Juvenile idiopathic arthritis: a literature review of recent evidence

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INTRODUCTION

Juvenile idiopathic arthritis (JIA) is a chronic autoimmune inflammatory joint disease. It is the most common rheumatic disease in children and adolescents. Juvenile idiopathic arthritis is defined as 'persistent arthritis of unknown aetiology that begins before the age 16 years and persists for at least 6 weeks'. It is diagnosed after excluding other causes.\(^1\)

The cause of JIA is unknown. It is suspected that environmental factors such as viral infections may trigger the condition in genetically susceptible children.\(^2\) However, it is unusual for more than one child in a family to have arthritis. As there is currently no cure for JIA, the aim of treatment is the induction of remission and control of the disease to minimise pain and function loss, and to maximise quality of life. Treatment has altered as a result of recent research into the best practice approach to managing children.

Objective

This literature review was conducted on behalf of The Royal Australian College of General Practitioners (RACGP) to inform the development of the evidence based Clinical guideline for the diagnosis and management of juvenile idiopathic arthritis (www.racgp.org.au/guidelines/juvenileidiopathicarthritis) and Recommendations for the diagnosis and management of juvenile idiopathic arthritis (www.racgp.org.au/guidelines/juvenileidiopathicarthritis/recommendations). The literature review updates a previous guideline, Juvenile idiopathic arthritis management guidelines (Provisional) (2006).\(^3\)

The objective of this review is to present the most recent evidence related to the diagnosis and management of JIA to inform the development of evidence based recommendations for general practitioners working in the Australian health care setting. The questions of specific interest to this literature review were:

1. What is the GP’s role in the diagnosis of JIA?
2. What are effective pharmacological, non-pharmacological (including ‘complementary’) and surgical interventions for children and adolescents with JIA?

Commonly used abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>ACR</td>
<td>American College of Rheumatology paediatric 30/50/70 criteria</td>
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<tr>
<td>AE</td>
<td>adverse event</td>
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<tr>
<td>ANA</td>
<td>antinuclear antigen</td>
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<tr>
<td>BMC</td>
<td>bone mineral content</td>
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<tr>
<td>BMD</td>
<td>bone mineral density</td>
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<tr>
<td>CDM</td>
<td>chronic disease management</td>
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<tr>
<td>CHAQ</td>
<td>Childhood Health Assessment Questionnaire</td>
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<tr>
<td>CI</td>
<td>confidence interval</td>
</tr>
<tr>
<td>COX-2</td>
<td>cyclo-oxygenase-2 selective inhibitors</td>
</tr>
<tr>
<td>CRP</td>
<td>C-reactive protein</td>
</tr>
<tr>
<td>DMARDs</td>
<td>disease modifying antirheumatic drugs</td>
</tr>
<tr>
<td>EPC</td>
<td>enhanced primary care</td>
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<tr>
<td>ES</td>
<td>effect size (0.2, small effect; 0.5, moderate effect; 0.8, large effect)</td>
</tr>
<tr>
<td>ESR</td>
<td>erythrocyte sedimentation rate</td>
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<tr>
<td>FBC</td>
<td>full blood count</td>
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<tr>
<td>GIT</td>
<td>gastrointestinal</td>
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<tr>
<td>GP</td>
<td>general practitioner</td>
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</table>
METHOD
The following method was used to identify research for inclusion in the literature review.

Inclusion/exclusion criteria

Types of studies
For evidence related to the diagnosis of JIA, initially only studies considered to be of National Health and Medical Research Council (NHMRC) Level 1 or Level 2 evidence (Table 1) that evaluated diagnostic strategies for JIA were considered for inclusion. Due to the paucity of evidence available, the search was expanded to include lower levels of evidence such as diagnostic case control studies and literature reviews. Studies reported in systematic reviews (SRs) already selected for inclusion were not subjected to individual critical appraisal to prevent replication of data.

For evidence related to the management of JIA, initially only papers considered to be of NHMRC Level 1 or Level 2 evidence (Table 1) that evaluated the effectiveness and/or safety of interventions for JIA in children aged 16 years or under were considered for inclusion. Due to the paucity of evidence available, the search was expanded to include lower levels of evidence such as comparative studies, case control studies, time series, case series and literature reviews. Randomised controlled trials (RCTs) reported in SRs already selected for inclusion in this literature review were not subjected to individual critical appraisal to prevent replication of data.

Types of participants
Studies that included children (aged 16 years or under) presenting with arthritic symptoms were considered for inclusion, as were studies that included children diagnosed as having JIA.
Table 1. NHMRC levels of evidence for intervention studies

<table>
<thead>
<tr>
<th>Level of evidence</th>
<th>Intervention studies</th>
<th>Diagnosis</th>
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</thead>
<tbody>
<tr>
<td>I</td>
<td>Evidence obtained from a systematic review of all relevant randomised controlled trials</td>
<td>A systematic review of Level II studies</td>
</tr>
<tr>
<td>II</td>
<td>Evidence obtained from at least one properly designed randomised controlled trial</td>
<td>A study of test accuracy with independent blinded comparison with a valid reference standard, among consecutive patients with a defined clinical presentation</td>
</tr>
<tr>
<td>III–1</td>
<td>Evidence obtained from well designed pseudo-randomised controlled trials (alternate allocation or some other method)</td>
<td>A study of test accuracy with independent blinded comparison with a valid reference standard, among non-consecutive patients with a defined clinical presentation</td>
</tr>
<tr>
<td>III–2</td>
<td>Evidence obtained from comparative studies with concurrent controls and allocation not randomised (cohort studies), case control studies, or interrupted time series with a control group</td>
<td>A comparison with reference standard that does not meet the criteria for Level II or Level III–1 evidence</td>
</tr>
<tr>
<td>III–3</td>
<td>Evidence obtained from comparative studies with historical control, two or more single arm studies, or interrupted time series without a parallel control group</td>
<td>Diagnostic case control evidence</td>
</tr>
<tr>
<td>IV</td>
<td>Evidence obtained from case series, either post-test or pre-test and post-test</td>
<td>Study of diagnostic yield (no reference standard)</td>
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</tbody>
</table>

**Types of interventions**
Interventions included any therapies used to manage JIA. Both pharmacological and non-pharmacological interventions were eligible for inclusion in this review.

**Levels of evidence**
Initial searches indicated a low volume of high level evidence (NHMRC Level I or Level II) addressing the review questions, therefore evidence of all levels (Table 1) was included in this literature review. In addition, literature reviews and consensus guidelines relevant to the diagnosis and management of JIA were considered for inclusion. The level of evidence assigned to each paper has been included throughout this literature review.

**Search strategy**
The Cochrane Library (including the CENTRAL Cochrane Controlled Trial Register) and the MEDLINE, EMBASE, and CINAHL databases were initially searched for evidence published between January 2000 and January 2007. Articles identified via personal contact with authors were also considered for inclusion. The following initial search strategies applied to the MEDLINE database and were adapted to apply to the other databases.
Search for evidence on diagnosis

- (‘juvenile spondyloarthritis’[Title/Abstract]) OR (‘seronegative enthesopathy’[Title/Abstract]) OR (‘juvenile chronic arthritis’[Title/Abstract]) AND (‘Diagnosis’[MeSH])
- (‘Spondylitis, Ankylosing/diagnosis’[MeSH]) OR (‘Arthritis, Psoriatic/diagnosis’[MeSH]) OR (‘Arthritis, Juvenile Rheumatoid/diagnosis’[MeSH]) OR (‘spondylarthropathies/diagnosis’[MeSH])
- Limited to: clinical trial, meta-analysis, practice guideline, review, controlled clinical trial, SRs.

Search for evidence on management

- (‘juvenile spondyloarthritis’[Title/Abstract]) OR (‘seronegative enthesopathy’[Title/Abstract]) OR (‘juvenile chronic arthritis’[Title/Abstract]) AND (‘Diet Therapy’[MeSH]) OR (‘Nursing’[MeSH]) OR (‘Rehabilitation’[MeSH]) OR (‘Surgery’[MeSH]) OR (‘Therapeutics’[MeSH]) OR (‘diet therapy’ [Subheading]) OR (‘nursing’[Subheading]) OR (‘rehabilitation’[Subheading]) OR (‘surgery’[Subheading]) OR (‘therapy’[Subheading]) OR (‘Spondylitis, Ankylosing/dt,nu,rh,su,th’[MeSH]) OR (‘Arthritis, Psoriatic/dt,nu,rh,su,th’[MeSH]) OR (‘Arthritis, Juvenile Rheumatoid/dt,nu,rh,su,th’[MeSH]) OR (‘spondylarthropathies/dt,nu,rh,su,th’[MeSH])
- Limited to: clinical trial, meta-analysis, practice guideline, randomised controlled trial, review, controlled clinical trial, SRs.

Critical appraisal

Critical appraisal of all studies that met the inclusion criteria for this literature review was conducted by two reviewers. There was a high level of consensus between reviewers with minor discrepancies in SIGN scoring resolved by a third reviewer.

Appraisal of systematic reviews

Systematic reviews and meta-analyses were appraised using a methodological checklist developed by the Scottish Intercollegiate Guidelines Network (SIGN). The SIGN checklist assesses description of aims and methodology; rigour of literature search; critical appraisal of included studies; appropriateness of methods of combining evidence; and an overall possibility of review bias, including conflict of interest. For this literature review, SRs and meta-analyses were given a score from 0 to 12 based on results of the SIGN methodological checklist (sections 1 and 2.1). Papers scored 2 for questions answered ‘well addressed’, 1 for questions answered ‘adequately addressed’ and 0 for questions answered as ‘poorly addressed’ or ‘not addressed’. When a question was answered as ‘not applicable’, this question was removed from the overall score for that review. Throughout this literature review, papers that achieved a SIGN checklist score above 9 are referred to as good quality; those that scored between 5 and 9 are referred to as being of moderate quality; and those that scored below 5 are referred to as being of low quality. To achieve a grading of good quality a review was required to provide a thorough outline of the aims and methods, use an appropriate search technique, include description of an appropriate critical appraisal process and pool studies in an appropriate manner. Appendix 1 provides a tabulated summary of methodological appraisal of included SRs and meta-analyses, together with their quality scores.
Appraisal of RCTs
Randomised controlled trials were appraised for methodological quality and scored using the Jadad scale that assesses randomisation, blinding and report of withdrawals. They were also appraised using a methodological checklist developed by SIGN. The SIGN checklist assesses quality of randomisation; blinding and concealment; between group differences at the commencement of, and throughout the trial; intention to treat analysis; and an overall possibility of study bias, including conflict of interest. For this literature review RCTs were scored from 0 to 20 based on the results of the SIGN methodological checklist, scoring 2 for questions answered ‘well addressed’, 1 for questions answered ‘adequately addressed’ and ‘0’ for questions answered as ‘poorly addressed’ or ‘not addressed’. When a question was answered as ‘not applicable’ this question was removed from the overall score for that RCT, thus some studies received a score out of 18. Throughout this literature review, studies that achieved a Jadad score of between 4 and 5 and a SIGN score above 16 are referred to as good quality; studies that were scored 3–4 on the Jadad scale and 10–15 on the SIGN checklist are referred to as being of moderate quality; and studies that scored 1–2 on the Jadad scale and below 10 on the SIGN checklist are referred to as being of low quality. To achieve a grading of high quality a study was required to have outlined appropriate methods for randomisation, blinding and allocation concealment; used equivalent populations and treated them in the same manner, aside from the intervention of interest; reported on withdrawals from the study; and used intention to treat analysis. Appendix 2 provides a tabulated summary of methodological appraisal of included RCTs, together with their quality scores.

Appraisal of other evidence
Literature reviews and other lower levels of evidence included in this report were considered by the two independent reviewers to be of sufficient quality, given the lack of evidence in this field. Consideration was given to the rigour of literature searching, selection of references, the author’s background (where known) and peer review.

Data extraction
The reviewers used the NHMRC RCT data extraction tool and the Joanna Briggs Institute data extraction tool for SRs to extract data from the included studies in a systematic manner. A table developed for this literature review was used to compile data from opinion papers and commentaries. A second reviewer checked data extraction for accuracy. Appendices 3 and 4 provide a tabulated summary of the findings extracted from each included paper.

SEARCH RESULTS
The initial search identified 120 diagnosis papers and 229 management papers that would potentially meet the review inclusion criteria. Two reviewers independently reviewed the titles and abstracts and identified those studies relevant to this literature review. Studies not selected included RCTs that were reviewed in included SRs, studies on interventions unavailable in Australia, studies not related to populations with JIA, and unreferenced reviews.

Two SRs and six papers reporting on five RCTs met inclusion criteria for the final review. Six papers of lower level evidence were used to provide evidence in areas where no higher level evidence was available. Table 2 provides a summary of the types of papers included in this review and the topics on which they provided evidence. For those studies excluded from the review during the critical appraisal stage, reasons for exclusion are outlined in Appendix 5.
Table 2. Summary of included studies in the literature review

<table>
<thead>
<tr>
<th>Intervention</th>
<th>SR/MA</th>
<th>RCT</th>
<th>Other studies</th>
<th>Literature review</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis of JIA</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>4</td>
</tr>
<tr>
<td>Care management/multidisciplinary care</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>3</td>
</tr>
<tr>
<td>Nutritional monitoring/calcium</td>
<td>-</td>
<td>3</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>Land based physical exercise</td>
<td>-</td>
<td>1</td>
<td>-</td>
<td>2</td>
</tr>
<tr>
<td>Aquatic exercise</td>
<td>-</td>
<td>1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Custom foot orthotics</td>
<td>-</td>
<td>1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Splinting</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Alternative physical therapies</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>Paracetamol</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>4</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>DMARDs</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>Weak/strong opioids</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Corticosteroid therapy</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>4</td>
</tr>
<tr>
<td>Biological modifying agents</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Surgical interventions</td>
<td>-</td>
<td>-</td>
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<td>-</td>
</tr>
</tbody>
</table>

EVIDENCE FOR THE DIAGNOSIS OF JIA

A range of evidence was found that addressed the review question regarding diagnosis of JIA. The evidence described below has been presented in tabulated format in Appendices 3 and 4.

Patient history and clinical examination

The literature search identified a USA clinical practice guideline on the management of JIA. The guideline was developed through a consensus process by professionals from a broad range of health care disciplines, as well as family members of children with JIA, and was supported by relevant references. This clinical practice guideline suggested that diagnosis of JIA should be based on a comprehensive patient history and clinical examination, with use of diagnostic tests to assist in differential diagnosis. The clinical practice guideline recommended taking a complete history with full description of symptoms. According to the guideline, consideration should be given to:

- the severity, onset, timing, and duration of pain, as well as aggravating and alleviating factors (eg. pain from JIA is often worse in the morning and after periods of inactivity)
- decrease in activity/avoidance of physical activity related to pain symptoms
- presence or absence of stiffness after inactivity
- persistent or worsening loss of function (eg. regression in physical skills)
• interference with activities of daily living, play, sports, and school
• any previous treatment that may have been used to manage symptoms and their efficacy.\(^6\) (Consensus practice guideline)

The clinical practice guideline outlined the following considerations in appropriate physical examination:

• range of motion in all joints (including temporomandibular joint, neck)
• presence of joint swelling
• presence of bony overgrowth
• muscle atrophy and/or weakness around involved joints
• signs or symptoms of significant trauma
• fever, especially characterised by a duration of more than 10 days without apparent cause or associated with a transient erythematous rash.\(^6\) (Consensus practice guideline)

In an extensive literature review that did not outline the search strategy or inclusion criteria, the importance of disease history and clinical examination in a diagnosis of JIA were highlighted. The authors suggested that a comprehensive patient history include the following:

• recent systemic illness and any preceding infections
• duration of any fever and rash
• characteristics of arthritis such as early morning stiffness, pain (at rest, at night, during activity)
• sexual history to rule out gonococcal arthritis
• sleep history, and
• vaccination history (in preparation for methotrexate therapy).\(^7\) (Literature review)

The literature search identified a review outlining the diagnosis and management of JIA within the Australian health care context. Written by Australian paediatric experts, this literature review supported other opinion regarding the importance of a comprehensive patient history and clinical examination in the diagnosis of JIA.\(^8\) (Literature review)

### Diagnostic investigations

One literature review reported relevant textual and research papers relating to the diagnosis, prognosis and management of JIA. Data from studies of various designs was included, although no critical appraisal of the study methods was conducted. This literature review reported that there is no specific test for diagnosis of JIA. Rheumatoid factor (RhF) and antinuclear antigen (ANA) screening tests should be conducted; however, children with infection or other pathology may have positive results, and these tests should not be used as a conclusive diagnosis of JIA. A full blood count (FBC) may show anaemia, raised white cell count, and platelet count consistent with inflammation. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) may also be elevated in children with JIA. Plain X-rays may be used to exclude trauma, malignancy or infection; however, arthritic changes are unlikely to be detected until late in the disease course.\(^9\) (Literature review)
A consensus clinical practice guideline on the management of JIA concurred that JIA cannot be diagnosed or confirmed by laboratory testing; however, some laboratory results may be useful in differential diagnosis. The guideline suggested that the following investigations may be helpful in excluding other diagnoses, and that their use should be guided by findings in history taking and clinical examination:

- ANA
- ESR
- FBC
- RhF
- CRP
- synovial fluid analysis, including bone marrow aspirate and biopsy
- plain X-rays.\(^6\) (Consensus practice guideline)

In one literature review, the authors suggested that the following diagnostic investigations may be relevant to assist in differential diagnosis:

- ANA
- liver and spleen enzymes
- synovial fluid examination and culture to exclude septic arthritis in patients with acute fever onset
- lyme serology (ELISA and immunoblot assays)
- varicella levels (in preparation for methotrexate therapy).\(^7\) (Literature review)

An Australian review reported on investigations currently used to assist in diagnosis of JIA. Plain X-rays may be used to exclude differential diagnosis (eg. bone infection, malignancy, trauma), although arthritic changes are unlikely to occur in early disease. Ultrasound, Doppler or magnetic resonance imaging (MRI) may be used to investigate other structures of the joint (eg. cartilage, blood flow) to assist in diagnosis. The following laboratory tests are often used to exclude differential diagnoses and to determine subset of JIA and risk of complications (eg. uveitis):

- FBC
- CRP
- ESR
- RhF
- ANA
- HLA B27 antigens
- anti-keratin (fillagrin) antibodies
- anti-cyclic citrullinated peptide antibodies.\(^8\) (Literature review)

**EVIDENCE FOR GENERAL CARE PRINCIPLES IN THE MANAGEMENT OF JIA**

**Paediatric rheumatology referral and multidisciplinary care**

In a well supported literature review drawing on textual and research studies, the experts proposed that input from a large multidisciplinary team is beneficial in the ongoing management of JIA. Early recognition and aggressive treatment of disease is likely to reduce the risk of many of the complications of JIA, therefore early referral to a paediatric rheumatologist or specialist is essential. Patients with JIA are likely to benefit from the input of a wide range of health care professionals, including (but not limited to) physiotherapists,
occupational therapists, podiatrists or orthotists, specialist nurses, community nursing teams, mental health workers, social workers, ophthalmologists, dentists, orthopaedic surgeons, and pain management teams. The GP has an ongoing role in providing appropriate referral and optimising communication between care providers.  

A clinical guideline supported the opinion that prompt referral to a paediatric rheumatologist is highly recommended to confirm diagnosis and initiate aggressive early management in children suspected of having JIA. Other health professionals including but not limited to physical and occupational therapists, social workers, psychologists, paediatric orthopaedists, ophthalmologists and rheumatology nurses should also be involved in the ongoing care of the child. The GP has a role in optimising communication between health professionals, the child and the child’s family. (Consensus clinical practice guideline)

**Ongoing monitoring**

One well supported literature review highlighted the importance of ophthalmology referral in the ongoing monitoring of disease complications arising from JIA. The authors reported that uveitis (inflammation of the uvea layer within the eye) occurs in 21% of patients with oligoarthritis JIA and 10% of polyarthritis JIA patients, being most common in girls who are ANA positive. Patients are usually asymptomatic, therefore regular screening by an ophthalmologist is recommended to reduce the risk of complications including glaucoma, cataracts, visual impairment, band keratopathy and posterior synechiae. The following risk based screening schedule is recommended:

- patients with oligoarthritis or polyarthritis who have +ve ANA and disease onset before 7 years of age: 3–4 monthly screening
- patients with oligoarthritis or polyarthritis who have +ve ANA but disease onset at 7 years of age or over: 6 monthly screening
- patients with oligoarthritis or polyarthritis who have -ve ANA: 6 monthly screening
- patients with systemic arthritis: annual screening. (Literature review)

**Psychosocial and educational support**

A consensus clinical practice guideline highlighted the relevance of psychosocial interventions to children with JIA and their families. The guideline prompted GPs to give consideration to:

- patient/family education
- psychosocial interventions/support services
- community resources, and
- school based resources. (Literature review)

A literature review outlining the management of JIA within the Australian health care context supported the above guideline and also recommended patient education and referral to psychosocial and support services for patients with JIA and their families. (Literature review)
EVIDENCE FOR NON-PHARMACOLOGICAL INTERVENTIONS FOR THE MANAGEMENT OF JIA

A range of evidence was found that addressed the review question regarding management of JIA. Evidence on non-pharmacological management strategies for JIA is presented below, and in tabulated format in Appendices 3 and 4.

Nutritional monitoring, dietary calcium and calcium supplementation

Nutritional monitoring

One review discussed the importance of nutritional monitoring in the management of JIA due to the increased risk of growth disturbance and delayed puberty. The authors recommend using dietary guidelines for healthy children based on gender and age when conducting nutritional assessment in children with JIA. The literature suggested that children with JIA are at increased risk of osteoporosis and osteopenia (especially related to corticosteroid therapy), and that management should include encouraging an appropriate caloric and calcium intake.7 (Literature review)

Dietary calcium intake

A moderate quality single blind RCT reported on the effectiveness of an educational and behavioural intervention in increasing dietary intake of calcium and improving overall BMD in children with JIA. Sixty-five families with a child aged 4–10 years (mean age 6 years) with a diagnosis of JIA consistent with ACR criteria were selected for inclusion in the study. Children taking oral calcium supplements or systemic corticosteroids were excluded from participation. Families were randomised to either the behavioural intervention group or the comparator group receiving enhanced standard of care (ESC). The behavioural intervention consisted of a family education program (separate parent and child groups) in which increasing calcium in a specific meal (eg. snacks, lunch, breakfast) was the focus for each of six sessions conducted over an 8 week period. The ESC group received three educational sessions over 8 weeks consisting of dietary advice and work with food diaries. In addition, all participants received baseline care consisting of education on increasing calcium to an ideal daily intake of 1500 mg/day. The active phase of the study lasted 8 weeks, and follow up was conducted at 6 and 12 months. The primary outcome measure was mean calcium intake. Secondary outcomes were change in vitamin D levels, change in total body bone mineral content (BMC) and change in BMC of arms/legs and lumbar spine.10,11

Using repeated ANOVA to measure changes in dietary calcium over time, with mean changes adjusted for age, height, gender and number of inflamed joints, no significant differences were observed in vitamin D levels between groups or over time. Children in both groups achieved a mean increase in calcium intake and maintained mean calcium levels above the recommended intake of 1500 mg/day compared to baseline after the 8 week intervention. This effect was sustained at 6 and 12 months. Mean calcium intake at 6 months was 1586 mg/day (54% of children ≥1500 mg/day) for the children in behavioural intervention compared to 1395 mg/day (25% of children ≥1500 mg/day) for those in ESC. At 12 months the behavioural intervention group maintained a mean calcium intake of 1547 mg/day (48% of children ≥1500 mg/day) compared to 1351 mg/day (35% of children ≥1500 mg/day) for the ESC group. These results were significant in favour of the behavioural intervention (F-test=14.39, p<0.001). The behavioural intervention was also found to have improvements on BMC at both 6 and 12 months compared to ESC. At 6 months the mean change from baseline in total BMC was 12.0% (±0.9%) for the behavioural intervention group while the mean change for the ESC group was 8.0% (±0.9%). At 12 months change from baseline in total BMC was 19.5% (±0.9%) for the behavioural intervention group and 16.1% (±0.9%) for the children randomised to the ESC group. These results translated to a 4% difference between groups at 6 months and a 2.9% difference with respect to total body BMC. The
findings for change in the BMC of arms and legs were similar; however, no significant differences were observed between the groups for lumbar spine BMC (see Appendix 2).10,11

Only 38% of eligible families agreed to participate, with significant differences between families who were consenting and those who declined to participate. Although a wide range of reasons were given for non-participation, parents who declined were more likely (F-test=4.63, p<0.05) to have an older child (mean=7.38 years ±2.06) than those who joined the study (mean=6.29 years ±1.95). In addition, children participating in the study were taking more medications than those who declined participation (2.94 ±1.73 vs. 1.31 ±0.22, F-test=10.15, p<0.01). Participants in the study were from English speaking backgrounds and were not currently taking oral calcium supplements or systemic corticosteroids. The findings from this study suggested that recommended daily calcium intake may be achieved through targeted behavioural intervention programs without nutritional supplements for some children with JIA; however further research is required on the effectiveness of this intervention for older children, those from different cultural backgrounds and those taking corticosteroids.10,11 (Level 2 evidence)

Calcium supplementation

A good quality double blinded RCT presented evidence on the effectiveness of calcium supplements in improving BMD in children with JIA compared to placebo. One hundred and ninety-eight children with JIA aged 6–18 years (mean age 11 years) were recruited to participate in the 24 month study. Children were ineligible for inclusion in the study if they were already taking a calcium supplement; had received systematic glucocorticoids in the 3 months before the study; were taking oral contraceptives; were smokers; were currently or previously pregnant; had another chronic illness known to effect bone mineralisation; or had a fasting random urine calcium:creatinine ratio of greater than 0.2. Participants meeting the inclusion criteria were primarily Caucasian females and had been diagnosed with any type of JIA using ACR criteria. Participants were randomised to either the intervention group receiving a 1000 mg oral calcium supplement (n=103) or to the control group receiving an oral placebo (n=95). These were administered daily for 24 months with a multivitamin capsule containing 400 IU vitamin D. Through random group allocation the intervention group included significantly more female participants (p=0.004). The primary outcome measure of total body BMD was measured at baseline, 6 months, 12 months and at completion of the trial (24 months). Adherence to the study regimen was determined through pill count.

During the 2 year study period, 28% of participants dropped out of the study, with no differences in the rate of dropout between the intervention and control groups (68 vs. 76% completion rate). Dropouts were not included in statistical analysis. At the end of the trial, mean total body BMD for the patients taking calcium supplements was 0.95 gm/cm² (±0.13, 6.7% increase from baseline) compared to 0.92 gm/cm² (±0.14, 5.8% increase from baseline) in the group taking placebo. When adjusted for age, disease state, adherence to regimen, height, and baseline total body BMD, there was a small but significant difference of 1% (p=0.03) in favour of calcium supplements. No adjustments were made for the between group gender imbalance, and any potential impact on the results was not included in the study discussion. Adherence to the calcium supplement intervention was reported as high, and only three patients in the intervention group withdrew from the trial due to adverse effects (nausea). This good quality RCT provided evidence that taking daily calcium supplements (1000 mg in conjunction with 400 IU vitamin D) for 24 months had a small positive effect above placebo on total body bone mass density in patients aged 6–18 years diagnosed with any type of JIA.12 (Level 2 evidence)

Land based physical exercise

One moderate quality RCT compared high intensity aerobic training with low intensity training in the management of children with JIA. Eighty children aged 8–16 years (mean age 11
years) were recruited for participation in this single blinded study conducted at 20 different exercise locations. Children who had significant cardiac, pulmonary or metabolic illness or moderate to severe hip pain on ambulation were excluded from participation, as were those already participating in more than 3 hours per week of physical (excluding aquatic) activity and those unable to participate in training or testing components of the protocol. Participants were randomised to receive either the high intensity exercise program (n=37) or the low intensity exercise program (n=37), both of which consisted of a 30 minute supervised exercise session and two 30 minute unsupervised, video assisted sessions each week for 12 weeks. The high intensity program consisted of a warm up period, cardiac exercise (dance and karate) and passive stretching, while those in the low intensity group participated in non-aerobic tai chi. Participants maintained their regular medication regimens and adjunct therapies throughout the study (details not reported). Primary outcome measures, taken by blinded assessors at baseline and within 2 weeks of completion of the intervention, included peak oxygen uptake (VO2peak measured in mL/kg/min); ROM assessed using the Pediatric Escola Paulista de Medicina Range of Motion scale (EPM scale); function measured on the self reported CHAQ; and health related quality of life (HRQOL) measured on a 10 cm VAS.

Six participants dropped out of the study (the main reason given was lack of time to participate) and their results were included in the per protocol analysis. Although both groups were offered incentives (eg. stickers) for adherence to the exercise regimen, adherence was greater in the low intensity exercise group (78 vs. 56%). Results for participants who adhered to at least 70% of the exercise regimen showed that after 12 weeks there was no difference between the groups on any outcome measures – VO2peak (between group p=0.80), ROM (between group p=0.35), CHAQ (between group p=0.80) and HRQOL (between group p=0.55). The only significant within group improvement in outcome measures was for the self reported CHAQ (mean difference –0.12, p<0.0001); however this finding may have been related to the Hawthorne effect or the incentive program. The study period may have been too short to achieve significant results, or the 2 week delay between completion of program and outcome measurement for some participants may have influenced the findings (changes may not have been sustained). No participants experienced adverse events or had worsening in outcome measures including HRQOL and CHAQ, and there was no difference between the groups in low level pain reported during training sessions. Children with JIA in this study who received both low and high intensity exercise programs for 12 weeks experienced no significant improvements above their regular therapy.13 (Level 2 evidence)

One literature review reported on physical activity in children with JIA. After conducting a broad search of MEDLINE, the authors reported that there was limited relevant research. The studies selected for inclusion were not subjected to quality appraisal and there is minimal to no reporting of the study methods. The review reported findings from a meta-analysis of five studies (type unspecified) that relative peak oxygen was 21.8% lower in children with JIA than in healthy controls, suggesting a reduced aerobic fitness in children with JIA. Findings from the studies suggested that these differences were related to disease duration (signs of reduced aerobic fitness were more common in patients with disease duration >2 years) but not disease activity nor severity. Despite the finding that children with JIA have decreased aerobic fitness, other studies have found that there is no significant difference in participation in physical activity between children with JIA and healthy controls.14

The same review reported findings from seven small studies investigating the effect of physical activity (land or aquatic) on children with JIA. The findings suggested that participation in moderate physical activity for at least 6 weeks (1–3 exercise sessions/week) can improve both muscle function and aerobic fitness in children with JIA. The following points were the most important considerations in physical activity in children with JIA:

- children with JIA can participate in exercise without disease exacerbation
• participation in either a water or land based exercise program at least twice a week for at least 6 weeks may help to reduce disease symptoms and improve general exercise endurance
• land exercise may lead to greater improvements in muscle strength, performance on timed tasks, and functional status than aquatic exercise
• weight bearing exercise is needed to develop optimal bone width and density during childhood
• individualised and supervised resistance exercise appears to be safe and effective for children with JIA
• the choice of exercise may depend on the child’s specific needs and preferences, and
• children with mild disease should be able to participate in most sports with proper screening. However, highly competitive contact sports pose a potential risk for damage to the joint surface and growth plate and should be avoided during periods of active joint disease.14 (Literature review)

Another literature review recommended that patients with JIA commence a comprehensive rehabilitation program early to correct loss of function and prevent permanent disability from uneven muscle development, muscle contracture, decreased flexibility, growth retardation and osteoporosis. The following points were highlighted:

• passive ROM exercises, isometric exercises, positioning, aquatic exercise and tai chi are all appropriate exercises for children with JIA
• to achieve an increase in aerobic capacity exercise needs to be performed at a moderate intensity for at least 30 min/day, and
• customised weight resistance programs for 3 days per week may be implemented to increase muscle strength.15 (Literature review)

Aquatic exercise

One poor quality non-blinded RCT reported on the effectiveness of aquatic training programs for children with JIA. Inclusion criteria required that participants be diagnosed with JIA and had experienced a disease remission phase of no longer than 6 months since diagnosis. All 54 participants had received local and/or systemic arthritis related therapy consisting of NSAIDs and/or DMARDs and/or immunosuppressive medication and/or steroids in the 6 months before inclusion. Children excluded from the trial were those who had evidence of systemic disease (eg. fever, malaise, low haemoglobin), had been a recipient of a bone marrow transplant, had exercise contraindicated by the physician, and those who had no water confidence. Participants were randomised to either the intervention group receiving aquatic training (n=27) or the control group receiving standard care (n=27). The aquatic training program consisted of aerobic exercises and flexibility and intensity training in a heated pool, conducted for 1 hour per week (20 sessions in total) in a group setting by a physical therapist. The primary outcome measure was functional ability measured on the parent completed CHAQ and on the Juvenile Arthritis Functional Assessment Scale (JAFAS) that assesses time taken to perform activities. Secondary outcome measures were health related quality of life measured using the JIA Quality of Life Questionnaire (JAQQ); physical fitness assessed with a maximal exercise test and a submaximal 6 minute walking test (time taken to walk 8 m); and number of swollen and/or tender joints assessed by a physiotherapist. Outcome measures were assessed before study commencement, at 3 months and at completion of the 20 week training program.

No significant differences were found on any of the outcome measures between the control and the intervention groups at the 20 week follow up. There was a non-statistical trend for children participating in the aquatic training to have an improvement in functional ability (27 vs. 5%) and a non-statistical trend for the control group to have a decline in quality of life (– 15 vs. 0%). Although the differences were not statistical, the intervention group had a 55%
decline in swollen and tender joints while the control group experienced a 21% increase. Lack of significant findings in this study may be a result of the small size (insufficient power to detect change in outcome measures); selection of outcome measures; insufficient study length; or, as the researchers suggest, may reflect the limited trainability of children. There was only one withdrawal from the study by the time the training program had been completed. The low dropout rate suggested this exercise intervention was acceptable to children and their families. As there was no indication that the intervention has a negative impact on health status, aquatic training is a safe exercise intervention for children with JIA who are water confident. (Level 2 evidence)

**Custom foot orthotics**

One low quality RCT investigated the effectiveness of foot orthotics in pain reduction and improvement of mobility for children aged over 4 years diagnosed with JIA and with active disease. Forty-seven children (mean age 12 years, 7 months; SD=3.7) with a history of persistent ankle/foot pain; no foot osseous anomaly; no joint injection within the previous 6 months; no previous use of shoe inserts; the ability to walk 50 feet without assistive devices; and with a stable medication regimen were recruited for participation. After inclusion in the 3 month study, all participants received supportive athletic shoes with a medial longitudinal arch support and shock absorbing soles. The non-blinded participants were then randomised to one of three study groups – an intervention group wearing adjunct, custom made semi-rigid foot orthotics with shock absorbing posts (n=15); an intervention group wearing adjunct, ready made flat neoprene shoe inserts (n=12); or the control group that wore athletic shoes alone (n=13). Seven participants lost to follow up were not reported in the statistical analysis. Blinded examiners conducted outcome measurement at baseline and after 3 months of orthotic therapy. The primary outcome measures were activity, disability, and pain measured using the Foot Function Index (FFI), a tool reported as being validated only in adult populations. Additional outcome measures included pain intensity measured by the Paediatric Pain Questionnaire VAS; and PedsQL, a standard test (completed by patient and parent) used to subjectively evaluate the child’s quality of life. Analysis included within group change over time, and between group comparisons of relative change over time.

There were significant improvements in activity/function (F-test=7.77, p=0.002), ambulation speed (F-test=4.93, p=0.013) and pain reduction (VAS: F-test=5.40, p=0.009; FFI: F-test=4.41, p=0.019) in the treatment group using custom made orthotics compared to those using either ready made orthotics or supportive shoes alone, although participants in the other groups also experienced improvements in some outcome measures. No significant improvements were observed in any of the groups for quality of life outcome measures (self reported: F-test=2.07, p=0.143; parent reported: F-test=3.01, p=0.063). The researchers concluded that semi-rigid foot orthotics with shock absorbing posts tend to reduce pain and improve speed of ambulation and other functions in children with lower extremity JIA; however neither 95% CI nor clinical effect size were reported for this study and there is no discussion of the power of the sample size to detect clinically significant change in outcome measures. Both the short duration of the trial and the non-blinding of participants may also have influenced the findings. Adverse events were not reported; however no participants withdrew from the study due to pain or discomfort. (Level 2 evidence)

**Splinting**

One good quality SR reported on splinting and orthotics in the management of children with JIA. This review sought to investigate the role of any orthotic devices in improving function and range of motion and decreasing pain and disability. Following an extensive search of eight major databases for primary studies and SRs of primary studies, only three trials meeting the inclusion criteria were identified. All three trials were un-randomised, uncontrolled before/after intervention case studies with small numbers of participants (n<20).
No data was pooled in meta-analysis due to heterogeneous methodology. One study assessed the effectiveness of night Seton skin traction (axis of tibia) combined with a daytime modified Engen’s extension orthosis. Five participants aged 1–6 years with knee contractures of 10 degrees or more, ability to ambulate, no previous history of traction use, and no intra-articular corticosteroid treatment within the past 10 days were recruited for the study. After a 14 day baseline period with no intervention, the participants were exposed to the experimental treatment of traction applied at night to both legs for a minimum of 2 hours combined with an extension orthosis applied twice daily for 30 minutes during weight bearing. Participants participated in concurrent physiotherapy and received medication throughout the treatment phase. The treatment phase lasted until contractures were cured, or for a maximum of 10 weeks. The primary outcome measure was ROM and patients acted as their own controls, with outcome measures from the completion of therapy compared to those taken after the initial baseline period. Adverse events were not reported. While analysis showed that night traction resulted in a reduction in knee flexion contractures and an improvement in both active and passive ROM, the large potential for bias reduced the generalisability and applicability of, as well as confidence in, the findings.18

The other two studies reported in this SR compared ready made wrist splints (Tweeklon or Droitwich) with custom made orthoplastic splints. Results from these splinting trials were conflicting. The first study investigated the effectiveness of a ready made Camp Droitwich hand splint compared to a custom made orthoplast cock-up splint. Twelve children aged over 12 years with a diagnosis of JIA and a history of wrist pain for at least 12 months participated in the trial, with right and left hands randomly assigned to splint type. After a baseline period with no intervention, the assigned splints were worn as much as possible during the day and resting splints were worn at night for the 6 month intervention period. Outcome measures of ROM and dexterity were compared between baseline and intervention measurement points, and between splint types. The researchers reported that both splint types corrected loss of dorsiflexion and ulnar deviation and improved dexterity. In the second study the effects of a Tweeklon splint in managing JIA with severe wrist and carpal involvement was investigated in 20 JIA patients with severe wrist and carpal involvement and compared to the effects of a custom made Vitrathene splint. Patients wore one type of splint on each hand for a period of 3 months and outcome measures including metacarpal flexion, ulnar deviation, tissue swelling, grip strength and pain were compared between pre- and post-intervention. Both types of splints achieved some positive outcomes for some patients but neither splint corrected ulnar deviation. The conflicting results and large potential for bias in these small, uncontrolled case studies reduced the generalisability and applicability of, as well as confidence in, the findings.18

Participants in the three studies included in the SR experienced difficulties applying the splints; required physiotherapist assistance to maintain and fit devices; and reported discomfort, sweating and, in the case of one participant, a severe skin reaction. The reviewers concluded that, based on low level evidence, although splinting seems to have some effect, it appears to be highly dependent on the age of the child, the type of orthosis used and the location of the affected joint.18 (Level 1 evidence)

Alternative physical therapies

A literature review provided opinion on alternative physical therapies in the management of JIA. The authors reported that heat therapy may have an effect in decreasing joint rigidity, pain and muscle spasms and increasing joint flexibility, and proposed the use of heat (eg. warm showers) to manage early morning stiffness. Cold is proposed as a therapy that may relieve pain and/or inflammation through vasoconstriction; however, potential adverse events include cold urticaria, cryoglobulinaemia, Raynaud phenomenon, and protest from the child. The review suggested that massage may also have an effect in relieving pain, decreasing
anxiety, promoting relaxation and preventing adhesions in subcutaneous tissues, but does not provide supporting evidence.\textsuperscript{15} (Literature review)

EVIDENCE FOR PHARMACOLOGICAL INTERVENTIONS FOR THE MANAGEMENT OF JIA

A range of evidence was found that addressed the review question regarding management of JIA. Evidence on pharmacological management strategies for JIA is presented below, and in tabulated format in Appendices 3 and 4.

Simple analgesics – paracetamol

The literature search failed to identify any SRs, RCTs or other clinical trials on the use of paracetamol in the management of JIA between 2000 and 2007. Numerous low level evidence sources, including a consensus practice guideline and a literature review set within the Australian context, recommended paracetamol be used as first line therapy in the management of pain in JIA.\textsuperscript{3,7,15} (Literature reviews)

NSAIDs

A low quality SR of 34 studies reported on the effectiveness of various pharmacological regimens in the management of JIA. Fourteen of the included studies (some of which were good quality RCTs) investigated the use of various NSAIDs for patients under 16 years of age with arthritis (type of arthritis and method of diagnosis were not reported). In this review, patients were classified as responders or non-responders using either the ACR 30 or the outcome measures specified by the author. Many of the trials were not placebo controlled and did not use randomisation and/or blinding techniques and limited research was available on the effectiveness of the majority of NSAIDs reported. The effectiveness of aspirin was investigated in seven small trials (471 participants) that compared aspirin in doses of 50–100 mg/kg/day to other NSAIDs (diclofenac, ibuprofen, tolmetin, naproxen, sulindac, fenoprofen) or placebo (one trial) for between 2 and 24 weeks. The effectiveness of naproxen was investigated in eight trials (943 participants) that compared naproxen in doses of 5–15 mg/kg/day to other NSAIDs (aspirin, piroxicam, diclofenac, tolmetin, meloxicam, rofecoxib) for 4–52 weeks. The effectiveness of other NSAIDs was reported in small trials. In these trials participants receiving all forms and doses of NSAIDs achieved significant improvements in outcome measures and no individual NSAID was shown to have a clear advantage over others. No differences were reported in the safety profiles of individual NSAIDs; however the reporting on adverse events in this review was minimal.\textsuperscript{19} (Level 1 evidence)
DMARDs

A literature review stated that in the Australian health care context, initiating DMARD therapy is the responsibility of a paediatric rheumatologist. Early referral is important so that aggressive therapy can be initiated immediately.8 (Literature review)

A low quality SR reported on 14 trials of varying design that investigated the use of DMARDs, immunosuppressive medications or systemic corticosteroids for the treatment of arthritis in patients aged less than 16 years. Neither critical appraisal of included studies nor meta-analysis of study results were conducted as part of this review. Two RCTs investigated the effectiveness of oral methotrexate compared to placebo. In a double blind crossover trial, 88 participants with systemic arthritis or oligoarthritis with polyarthritis course received an 8 week course of oral methotrexate 15–20 mg/m²/wk preceded or followed by an 8 week placebo course. The primary outcome measure taken at 8 and 16 weeks was classification as responder or non-responder on ACR 30. The results for participants with systemic arthritis showed 25% were responders on ACR 30 following the oral methotrexate course, compared to 16% following the placebo course. For participants diagnosed with oligoarthritis, 48% were responders on ACR 30 after taking oral methotrexate, compared to 18% following the placebo course. In the second RCT, 127 participants diagnosed with any type of JIA and with at least three joints with active disease were randomised to receive either oral methotrexate 5 mg/m²/wk, oral methotrexate 10 mg/m²/wk, or placebo for 26 weeks. The primary outcome measure for this trial was classification as responder or non-responder on the Composite Index. The results showed 32% of participants receiving low dose oral methotrexate were classified as Composite Index responders ($p=NS$), compared to 65% of high dose methotrexate participants ($p=reported as significant$) and 36% of those taking placebo. Details of these trials were insufficient to determine the quality of study designs and methods. While the results suggested that oral methotrexate is effective in doses of 10 mg/m²/wk for patients with oligoarthritis with polyarthritis course, the volume of evidence on efficacy and safety was insufficient to reach any conclusions.19 (Level 1 evidence)

The review included results from two double blind RCTs on the effectiveness of sulfasalazine in the management of JIA. In the first trial, 69 participants with oligoarthritis or polyarthritis were randomised to receive sulfasalazine 50 mg/kg/day (maximum 2 g) or a daily placebo. After 24 weeks of therapy, 44% of participants taking sulfasalazine were responders on ACR 30 compared to 21% of the placebo group. Participants taking sulfasalazine were reported to have experienced a higher rate of adverse effects. In the second RCT, 33 participants with enthesitis related arthritis received sulfasalazine 30–60 mg/kg/day (maximum 2 g) or a daily placebo. After 26 weeks, 46% of those receiving sulfasalazine had a reduction in number of active joints (assessment tool not reported) compared to 42% from the placebo group. The volume of evidence on efficacy and safety of sulfasalazine in patients with JIA was both insufficient and conflicting, and no conclusions could be reached.19 (Level 1 evidence)

The review presented two RCTs that compared D-penicillamine to placebo. In a 26 week trial, 74 participants with oligoarthritis or polyarthritis received D-penicillamine 10 mg/kg/day or placebo. Of those taking D-penicillamine, 55% showed improvement on physician global scale compared to 28% of those who received the placebo. In a 52 week double blind RCT 162 participants with polyarthritis received either D-penicillamine 10 mg/kg/day, hydroxychloroquine 6 mg/kg/day or placebo. The primary outcome measure was classification as responder on non-responder, where a responder was a participant who achieved at least 25% reduction in active joints on the Composite Index and improvement on both the physician and patient global assessment. While 32% of those taking placebo were classified as responders, 42% of the D-penicillamine group were responders after 52 weeks of therapy (hydroxychloroquine, 30% responders). Insufficient details of these studies were presented to appraise quality of the design and methods; however there was limited support for the use of D-penicillamine therapy in JIA.19 (Level 1 evidence)
Corticosteroid therapy

Systemic corticosteroids

A low quality SR included one study that compared pulse intravenous (IV) methylprednisolone therapy to oral methylprednisolone for management of systemic arthritis. In this randomised open trial, 22 participants received either the IV regimen (IV methylprednisolone 5 mg/kg/day for 3 days then 2.5 mg/kg/day for 5 days, then oral methylprednisolone 1 mg/kg/day) or the oral regimen (oral methylprednisolone 1 mg/kg/day). At 26 weeks, 74% of those who received the IV regimen achieved a reduction in daily oral corticosteroid dose, compared to 34% of those taking the oral regimen. The small volume of evidence comparing systemic corticosteroid regimens in patients prevented any conclusions being reached.19 (Level 1 evidence)

An Australian review reported that due to well documented side effects and the requirement for weaning therapy, oral and parenteral corticosteroids should be avoided wherever possible. When used (eg. as bridging therapy while awaiting the effects of DMARDs or during an acute flare) they should be prescribed by a paediatric rheumatologist. Due to the increased risk of osteoporosis, calcium and vitamin D supplements should be considered during oral corticosteroid therapy.8 (Literature review)

Another review also recommended that calcium supplements of 1200–1500 mg/day administered with 400 units of vitamin D should be considered when the patient is taking a corticosteroid course due to increased risk of osteoporosis.7 (Literature review)

Intra-articular corticosteroid injections

A low quality SR reported results from three good quality double blind RCTs investigating the effectiveness of intra-articular corticosteroid injections in the management of oligoarthritis or polyarthritis in participants aged under 16 years. Participants were classified as responders or non-responders using either ACR 30 or the outcome measures specified in individual studies. Two studies comparing the effectiveness of long acting triamcinolone hexacetonide (TH) to triamcinolone acetonide (TA) over 24 months reported improvements in all participants, with longer lasting improvement reported in groups receiving TH. No meta-analysis was conducted to determine if the results were significant. A third study compared the effectiveness of TH to betamethasone in reducing knee circumference at 6 weeks in 23 participants with knee oligoarthritis. In this small study participants receiving triamcinolone hexacetonide reported an average reduction in knee circumference of 1.7 cm, while those receiving betamethasone reported an average increase in knee circumference of 1 cm (p=not stated). The studies reported in this review suggested that triamcinolone hexacetonide is more effective and has a longer effect than other forms of intra-articular corticosteroids; however this finding was based on a small volume of evidence and adverse events experienced by participants in these studies were not reported.19 (Level 1 evidence)

A number of literature reviews reported that intra-articular corticosteroids are an established treatment in the management of local joint inflammation in children with JIA that may contribute to a decrease in long term joint complications with fewer side effects than systemic corticosteroids. Intra-articular corticosteroid therapy should be prescribed by a paediatric rheumatologist and administered under sedation as a day case procedure. A regimen guideline of 3 monthly injections with a maximum of three injections per joint annually was proposed.6–9 (Literature reviews)

Topical corticosteroids

A literature review by Australian paediatric experts reported that there is currently no evidence of effectiveness of topical NSAIDs in the management of JIA.8 (Literature review)
Biological modifying agents

A low quality SR reported results from studies investigating the effectiveness of biological modifying agents in the management of JIA in participants aged less than 16 years. Two RCTs compared the effectiveness of IV immunoglobulin compared to placebo. In the first trial 19 participants with polyarthritis received either IV immunoglobulin (2 g/kg/month) or placebo. After 16 weeks, 80% of participants in the placebo group experienced a ‘flare’ (definition of flare not provided) compared with 20% of those receiving IV immunoglobulin. Participants in the second RCT (n=31) had a diagnosis of systemic arthritis. After 26 weeks, 50% of participants who received IV immunoglobulin (1.5 g/kg/month) displayed improvement measured by physician global assessment compared to 27% of those taking placebo. The findings of these small studies suggested that IV immunoglobulin may be effective in reducing symptoms from JIA. However, no critical appraisal or pooled meta-analysis was conducted, adverse events were not reported and there is insufficient research to reach conclusions regarding clinical use.19 (Level 1 evidence)

The SR reported results from a small double blind RCT (n=51) in which the effectiveness of subcutaneous etanercept in the management of polyarthritis was compared to placebo. At 16 weeks, 28% of participants who received twice weekly subcutaneous etanercept 0.4 mg/kg experienced a ‘flare’ (definition of flare not provided) compared to 81% of participants in the placebo group. Further data was not reported, therefore there is insufficient research on which to make conclusions on the effectiveness of this therapy.19 (Level 1 evidence)

DISCUSSION

Limitations of the review

Search limitations
The literature review builds on an existing review3 and presents the best evidence available up to January 2007. The search strategy did not include a search for grey literature (eg. conference proceedings), therefore publication bias may have occurred. However, experts in the field informed the methods of this review and identified any known recent research.

Interventions and studies included
Although an initial attempt was made to limit the evidence presented in this review to research meeting NHMRC Level 1 and Level 2 evidence, there was a paucity of high level evidence available. After an expanded search this review included lower levels of evidence such as previous literature reviews and consensus papers. As such, many of the interventions reported in this literature review are supported by only low level evidence.

Evidence that is presented relates to the diagnosis and care management of JIA and pharmacological and non-pharmacological interventions for management. No evidence was identified in the literature relating to surgical interventions; complementary/alternative physical therapies (eg. TENS, acupuncture); or vitamin, herbal or other medicinal therapies in the management of JIA.

Some of the pharmacological studies included in this literature review (as well as RCTs reported in SRs) were conducted or sponsored by pharmaceutical companies with interests in the intervention medication. This factor was considered in the critical appraisal process.
Implications for practice and research

The most recent evidence available on the management of JIA presented in this review supported the recommendations presented in *Juvenile idiopathic arthritis management guidelines (Provisional)*.³

Implications for practice

There was support from current best available evidence for the following considerations in the diagnosis and care management of JIA:

- early diagnosis through clinical examination and diagnostic investigations including ESR, CRP and FBC
- referral to a paediatric rheumatologist
- involvement of the multidisciplinary health care team
- individualised care planning, and
- ongoing disease monitoring including dietary (calcium) intake and regular screening for comorbidity.

There was support from current best available evidence for the use of the following non-pharmacological interventions in the management of JIA:

- patient education and psychosocial support
- increase in calcium intake, with consideration to calcium supplementation for some patients
- land based exercise
- individualised use of splints and foot orthoses for some patients, and
- thermotherapy.

There was support from current best available evidence for the following pharmacological interventions in the management of JIA:

- paracetamol, and
- oral NSAIDs.

The evidence presented in this literature review has been used to develop recommendations and clinical guidelines for Australian GPs to assist in the management of JIA. The companion documents to this literature review, *Clinical guideline for the diagnosis and management of juvenile idiopathic arthritis* (www.racgp.org.au/guidelines/juvenileidiopathicarthritis) and *Recommendations for the diagnosis and management of juvenile idiopathic arthritis* (www.racgp.org.au/guidelines/juvenileidiopathicarthritis/recommendations), provide graded recommendations for the use of the interventions supported by the evidence in this literature review, together with guidelines for their implementation.

Implications for research

There is a strong need for well conducted RCTs investigating interventions for JIA to provide a higher evidence base for the management of this condition. Many interventions lack any well conducted research and other interventions, particularly pharmacological studies, require larger, more robust trials to determine the efficacy and safety of various pharmacological management options.
ACKNOWLEDGMENTS

This literature review was supported by the RACGP and the Australian Department of Health and Aging. The following experts were involved in the development of the review as part of the RACGP JIA Working Group: Dr Jane Munro (Chair), Dr Shane Brun, Dr Morton Rawlin, Ms Pam Webster (consumer representative), Professor Karen Grimmer-Somers (NHMRC advisor), Amy Jasper, Dr Jiri Rada, and Emily Haesler.

REFERENCES


## APPENDIX 1. CRITICAL APPRAISAL OF SYSTEMATIC REVIEWS

### Pharmacological management studies

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<th>Review</th>
<th>Types of studies</th>
<th>Methodology</th>
<th>Outcomes measures</th>
<th>Analysis performed</th>
<th>ES and 95% CI</th>
<th>Comments</th>
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<tr>
<td>Hashkes et al., 2005&lt;sup&gt;19&lt;/sup&gt;</td>
<td>34 RCTs (28 double blind): 14 NSAIDs, 14 DMARDs, or immunosuppressive medications or systemic corticosteroids; three IA corticosteroid; three biological modifying agents. Also CCTs, case control and case series, with any uncontrolled trial requiring at least 10 participants for inclusion.</td>
<td>Searched MEDLINE, EMBASE and Cochrane Library from 1966 to 2005; search of conference proceedings, general search on common drugs; no critical appraisal process described.</td>
<td>Patients were classified as responders or non-responders using either of the following outcome measures: a) for post-1997 studies: validated consensus outcome measures of the ACR 30 b) for pre-1997 studies: outcome measure specified by author.</td>
<td>Tabulated and narrative summary. Insufficient similarity between trials for meta-analysis.</td>
<td>Not presented.</td>
<td>For most drugs presented in this review there was minimal research available. Many of the trials presented are not placebo controlled, have not used randomisation and/or blinding techniques, and no information is provided on the quality of the data. Only minimal results are presented.</td>
</tr>
</tbody>
</table>

### Splinting

<table>
<thead>
<tr>
<th>Review</th>
<th>Types of studies</th>
<th>Methodology</th>
<th>Outcomes measures</th>
<th>Analysis performed</th>
<th>ES and 95% CI</th>
<th>Comments</th>
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<tr>
<td>Muggli, 2002&lt;sup&gt;20&lt;/sup&gt;</td>
<td>Three before/after intervention case series.</td>
<td>Searched seven major databases; most searches for 2002 only. Included ‘best available evidence’ (defined as research that is least susceptible to bias).</td>
<td>Function, ROM, deformity, and pain.</td>
<td>Tabulated and narrative summary. Insufficient similarity between trials for meta-analysis.</td>
<td>Not presented.</td>
<td>The studies did not assess any effect on pain; however one study reported that pain was not a prominent feature.</td>
</tr>
</tbody>
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## APPENDIX 2. CRITICAL APPRAISAL OF RCTS

### Interventions to improve calcium intake

<table>
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<tr>
<th>Study</th>
<th>Random allocation</th>
<th>Follow up</th>
<th>ITT analysis</th>
<th>Comparable at baseline</th>
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<th>ES and 95% CI</th>
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<th>Jadad score</th>
<th>SIGN score</th>
<th>Quality</th>
<th>Comments</th>
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</thead>
<tbody>
<tr>
<td>Lovell et al, 2005</td>
<td>Computer generated block sequence.</td>
<td>68% calcium supplements 76% placebo group. No difference between groups.</td>
<td>No.</td>
<td>Significantly more females in calcium group (p=0.004).</td>
<td>Yes.</td>
<td>Double blind.</td>
<td>Total body BMD Calcium group Mean 0.95 gm/cm² (±0.13); 6.7% increase from baseline. Placebo group Mean 0.92 gm/cm² (±0.14); 5.8% increase from baseline. Significant in favour of calcium when adjusting for age, disease stage, adherence, height, baseline TB BMD and weight; p=0.03.</td>
<td>There was a high level of adherence to the treatment regimen over 24 months as determined through pill count. This study was only powered for 20% dropout and dropout exceeded this rate.</td>
<td>4/5</td>
<td>16/20</td>
<td>Good.</td>
<td></td>
</tr>
<tr>
<td>Stark et al, 2006 AND Stark et al, 2005</td>
<td>Computer generated block sequence.</td>
<td>78% behavioural intervention 73% standard care. No difference between groups.</td>
<td>No ITT analysis. No baseline data for at least half of the patients who withdrew.</td>
<td>Yes.</td>
<td>Yes.</td>
<td>Single blinded participants were not blinded due to nature of intervention.</td>
<td>Change in TB BMC Behavioural intervention group Base to 6 months: 114.7 g ±7.6; 12.0% (±0.9) change Base to 12 months: 165.6 g ±7.5; 19.5% (±0.9) change (p&lt;0.002, % p&lt;0.005 over time). ESC group Base to 6 months: 74.9 g ±7.7; 8.0% (±0.9) change Base to 12 months: 141.6 g ±7.5; 16.1% (±0.9) change.</td>
<td>Eligible families with older children were more likely to decline to be involved in this study; therefore the effect of this intervention on different age groups may not be the same. This intervention was limited to English speaking families of which more than 90% were Caucasian. The results may not be applicable to different cultural groups.</td>
<td>3/5</td>
<td>15/20</td>
<td>Moderate.</td>
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<tr>
<td>Stark, et al, 2006&lt;sup&gt;10&lt;/sup&gt; AND Stark et al, 2005&lt;sup&gt;11&lt;/sup&gt;</td>
<td>Mean serum 25-hydroxyvitamin D (ng/mL)</td>
<td>Mean calcium intake</td>
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<td><strong>Behavioural intervention group</strong>&lt;br&gt;Base: 32±10 (95% CI: 16–57)&lt;br&gt;6 months: 35±9 (95% CI: 19–51)&lt;br&gt;12 months: 37±8 (95% CI: 25–52)&lt;br&gt;(p&gt;0.05, within group and between group).</td>
<td><strong>Behavioural intervention group</strong>&lt;br&gt;Baseline: 972 mg/day (±372)&lt;br&gt;At 8 weeks: 1811 mg/day (±324) (92% of children ≥1500 mg/day)&lt;br&gt;6 months: 1586 mg/day (54% of children ≥1500 mg/day)&lt;br&gt;12 months: 1547 mg/day (48% of children ≥1500 mg/day)&lt;br&gt;(group x time variance F=14.39; p&lt;0.001).</td>
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<td><strong>ESC group</strong>&lt;br&gt;Base: 36±12 (95% CI: 20–60)&lt;br&gt;6 months: 35±13 (95% CI: 20–72)&lt;br&gt;12 months: 32±8 (95% CI: 22–52).</td>
<td><strong>ESC group</strong>&lt;br&gt;Baseline: 961 mg/day (±438)&lt;br&gt;At 8 weeks: 1281 mg/day (±358) (17% of children ≥1500 mg/day)&lt;br&gt;6 months: 1395 mg/day (25% of children ≥1500 mg/day)&lt;br&gt;12 months: 1351 mg/day (35% of children ≥1500 mg/day).</td>
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</table>

**Change in arms/legs BMC**
- **Behavioural intervention group**
  - Base to 6 months: 66.3 g ±4.3; 16.2% (±1.4) change
  - Base to 12 months: 95.4 g ±4.32; 27.0% (±1.4) change
  - (p<0.003, % p<0.0007 over time).
- **ESC group**
  - Base to 6 months: 39.5 g ±4.4; 9.1% (±1.4) change
  - Base to 12 months: 98.0 g ±4.5; 21.7% (±1.6) change.

**Change in lumbar spine BMC**
- **Behavioural intervention group**
  - Base to 6 months: 0.028 g ±0.004; 5.1% (±0.7) change
  - Base to 12 months: 0.037 g ±0.004; 3.8% (±0.8) change
  - (p<0.012, % p<0.19 over time).
- **ESC group**
  - Base to 6 months: 0.028 g ±0.004; 5.1% (±0.7) change
  - Base to 12 months: 0.037 g ±0.004; 3.8% (±0.8) change.
Physical exercise

<table>
<thead>
<tr>
<th>Study</th>
<th>Random allocation</th>
<th>Follow up at baseline</th>
<th>ITT analysis</th>
<th>Comparable at baseline</th>
<th>Comparable treatment</th>
<th>Blinding</th>
<th>ES and 95% CI</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Singh-Grewal et al., 2007</td>
<td>Block randomisation balanced for pubertal stage and degree of disability measured by Childhood Health Assessment Questionnaire (CHAQ).</td>
<td>78% control group, 56% treatment group.</td>
<td>ITT per protocol and also analysed on participants who adhered to &gt;70% of programs.</td>
<td>Both groups offered incentive for adherence (eg. stickers). Patients maintained medication regimens, which were not reported.</td>
<td>Assessors blinded. Participants not blinded due to nature of intervention.</td>
<td>Peak oxygen uptake (mL/kg/min) Control: baseline: 35.7 (±7.8); 12 weeks: 36.2 (±8.0) Intervention: baseline: 33.3 (±6.8); 12 weeks: 34.8 (±8.8) between group p=0.80. ROM (EPM score) Control: baseline: 0 (±0.1); 12 weeks: 0.1 (±0.4) Intervention: baseline: 0.1; (±0.1) 12 weeks: 0.1 (±0.2) between group p=0.35. CHAQ score Control: baseline: 0.32 (±0.45); 12 weeks: 0.21 (±0.35) Intervention: baseline: 0.34 (±0.49); 12 weeks: 0.22 (±0.37) between group p=0.80 Within group mean difference: −0.12, p&lt;0.0001. HRQOL 10 cm VAS Control: baseline: 8.3 (±1.9); 12 weeks 8.5 (±1.7) Intervention: baseline: 7.7 (±1.8); 12 weeks: 7.8 (±1.9) between group p=0.55.</td>
<td>Finding of improvement in self reported outcome measures may result from Hawthorne effect. The exercise regimen may not have been intensive enough to show significant improvement in the time frame.</td>
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<thead>
<tr>
<th>Jadad score</th>
<th>SIGN score</th>
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<tr>
<td>3/5</td>
<td>15/20</td>
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Quality Moderate.
## Aquatic fitness training

<table>
<thead>
<tr>
<th>Study</th>
<th>Random allocation</th>
<th>Follow up</th>
<th>ITT analysis</th>
<th>Comparable groups baseline</th>
<th>Comparable treatment</th>
<th>Blinding</th>
<th>ES and 95% CI</th>
<th>Comments</th>
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</thead>
<tbody>
<tr>
<td>Takken et al., 2003</td>
<td>Randomisation method not stated. Patients were stratified by disease subclass.</td>
<td>One dropout from training program</td>
<td>Yes.</td>
<td>Not reported.</td>
<td>Medication regimens or other treatments not reported.</td>
<td>Investigators and subjects blinded for previous measurements at each stage of evaluation; not blinded for group allocation.</td>
<td>Functional ability (CHAQ)</td>
<td>The study found no significant effect of an aquatic fitness training program in children with JIA. However, there was a trend toward improved joint status. Lack of improvements could be the result of a limited trainability of children.</td>
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<td>Functional ability (JAFAS)</td>
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<td>Health related quality of life (JAQQ)</td>
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<td>Swollen and tender joints</td>
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<td>Joint ROM (PEPM ROM)</td>
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<td>Physical fitness – peak oxygen</td>
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<td>Physical fitness – 6 metre walk</td>
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</table>

**ES and 95% CI**

**Comments**

**Jadad score**

**SIGN score**

**Quality**

**Low.**
### Custom foot orthotics

<table>
<thead>
<tr>
<th>Study</th>
<th>Random allocation</th>
<th>Follow up</th>
<th>ITT analysis</th>
<th>Compar- able groups baseline</th>
<th>Compar- able treatment</th>
<th>Blinding</th>
<th>ES and 95% CI</th>
<th>Comments</th>
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</thead>
<tbody>
<tr>
<td>Powell et al, 2005&lt;sup&gt;1&lt;/sup&gt;</td>
<td>No.</td>
<td>Yes.</td>
<td>Not stated.</td>
<td>Blinded assessors.</td>
<td>Pain (Paediatric Pain Questionnaire VAS 0–10) Group 1 (orthotics): baseline: 5.23 (SD 2.01); follow up: 1.32 (SD 1.30) Group 2 (inserts): baseline: 3.50 (2.42); follow up: 2.84 (2.88) Group 3 (shoes only): baseline: 4.74 (1.98); follow up: 2.82 (2.01) F-test (group by time)=5.40; df=2.37; p=0.009.</td>
<td>To reduce the placebo effect on the groups that received shoe inserts or orthotics, all patients were instructed that the three interventions had been shown to improve foot pain. The relatively short duration of the study is a potential limitation.</td>
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<td>Timed walk Group 1: baseline: 7.76 (1.25); follow up: 7.03 (1.12) Group 2: baseline: 7.40 (1.10); follow up: 7.98 (1.30) Group 3: baseline: 8.62 (2.45); follow up: 8.36 (2.44) F-test=4.93; df=2.37; p=0.013.</td>
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<td>Foot Function Index (FFI) – activity limitation Group 1: baseline: 26.15 (12.85); follow up: 8.54 (11.06) Group 2: baseline: 14.88 (14.33); follow up: 19.96 (19.73) Group 3: baseline: 24.23 (25.80); follow up: 27.92 (27.89) F-test=7.77; df=2.37; p=0.002.</td>
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<td>FFI – foot pain Group 1: baseline: 42.13 (20.86); follow up: 18.35 (17.05). Group 2: baseline: 31.48 (18.33); follow up: 30.46 (25.56). Group 3: baseline: 42.38 (21.05); follow up: 37.54 (25.47). F-test=4.41; df=2.37; p=0.019.</td>
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<td>FFI – disability Group 1: baseline: 40.27 (23.68); follow up: 15.60 (13.51) Group 2: baseline: 30.97 (18.85); follow up: 29.98 (25.26) Group 3: baseline: 37.08 (23.00); follow up: 34.15 (26.35) F-test=4.14; df=2.37; p=0.024.</td>
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<td>PedsQL physical functioning – self report Group 1: baseline: 56.39 (15.66); follow up: 71.88 (15.88) Group 2: baseline: 54.38 (15.04); follow up: 55.94 (17.46) Group 3: baseline: 50.78 (14.60); follow up: 59.78 (18.80) F-test=2.07; df=2.37; p=0.143.</td>
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<td>PedsQL physical functioning – parent report Group 1: baseline: 48.66 (19.45); follow up: 64.96 (19.92) Group 2: baseline: 52.81 (8.13); follow up: 55.31 (15.80) Group 3: baseline: 53.39 (17.50); follow up: 55.95 (13.97) F-test=3.01; df=2.37; p=0.063.</td>
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<th>Jadad score</th>
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<tr>
<td>2/5</td>
<td>10/18</td>
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</table>

Quality Low.
## APPENDIX 3. SUMMARY OF SYSTEMATIC REVIEWS

### Pharmacological management

<table>
<thead>
<tr>
<th>Review</th>
<th>Participants</th>
<th>Interventions tested</th>
<th>Comparator</th>
<th>Results including adverse effects</th>
<th>Conclusions – relevance of outcomes</th>
<th>SIGN score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hashkes et al, 2005</td>
<td>Patients aged 16 years or under with any form of arthritis (method of diagnosis not stated).</td>
<td>NSAIDs Drugs and doses trialled: Tolmetin 15–30 mg/kg, Aspirin 50–100 mg/kg, Naproxen 6.5–15 mg/kg, Ketoprofen 50 or 100 mg, Indomethacin 50 or 100 mg, Rofecoxib 0.3–0.6 mg/kg, Meloxicam 0.125–0.375 mg/kg, Diclofenac 2–3 mg/kg, Sulindac 50, 75, or 150 mg, Fenoprofen 900–1800 mg/m², Ibuprofen 30–40 mg/kg, Piroxicam 5, 10, or 15 mg.</td>
<td>Varied between trials, see results.</td>
<td>NSAIDS Diclofenac vs. aspirin vs. placebo. 2 week double blind RCT; 45 participants with all types of arthritis. Diclofenac 2–3 mg/kg: 73% improved on physician 4 point scale; aspirin 50–100 mg/kg: 50%; placebo: 27% improved; significantly fewer adverse effects in diclofenac group vs. aspirin. Tolmetin vs. aspirin. 12 week double blind RCT; 107 participants with all types of arthritis. Tolmetin 15–30 mg/kg: 25% improved in index of active joints; aspirin 50–100 mg/kg: 26% improved in index of active joints; similar adverse effects. Naproxen vs. aspirin. 16 week randomised double blind crossover trial (8 weeks each drug); 18 participants with unstated type of arthritis. Naproxen 6.5 mg/kg: 46% preferred by physician; aspirin 60 mg/kg: 27% preferred by physician; equal efficacy in 27% of patients. 24 week double blind RCT; 80 participants with oligoarthritis or polyarthritis. Naproxen 10 mg/kg: 39% improved in index of active joints; aspirin 75 mg/kg: 22% improved in index of active joints; more patients discontinued aspirin due to adverse effects. Sulindac vs. aspirin. 6 week randomised double blind crossover trial (3 weeks each drug); 30 participants with all types arthritis. Sulindac 50, 75, or 150 mg: 22% improved on physician global assessment; aspirin 1500, 2700, or 3600 mg: 25% improved on physician global assessment. Fenoprofen vs. aspirin. 12 week double blind RCT; 99 participants with all types of arthritis. Fenoprofen 900–1800 mg/m²: 62% improved on physician global assessment; aspirin 1500–3000 mg/m²: 63% improved on physician global assessment; more patients discontinued aspirin due to adverse effects.</td>
<td>Low quality SR of (some high quality) trials provided evidence that: - no individual NSAID has been shown to have a clear advantage over others - systemic corticosteroids are not disease modifying - there is decrease in synovial volume after intra-articular corticosteroid injections. The adverse effects are few and long acting triamcinolone hexacetonide is more effective and has a longer effect than other forms of injectable corticosteroids - the greatest efficacy of methotrexate was seen in patients with extended oligoarthritis; no significant effect was found in patients with systemic arthritis - there was limited to no support for the efficacy of hydroxychloroquine, oral gold, or D-penicillamine in the treatment of JIA - from a number of small, mostly uncontrolled trials, there were conflicting findings regarding the efficacy of sulfasalazine - there was insufficient research on many of the treatments presented in this review.</td>
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**NSAIDS continued**

**Naproxen vs. piroxicam**  
8 week randomised double blind crossover trial (4 weeks each drug); 47 participants with oligoarthritis or polyarthritis.  
Naproxen 15 mg/kg: 24% preferred by physician; piroxicam 5, 10, 15, or 20 mg: 26% preferred by physician.  
12 week double blind RCT; 26 participants with polyarthritis.  
Naproxen 12.5 mg/kg: 38% improved on physician global scale; piroxicam 5, 10, or 15 mg: 67% improved on physician global scale.

**Ketoprofen vs. indomethacin**  
4 week randomised double blind crossover trial (2 weeks each drug); 30 participants with all types of arthritis.  
Ketoprofen 50 or 100 mg: 25% preferred by patient; indomethacin 50 or 100 mg: 75% preferred by patient; no difference in adverse effects.

**Naproxen vs. tolmetin vs. diclofenac**  
8 week randomised double blind trial; 28 participants with oligoarthritis or polyarthritis.  
Naproxen 10 mg/kg: 89% no change or improved on physician global scale; diclofenac 2 mg/kg: 88% no change or improved on physician global scale; tolmetin 25 mg/kg: 86% no change or improved.

**Ibuprofen vs. aspirin**  
12 week double blind RCT; 92 participants with all types of arthritis.  
Ibuprofen 30–40 mg/kg: 79% improved on physician global scale; aspirin 60–80 mg/kg: 77% improved on physician global scale; more adverse effects in aspirin group.

**Naproxen vs. meloxicam**  
52 week double blind RCT; 225 participants with oligoarthritis or polyarthritis.  
Naproxen 10 mg/kg: 74% responders; meloxicam 0.125 mg: 77% responders on ACR 30; meloxicam 0.25 mg: 76% responders on ACR 30.

**Rofecoxib low dose vs. rofecoxib high dose vs. naproxen**  
12 week double blind RCT; 310 participants with oligoarthritis or polyarthritis.  
Rofecoxib 0.3 mg/kg (maximum 12.5 mg): 46% responders on ACR 30; Rofecoxib 0.6 mg/kg (max 25 mg): 54% responders on ACR 30; naproxen 15 mg/kg: 55% responders on ACR 30; only low dose rofecoxib group had significantly less gastrointestinal adverse effects.

**DMARDs or immunosuppressive medications or systemic corticosteroids**

**Intramuscular gold vs. D-penicillamine**  
50 week randomised open trial; 77 participants with oligoarthritis or polyarthritis.  
Intramuscular gold 0.7 mg/kg/injection: 59% had at least 50% improvement on physician global scale; D-penicillamine 10 mg/kg/day: 50% had at least 50% improvement on physician global scale.

**Hydroxychloroquine vs. Intramuscular gold vs. D-penicillamine**  
50 week randomised open trial; 72 participants with oligoarthritis or polyarthritis.  
Hydroxychloroquine 5 mg/kg/day: 71% had at least 50% improvement on physician global scale; Intramuscular gold 0.7 mg/kg per injection: 67% had at least 50% improvement on physician global scale; D-penicillamine 10 mg/kg/day: 67% had at least 50% improvement on physician global scale.

**D-penicillamine vs. placebo**  
26 week double blind RCT; 74 participants with oligoarthritis or polyarthritis.  
D-penicillamine 10 mg/kg/day: 55% improved on physician global scale; placebo: 28% improved on physician global scale.

**Sulfasalazine vs. chloroquine**  
26 week double blind RCT; 39 participants with oligoarthritis or polyarthritis.  
Assessed as improving based on four criteria: active joints, pain, morning stiffness, ESR, functional capacity.  
Sulfasalazine 20–30 mg/kg/day: 48% improved; chloroquine 3–4 mg/kg/day: 28% improved; more adverse reactions with sulfasalazine.

**Hydroxychloroquine vs. D-penicillamine vs. placebo**  
52 week double blind RCT; 162 participants with polyarthritis.  
Assessed on the Composite Index and considered a responder if assessed as having at least 25% reduction in active joints and improvement in physician and patient global assessment.  
Hydroxychloroquine 6 mg/kg/day: 30% responders; D-penicillamine 10 mg/kg/day: 42% responders; placebo: 32% responders.

**Azathioprine vs. placebo**  
16 week double blind RCT; 32 participants with all types of arthritis.  
Azathioprine 2–2.5 mg/kg/day: 41% improved by at least 25% in index of joints; placebo: 27% improved by at least 25% in index of joints.
### Oral gold vs. placebo

**26 week double blind RCT; 231 participants with all types of arthritis with at least three active joints.**
- Oral gold 0.15–0.2 mg/kg/day: 34% responders on Composite Index; placebo: 46% responders on Composite Index.

### Parenteral methotrexate low dose vs. high dose

**26 week randomised open trial; 80 participants with polyarthritis.**
- Parenteral methotrexate 15 mg/m²/wk: 6% responders on ACR 30; parenteral methotrexate 30 mg/m²/wk: 58% responders on ACR 30.

### Oral methotrexate low dose vs. high dose vs. placebo

**26 week double blind RCT; 127 participants with all types of arthritis with at least three active joints.**
- Oral methotrexate 5 mg/m² body surface area per week: 32% responders on Composite Index; oral methotrexate 10 mg/m² body surface area per week: 65% responders on Composite Index; significant effect only of methotrexate 10 mg/m².

### Pulse IV methylprednisolone therapy vs. oral methylprednisolone

**26 week randomised open trial; 22 participants with systemic arthritis.**
- Intravenous methylprednisolone 5 mg/kg per day for 3 days then 2.5 mg/kg/day for 5 days then oral 1 mg/kg/day: 74% had reduction in daily oral corticosteroid dose at 6 months; oral methylprednisolone 1 mg/kg/day: 34% had reduction in daily oral corticosteroid dose at 6 months; significantly less cumulative dose in initial IV group.

### Sulfasalazine vs. placebo

**24 week double blind RCT; 69 participants with oligoarthritis or polyarthritis.**
- Sulfasalazine 50 mg/kg/day, maximum 2 g/day: 44% responders on ACR 30; placebo: 21% responders on ACR 30; more sulfasalazine adverse effects.

### Intra-articular corticosteroid injections

#### Triamcinolone hexacetonide vs. triamcinolone acetonide

**24 month randomised, blinded assessment trial; 85 participants with oligoarthritis.**
- Responders were patients who had at least 60% decrease in articular score.
  - At 6 months: triamcinolone hexacetonide 1–40 mg/kg: 81% responders; triamcinolone acetonide 1–40 mg/kg: 53% responders.
  - At 12 months: triamcinolone hexacetonide 1–40 mg/kg: 67% responders; triamcinolone acetonide 1–40 mg/kg: 43% responders.
  - At 24 months: triamcinolone hexacetonide 1–40 mg/kg: 60% responders; triamcinolone acetonide 1–40 mg/kg: 33% responders.

#### Triamcinolone hexacetonide vs. betamethasone

**6 week double blind RCT; 23 participants with knee oligoarthritis.**
- Triamcinolone hexacetonide (no dose stated): –1.7 cm difference in knee circumference; betamethasone (no dose stated): +1.0 cm difference in knee circumference.

### Biological modifying agents

#### Intravenous immunoglobulin vs. placebo

**16 week double blind RCT; 19 participants with polyarthritis.**
- Intravenous immunoglobulin 2 g/kg/mth: 20% had a flare (definition of flare not provided); placebo: 80% had a flare.

#### Subcutaneous etanercept vs. placebo

**16 week double blind RCT; 51 participants with polyarthritis course.**
- Subcutaneous etanercept 0.4 mg/kg twice weekly: 28% had a flare (definition of flare not provided); placebo: 81% had a flare.
## Splints/orthotic management

<table>
<thead>
<tr>
<th>Review</th>
<th>Participants</th>
<th>Interventions tested</th>
<th>Comparator(s)</th>
<th>Results including adverse effects</th>
<th>Conclusions – relevance of outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muggli, 2002</td>
<td>Children with juvenile chronic arthritis, juvenile rheumatoid arthritis or juvenile idiopathic arthritis.</td>
<td>Use of ready made wrist splints and other orthotic devices.</td>
<td>Three before and after intervention case studies. No SRs or other higher level studies met the inclusion criteria.</td>
<td>None.</td>
<td>Night traction resulted in a reduction of knee flexion contractures with an improvement in active as well as passive range of motion. Ready made splints and custom made splints resulted in an improvement of dexterity. One study reported that both splints (Droitwich plus custom made) corrected ulnar deviation. Another study, which used the Tweeklon plus a custom made splint, reported no effect on ulnar deviation. The findings, which come from three before/after studies with a low level of evidence, are small, and although they suggest orthotics may have a role in management of JIA for some patients, the findings cannot be generalised to other children with JIA. To date, no clinical trials for splinting in JIA have been undertaken, and although splinting seems to have some effect, it appears to be highly dependent on the age of the child, the type of orthosis used, and the location of the affected joint. There is as yet no high level of evidence indicating the effectiveness of any type of orthosis in JIA.</td>
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**APPENDIX 4. SUMMARY OF RCTS**

### Interventions to improve calcium intake

| Study                      | Participants                                                                 | Interventions tested                                                                 | Comparator(s)                                                                                      | Outcome measures                                                                 | Results                                                                                       | Adverse events                                                                 | Conclusions – relevance of outcomes                                                                 |
|----------------------------|------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|
| Lovell et al, 2005         | 198 patients 6–18 years of age with JIA meeting ACR criteria. Mean age 11 years; primarily Caucasian females. | 1000 mg oral calcium supplement daily with one multivitamin tablet with 400 IU vitamin D for 24 months. | Oral placebo control daily with one multivitamin tablet with 400 IU vitamin D for 24 months. | Total body BMD.                                                                             | A relatively small difference (~1%) between the calcium and placebo groups improvement in total body BMD over 24 months occurred. | No serious adverse events reported. Study medication was discontinued due to nausea in three patients receiving calcium. | This good quality RCT provides evidence that daily calcium supplements (in conjunction with vitamin D) has a small, positive effect above placebo on total body BMD in patients aged 6–18 years diagnosed with any type of JIA. Some patients may experience nausea as a side effect. |
| Stark et al, 2006 AND Stark et al, 2005 | 65 families with a child aged 4–10 years with a diagnosis of JIA consistent with ACR criteria. Participants were from English speaking backgrounds and were not taking oral calcium supplements or systemic corticosteroids. Mean age 6 years (older children were more likely to decline to participate). | Behavioural intervention Six visits over 8 weeks; separate child and parent education groups focusing on a different meal in each session. Active phase 8 weeks, followed up at 6 and 12 months. | Enhanced standard of care (ESC) Three visits over 8 weeks consisting of dietary assistance and work with food diaries. Active phase 8 weeks, followed up at 6 and 12 months. Baseline care (both groups) aimed to increase calcium intake to 1500 mg/day, and included education on how to record and graph child’s intake; activity for children; and high calcium snack. Both groups received same nutritional information. | Total body bone mineral content (TB BMC) Arms/legs bone mineral content (AL BMC) Lumbar spine bone mineral content (LS BMC) Height and weight Vitamin D status. | No significant between group differences or over time in vitamin D levels. Behavioural intervention had greater increase in TB BMC than the control with a 4% difference between groups at 6 months and a 2.9% difference between groups at 12 months. A similar difference was observed for AL BMC with a 7.1% difference between groups at 6 months and a 5.3% difference between groups at 12 months. There was no significance between group differences for LS BMC. Those exposed to the behavioural intervention achieved between a 2.9% and 5.3% improvement in BMC 12 months after the 8 week intervention, depending upon the outcome measure. Children in both groups achieved increase in calcium and maintained average calcium levels above the goal intake of 1500 mg/day, maintaining this increase over the 12 month follow up period. | None reported. | This moderate quality RCT provides evidence that an educational program focused on improving dietary intake of calcium in children with JIA contributes to an increase in overall calcium intake and a corresponding improvement in BMC. The findings suggested that recommended daily calcium intake can be achieved without dietary supplement. Families with younger children with JIA were more prepared to participate in the interventions. |
### Custom foot orthotics

<table>
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<tr>
<th>Study</th>
<th>Participants</th>
<th>Interventions tested</th>
<th>Comparator(s)</th>
<th>Outcome measures</th>
<th>Results</th>
<th>Adverse events</th>
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</table>
| Powell et al., 2005    | 47 participants aged over 4 years diagnosed with JIA. Inclusion criteria: presence of active disease, history of persistent ankle/foot pain, no foot osseous anomaly, stable medication, no joint injection for <6 months, no previous use of shoe inserts and ability to walk 50 feet without assistive devices. 75% female; mean age 12 years 7 months (SD 3.7). | Group 1: Custom orthotics: custom made, semi-rigid orthotics with shock absorbing post.  
Group 2: Shoe inserts: pre-fabricated, ready made shoe inserts. | Group 3: Supportive athletic shoes with shock absorbing soles. | Pain intensity on Paediatric Pain Questionnaire VAS  
Timed walking  
Foot Function Index (FFI). | The group using the custom made orthotics had significant reductions in pain and disability levels, improvement in speed of ambulation and increased function. Semi-rigid foot orthotics with shock absorbing posts tend to reduce pain and improve speed of ambulation and other functions in children with lower extremity JIA. Children using prefabricated inserts or athletic shoes also showed improvements in outcome measures, although the findings for these groups were smaller than for the orthotics group. Ready made shoe inserts and supportive athletic shoes are less able to perform the above functions. | No adverse effects were reported. |

### Physical exercise

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<th>Comparator(s)</th>
<th>Outcome measures</th>
<th>Results</th>
<th>Adverse events</th>
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</table>
| Singh-Grewal et al., 2007 | 80 patients with JIA aged 8–16 years. Exclusion criteria: cardiac, pulmonary or metabolic illness; moderate to severe hip pain on ambulation; already participating in more than 3 hours physical activity. | 12 week exercise program consisting of one supervised and two unsupervised (video assisted) sessions per week for 30 minutes (n=37). | 12 week exercise program consisting of one supervised and two unsupervised (video assisted) sessions per week for 30 minutes. Intervention was non-aerobic tai chi (n=37). | Sub-maximal oxygen uptake (VO2 submax) and heart rate measured after 5 minutes treadmill at 1.5 km/hr and at 3 km/hr.  
Peak oxygen uptake (VO2 peak) and heart rate measured after 6–10 minutes treadmill at 1.5 km/hr and at 3 km/hr.  
Range of motion on EPM scale.  
Function on CHAQ health related quality of life. | All groups achieved improvement in self reported physical function measured by CHAQ. Effect size not reported. NS differences in any outcome measures between groups. | No adverse events reported for any groups. No worsening of joint activity counts, CHAQ, QOL or HRQOL. No difference in low levels of pain reported in both groups during training sessions. |
### Aquatic fitness training

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<tr>
<th>Study</th>
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<th>Interventions tested</th>
<th>Comparator(s)</th>
<th>Outcome measures</th>
<th>Results</th>
<th>Adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Takken et al, 2003</td>
<td>54 patients diagnosed with JIA (EULAR criteria or ILAR criteria) with remission without medication of no longer than 6 months in the absence of joint pain, tenderness and/or morning stiffness and normal ESR. All patients had received a local and/or systemic arthritis related therapy consisting of NSAIDs and/or DMARDs and/or immunosuppressive medication and/or steroids in the last 6 months before inclusion.</td>
<td>Aquatic training (n=27): conducted in a group setting in a heated pool by a physical therapist. Sessions were for 1 hour/week for 20 sessions. Consisted of aerobic exercise, flexibility and intensity training. Heart rate monitoring used to assess training intensity.</td>
<td>Control group (n=27): regular care and assessment only.</td>
<td>Functional ability using CHAQ and JAFAS. Health related quality of life using JIA Quality of Life Questionnaire. Joint status assessed by a physiotherapist. Physical fitness: max exercise, and submax 6 minute walk test.</td>
<td>Although there was no significant effect of the intervention on functional ability, the experimental group improved 27% in CHAQ score, while the control group improved only 5%. There was also a trend for the control group to deteriorate in HRQOL. The number of swollen and tender joints decreased in the intervention group (−55%), while it increased in the control group (+21%); however the difference was not statistical.</td>
<td>None reported.</td>
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## APPENDIX 5. EXCLUDED STUDIES

<table>
<thead>
<tr>
<th>Paper</th>
<th>Type of study</th>
<th>Reason for exclusion</th>
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<tbody>
<tr>
<td>Wallen M, Gillies D. Intra-articular steroids and splints/rest for children with juvenile idiopathic arthritis and adults with rheumatoid arthritis. Cochrane Database Syst Rev 2006;1.</td>
<td>SR</td>
<td>None of the studies included in this review included participants with JIA.</td>
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