). The studies were heterogeneous with regard to study quality, the chronic painful conditions that were investigated, the dose of vitamin D given, co-interventions, and the outcome measures reported. Only two studies reported responder pain outcomes; the other studies reported treatment group average outcomes only. Overall, there was no consistent pattern that vitamin D treatment was associated with greater efficacy than placebo in any chronic painful condition (low quality evidence). Adverse events and withdrawals were comparatively infrequent, with no consistent difference between vitamin D and placebo (good quality evidence).

Authors' conclusions

The evidence addressing the use of vitamin D for chronic pain now contains more than twice as many studies and participants than were included in the original version of this review. Based on this evidence, a large beneficial effect of vitamin D across different chronic painful conditions is unlikely. Whether vitamin D can have beneficial effects in specific chronic painful conditions needs further investigation.

PLAIN LANGUAGE SUMMARY

Vitamin D for the treatment of chronic painful conditions in adults

Chronic pain is pain of moderate or severe intensity lasting three months or more. It can have a variety of causes, but most comes from musculoskeletal conditions such as arthritis, or pain in muscles. Chronic pain usually affects older people more than younger people. Chronic pain is disabling, and has a large negative impact on quality of life.

Vitamin D has a variety of roles in the body. It is made in the skin through the action of sunlight and can also be obtained from food. A lack of vitamin D has been implicated in a number of conditions, including chronic pain. Additionally, associations of such diverse types of pain as headache, abdominal pain, knee pain, and back pain with season of the year and latitude provide indirect support for a role for vitamin D. The possibility of a link between low levels of vitamin D and chronic pain has attracted interest because - if it were true - vitamin D would be an inexpensive and relatively safe treatment.

We searched scientific databases for studies comparing vitamin D supplementation with placebo (a dummy treatment) or active medicines for the treatment of chronic painful conditions in adults. The evidence is current to February 2015.

There is a small amount of evidence supporting this link but it is not of high quality and may not be reliable. This update of a review sought high quality evidence from randomised controlled trials (studies where participants are randomly allocated to receive one of several treatments) on vitamin D for chronic painful conditions.

We found no consistent pattern that vitamin D treatment was better than placebo for any chronic painful condition, but the studies had methodological shortcomings (low quality evidence).

More research is needed to determine if vitamin D is a useful pain treatment in any particular chronic painful condition. That research should examine whether any effect is restricted to people who are vitamin D deficient. It should also examine how much vitamin D is required, and for how long, before beneficial effects occur.

BACKGROUND

This review is an update of a previously published review in the Cochrane Database of Systematic Reviews (Issue 1, 2010) on 'Vitamin D for the treatment of chronic painful conditions in adults'.

Vitamin D (calciferol) is a fat-soluble vitamin that is synthesised from a precursor in the skin after exposure to ultraviolet B (UVB) radiation from the sun, and it is also obtained from dietary sources (eg oily fish, vitamin D-fortified milk and breakfast cereals, or dietary supplements). Vitamin D can be of plant origin (vitamin D_2 or ergocalciferol) or of animal origin (vitamin D_3 or cholecalciferol). Vitamin D from the skin and diet is metabolised in the liver to 25-hydroxyvitamin D, and further metabolised in the kidneys to its active form, 1,25-dihydroxyvitamin D. Vitamin D exerts its effects by modulating gene expression after binding to a nuclear vitamin D receptor. Most tissues in the human body express vitamin D receptors (Holick 2007), supporting the concept of a wide-ranging importance of vitamin D.

Vitamin D deficiency can arise from a number of causes including insufficient UVB exposure, decreased bioavailability (eg malabsorption disorders), or diseases that affect the metabolism of vitamin D, such as liver and kidney disease. Some medications can also cause vitamin D deficiency. These include anticonvulsants, glucocorticoids, and antiretroviral drugs (Holick 2007).

Lack of vitamin D is known to be implicated in diseases of the musculoskeletal system, where its deficiency is classically a cause of rickets (in children) and osteomalacia (in adults). Insufficient vitamin D has been implicated in a range of diseases involving other body systems, including metabolic, autoimmune, psychiatric, respiratory, and cardiovascular disorders; cancers (especially colon, prostate, and breast cancer); and chronic pain (Gröber 2013; Holick 2007). It has been suggested that there is widespread vitamin D deficiency or insufficiency in many populations and that sensible sun exposure and vitamin D supplementation may be called for (Gröber 2013; Holick 2007). Indeed, one meta-analysis found a reduced all-cause mortality with vitamin D supplementation (Autier 2007). One more recent Cochrane review found that, overall, vitamin D slightly decreased mortality, but further analyses suggested that the benefit in terms of vitamin D supplementation decreasing mortality was more limited; there may be benefit with vitamin D_3 supplementation for elderly people (Bjelakovic 2014).

The Institute of Medicine recommends a dietary intake of 600 international units (IU) of vitamin D (800 IU for people older than 70 years) (IOM 2011), other publications recommend higher intakes, at least without adequate sun exposure (Gröber 2013; Holick 2007). One IU corresponds to 25 ng of vitamin D.

The precise definition of vitamin D deficiency is a matter of debate. It has been argued that serum 25-hydroxyvitamin D levels below 20 ng/mL signify pronounced deficiency and that levels between 21 and 29 ng/mL signify moderate deficiency, or insufficiency (Gröber 2013; Hossein-nezhad 2013). It has further been suggested that a 25-hydroxyvitamin D level between 40 and 60 ng/mL is ideal and that toxicity is expected only at levels greater than 150 ng/mL (Gröber 2013). For the purpose of this review, we have regarded levels of vitamin D below 20 ng/mL as evidence of deficiency, levels between 20 and 29 ng/mL as evidence of insufficiency, and levels of 30 ng/mL or greater as evidence of sufficiency.

Description of the condition

Chronic pain is generally described as pain experienced on most days for at least three months. Chronic pain in its various forms is very common, one of the most common health problems of all: one recent review of prevalence studies estimated the average prevalence of non-cancer chronic pain in adults at about 20% (Moore 2014), with some individual studies claiming substantially higher prevalence rates. The prevalence of benign chronic back pain alone has been estimated to be between 2% and 40%, depending on the population studied (Verhaak 1998). The prevalence of arthritis was estimated at almost 16% in one large multinational study (Alonso 2004). Fibromyalgia is another chronic pain disorder that affects 1% to 6% of the population (Bannwarth 2009; Mas 2008; McQuay 2007; Vincent 2013). Furthermore, acute pain can become chronic. For example, one systematic review showed that chronic pain after surgery was surprisingly common, up to 47% after thoracic surgery (Perkins 2000). Not surprisingly, chronic pain conditions can have a profound effect on functioning and quality of life (Alonso 2004; Mas 2008; Moore 2014), with considerable economic and social impact. Chronic pain is a common cause of sickness absence from work (Moore 2014; Saastamoinen 2009).

Low levels of 25-hydroxyvitamin D have been linked with a higher incidence of chronic pain (Atherton 2009; Benson 2006; Lotfi 2007). Additionally, associations of such diverse types of pain as headache, abdominal pain, knee pain, and back pain with season of the year and latitude may suggest that 25-hydroxyvitamin D levels are important in this context (Mitsikostas 1996; Saps 2008; Zeng 2004). Therefore, it seems possible that vitamin D deficiency may be involved in the aetiology of chronic pain.

Description of the intervention

Vitamin D supplementation can be given orally or parenterally. A number of different preparations and dosing regimens of vitamin D treatment have been employed in clinical practice. This review considered all vitamin D preparations and dosing regimens when used in the treatment of chronic pain. Treatment with vitamin D holds great appeal because it is inexpensive; has relatively few, usually mild, adverse effects; and there is a positive public perception of vitamin supplementation that could result in high rates of adherence. Excessive vitamin D intake can result in hypercalcaemia, but this is rare.

How the intervention might work

Vitamin D supplementation increases 25-hydroxyvitamin D blood levels (25-hydroxyvitamin D is the form of the vitamin usually measured and recommended to be measured (Holick 2011), with assays normally detecting vitamin D_2 and vitamin D_3) and can, therefore, potentially correct the effects of vitamin D deficiency (Gröber 2013; Holick 2007). The details of how this might work (molecular mechanism, time to effect, extent of reversibility of pain potentially associated with vitamin D deficiency) are unclear at present.

Why it is important to do this review

At the time that the original version of this Cochrane review was written, no systematic review of vitamin D supplementation in chronic pain had been published in the Cochrane Database of Systematic Reviews. A systematic review of vitamin D treatment

for chronic pain was necessary to answer the questions of whether chronic pain could be helped by vitamin D supplementation and, indirectly, whether low levels of 25-hydroxyvitamin D in people with chronic pain were causal or coincidental.

Our initial review on this topic was published in "*Pain*". This was based on a MEDLINE (PubMed) search and used evidence from a variety of study architectures (Straube 2009). We felt it was important to develop this further by using a more extensive search strategy and, at the same time, more stringent inclusion criteria to focus on the high quality evidence that is most relevant to clinical practice for publication in *The Cochrane Library*. The original version of this Cochrane review was published in 2010 (Straube 2010). A number of studies investigating vitamin D for chronic painful conditions have been published since that time, so that an update of our Cochrane review was called for.

OBJECTIVES

To assess the efficacy and safety of vitamin D supplementation in chronic painful conditions when tested against placebo or against active comparators.

METHODS

Criteria for considering studies for this review

Types of studies

We included studies if they were randomised, double-blind, controlled trials of vitamin D supplementation compared with placebo or with active interventions in the treatment of chronic painful conditions. Randomisation and double-blinding are known to minimise bias and were therefore deemed essential study features (Moore 2006; Moore 2010). Parallel-group design and cross-over studies were both acceptable.

We excluded the following types of report.

- Review articles, case series, case reports, and clinical observations.
- Studies of experimentally induced pain.
- Studies where pain relief (or pain intensity with baseline level) was not measured or not patient-reported.

Types of participants

Studies of adults (generally over 15 years of age) with all types of chronic pain conditions were eligible for inclusion. To qualify for inclusion, all study participants needed to have a chronic painful condition. Studies in conditions that were painful in some people but could be asymptomatic in other people (eg osteoporosis) did not qualify for inclusion if they did not explicitly state that all study participants had chronic pain.

Types of interventions

We compared vitamin D supplementation (oral or parenteral) with placebo or active comparator, with no restriction regarding type, dose, and frequency of vitamin D treatment. We included studies that investigated combined treatment with vitamin D and other concurrent interventions only if the other interventions were also given to the comparator group, because we wanted to isolate the treatment effect due to vitamin D.

Types of outcome measures

We collected data on participant characteristics (age, sex, and condition to be treated) and on baseline and end-of-trial 25-hydroxyvitamin D levels where they were reported.

Primary outcomes

The primary outcome was patient-reported clinically significant pain relief. We used the following hierarchy of outcome measures, in order of preference.

- Number of participants with at least 50% pain relief.
- Number of participants reporting a global impression of change of "much" or "very much" improvement.
- Number of participants with undefined (any) improvement in pain.

Secondary outcomes

- Other patient-rated pain outcomes (typically reported as group mean values).
- Numbers of participants with adverse events: any adverse event, any serious adverse event.
- Numbers of withdrawals: all-cause, lack of efficacy, and adverse event withdrawals.
- Quality of life (any scale).

Search methods for identification of studies

We identified studies primarily by searching electronic databases, with no language restriction.

Electronic searches

For the original version of this review, the following electronic databases were searched, as far back as they would allow, without specified start dates: Cochrane Central Register of Controlled Trials (CENTRAL; Issue 3, 2009), MEDLINE (to September 2009), EMBASE (to September 2009), and the Oxford Pain Relief Database (Jadad 1996a).

For this update of the review, the trials search co-ordinator of the Cochrane Pain, Palliative and Supportive Care group and the review authors conducted searches in the databases listed below.

- CENTRAL (via CRSO, 2009 to 2 February 2015).
- MEDLINE (via Ovid, September 2009 to 2 February 2015).
- EMBASE (via Ovid, September 2009 to 2 February 2015).

See Appendix 1 for the CENTRAL search strategy, Appendix 2 for the MEDLINE search strategy, and Appendix 3 for the EMBASE search strategy.

We also searched MEDLINE (via PubMed) in December 2014 using a number of search terms to identify chronic diseases in combination with terms to identify vitamin D treatment, and we searched using the "related citations" feature in PubMed for each of the included studies.

The Oxford Pain Relief Database is no longer being updated and was not searched again for this update.

Searching other resources

We searched additional studies for this update from the reference lists of the retrieved articles and reviews in the field. We searched two online trial registries for trials that have not yet been published or are still ongoing: ClinicalTrial.gov (clinicaltrials.gov) and the World Health Organization (WHO) International Clinical Trial Registry Platform (ICTRP) (apps.who.int/trialsearch/). These trial registries were searched on 3 December 2014. We did not contact manufacturers of vitamin D preparations since vitamin D does not have an indication in chronic pain.

Data collection and analysis

Review authors were not blinded to the study authors' names and institutions, journal of publication, or study results at any stage of the review. Two review authors independently selected the studies identified for this review update for inclusion, assessed methodological study quality, and extracted data. We resolved disagreements through discussion.

Selection of studies

We assessed titles and abstracts of publications identified by the searches on screen to eliminate studies that obviously did not satisfy the inclusion criteria. We obtained full publications of the remaining studies to determine inclusion in the review.

Data extraction and management

Two review authors independently extracted data using a standard form.

Assessment of risk of bias in included studies

We used the Oxford Quality Scale score as the basis for inclusion, limiting inclusion to studies that were randomised and double-blind as a minimum (Jadad 1996b).

We also assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011); we assessed the following for each study.

- Random sequence generation (checking for possible selection bias). We assessed the method used to generate the allocation sequence as: low risk of bias (any truly random process, eg random number table; computer random number generator); unclear risk of bias (method used to generate sequence was not clearly stated). We excluded studies using a non-random process that were therefore at high risk of bias (eg odd or even date of birth; hospital or clinic record number).
- Allocation concealment (checking for possible selection bias). The method used to conceal allocation to interventions before assignment determines whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment. We assessed the methods as: low risk of bias (eg telephone or central randomisation; consecutively numbered sealed opaque envelopes); unclear risk of bias (method was not clearly stated). We excluded studies that did not conceal allocation and were therefore at high risk of bias (eg open list).
- Blinding of outcome assessment (checking for possible detection bias). We assessed the methods used to blind study participants and outcome assessors from knowledge of which intervention a participant received. We assessed the methods as: low risk of bias (study stated that it was blinded and described the method used to achieve blinding, eg identical tubes containing gel, or identical plasters; matched in appearance and smell); unclear risk of bias (study stated that it was blinded but did not provide an adequate description of how blinding was achieved). We excluded studies that were not double-blind and therefore at high risk of bias.
- Incomplete outcome data (checking for possible attrition bias due to the amount, nature, and handling of incomplete outcome data). We assessed the methods used to deal with incomplete data as: low risk of bias (less than 10% of participants did not complete the study or used 'baseline observation carried forward' analysis, or both); unclear risk of bias (used 'last observation carried forward' analysis and 10% of participants or more did not complete the study); or high risk of bias (used 'completer' analysis and 10% of participants or more did not complete the study).
- Size (checking for possible biases confounded by small size). Small studies overestimate treatment effects, probably due to methodological weaknesses (Dechartres 2013; Nüesch 2010). We assessed studies as at low risk of bias if they had at least 200 participants in each treatment arm, at unclear risk if they had 50 to 199 participants, and at high risk if they had fewer than 50 participants.

Measures of treatment effect

We planned to estimate treatment effect for dichotomous outcomes by calculating risk ratio (RR) to establish statistical difference, and numbers needed to treat to benefit (NNT) and pooled percentages as absolute measures of benefit or harm (Cook 1995; Morris 1995). We did not plan to pool continuous outcome data because response to treatment does not usually follow a normal (Gaussian) distribution.

However, because of clinical and methodological heterogeneity between the studies, we did not undertake any pooled analysis.

Unit of analysis issues

Randomisation was to the individual participant.

Dealing with missing data

Analysis was conducted according to the intention-to-treat (ITT) principle. Missing data and imputation methods were incorporated in the risk of bias assessment.

Assessment of heterogeneity

We planned to examine the heterogeneity of studies with regard to intervention effects visually using L'Abbé plots (L'Abbé 1987). However, we performed no pooled analysis.

Assessment of reporting biases

We did not formally assess reporting biases.

Data synthesis

We planned to pool data where the same or comparable measures were used. We did not carry out any data synthesis because of substantial clinical and methodological heterogeneity in the included studies.

Subgroup analysis and investigation of heterogeneity

We planned subgroup analyses for different painful conditions, but we performed no pooled analysis.

Sensitivity analysis

We planned sensitivity analyses for different treatment regimens and for participants with different baseline levels of 25-hydroxyvitamin D (the effects of vitamin D treatment might differ in people who are deficient or insufficient in 25-hydroxyvitamin D versus people who have sufficient levels), but we performed no pooled analysis.

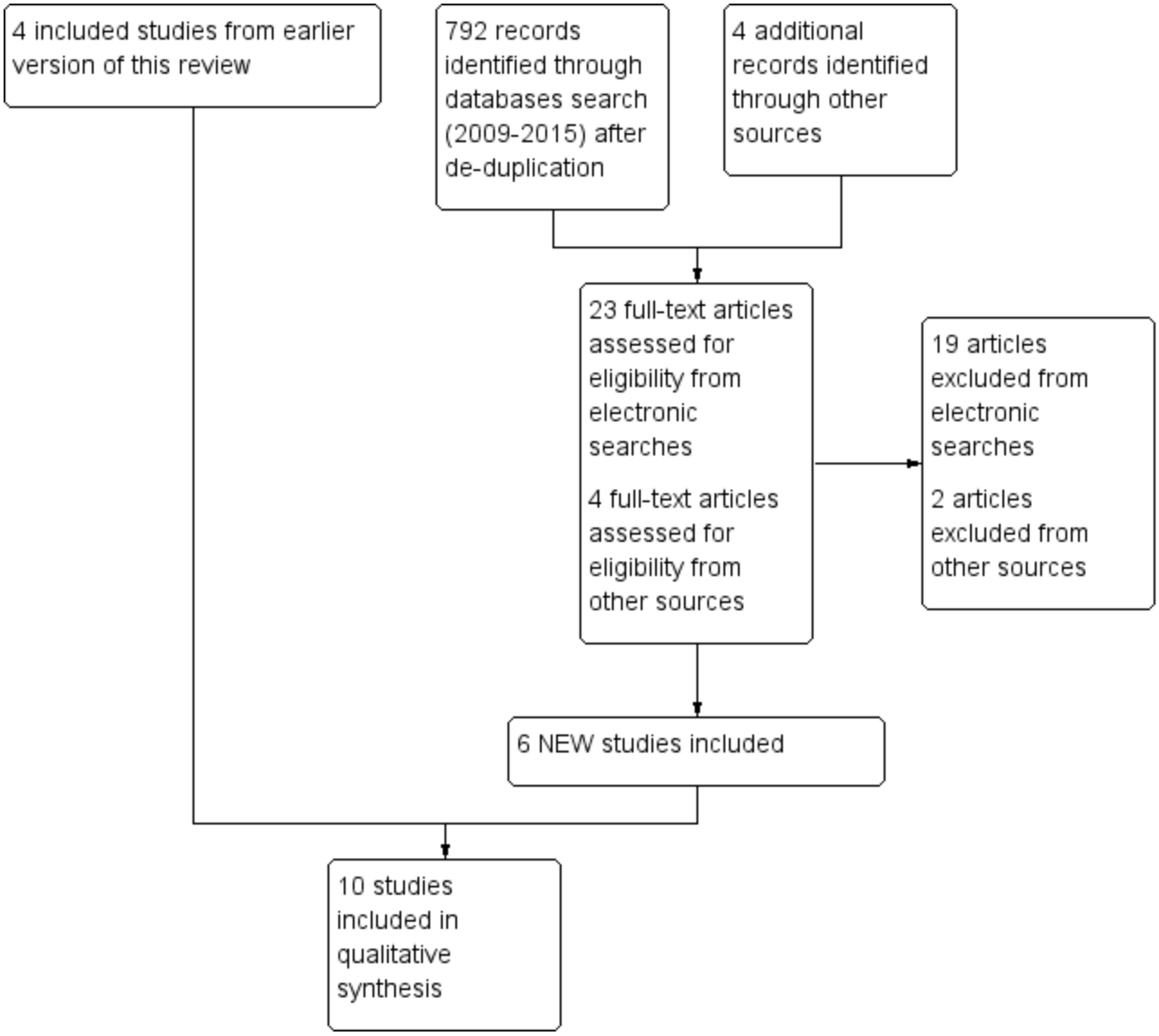
RESULTS

Description of studies

Results of the search

The electronic database searches in CENTRAL (Appendix 1), MEDLINE (Appendix 2), and EMBASE (Appendix 3) conducted for this update identified 792 hits after de-duplication, of which 769 were excluded based on titles and abstracts. We examined 23 articles fully, and included four studies (McAlindon 2013; Sanghi 2013a; Schreuder 2012; Wepner 2014). Other searches identified four studies to be examined as full texts, of which we included two (Hansen 2014; Salesi 2012) (Figure 1).

Figure 1. Study flow diagram. Six NEW studies



In addition, we found 12 studies ongoing (ACTRN12610000322033; Cao 2012; CTRI/2014/06/004658; EUCTR 2009-015835-34-IT; EUCTR 2014-000047-33-NL; ISRCTN94818153; NCT00279461; NCT01023490; NCT01351805; NCT01426347; NCT02002000; NCT02243800). Details are in the Characteristics of ongoing studies table. We were unable to determine exactly how many participants were enrolled in these studies.

Included studies

For this update, we included six new studies with 517 participants (Hansen 2014; McAlindon 2013; Salesi 2012; Sanghi 2013a; Schreuder 2012; Wepner 2014), and four studies with 294 participants from the earlier review (Brohult 1973; Di Munno 1989; Warner 2008; Yamauchi 1989).

The 10 included studies assessed people with rheumatoid arthritis (Brohult 1973; Hansen 2014; Salesi 2012; Yamauchi 1989), knee osteoarthritis (McAlindon 2013; Sanghi 2013a), polymyalgia rheumatica (Di Munno 1989), 'non-specific' musculoskeletal pain (Schreuder 2012), 'diffuse' musculoskeletal pain (Warner 2008), and fibromyalgia (Wepner 2014). The mean age ranged from 42 to 68 years, and most studies included more women than men (range of women 41% to 100%).

Vitamin D preparation, dose, and duration varied considerably between the studies. Yamauchi 1989 used 1-hydroxycholecalciferol, Di Munno 1989 and Salesi 2012 used 25-hydroxyvitamin D, the other studies used calciferol preparations. Wepner 2014 gave some people in the active treatment group as little as 1200 IU of calciferol daily for 25 weeks, Brohult 1973 gave 100,000 IU of calciferol daily for one year. McAlindon 2013 used dose adjustments to keep vitamin D levels in a target range and treated over two years. Schreuder 2012 gave a single dose of 150,000 IU vitamin D.

Not all studies reported concentrations of vitamin D or metabolites in blood at the start and end of the treatment period. For those studies that did, results for placebo and treatment are in Appendix 4, and in Figure 2 and Figure 3. This shows that most studies demonstrated major change with treatment but not placebo, but only two had initial serum 25-hydroxyvitamin D levels below 20 ng/mL signifying pronounced deficiency (Schreuder 2012; Warner 2008), one had initial levels of about 40 ng/mL (Salesi 2012), and that others had levels in the insufficiency range (Hansen 2014; McAlindon 2013; Wepner 2014). Weighted mean levels with placebo rose by 3 ng/mL and with active treatment by 14 ng/mL.

Figure 2. Vitamin D concentrations at start and end of treatment with placebo. The size of the symbols is proportional to the number of participants (inset scale).

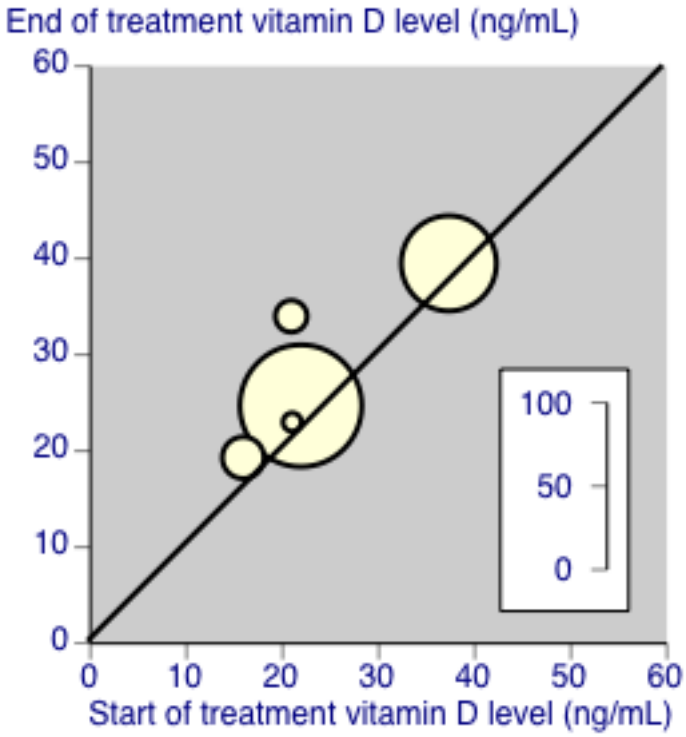
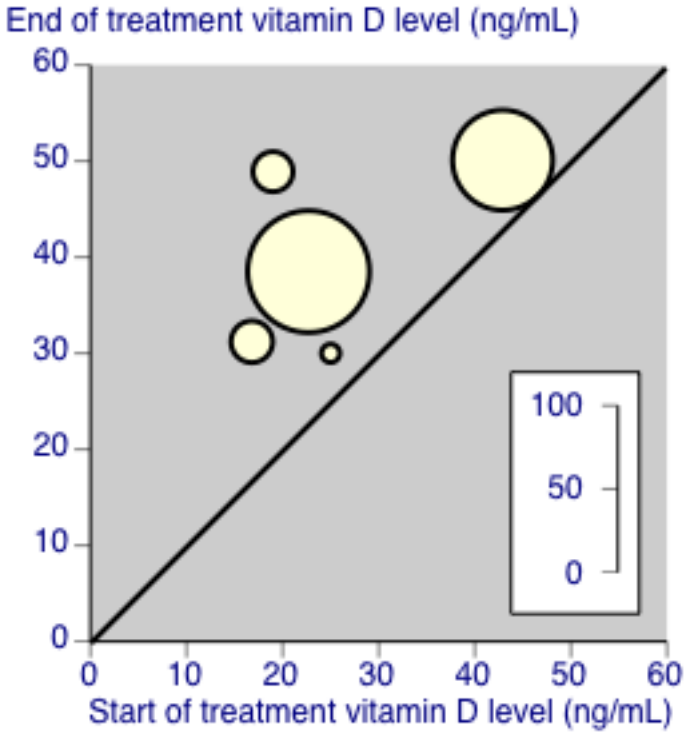


Figure 3. Vitamin D concentrations at start and end of treatment with vitamin D supplementation (active treatment). The size of the symbols is proportional to the number of participants (inset scale).



Full details are in the Characteristics of included studies table.

Excluded studies

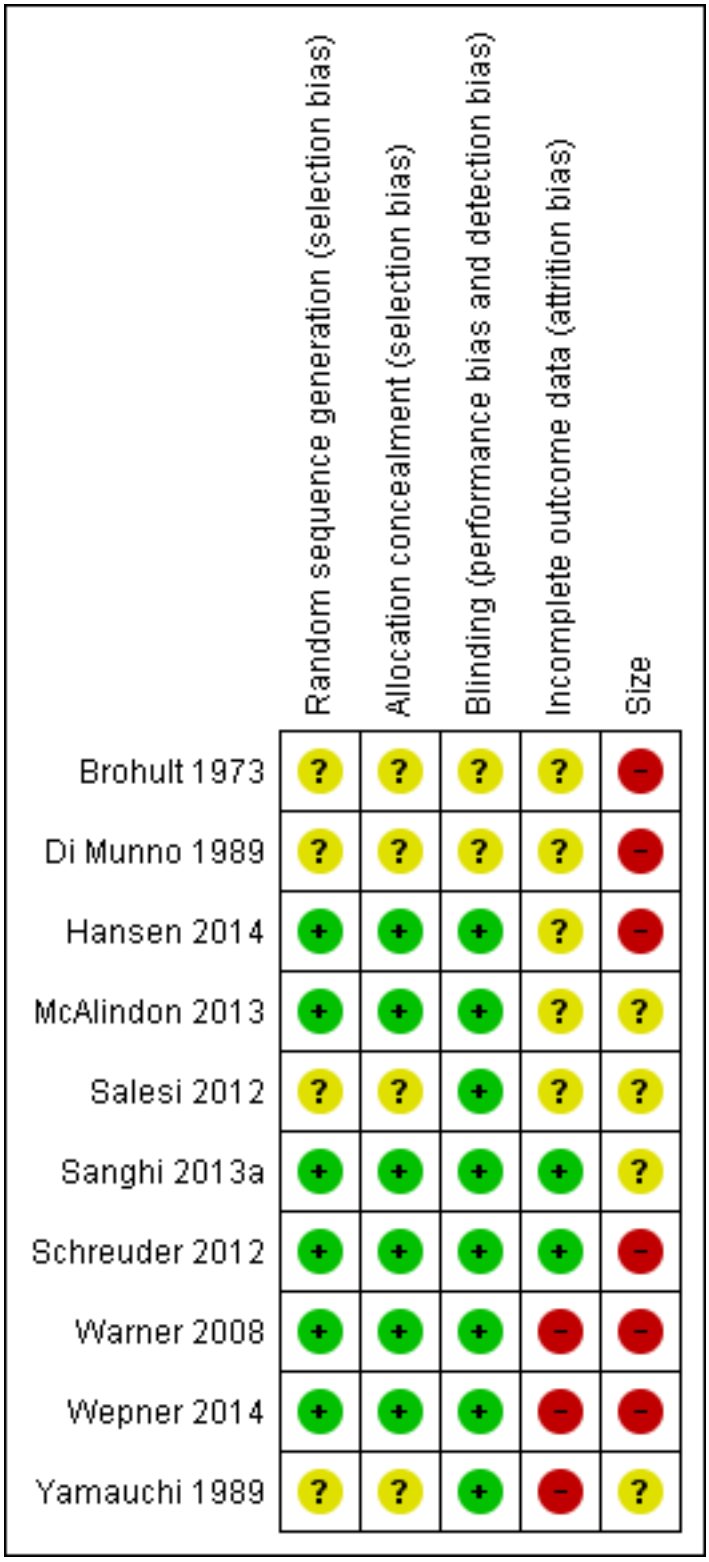
We excluded 21 studies from records identified in searching for this update; 11 studies were excluded in the original review (Abou-Raya 2014; Arden 2006; Arden 2014; Björkman 2008; Chlebowski 2013; de Nijs 2006; Ding 2013; Dottori 1982; Felson 2013; Gendelman 2014; Grove 1981; Kessenich 2010; Knutsen 2014; Kragstrup 2011; Krocker 2008; Lyritis 1994; Mascitelli 2012; McAlindon 2010; Osunkwo 2012a; Osunkwo 2012b; Osunkwo 2012c; Ringe 2000; Ringe 2004; Ringe 2005; Ringe 2007; Sakalli 2012; Sanghi 2011; Sanghi 2012; Sanghi 2013b; Sanghi 2014; Wicherts 2011; Wynn 2013). Exclusions were largely because studies were reported as short conference abstracts rather than full publications, were not double-blind randomised controlled trials, or because it was not clear that all participants had a chronic painful condition. Full details are in the Characteristics of excluded studies table.

Risk of bias in included studies

Five studies scored the maximum of 5/5 on the Oxford Quality Scale (McAlindon 2013; Sanghi 2013a; Schreuder 2012; Warner 2008; Wepner 2014), one scored 4/5 (Hansen 2014), three scored 3/5 (Brohult 1973; Salesi 2012; Yamauchi 1989), and one scored 2/5 (Di Munno 1989). We have reported individual scores in the Characteristics of included studies table. Points were lost mainly due to failure to describe methods of randomisation and blinding adequately.

We assessed the risk of bias in included studies using the 'Risk of bias' tool, and have summarised the findings below and in Figure 4. Details for each study are in the Characteristics of included studies table.

Figure 4. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.



Allocation

All the studies stated that they were randomised, but four did not provide adequate descriptions of the methods used to generate the random sequence or conceal the random allocation (Brohult 1973; Di Munno 1989; Salesi 2012; Yamauchi 1989).

Blinding

All the studies blinded participants and study personal, but two did not provide adequate descriptions of the methods used to blind the interventions (Brohult 1973; Di Munno 1989).

Incomplete outcome data

Warner 2008, Wepner 2014, and Yamauchi 1989 were at high risk of bias due to incomplete outcome data. The other studies were at unclear or low risk.

Selective reporting

While there was no clear evidence of selective reporting, only six of the 10 studies reported on vitamin D levels at the beginning and end of the trial (Hansen 2014; McAlindon 2013; Salesi 2012; Sanghi 2013a; Warner 2008; Wepner 2014). The others did not report either time point (Brohult 1973; Di Munno 1989; Yamauchi 1989), or only baseline vitamin D levels (Schreuder 2012).

Other potential sources of bias

None of the included studies enrolled 200 or more participants per treatment arm, which we consider is the minimum required to give confidence in the results. Six studies enrolled fewer than 50 participants in each treatment arm and we judged them to be at high risk of bias (Brohult 1973; Di Munno 1989; Hansen 2014; Schreuder 2012; Warner 2008; Wepner 2014). The remaining four studies enrolled between 50 and 199 participants per treatment arm and we judged them to be at unclear risk of bias (McAlindon 2013; Salesi 2012; Sanghi 2013a; Yamauchi 1989).

Effects of interventions

Because the studies were heterogeneous with regard to the included participants, interventions (amount and schedule of administration of vitamin D, co-interventions), duration, and outcomes reported, we did not undertake a pooled analysis. Below, we discussed the studies by type of outcomes (efficacy or safety) and by the conditions treated.

Efficacy outcomes

Appendix 4 summarises the efficacy outcomes in individual studies.

Rheumatoid arthritis

Four studies investigated participants with rheumatoid arthritis (Brohult 1973; Hansen 2014; Salesi 2012; Yamauchi 1989).

In a trial of calciferol 100,000 IU daily conducted over 12 months, Brohult 1973 showed that the consumption of analgesics and anti-inflammatory drugs decreased significantly in the calciferol group while there was no change in the placebo group (no direct between groups comparison was reported). Hansen 2014 investigated ergocalciferal 50,000 IU plus calcium initially three times weekly and then twice monthly for a total duration of 12 months, finding a worse outcome with vitamin D than with placebo (just calcium) in one pain comparison; the Patient Assessment of Global Health was also worse with vitamin D. Salesi 2012 gave participants vitamin D 50,000 IU weekly plus methotrexate or methotrexate alone for a duration of 12 weeks. There was no difference between the groups in visual analogue scale pain scores. None of these three studies investigated our preferred responder pain outcomes. One trial of alfacalcidol (1-hydroxycholecalciferol) over 16 weeks found that similar proportions of participants reported "very much" or "much" improvement in the Patient Global Impression of Change in the two treatment groups (alfacalcidol 1 to 2 µg) and in the placebo group (Yamauchi 1989).

Overall, the studies in rheumatoid arthritis did not show a consistent direction of effect of vitamin D. Hansen 2014 and Salesi 2012 reported baseline and end-of-trial vitamin D levels, finding greater increases in vitamin D levels with vitamin D than placebo, but the increases were small to moderate on average. Only in Hansen 2014 did participants have vitamin D levels in the insufficiency range at the start of the trial and reach sufficiency (30 ng/mL) with vitamin D treatment. In Salesi 2012, the participants were already vitamin D sufficient at the start of the treatment.

Knee osteoarthritis

Two studies investigated vitamin D for knee osteoarthritis (McAlindon 2013; Sanghi 2013a).

McAlindon 2013 initially administered cholecalciferol 2000 IU daily with later dose adjustments, or placebo. The active treatment moved participants from vitamin D insufficiency at the beginning of the trial well into the sufficiency range at trial end, after two years. Pain responder outcomes were not reported. Western Ontario and McMaster Universities Arthritis Index (WOMAC) pain and function score changes were not significantly different between the groups. Sanghi 2013a administered vitamin D 60,000 IU daily for 10 days followed by the same dose given once a month, or placebo, for 12 months. This moved participants in the active treatment group from vitamin D deficiency at trial beginning to sufficiency at trial end. Although Sanghi 2013a did not report any responder pain outcomes, the comparison of average visual analogue pain scale changes revealed a significant difference in favour of the vitamin D treatment. WOMAC pain score changes and total score changes also indicated superiority of vitamin D over placebo in that study.

Other painful conditions

One trial of 25-hydroxyvitamin D (35 µg daily for 25 days a month) for nine months in people with polymyalgia rheumatica found that subjective pain on movement decreased in both vitamin D and placebo groups over time, with little difference between the groups (no statistics for between-group comparisons reported) (Di Munno 1989).

Schreuder 2012 investigated non-specific musculoskeletal pain in non-Western immigrants who were vitamin D deficient at the onset of the study, and used a one-time treatment of vitamin D 150,000 IU or placebo. After six weeks, the combined outcome of "much less pain" and "less pain" revealed a significant difference in favour of vitamin D. End-of-trial vitamin D levels were not reported.

One study of ergocalciferol 50,000 IU for the treatment of diffuse musculoskeletal pain over three months investigated pain with a visual analogue scale (finding no significant difference between vitamin D and placebo groups) and with a functional pain score (with an outcome that slightly favoured placebo in one comparison) (Warner 2008) (Appendix 4). In Warner 2008, participants were, on average, vitamin D deficient at trial onset and at the lower end of the sufficiency range at trial end in the active treatment group. Although vitamin D levels also increased in the placebo group, people in the placebo group on average remained in the deficiency range at trial end.

Wepner 2014 treated participants with fibromyalgia with cholecalciferol 1200 to 2400 IU daily (dose depending on vitamin D levels) or placebo. Both active and placebo groups were on the borderline of the vitamin D deficiency and insufficiency ranges (around 20 ng/mL), and both groups were in the sufficiency range after 25 weeks of treatment. Although responder pain outcomes were not reported, some other pain and quality of life outcomes suggested benefit with vitamin D.

Safety outcomes

Appendix 5 summarises the adverse event and withdrawal outcomes in the individual studies.

Overall, adverse events were infrequent and, where reported, the numbers of participants with any adverse event or with any serious adverse events did not seem to differ systematically between vitamin D and placebo groups. Salesi 2012 found 7/60 participants had adverse events with methotrexate plus vitamin D versus 3/57 with methotrexate alone.

All-cause withdrawals were reported in all but two studies, with no consistent difference between vitamin D and placebo. Lack of efficacy withdrawals and adverse event withdrawals, when reported, also did not show a consistent difference between active treatment and placebo.

Wepner 2014 reported that one person receiving vitamin D had mild hypercalcaemia (2.71 mmol/L); the study medication was interrupted and the serum calcium level returned to the normal range. Brohult 1973 reported that after 10 months of treatment, one participant in the calciferol group had a serum calcium level (3.5 mmol/L) that exceeded the upper limit of the normal range, and that two participants in the calciferol group reported polydipsia and increased frequency of urination on one occasion (these can be symptoms of hypercalcaemia, but they are not specific for it). None of the other trials reported cases with hypercalcaemia as an adverse event.

DISCUSSION

Summary of main results

This updated review found no convincing beneficial effect of vitamin D supplementation on chronic pain. The review has more information than a previous version of the review that reached similar conclusions.

This result has to be interpreted with caution. A major concern must be whether the studies were sufficiently sensitive to detect a difference with treatment. Only one study demonstrated unequivocal vitamin D deficiency before treatment, with 25-hydroxyvitamin D levels below 10 ng/mL (Schreuder 2012). Other studies had initial values generally of 20 ng/mL or higher. The effects of vitamin D supplementation on 25-hydroxyvitamin D levels was modest; although the five studies reporting end-of-study levels reported average 25-hydroxyvitamin D levels above 30 ng/mL, two were borderline, and the weighted mean increase of 14 ng/mL was only a 50% increase on the initial level of 28 ng/mL. Some trial participants were vitamin D sufficient at the onset of the trial (Salesi 2012), thus, a vitamin D effect might be difficult to demonstrate in any case. Therefore, there would appear to be major questions as to whether the studies had designs able to sensitively demonstrate effects of vitamin D on pain.

Another reason why results have to be interpreted with caution is that responder outcomes of clinically useful benefit were reported only infrequently (Dworkin 2008; Moore 2010). Relying on group mean values for pain intensity or pain relief is problematic because the underlying distributions of individual data are often skewed, and using average data from such skewed distributions can produce misleading results (McQuay 1996; Moore 2013). This is why dichotomous responder analysis has been suggested to produce more useful results in clinical practice both in the acute (Moore 1998), and chronic (Moore 2008), pain settings.

With these caveats in mind, we found that there was no consistent effect of vitamin D on pain in rheumatoid arthritis. In knee osteoarthritis, one (smaller and shorter) study reported significantly better outcomes with vitamin D (Sanghi 2013a), while another (larger and longer) study found no difference between the groups (McAlindon 2013). With other painful conditions there is some suggestion of benefit in fibromyalgia (Warner 2008), and non-specific musculoskeletal pain in non-Western immigrants (Schreuder 2012), while there was no evidence of superiority of vitamin D over placebo in one study on polymyalgia rheumatica (Di Munno 1989). One study on diffuse musculoskeletal pain even reported benefit with placebo in one outcome (Warner 2008). Overall, there is no consistent pattern that vitamin D treatment was associated with greater efficacy than placebo in chronic painful conditions. Adverse events and withdrawals were comparatively infrequent, also with no consistent difference between vitamin D and placebo.

Overall completeness and applicability of evidence

A number of potentially eligible studies had methodological limitations and had to be excluded from this review. Other potentially eligible studies were identified by searching trial registries but were not (yet) published and did not have data available for analysis. The 10 studies included in this review were conducted at different times; in different locations; treating a number of painful conditions in participants with vitamin D levels in the deficiency, insufficiency, and sufficiency ranges with different vitamin D doses and schedules of administration over different periods of time; and assessing different outcomes. This heterogeneity meant that no meaningful pooled analysis could be undertaken.

Because of these limitations and the infrequent use of the responder pain outcomes now thought to be most informative of clinical benefit, the evidence has to be judged to be incomplete. Based on the included studies, there is no clearly demonstrable benefit associated with vitamin D in chronic pain in adults. It can be argued that if substantial benefit was present across different chronic painful conditions, it would have become apparent; however, this was not the case.

Quality of the evidence

Though the included studies were largely assessed to be at low or unclear risk of bias, the relative paucity of trials and participants in high quality studies, together with the inadequacy of outcome measures used, implies that the evidence base regarding the use of vitamin D in chronic painful conditions is weak.

Potential biases in the review process

Because of adherence to quality criteria and an extensive search strategy, biases in the review process were minimised.

Agreements and disagreements with other studies or reviews

This review agrees with a previous review on the subject in that there is little high quality evidence for an effect of vitamin D in chronic pain, despite the existence of a number of studies of lower methodological quality (not double-blind randomised controlled trials) that suggest an effect (Straube 2009). As we have previously stated, there is a 'beguiling attraction' in a link between low 25-hydroxyvitamin D levels and chronic pain (Straube 2009). If effective, vitamin D would be a simple and inexpensive treatment with limited adverse effects. However, good evidence for this effectiveness is lacking.

There are a number of examples where early observational studies and treatment studies of lower methodological quality appear to demonstrate effects that are not subsequently confirmed by high quality trials. For example, the use of hyperbaric oxygen in multiple sclerosis appeared beneficial based on observational and non-randomised studies, but subsequent randomised controlled trails found no benefit (Bennett 2001). Likewise, for the use of transcutaneous electrical nerve stimulation for postoperative pain, non-randomised trials were largely positive while randomised trials were largely negative (Carroll 1996). Our previous review on vitamin D for chronic pain came to a similar conclusion when comparing high and low quality treatment studies (Straube 2009). This present review, updated to include 10 studies, relied on a wider search and more strict inclusion criteria than our previous review (Straube 2009), but also did not identify consistent evidence of an effect of vitamin D.

AUTHORS' CONCLUSIONS

Implications for practice

For people with chronic pain

The evidence base did not indicate that vitamin D supplementation for chronic painful conditions in adults is beneficial in terms of bringing about pain relief, though the evidence is insufficient to reach a definitive conclusion for clinical practice.

For clinicians

The evidence base did not indicate that vitamin D supplementation for chronic painful conditions in adults is beneficial in terms of bringing about pain relief. Frank vitamin D deficiency or insufficiency may dictate vitamin D treatment, but pain intensity reduction should not be expected.

For policy makers

There is no evidence that vitamin D supplementation reduces pain in people with chronic pain.

For funders

Treating chronic pain with vitamin D is unlikely to have any benefits, or be cost-effective.

Implications for research

General

Even though this Cochrane review update now includes more than twice as many studies and participants as the original review (Straube 2010), there is still a need for more work in this area. A number of studies that have been identified by searching online trial registries seem to be ongoing, so that there is the possibility of having more data available to assess the effect of vitamin D in chronic pain in the future. Even though the present evidence does not suggest a beneficial effect, such an effect of vitamin D on chronic pain is theoretically possible, even in the absence of a clearly identifiable mode of action, because of the wide range of effects of vitamin D (Holick 2007), and the many molecular and neural mechanisms involved in the pathogenesis of various chronic pain conditions. While there is little evidence from double-blind randomised controlled trials, other study types do suggest that there may be a link (Straube 2009). Because vitamin D is inexpensive and relatively safe, a use in chronic pain could be advocated even if the benefit was of modest size.

Design

Large, double-blind, randomised controlled trials in a variety of chronic pain conditions conducted over long enough periods of time with multiple assessments to capture short, medium, and long term effects are called for. To provide the highest quality evidence, these trials need to be stratified by baseline 25-hydroxyvitamin D levels, with defined treatments, with clinically relevant pain outcomes (such as the primary outcomes that this review looked for), and ideally with outcomes analysed by post-treatment 25-hydroxyvitamin D level. Because it is unclear whether vitamin D has an effect at all, trials need to include a placebo group; and because it is unclear which dose of vitamin D - if any - is effective, different treatment regimens need to be compared. Finally, trials need to report on adverse events and give details of withdrawals and drop-outs (all-cause, lack of efficacy, and adverse event withdrawals), as is now established standard in the pain field.

Measurement (endpoints)

Standard pain outcomes should be used. The ideal outcome is people achieving at least 50% pain intensity reduction, or being in a final pain state of no worse than mild pain.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Brohult 1973

Methods	Randomised, double-blind, placebo-controlled study. Duration: 12 months
Participants	Participants (N = 49) with rheumatoid arthritis of at least 2 years' duration (average duration of disease 7 years). Mean age 52 years (range 18-69 years), 68% women
Interventions	Calciferol 100,000 IU/day (no more details given) (n = 24) Placebo (n = 25)
Outcomes	Consumption of analgesics and antiinflammatory drugs, all-cause withdrawals, lack of efficacy withdrawals (worsening of disease), adverse event withdrawals (death)
Notes	Oxford Quality Score: R1, D1, W1 = 3/5

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Stated to be randomised. 1 of the authors chose whether participants received placebo or active treatment, but it is not stated by which method
Allocation concealment (selection bias)	Unclear risk	1 of the authors chose whether participants received placebo or active treatment (though it is not stated how) and was, therefore, possibly aware of the allocation
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Stated to be double-blind. 1 of the authors was blinded but the other was possibly aware of treatment allocation. However, the authors arrived at their assessments independently and the other author's opinion (not aware of allocation or blood calcium data) was adopted in case of disagreement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	10/49 participants dropped out; last observation carried forward was used
Size	High risk	< 50 participants in each treatment arm

Di Munno 1989

Methods	Randomised, double-blind, placebo-controlled study. Duration: 9 months
Participants	Participants (N = 24) with polymyalgia rheumatica of recent onset, receiving 6-metholprednisolone. Mean age 67.9 years (range 51-82 years), 63% women
Interventions	25-hydroxyvitamin D_3 35 µg/day for 25 days/month (n = 12) Placebo (n = 12) All participants received calcium 500 mg/day
Outcomes	Pain on movement, any adverse events, and serious adverse events
Notes	Oxford Quality Score: R1, D1, W0 = 2/5

Risk of bias

Di Munno 1989 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Stated to be randomised. Method of sequence generation not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Stated to be double-blind. Method of blinding not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Drop-outs and imputation method not stated
Size	High risk	< 50 participants in each treatment arm

Hansen 2014

Methods	Randomised, double-blind, placebo-controlled study. Duration: 12 months
Participants	Participants (N = 22) with rheumatoid arthritis. Vitamin D: 36% women, mean (± SD) age 63 ± 12 years. Placebo: 55% women, mean (± SD) age 53 ± 11 years
Interventions	Ergocalciferol 50,000 IU 3 times/week for 4 weeks, then 50,000 IU twice monthly for 11 months (n = 11) Placebo (n = 11) All participants received calcium 500 mg 3 times daily throughout the study and were asked to apply sunscreen between May and September
Outcomes	11-point pain scale, Health Assessment Questionnaire, Patient Assessment of Global Health, and baseline and end-of-trial vitamin D levels
Notes	Oxford Quality Score: R2, D2, W0 = 4/5

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block randomisation
Allocation concealment (selection bias)	Low risk	Randomisation done by research pharmacy
Blinding (performance bias and detection bias) All outcomes	Low risk	"Matching placebo"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Drop-outs and imputation method not stated

Hansen 2014 *(Continued)*

Size	High risk	< 50 participants in each treatment arm

McAlindon 2013

Methods	Randomised, double-blind, placebo-controlled study. Duration: 2 years
Participants	Participants (N = 146) with symptomatic knee osteoarthritis. 61% women, mean (± SD) age 62.4 ± 8.5 years
Interventions	Cholecalciferol 2000 IU daily initially, with subsequent dose adjustments in 2000 IU increments at 4, 8, and 12 months to keep 25-hydroxyvitamin D levels between 36 and 100 ng/mL (n = 73) Placebo (n = 73)
Outcomes	Western Ontario and McMaster Universities Arthritis Index, any adverse events, serious adverse events, all-cause withdrawals, and baseline and end-of-trial vitamin D levels
Notes	Oxford Quality Score: R2, D2, W1 = 5/5

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Stratified randomisation system, 1 : 1 assignments in permuted blocks of 6, randomisation list generated by study statistician
Allocation concealment (selection bias)	Low risk	Randomisation list provided by study statistician to research pharmacy, list was concealed from the investigative team. "Labeling and dispensing of study pills was performed by the research pharmacy"
Blinding (performance bias and detection bias) All outcomes	Low risk	Identical placebo, dummy dose changes in placebo group. "Monitoring of laboratory test results was performed by the pathology department staff, independently of the clinical team"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	22/146 participants dropped out; multiple imputation used
Size	Unclear risk	> 50 but < 200 participants in each treatment arm

Salesi 2012

Methods	Randomised, double-blind, placebo-controlled study. Duration: 12 weeks
Participants	Participants (N = 117) with rheumatoid arthritis and on treatment with methotrexate, 98 completers (91% women). Median methotrexate dose at baseline 10 mg/week. Vitamin D: mean (± SD) age 49.9 ± 13 years. Placebo: mean (± SD) age 50 ± 12.7 years
Interventions	25-hydroxyvitamin D 50,000 IU/week (plus methotrexate, n = 60) Placebo (plus methotrexate, n = 57)

Salesi 2012 *(Continued)*

Outcomes	Visual analogue pain scale, any adverse events, serious adverse events, all-cause withdrawals, lack of efficacy withdrawals, adverse event withdrawals, and baseline and end-of-trial vitamin D levels
Notes	Oxford Quality Score: R1, D1, W1 = 3/5

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Stated to be randomised. Method of sequence generation not described
Allocation concealment (selection bias)	Unclear risk	No details given
Blinding (performance bias and detection bias) All outcomes	Low risk	"Matching placebo"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	19 of 117 participants dropped out; imputation method not stated
Size	Unclear risk	> 50 but < 200 participants in each treatment arm

Sanghi 2013a

Methods	Randomised, double-blind, placebo-controlled study. Duration: 12 months
Participants	Participants (N = 106) with knee osteoarthritis and vitamin D insufficiency (≤ 50 nmol/L); 103 completers. Vitamin D: 69% women, mean (± SD) age 53.2 ± 9.6 years; placebo: 59% women, mean (± SD) age 53.0 ± 7.4 years
Interventions	Cholecalciferol 60,000 IU/day for 10 days, then 60,000 IU once a month for 12 months (n = 53) Placebo (n = 53)
Outcomes	Visual analogue pain scale, Western Ontario and McMaster Universities Arthritis Index, all-cause withdrawals, and baseline and end-of-trial vitamin D levels
Notes	Oxford Quality Score: R2, D2, W1 = 5/5

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated random allocation sequence
Allocation concealment (selection bias)	Low risk	Random allocation sequence generated by study statistician. Stated that the allocation process was done in a completely concealed manner and that investigator, participants, and staff were unaware of the sequence

Sanghi 2013a *(Continued)*

Blinding (performance bias and detection bias) All outcomes	Low risk	States that the investigator, participants, and pharmacist dispensing the interventions were all blinded to group assignment. Vitamin D and placebo given as capsules
Incomplete outcome data (attrition bias) All outcomes	Low risk	3/106 participants dropped out
Size	Unclear risk	> 50 but < 200 participants in each treatment arm

Schreuder 2012

Methods	Randomised, double-blind, placebo-controlled study. Total duration: 12 weeks. Semi-cross-over at week 6 (main outcome assessed then)
Participants	Non-Western immigrants (N = 84) presenting to general practitioner with non-specific musculoskeletal pain and with 25-hydroxyvitamin D levels < 50 nmol/L. 76% women, mean (± SD) age 41.9 ± 10.4 years
Interventions	Vitamin D_3 150,000 IU as a single dose (n = 44) Placebo (n = 40) (Re-randomisation at week 6 with all placebo participants receiving vitamin D, and vitamin D participants receiving either placebo or a second dose of vitamin D)
Outcomes	5-point pain scale, visual analogue pain scale, any adverse events, all-cause withdrawals, and baseline vitamin D level
Notes	Oxford Quality Score: R2, D2, W1 = 5/5

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Computer-generated randomisation list"
Allocation concealment (selection bias)	Low risk	Pharmacists unaware of treatment allocation dispensed vitamin D or placebo
Blinding (performance bias and detection bias) All outcomes	Low risk	Placebo had same appearance and taste as active treatment. Participants, general practitioners, and interviewers were blinded during the whole trial period
Incomplete outcome data (attrition bias) All outcomes	Low risk	5/84 participants dropped out
Size	High risk	< 50 participants in each treatment arm

Warner 2008

Methods	Randomised, double-blind, placebo-controlled study. Duration: 3 months

Warner 2008 *(Continued)*

Participants	Participants (N = 50) with diffuse musculoskeletal pain and 25-hydroxyvitamin D levels between 9 and 20 ng/mL. Mean (± SD) age 56.2 ± 9.3 years, 100% women
Interventions	Ergocalciferol 50,000 IU/week (n = 25) Placebo (n = 25)
Outcomes	Visual analogue pain scale, functional pain score, all-cause withdrawals, adverse event withdrawals, and baseline and end-of-trial 25-hydroxyvitamin D levels
Notes	Oxford Quality Score: R2, D2, W1 = 5/5

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number table
Allocation concealment (selection bias)	Low risk	Vitamin D and placebo capsules (identical appearance) dispensed in identical prescription containers by hospital pharmacy
Blinding (performance bias and detection bias) All outcomes	Low risk	Colour matched, identical appearing capsules of vitamin D and placebo
Incomplete outcome data (attrition bias) All outcomes	High risk	8/50 participants dropped out; completer analysis was used
Size	High risk	< 50 participants in each treatment arm

Wepner 2014

Methods	Randomised, double-blind, placebo-controlled study. Duration: 25 weeks of treatment, follow-up examination at week 49
Participants	Participants (N = 42) with fibromyalgia and serum calcifediol levels < 32 ng/L; 30 completers (90% women): mean (± SD) age 48.4 ± 5.3 years, range 35-55 years
Interventions	Cholecalciferol (in triglyceride solution) 1200 or 2400 IU daily, depending on vitamin D level Placebo: triglyceride solution
Outcomes	Visual analogue pain scale, Short Form (36) Health Survey (SF-36), Fibromyalgia Impact Questionnaire, all-cause withdrawals, and baseline and end-of-trial 25-hydroxyvitamin D levels
Notes	Oxford Quality Score: R2, D2, W1 = 5/5

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number generator

Wepner 2014 *(Continued)*

Allocation concealment (selection bias)	Low risk	Random allocation done by statistician who was not involved in testing or treatment
Blinding (performance bias and detection bias) All outcomes	Low risk	Cholecalciferol in triglyceride solution as active, triglyceride solution alone as placebo. Mock dose changes in placebo group
Incomplete outcome data (attrition bias) All outcomes	High risk	12/42 participants dropped out, completer analysis
Size	High risk	< 50 participants in each treatment arm

Yamauchi 1989

Methods	Randomised, double-blind, placebo-controlled study. Duration: 16 weeks
Participants	Participants (N = 171) with rheumatoid arthritis. Data for 140 participants (excluding 31 drop-outs): mean age not reported; age groups: < 29 years (n = 3), 30-39 years (n = 12), 40-49 years (n = 19), 50-59 years (n = 51), 60-69 years (n = 32), > 70 years (n = 23); 83% women
Interventions	Alfacalcidol (1-hydroxycholecalciferol) 1.0 µg/day (n = 59) Alfacalcidol 2.0 µg/day (n = 55) Placebo (n = 57)
Outcomes	Patient Global Impression of Change, any adverse events, serious adverse events, all-cause withdrawals, adverse event withdrawals, and lack of efficacy withdrawals
Notes	Oxford Quality Score: R1, D1, W1 = 3/5

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomly allocated by 'controller'; no further details given
Allocation concealment (selection bias)	Unclear risk	Administered by (presumably independent) 'controller'
Blinding (performance bias and detection bias) All outcomes	Low risk	Identical placebo; verified by 'controller'
Incomplete outcome data (attrition bias) All outcomes	High risk	31/171 participants dropped out; completer analysis was used
Size	Unclear risk	> 50 but < 200 participants in each treatment arm

IU: international unit; N: total number in study population, n: number in a treatment arm; SD: standard deviation.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Abou-Raya 2014	Abstract only
Arden 2006	Not all participants had chronic pain. Did not report on outcomes of vitamin D therapy
Arden 2014	Abstract only
Björkman 2008	Pain not always self rated ("self- or nurse-reported"). No other outcomes of interest
Chlebowski 2013	Included women who did not have pain
de Nijs 2006	Participants were not required to have chronic pain
Ding 2013	Letter to the editor, not a trial
Dottori 1982	Not explicitly described as double-blind
Felson 2013	Commentary, not a trial
Gendelman 2014	Abstract only
Grove 1981	Fluoride and calcium administered concurrently with calciferol but not given to comparator group
Kessenich 2010	Case report
Knutsen 2014	Not all participants had chronic pain
Kragstrup 2011	Editorial, not a trial
Krocker 2008	All participants received vitamin D. Described as "pseudorandomised". Not described as double-blind
Lyritis 1994	Not clear that all participants had chronic pain
Mascitelli 2012	Letter to the editor, not a trial
McAlindon 2010	Abstract only
Osunkwo 2012a	Abstract only
Osunkwo 2012b	Abstract only
Osunkwo 2012c	Trial in children and adolescents
Ringe 2000	Not clear that all participants had chronic pain. Not described as double-blind
Ringe 2004	Not clear that all participants had chronic pain. Not described as double-blind
Ringe 2005	Not clear that all participants had chronic pain. Not described as double-blind. Reports on same results as Ringe 2004
Ringe 2007	Not clear that all participants had chronic pain. Not described as double-blind
Sakalli 2012	Not clear that all participants had chronic pain

Study	Reason for exclusion
Sanghi 2011	Abstract only
Sanghi 2012	Abstract only
Sanghi 2013b	Abstract only
Sanghi 2014	Abstract only
Wicherts 2011	Not limited to participants with chronic pain
Wynn 2013	Review, not a trial

Characteristics of ongoing studies *[ordered by study ID]*

ACTRN12610000322033

Trial name or title	The Role of Vitamin D in the Treatment of Nerve Pain in Diabetes
Methods	Randomised, placebo-controlled study, parallel groups. Duration: 6 months
Participants	Participants with type 2 diabetes and with painful neuropathy with a serum 25-hydroxyvitamin D level < 20 ng/mL Estimated enrolment: N = 60
Interventions	Intramuscular vitamin D injection (300,000 IU) at baseline Placebo injection (normal saline) at baseline
Outcomes	Pain scores visual analogue scale and McGill short form pain questionnaire, SF-36
Starting date	1 April 2010
Contact information	Paul Lee, Department of Endocrinology, Garvan Institute of Medical Research, 384 Victoria Street, Darlinghurst, New South Wales 2010, Australia
Notes	

Cao 2012

Trial name or title	Does Vitamin D Supplementation Prevent Progression of Knee Osteoarthritis? A Randomised Controlled Trial
Methods	Randomised, double-blind, placebo-controlled study, parallel group. Duration: 2 years
Participants	Men and women with symptomatic knee osteoarthritis for at least 6 months with a pain visual analogue scale score of at least 20 mm; serum vitamin D level of > 5 ng/mL and < 24 ng/mL Estimated enrolment: N = 400
Interventions	Cholecalciferol 50,000 IU tablets given once monthly for 2 years Placebo tablets

Cao 2012 *(Continued)*

Outcomes	Knee pain, assessed with Western Ontario and McMaster Universities Arthritis Index (WOMAC)
Starting date	1 August 2010
Contact information	Changhai Ding, Menzies Research Institute, 17 Liverpool St, Hobart 7000, Tasmania; Department of Epidemiology & Preventive Medicine, 99 Commercial Rd, Melbourne 3004, Victoria, Australia
Notes	

CTRI/2014/06/004658

Trial name or title	Effect of Vitamin D Supplementation on Progression of Osteoarthritis Knee
Methods	Randomised, double-blind, parallel group study. Duration: 2 years
Participants	Men and women diagnosed with knee osteoarthritis with serum 25-hydroxyvitamin D level ≤ 20 ng/mL
Interventions	Cholecalciferol 60,000 IU for 10 days continuously, then 60,000 IU once a month for 2 years Placebo
Outcomes	Knee pain, quality of life
Starting date	22 July 2014
Contact information	R N Srivastava, Dept. of Orthopaedic Surgery, King George's Medical University, Lucknow, Uttar Pradesh, 226003, India
Notes	

EUCTR 2009-015835-34-IT

Trial name or title	Vitamin D Effect on T Lymphocytes and Osteoclastogenesis in Rheumatoid Arthritis
Methods	Randomised, double-blind, placebo-controlled, parallel group study
Participants	Women with rheumatoid arthritis
Interventions	Cholecalciferol solution (300,000 IU) Placebo solution
Outcomes	
Starting date	9 April 2010
Contact information	
Notes	

EUCTR 2014-000047-33-NL

Trial name or title	The Effect of Intensive Muscle Strength Training and Vitamin D Supplements in Persons with Knee Osteoarthritis
Methods	Randomised, double-blind, placebo-controlled, parallel group study. Duration: 12 months
Participants	Participants with knee osteoarthritis and vitamin D deficiency defined as 25-hydroxyvitamin D levels > 6 ng/mL and < 20 ng/mL (in winter) or < 28 ng/mL (in summer)
Interventions	Cholecalciferol (1200 IU) Placebo
Outcomes	Knee pain, global perceived effect
Starting date	20 March 2014
Contact information	Trial co-ordinator, Dr. Jan van Breemenstraat, 1056AB, Amsterdam, The Netherlands
Notes	

ISRCTN94818153

Trial name or title	A Randomised, Double-Blind, Placebo-Controlled Trial of Vitamin D Supplementation in the Management of Symptomatic Knee Osteoarthritis (the VIDEO study)
Methods	Randomised, double-blind, placebo-controlled study. Duration: 36 months
Participants	Men and women with primary knee osteoarthritis Estimated enrolment: N = 800
Interventions	Cholecalciferol 800 IU/day Placebo
Outcomes	Pain, quality of life
Starting date	1 February 2004
Contact information	Richard Keen, Metabolic Unit, Royal National Orthopaedic Hospital Stanmore, Brockley Hill, Stanmore, HA7 4LP, UK
Notes	Trial status: completed (end date: 31 August 2011)

NCT00279461

Trial name or title	Vitamin D Deficiency Causes Immune Dysfunction and Enables or Perpetuates the Development of Rheumatoid Arthritis
Methods	Randomised, double-blind, parallel group, placebo-controlled study. Duration: 6 months
Participants	Men and women with rheumatoid arthritis and a 25-hydroxyvitamin D level < 30 ng/mL

NCT00279461 *(Continued)*

	Estimated enrolment: N = 50
Interventions	Cholecalciferol 2000 IU capsule daily for 6 months Placebo capsule
Outcomes	American College of Rheumatology response criterion of 20% improvement (ACR20)
Starting date	May 2009
Contact information	Ernesto N Levy, erlevy@iupui.edu
Notes	

NCT01023490

Trial name or title	Vitamin D Treatment to Patients Suffering from Chronic Pain and Vitamin D Hypovitaminosis
Methods	Randomised, double-blind, parallel group, placebo-controlled study. Duration: 1 year
Participants	Men and women with chronic pain and hypovitaminosis D Estimated enrolment: N = 12
Interventions	Vitamin D (34,500 IU/week) Placebo
Outcomes	Pain intensity
Starting date	January 2010
Contact information	
Notes	Trial status: completed October 2012. Other study ID: TASMC-09-SB-0494-CTIL

NCT01351805

Trial name or title	Vitamin D and Fish Oil for Autoimmune Disease, Inflammation and Knee Pain
Methods	Randomised, double-blind, placebo-controlled study
Participants	The parent trial of this study, VITamin D and OmegA-3 TriaL (VITAL; NCT 01169259), is a randomised controlled trial in 25,876 US men and women investigating the effects of daily dietary supplementation with cholecalciferol or omega-3 fatty acids This study (NCT01351805) is conducted among VITAL participants. The study will examine whether vitamin D or fish oil have effects on autoimmune disease incidence, biomarkers of systemic inflammation, and chronic knee pain. It involves a randomly selected subcohort of 2000 participants analysed for changes in biomarkers of systemic inflammation. Approximately 2000 participants with chronic knee pain at baseline are to be followed regarding their knee pain as a subcohort
Interventions	Marine omega-3 fatty acids (eicosapentaenoic acid (EPA) 465 mg and docosahexaenoic acid (DHA) 375 mg)

NCT01351805 *(Continued)*

	Cholecalciferol 2000 IU/day Placebo Marine omega-3 fatty acids (EPA 465 mg and DHA 375 mg) plus cholecalciferol 2000 IU/day
Outcomes	Severity of knee pain
Starting date	January 2011
Contact information	
Notes	Study ongoing, but not recruiting participants

NCT01426347

Trial name or title	Treatment of Vitamin D Deficiency in Patients with Rheumatoid Arthritis
Methods	Randomised, double-blind, parallel group, placebo-controlled study. Duration: 6 months
Participants	Men and women with rheumatoid arthritis Estimated enrolment, N = 140
Interventions	Ergocalciferol 50,000 IU/week for 16 weeks Placebo
Outcomes	AIMS-SF (probably refers to: Arthritis Impact Measurement Scale-Short Form)
Starting date	January 2009
Contact information	
Notes	

NCT02002000

Trial name or title	Chronic Pain and Vitamin D (DOVID)
Methods	Randomised, double-blind, parallel group, placebo-controlled study. Duration: 3 months
Participants	Men and women with chronic, diffuse musculoskeletal pain with 25-hydroxyvitamin D deficiency < 20.8 ng/mL Estimated enrolment: N = 100
Interventions	Cholecalciferol, 3 doses: 200,000 IU at baseline, 200,000 IU on day 15, and 200,000 IU on day 30 Placebo
Outcomes	Brief Pain Inventory, SF-36
Starting date	December 2013

NCT02002000 *(Continued)*

Contact information	Anne-Marie Schott, anne-marie.schott-pettelaz@chu-lyon.fr Julie Haesebaert, julie.haesebaert@chu-lyon.fr
Notes	

NCT02243800

Trial name or title	Study of the Efficacy and Safety of Cholecalciferol Supplementation on the Activity of Rheumatoid Arthritis in Patients with Vitamin D Deficiency
Methods	Randomised, double-blind, parallel group, placebo-controlled study. Duration: 24 weeks
Participants	Men and women with rheumatoid arthritis with a serum 25-hydroxyvitamin D < 30 ng/mL Estimated enrolment: N = 164
Interventions	Cholecalciferol Placebo
Outcomes	Visual analogue score pain, quality of life (SF-36 and others)
Starting date	November 2011
Contact information	Patrick Lacarin, placarin@chu-clermontferrand.fr
Notes	

N: total number in study population; SF-36: Short Form (36) Health Survey

APPENDICES

Appendix 1. CENTRAL (CRSO) search strategy

1. MESH DESCRIPTOR vitamin D EXPLODE ALL TREES
2. (vitamin D):TI,AB,KY
3. (vitamin D2):TI,AB,KY
4. (vitamin D3):TI,AB,KY
5. (1-alpha hydroxyvitamin D3):TI,AB,KY
6. (1-alpha hydroxy-vitamin D3):TI,AB,KY
7. (1-alpha hydroxycalciferol):TI,AB,KY
8. 1-alpha-hydroxy-calciferol:TI,AB,KY
9. (1,25 dihydroxyvitamin D3):TI,AB,KY
10. (1,25-dihydroxy-vitamin D3):TI,AB,KY
11. (1,25 dihydroxycholecalciferol):TI,AB,KY
12. 1,25-dihydroxycholecalciferol:TI,AB,KY
13. 25-hydroxycholecalciferol:TI,AB,KY
14. (25 hydroxycholecalciferol):TI,AB,KY
15. (25 hydroxyvitamin D):TI,AB,KY
16. (25-hydroxy-vitamin D):TI,AB,KY
17. alfacalcidol:TI,AB,KY
18. calcidiol:TI,AB,KY

19.calcitriol:TI,AB,KY
20.calcifediol:TI,AB,KY
21.calciferol:TI,AB,KY
22.ergocalciferol:TI,AB,KY
23.cholecalciferol:TI,AB,KY
24.#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23
25.pain*:TI,AB,KY
26.MESH DESCRIPTOR pain EXPLODE ALL TREES
27.#25 OR #26
28.#24 AND #27
29.2009 TO 2015:YR
30.#28 AND #29

Appendix 2. MEDLINE (OVID) search strategy

1. exp Vitamin D/
2. vitamin D.tw.
3. vitamin D2.tw.
4. vitamin D3.tw.
5. 1-alpha hydroxyvitamin D3.tw.
6. 1-alpha-hydroxy-vitamin D3.tw.
7. 1-alpha hydroxycalciferol.tw.
8. 1-alpha-hydroxy-calciferol.tw.
9. 1,25 dihydroxyvitamin D3.tw.
10.1,25-dihydroxy-vitamin D3.tw.
11.1,25 dihydroxycholecalciferol.tw.
12.1,25-dihydroxycholecalciferol.tw.
13.25-hydroxycholecalciferol.tw.
14.25 hydroxycholecalciferol.tw.
15.25 hydroxyvitamin D.tw.
16.25-hydroxy-vitamin D.tw.
17.alfacalcidol.tw.
18.calcidiol.tw.
19.calcitriol.tw.
20.calcifediol.tw.
21.calciferol.tw.
22.ergocalciferol.tw.
23.cholecalciferol.tw.
24.or/1-23
25.pain*.tw.
26.exp pain/
27.25 or 26
28.24 and 27
29.randomized controlled trial.pt.
30.controlled clinical trial.pt.
31.randomized.ab.
32.placebo.ab.
33.drug therapy.fs.
34.randomly.ab.
35.trial.ab.
36.groups.ab.
37.29 or 30 or 31 or 32 or 33 or 34 or 35 or 36

38.exp animals/ not humans.sh.
39.37 not 38
40.28 and 39
41.(200909*or 200910* or 200911* or 200912* or 2010* or 2011* or 2012* or 2013* or 2014* or 2015*).ed.
42.40 and 41

Appendix 3. EMBASE (OVID) search strategy

1. exp Vitamin D/
2. vitamin D.tw.
3. vitamin D2.tw.
4. vitamin D3.tw.
5. 1-alpha hydroxyvitamin D3.tw.
6. 1-alpha-hydroxy-vitamin D3.tw.
7. 1-alpha hydroxycalciferol.tw.
8. 1-alpha-hydroxy-calciferol.tw.
9. 1,25 dihydroxyvitamin D3.tw.
10. 1,25-dihydroxy-vitamin D3.tw.
11. 1,25 dihydroxycholecalciferol.tw.
12. 1,25-dihydroxycholecalciferol.tw.
13. 25-hydroxycholecalciferol.tw.
14. 25 hydroxycholecalciferol.tw.
15. 25 hydroxyvitamin D.tw.
16. 25-hydroxy-vitamin D.tw.
17. alfacalcidol.tw.
18. calcidiol.tw.
19. calcitriol.tw.
20. calcifediol.tw.
21. calciferol.tw.
22. ergocalciferol.tw.
23. cholecalciferol.tw.
24. or/1-23
25. pain*.tw.
26. exp pain/
27. 25 or 26
28. 24 and 27
29. random$.tw.
30. factorial$.tw.
31. crossover$.tw.
32. cross over$.tw.
33. cross-over$.tw.
34. placebo$.tw.
35. (doubl$ adj blind$).tw.
36. (singl$ adj blind$).tw.
37. assign$.tw.
38. allocat$.tw.
39. volunteer$.tw.
40. Crossover Procedure/
41. double-blind procedure.tw.
42. Randomized Controlled Trial/
43. Single Blind Procedure/
44. or/29-43
45. (animal/ or nonhuman/) not human/

46.44 not 45
47.28 and 46
48.(200909*or 200910* or 200911* or 200912* or 2010* or 2011* or 2012* or 2013* or 2014* or 2015*).dd.
49.47 and 48
50.limit 49 to embase

Appendix 4. Summary of outcomes in individual studies: efficacy

Study ID	Condition	Intervention	Baseline 25-hydroxyvitamin D (ng/mL) (± SD)	End-of-trial 25-hydroxyvitamin D (ng/mL) (± SD)	≥ 50% pain relief	PGIC much or very much improved	Any pain improvement	Other pain outcomes (95% CI)	QoL Improvement (95% CI)
Rheumatoid arthritis									
Brohult 1973	Rheumatoid arthritis	(1) Calciferol 100,000 IU/day, n = 24 (2) Placebo, n = 5	No data	No data	No data	No data	No data	Consumption of "analgesics and anti-inflammatory medicines" decreased significantly in calciferol group (P value < 0.01),	No data

(Continued)

								no change in control group (no direct between groups comparison reported)	
Hansen 2014	Rheumatoid arthritis	(1) Ergocalciferol 50,000 IU, 3 times/week for 4 weeks, then twice monthly for 11 months, plus calcium 500 mg 3 times daily, n = 11 (2) Placebo plus calcium 500 mg 3 times daily, n = 11	(1) 25 ± 24 (2) 21 ± 9	(1) 30 ± 11 (2) 23 ± 11	No data	No data	No data	Change in pain (scale 0 to 10) (1) 2.9 (95% CI 1.8 to 4.1) to 3.9 (95% CI 2.6 to 5.2) (2) 2.9 (95% CI	Change in: Health Assessment Questionnaire (scale 0 to 3; 3 is worst functional status) (1) 0.61 (95% CI 0.35 to 0.87) to 0.68 (95% CI 0.39 to 0.96) (2) 0.61 (95% CI 0.35 to 0.87) to 0.44 (95% CI 0.15 to 0.73) No significant difference at end of trial Patient Assessment of Global Health (scale 0 to 5; 5 is poor health) (1) 2.4 (95% CI 2.0 to 2.8) to 3.2 (95% CI 2.6 to 3.7) (2) 2.4 (95% CI 2.0 to 2.8) to 2.2 (95% CI 1.7 to 2.7) Significant difference for end-of-trial values; worse with vitamin D Also significant decline in physical function domain of SF-36 in vitamin D-treated participants

(Continued)

								1.8 to 4.1) to 2.4 (95% CI 1.1 to 3.7) Significant difference (P value = 0.03) for end-of-trial values between groups; worse pain in vitamin D group	
Salesi 2012	Rheumatoid arthritis	(1) Methotrexate (7.5-20 mg/week) plus vitamin D 50,000 IU/week, n = 60	(1) 43 ± 11 (2) 37 ± 13	(1) 50 ± 9.0 (2) 40 ± 12	No data	No data	No data	Change in visual	No data

(Continued)

	(2) Methotrexate (7.5-20 mg/ week plus placebo, n = 57			
			ana- logue scale (0 to 100): (1) 63 ± 18 to 46 ± 20 (2) 61 ± 22 to 39 ± 20	Sig- nifi- cant im- prove- ments in both groups, no sig- nifi- cant dif- fer- ence be- tween groups at ei-

(Continued)

								ther time point	
Yamauchi 1989	Rheumatoid arthritis	(1) Alfacalcidol 1 µg/day, n = 59 (2) Alfacalcidol 2 µg/day, n = 55 (3) Placebo, n = 57	No data	No data	No data	(1) 8/59 (2) 7/55 (3) 8/57	No data	No data	No data
Knee osteoarthritis									
McAlindon 2013	Knee osteoarthritis	(1) Cholecalciferol 2000 IU daily, initially, with adjustments at 4, 8, and 12 months for a target vitamin D level of 36-100 ng/mL, n = 73 (2) Placebo, n = 73	(1) 23 ± 11 (2) 22 ± 8.3	(1) 39 (2) 25	No data	No data	No data	WOMAC knee pain score (range 0 to 20) change baseline to trial end (1) -2.3 (95% CI -3.2 to -1.4) (2) -1.5 (95% CI -2.3 to -0.6) No sig-	WOMAC function score change (1) -7.0 (95% CI -9.8 to -4.2) (2) -3.8 (95% CI -6.0 to -1.7) No significant difference between groups

(Continued)

								nificant difference between groups	
Sanghi 2013a	Knee osteoarthritis	(1) Vitamin D 60,000 IU/day for 10 days, followed by 60,000 IU once a month for 12 months, n = 53 (2) Placebo, n = 53	(1) 15 ± 3.0 (2) 14 ± 3.0	(1) 33 (2) 15	No data	No data	No data	Visual analogue pain scale change (1) -0.26 (95% CI -2.8 to -1.4) (2) 0.13 (95% CI -0.03 to 0.29) Significant difference (P value = 0.02)	WOMAC total score change (1) -2.1 (95% CI -2.8 to -1.4) (2) 1.4 (95% CI 0.95 to 1.86) Significant difference (P value < 0.001)

(Continued)

								WOMAC pain score change (1) -0.55 (95% CI -0.07 to 1.02) (2) 1.2 (95% CI 0.82 to 1.2) Significant difference (P value < 0.001)	
Other									
Di Munno 1989	Polymyalgia rheumatica	(1) 25-Hydroxyvitamin D 35 µg/day for 25 days/month, n = 12 (2) Placebo, n = 12 All had calcium 500 mg and 6-methylprednisolone	No data	No data	No data	No data	No data	Subjective pain on movement (scale 0 to 4):	No data

(Continued)

								significantly decreased in both groups over time, no great difference between groups (no statistics for between groups comparison reported)	
Schreuder 2012	Non-specific musculoskeletal pain	(1) Vitamin D_3 150,000 IU once, n = 44 (2) Placebo, n = 40	(1) 7.9 ± 4.3 (2) 7.9 ± 3.5	No data	"much less pain" (5-point scale) (1) 2/44 (2) 1/40	No data	"much less pain" or "less pain" (5-point scale) (1) 15/44 (2) 7/40	Visual analogue scale for pain: no significant	No data

(Continued)

							Significant difference (P value = 0.04)	cant improvement with vitamin D	
Warner 2008	Diffuse musculoskeletal pain	(1) Ergocalciferol 50,000 IU/week, n = 25 (2) Placebo, n = 25	(1) 17 ± 2.9 (2) 16 ± 3.6	(1) 31 ± 6.2 (2) 19 ± 6.5 (P value < 0.001)	No data	No data	No data	Visual analogue scale: no significant difference between groups; functional pain score: slightly favours placebo (P value = 0.05)	No data
Wepner 2014	Fibromyalgia	(1) Cholecalciferol 1200-2400 IU daily, depending on vitamin D level, n = 24	(1) 19 ± 5.9	(1) 49 ± 11	No data	No data	No data	Visual	SF-36 scores showed no significant time or groups effect in the physical and metal health summaries. A group-specific signifi-

				ana-logue scale score change week 1 to week 25 (1) 69 ± 12 to 53 ± 29 (2) 62 ± 20 to 65 ± 16
A 2 groups x 4 time points vari-ance analy-sis showed a sig-nifi-cant group ef-fect (P	cance was seen in the physical functioning subscale: the treatment group improved (P value = 0.014); the placebo group remained unchanged (P value = 0.480) FIQ scores, week 1 to week 25: (1) 43 ± 12 to 44 ± 16 (2) 42 ± 17 to 48 ± 12 No group-specific effects seen overall (P val-ue = 0.615); FIQ question on morning fatigue: a signifi-cantly better outcome was observed for the intervention group (P value = 0.007)			

(Continued)

	(2) Placebo, n = 18	(2) 21 ± 6.3	(2) 34 ± 12

(Continued)

							value = 0.025)

CI: confidence interval; FIQ: Fibromyalgia Impact Questionnaire; n = number; PGIC: Patient Global Impression of Change; QoL: quality of life; SD: standard deviation; SF-36: Short Form (36) Health Survey; WOMAC: Western Ontario and McMaster Universities Arthritis Index.

Yamauchi 1989 included 191 participants in total (65 in the placebo, 64 in the alfacalcidol 1 µg, and 62 in the alfacalcidol 2 µg). Of these, 20 (8, 5, and 7 in the previously mentioned groups) were excluded after randomisation due to violation of inclusion criteria or concurrent drugs. These 20 participants who were excluded from the original study due to protocol violation were not included in our intention-to-treat analysis.

Appendix 5. Summary of outcomes in individual studies: adverse events and withdrawals

Study ID	Condition	Intervention	Any AE	Serious AE	All-cause withdrawal	LoE with-drawal	AE with-drawal
Rheumatoid arthritis							
Brohult 1973	Rheumatoid arthritis	(1) Calciferol 100,000 IU/day, n = 24 (2) Placebo, n = 25	No data	No data	(1) 4/24 (2) 6/25	Worsening of disease: (1) 3/24 (2) 6/25	Mortality: (1) 1/24 (PE) (2) 0/25
Hansen 2014	Rheumatoid arthritis	(1) Ergocalciferol 50,000 IU , 3 times/week for 4 weeks, then twice monthly for 11 months, plus 500 mg calcium 3 times daily, n = 11 (2) Placebo plus 500 mg calcium 3 times daily, n = 11	No data	No data	No data	No data	No data
Salesi 2012	Rheumatoid arthritis	(1) Methotrexate 7.5-20 mg/week plus vitamin D 50,000 IU/week, n = 60 (2) Methotrexate (7.5-20 mg/week) plus placebo, n = 57	(1) 7/60 (2) 3/57	Due to intervention: (1) 0/60 (2) 0/57 Also 1 death due to heart disease in (1)	(1) 10/60 (2) 9/57	(1) 0/60 (2) 0/57	(1) 1/60 (2) 1/57
Yamauchi 1989	Rheumatoid arthritis	(1) Alfacalcidol 1 µg/day, n = 59 (2) Alfacalcidol 2 µg/day, n = 55 (3) Placebo, n = 57	(1) 1/59 (2) 2/55 (3) 3/57	(1) 1/59 (2) 0/55 (3) 0/57	(1) 14/59 (2) 9/55 (3) 8/57	(1) 1/59 (2) 0/55 (3) 0/57	(1) 1/59 (2) 2/55 (3) 3/57
Knee osteoarthritis							
McAlindon 2013	Knee osteoarthritis	(1) Cholecalciferol 2000 IU daily, initially, with adjustments at 4, 8, and 12 months for a target vitamin D level of 36-100 ng/mL, n = 73 (2) Placebo, n = 73	(1) 47/73 (2) 46/73	(1) 16/73 (2) 16/73	(1) 9/73 (2) 13/73	1) 0/73 (2) 0/73 (2 with unclear ("other") reason for drop-out)	1) 0/73 (2) 0/73 (2 with unclear ("other") reason for drop-out)
Sanghi 2013a	Knee osteoarthritis	(1) Vitamin D 60,000 IU/day for 10 days, followed by 60,000 IU once per month for 12 months, n = 53	No data	No data	(1) 1/53	(1) 0/53	(1) 0/53

(Continued)

		(2) Placebo, n = 53			(2) 2/53	(2) 0/53	(2) 0/53
Other							
Di Munno 1989	Polymyalgia rheumatica	(1) 25-Hydroxyvitamin D 35 µg/day for 25 days/month, n = 12 (2) Placebo, n = 12 All had calcium 500 mg and 6-methylprednisolone	(1) 0/12 (2) 0/12	(1) 0/12 (2) 0/12	No data	No data	No data
Schreuder 2012	Non-specific musculoskeletal pain	(1) Vitamin D_3 150,000 IU once, n = 44 (2) Placebo, n = 40	"did not find any adverse effects of vitamin D supplementation"	Presumably none	(1) 1/44 (2) 4/40	(1) 0/44 (2) 0/40	(1) 0/44 (2) 0/40
Warner 2008	Diffuse musculoskeletal pain	(1) Ergocalciferol 50,000 IU ergocalciferol/week, n = 25 (2) Placebo, n = 25	No data	No data	(1) 3/25 (2) 5/25	No data	(1) 0/25 (2) 0/25
Wepner 2014	Fibromyalgia	(1) Cholecalciferol 1200-2400 IU daily, depending on vitamin D level, n = 24 (2) Placebo, n = 18	No data	No data	(1) 9/24 (2) 3/18	No data	No data

AE: adverse event; LoE: lack of efficacy; n: number; PE: pulmonary embolus.

Yamauchi 1989 reported that there were 2 participants with adverse events in the placebo groups. However, because there were 3 adverse event withdrawals in that group the number of participants with adverse events is given as 3 in the above table.

WHAT'S NEW

Date	Event	Description
18 February 2020	Amended	Clarification added to Declarations of interest.
22 March 2018	Review declared as stable	See Published notes.

HISTORY

Protocol first published: Issue 2, 2009
Review first published: Issue 1, 2010

Date	Event	Description
30 April 2015	Review declared as stable	This review will be assessed for further updating in 2018.
16 February 2015	New citation required but conclusions have not changed	New studies did not change the overall conclusion that there is a lack of good evidence supporting the use of vitamin D for chronic pain. Issues around study design are highlighted.
2 February 2015	New search has been performed	New searches identified six new studies (517 participants) for inclusion and 21 studies for exclusion.
12 December 2014	Amended	Work on the update has started. Searches have been completed.
27 June 2012	Amended	Contact details updated.
25 April 2012	Review declared as stable	The authors will update this review in 2014 or sooner if evidence comes to light to alter the current conclusions.
24 September 2010	Amended	Contact details updated.

CONTRIBUTIONS OF AUTHORS

For this update, CS and SS assessed the studies identified by the searches, extracted data and performed the quality scoring.

SS has drafted the review update manuscript.

All review authors read and approved the final manuscript.

SS will be responsible for further updates.

DECLARATIONS OF INTEREST

SS has no conflicts relating to this review or any similar product.

SD has no conflicts relating to this review or any similar product.

CS has no conflicts relating to this review or any similar product.

RAM has no conflicts relating to this review or any similar product.

For transparency, SS, SD, and RAM have received research support from charities, government, and industry sources at various times, but none relate to this review. SD and RAM are funded by the NIHR for work on a series of reviews informing the unmet need of chronic pain and providing the evidence for treatments of pain.

This review was identified in a 2019 audit as not meeting the current definition of the Cochrane Commercial Sponsorship policy. At the time of its publication it was compliant with the interpretation of the existing policy. As with all reviews, new and updated, at update this review will be revised according to 2020 policy update.

SOURCES OF SUPPORT

Internal sources

- Oxford Pain Research Trust, UK.

  General institutional support

External sources

- The National Institute for Health Research (NIHR), UK.

  NIHR Cochrane Programme Grant: 13/89/29 - Addressing the unmet need of chronic pain: providing the evidence for treatments of pain

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

After the search and examination of the retrieved studies it was decided, at the stage of the original version of this review, to include an additional secondary outcome ("other patient-rated pain outcomes"). For the 2015 update, the risk of bias assessment has been extended to bring it into line with current standards.

NOTES

A restricted search in March 2018 did not identify any potentially relevant studies likely to change the conclusions. Therefore, this review has now been stabilised following discussion with the authors and editors. There is ongoing relevant work and therefore the review will be re-assessed for updating in two years. If appropriate, we will update the review before this date if new evidence likely to change the conclusions is published, or if standards change substantially which necessitate major revisions

INDEX TERMS

Medical Subject Headings (MeSH)

Arthritis, Rheumatoid [drug therapy]; Chronic Pain [*drug therapy] [etiology]; Ergocalciferols [adverse effects] [therapeutic use]; Hydroxycholecalciferols [adverse effects] [therapeutic use]; Musculoskeletal Pain [drug therapy]; Osteoarthritis, Knee [drug therapy]; Polymyalgia Rheumatica [drug therapy]; Randomized Controlled Trials as Topic; Vitamin D [adverse effects] [*therapeutic use]; Vitamin D Deficiency [complications] [drug therapy]; Vitamins [adverse effects] [*therapeutic use]

MeSH check words

Adult; Humans