EXTENDED REPORT


Accepted 21 July 2003

Objectives: To update the EULAR recommendations for management of knee osteoarthritis (OA) by an evidence based medicine and expert opinion approach.

Methods: The literature search and guidelines were restricted to treatments for knee OA pertaining to clinical and/or radiological OA of any compartment of the knee. Papers for combined treatment of knee and other types of OA were excluded. Medline and Embase were searched using a combination of subject headings and key words. Searches for those treatments previously investigated were conducted for January 1999 to February 2002 and for those treatments not previously investigated for 1966 to February 2002. The level of evidence found for each treatment was documented. Quality scores were determined for each paper, an effect size comparing the treatment with placebo was calculated, where possible, and a toxicity profile was determined for each treatment modality.

Results: 497 new publications were identified by the search. Of these, 103 were intervention trials and included in the overall analysis, and 33 treatment modalities were identified. Previously identified publications which were not exclusively knee OA in the initial analysis were rejected. In total, 545 publications were included. Based on the results of the literature search and expert opinion, 10 recommendations for the treatment of knee OA were devised using a five stage Delphi technique. Based on expert opinion, a further set of 10 items was identified by a five stage Delphi technique as important for future research.

Conclusion: The updated recommendations support some of the previous propositions published in 2000 but also include modified statements and new propositions. Although a large number of treatment options for knee OA exist, the evidence based format of the EULAR Recommendations continues to identify key clinical questions that currently are unanswered.

Osteoarthritis (OA) is the most common form of arthritis in Western populations. It is characterised pathologically by both focal loss of articular cartilage and marginal and central new bone formation. OA of the knee, the principal large joint to be affected, results in disabling knee symptoms in an estimated 10% of people older than 55 years, a quarter of whom are severely disabled. The risk of disability attributable to knee OA alone is as great as that due to cardiac disease and greater than that due to any other medical disorder in the elderly. A recent World Health Organisation report on the global burden of disease indicates that knee OA is likely to become the fourth most important global cause of disability in women and the eighth most important in men. The annual costs attributable to knee OA are immense. There is therefore a burden on health from both morbidity and cost. Radiographic evidence of knee OA in men and women aged over 65 is reported in 30% of subjects, around one third of whom are symptomatic. Annual arthroplasty rates in Europeans over the age of 65 vary from country to country but are of the order of 0.5–0.7 per 1000.

The aetiology of knee OA is multifactorial and includes both generalised constitutional factors (for example, aging, sex, obesity, heredity, reproductive variables) and local adverse mechanical factors (for example, trauma, occupational and recreational usage, alignment). There is a significant genetic component to the prevalence of knee OA, with heritability estimates from twin studies of 0.39–0.65 independent of known environmental or demographic confounders.

Knee OA is associated with symptoms of pain and functional disability. Physical disability arising from pain and loss of functional capacity reduces quality of life and increases the risk of further morbidity and mortality. Current treatments aim at alleviating these symptoms by several different methods:

- Non-pharmacological treatments (for example, education, exercise, lifestyle changes)
- Pharmacological treatments (for example, paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs), topical treatments)

Abbreviations: ES, effect size; HA, hyaluronic acid; NSAIDs, non-steroidal anti-inflammatory drugs; OA, osteoarthritis; QS, quality score; RCT, randomised controlled trial; TKR, total knee replacement

www.annrheumdis.com
* Invasive interventions (for example, intra-articular injections, lavage, arthroplasty).

The objectives of management are to:
* Educate the patient about OA and its management
* Alleviate pain
* Improve function and decrease disability
* Prevent or retard progression of the disease and its consequences.

Current evidence to support the various treatments in current use, however, is very variable.

Guidelines on the management of knee and hip OA have been published by the Royal College of Physicians and the American College of Rheumatology. In 1998, EULAR commissioned a steering group to review the evidence for the treatment of knee OA. Recommendations for treatment were developed as a result of this evidence based review and presented in 2000. These guidelines, however, were restricted to a limited number of treatment modalities and only reviewed evidence up until December 1998. We therefore have updated the recommendations by extending the literature search to February 2002 and by including all treatments used in knee OA.

**METHODS**

**Membership of guidelines steering group committee**
The members of the expert committee on knee OA reconvened in November 2001 to establish the methodology in updating the evidence base and recommendations for the treatment of knee OA. The initiative, endorsed by ESCISIT, involved a committee of experts in OA (19 rheumatologists, four orthopaedic surgeons) and one research fellow from 13 European countries.
The aims of the committee were:
* To describe all the therapeutic modalities used in the treatment of knee OA and to review the current level of evidence attributable to each of these treatments
* To produce a list of 10 recommendations for the management of knee OA and to examine the degree to which these recommendations are supported both by research evidence and the consensus of expert opinion
* To specify 10 recommendations for the future research agenda for the management of knee OA.

**Evidence based review**

**Search strategy**
To maintain continuity from the previous search, Medline OVID and BIDS Embase were the databases searched systematically. The searches for those treatment modalities previously investigated were conducted for the period January 1999 to February 2002 and for those modalities not previously investigated from 1966 to February 2002. In the search strategy, all English and other European language publications in the form of systematic reviews, meta-analyses, randomised controlled trials (RCTs), controlled trials, and observational studies were included. Publications in non-European languages were excluded.

**Selection of manuscripts**
All trials that assessed the effects of a treatment for knee OA on pain and/or function were included. Thirty three such individual treatment modalities were identified; NSAIDs are divided into two subsets, conventional (non-selective) NSAIDs and COX 2 selective NSAIDs (coxibs), but overall recognised as one group (table 1). For the purpose of the review knee OA was defined as patients with clinical and/or radiological evidence of knee OA. Only papers exclusively studying knee OA were included at all stages of the analysis; those combining hip and knee OA were excluded. The previous literature search included papers combining hip and knee OA in its qualitative data; these were reviewed and if the results for hip and knee OA could not be separated from one another, the publication was rejected.

**Quality scoring of manuscripts**
The methodological design of each study was scored according to a predetermined proforma. This methodological checklist provided a quality assessment of the information provided by each individual publication, particularly addressing study design and methodology and the statistical power of each study. Studies were scored 0–1 for 26 questions and 0–2 for one question, giving a maximum total of 28. Power calculations were scored as 1 if present and 0 if absent. If probability values were reported in the results, a score of 1 was given and 0 if absent. A single assessor scored English language publications and a second assessor validated these scores in a blinded fashion. Non-English European language publications were assessed by individual members of the EULAR steering group committee fluent in the language of the publication. All quality scores were collected and recorded centrally.

**Estimation of a treatment effect size**
Quantitative analysis of treatment effect was assessed, where possible, by calculating the effect size (ES) for validated outcome measures of pain and function. A software package was used for this purpose. An ES is the standardised mean difference between a treatment group and a control group for an outcome variable—in this case, pain and function. It reflects the magnitude of difference between two groups in standardised terms and is free of units. The mean and distribution of values for the baseline placebo and active treatment, and end point placebo and active treatment, and difference from baseline to end point were tabulated for each of the outcome measures recorded.
The ES and data displayed in this paper in all cases are calculated against placebo. Clinically, an ES of 0.2 is considered small, 0.5 is moderate (and would be recognised clinically), and greater then 0.8 is large. All data were collected and recorded centrally.

**Categorising evidence**
Categories of evidence were adapted from the classification of the United States Agency for Health Care Policy and Research. Evidence was categorised according to study design reflecting susceptibility to bias. Table 2 shows the categories in descending order of importance. Questions posed by the recommendations were answered using the best evidence available. If, for example, a question could be answered by category 1 evidence then weaker design publications were not reviewed.

**Strength of recommendation**
The strength of recommendation for an intervention was graded A-D (table 3) by members of the editing subcommittee of the task force, after examination of the evidence in detail. The strength of recommendations is based not only on the level of evidence but also upon consideration of the following: the ES of the intervention; the side effect profile; the applicability of the evidence to the population of interest; practicality of delivery; and economic considerations. In this way the different treatments could be scored in a pragmatic manner more applicable to everyday clinical practice.

**Assessment by expert panel opinion**
Experts’ opinion approach
After informing the expert committee about the results of the literature search and the level of evidence found for each treatment modality, two sets of 10 recommendations were...
proposed following a five stage Delphi technique: (a) the final expert evidence and opinion based recommendations for treatment, and (b) recommendations for future research agendas.

Toxicity profile
Once the definitive list of the treatments and their level of evidence was communicated, the committee ranked the potential toxicity of each intervention. This was expressed as a 100 mm visual analogue scale, in which 0 was “not toxic at all” and 100 was “very toxic.” Figure 1 shows the results obtained.

It was felt by members of the panel after the initial opinion had been sought that the NSAID group should be subdivided into conventional NSAIDs and coxibs. This was therefore performed at a later meeting.

Level of evidence of the experts’ opinion approach
The researchers who undertook the literature search evaluated the level of evidence in order to answer the questions posed by the 10 recommendations for management of knee OA as proposed by the panel.

RESULTS
Evidence based approach
497 new publications were identified by the search strategy. Of these, 103 were intervention trials and therefore included in the overall analysis; 99 of these were intervention trials using at least one of the 33 treatment modalities identified, 3 were systematic reviews, and 1 was a meta-analysis. The previously identified publications were also reviewed and those that were not exclusively knee OA in the initial analysis were rejected. In total, 545 publications were included. Treatments that are no longer in use (for example, acetylsalicylic acid) were rejected. In total, 545 publications were included.

Table 1 Treatment modalities identified for the treatment of knee OA

<table>
<thead>
<tr>
<th>Category</th>
<th>Pharmacological</th>
<th>Intra-articular</th>
<th>Surgical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Education</td>
<td>Education</td>
<td>Corticosteroid</td>
<td>Arthroscopy</td>
</tr>
<tr>
<td>Exercise</td>
<td>Paracetamol</td>
<td>Hyaluronic acid</td>
<td>Osteotomy</td>
</tr>
<tr>
<td>Insoles</td>
<td>NSAIDs</td>
<td>Tidal irrigation</td>
<td>UKR</td>
</tr>
<tr>
<td>Orthotic devices</td>
<td>Opioid analgesics</td>
<td>TENS, spinal cord stimulation</td>
<td>TKR</td>
</tr>
<tr>
<td>Weight loss</td>
<td>SYSADOA</td>
<td>Topical NSAID</td>
<td>TKR</td>
</tr>
<tr>
<td>Laser</td>
<td>Psychotropic drugs</td>
<td>Acupuncture</td>
<td>Supplies</td>
</tr>
<tr>
<td>Spa</td>
<td>Topical NSAID</td>
<td>Vitamins/minerals</td>
<td>Telephone</td>
</tr>
<tr>
<td>Telephone</td>
<td>Topical capsacin</td>
<td>Pulsed EMF</td>
<td>Ultrasound</td>
</tr>
<tr>
<td>Telephone</td>
<td>Topical capsacin</td>
<td>Ultrasound</td>
<td>TENS</td>
</tr>
<tr>
<td>Telephone</td>
<td>Topical capsacin</td>
<td>TENS</td>
<td>Acupuncture</td>
</tr>
<tr>
<td>Nutrients</td>
<td>Nutrients</td>
<td>Nutrients</td>
<td>Nutrients</td>
</tr>
<tr>
<td>Herbal remedies</td>
<td>Herbal remedies</td>
<td>Herbal remedies</td>
<td>Herbal remedies</td>
</tr>
</tbody>
</table>

EMF, electromagnetic field therapy; TENS, transcutaneous electrical nerve stimulation; NSAIDs, non-steroidal anti-inflammatory drugs; SYSADOA, SYSmptomatic Slow Acting Drugs for OA (includes avocado/soybean unsaponifiables (ASU), chondroitin, diacerein and glucosamine); UKR, unicompartmental knee replacement; TKR, total knee replacement.

The researchers who undertook the literature search evaluated the level of evidence in order to answer the questions posed by the 10 recommendations for management of knee OA as proposed by the panel.

Toxicity profile
Once the definitive list of the treatments and their level of evidence was communicated, the committee ranked the potential toxicity of each intervention. This was expressed as a 100 mm visual analogue scale, in which 0 was “not toxic at all” and 100 was “very toxic.” Figure 1 shows the results obtained.

It was felt by members of the panel after the initial opinion had been sought that the NSAID group should be subdivided into conventional NSAIDs and coxibs. This was therefore performed at a later meeting.

Level of evidence of the experts’ opinion approach
The researchers who undertook the literature search evaluated the level of evidence in order to answer the questions posed by the 10 recommendations for management of knee OA as proposed by the panel.

RESULTS
Evidence based approach
497 new publications were identified by the search strategy. Of these, 103 were intervention trials and therefore included in the overall analysis; 99 of these were intervention trials using at least one of the 33 treatment modalities identified, 3 were systematic reviews, and 1 was a meta-analysis. The previously identified publications were also reviewed and those that were not exclusively knee OA in the initial analysis were rejected. In total, 545 publications were included. Treatments that are no longer in use (for example, acetylsalicylic acid) were rejected. In total, 545 publications were included.

Table 2 Categories of evidence

<table>
<thead>
<tr>
<th>Category</th>
<th>Evidence from:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1A</td>
<td>Meta-analysis of RCTs</td>
</tr>
<tr>
<td>1B</td>
<td>At least one RCT</td>
</tr>
<tr>
<td>2A</td>
<td>At least one controlled study without randomisation</td>
</tr>
<tr>
<td>2B</td>
<td>At least one quasi-experimental study</td>
</tr>
<tr>
<td>3</td>
<td>Descriptive studies, such as comparative, correlation or case-control studies</td>
</tr>
<tr>
<td>4</td>
<td>Expert committee reports or opinions and/or clinical experience of respected authorities</td>
</tr>
</tbody>
</table>

The researchers who undertook the literature search evaluated the level of evidence in order to answer the questions posed by the 10 recommendations for management of knee OA as proposed by the panel.

Table 3 Strength of recommendation

<table>
<thead>
<tr>
<th>Category</th>
<th>Directly based on:</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Category 1 evidence</td>
</tr>
<tr>
<td>B</td>
<td>Category 2 evidence or extrapolated recommendation from category 1 evidence</td>
</tr>
<tr>
<td>C</td>
<td>Category 3 evidence or extrapolated recommendation from category 1 or 2 evidence</td>
</tr>
<tr>
<td>D</td>
<td>Category 4 evidence or extrapolated recommendation from category 2 or 3 evidence</td>
</tr>
</tbody>
</table>
Assessment of the propositions

The propositions are ranked in order of importance as debated by the expert opinion panel.

1. The optimal management of knee OA requires a combination of non-pharmacological and pharmacological treatment modalities

Although this statement is logical and represents common clinical practice, there is little direct evidence from appropriately designed factorial RCTs to support this statement. There is, however, a wealth of indirect evidence from RCTs in which all subjects were receiving analgesics or NSAIDs at baseline that non-pharmacological treatments offer additional benefit over and above analgesic or NSAID usage. These have demonstrated that exercise programmes15(quality score (QS) 26), physiotherapy16 (QS 26), weight loss combined with exercise17(QS 21), education18 (QS 12), and wedged insoles19 20 (QS 10, 11) offer additional benefit when used with an analgesic or NSAID regimen. There is therefore a reasonable evidence base to support this statement (1B).

2. The treatment of knee OA should be tailored according to:

- Knee risk factors (obesity, adverse mechanical factors, physical activity)
- General risk factors (age, comorbidity, polypharmacy)
- Level of pain intensity and disability
- Sign of inflammation—for example, effusion
- Location and degree of structural damage.

This statement represents ideal practice and includes clinical markers that are often used to guide clinical decisions. Clinical trials predominantly investigate the efficacy of one or two specific monotherapies in highly selected homogeneous populations of otherwise fit subjects with knee OA. These data therefore are not directly applicable to the whole population of subjects with OA. Those studies that have examined the predictors of response to treatment often have limited statistical power, and therefore results are often inconclusive. An example is the presence of an effusion predicting a response to intra-articular steroids where two studies have shown conflicting results21 22(QS 22, 17). One RCT involving 84 patients confirmed short term symptom benefit of steroid over placebo and found a better outcome in those with an effusion. However, a randomised crossover study of methylprednisolone versus saline found no clinical predictors of response, suggesting that steroid injection should not be reserved just for those with effusion alone.

As well as the expected relative benefits, potential dangers and costs of the intervention must clearly be taken into account. This has relevance to both medical and surgical interventions. The holistic approach to the patient is universally accepted: it has obvious validity but no research based justification specific to knee OA.

3. Non-pharmacological treatment of knee OA should include, education, exercise, appliances (sticks, insoles, knee bracing) and weight reduction

Education and provision of information should form an integral part of the management of any chronic disease. This is a professional obligation and should include details of the disease, its investigations, and management. Practitioners should tailor any treatment to the individual needs of the patient and this concept can be discussed within education. Several large RCTs and a meta-analysis have demonstrated the benefits of different educational techniques in reducing pain and increasing coping skills, but with little impact on function in patients with knee OA.23 Education has also been shown to result in fewer visits to
primary care and therefore also has a cost implication. In a study of 211 patients with knee OA, 80% of the costs of delivering effective self care education were offset within a year by the reduced frequency and costs of primary care visits. Education techniques shown to be effective include individualised education packages (QS 12), regular telephone calls (QS 17), group education (QS 20), patient coping skills (QS 13), and spouse assisted coping skills training (QS 15).

There is evidence from large RCTs that joint-specific exercises reduce pain and improve function in patients with knee OA. However, the optimal exercise regimen has not yet been determined. Exercise can be divided into joint-specific strength and range of motion exercises and general aerobic conditioning and can be either directly supervised on land or water or offered as a home based, self directed programme. A two centre RCT of 439 older patients with knee OA demonstrated that the cumulative incidence of disability for activities of daily living was lower in both exercise groups (aerobic exercise and resistance exercise) than in a no-exercise control group (QS 24). The effectiveness of home exercise on knee OA has been explored in several RCTs, showing reduced pain scores and improved function (QS 26, 20, 19). No differences were found between a land based exercise programme and an aquatic programme, although both showed significant improvements in pain and function (QS 17). Importantly, some of these studies report long term improvements (6–18 months). ES for exercise ranged from 0.57 to 1.0.

One RCT in 119 patients demonstrated that the pain and function of patients with varus knee OA using a knee brace improved significantly compared with those who did not use a brace (QS 20). An RCT comparing laterally wedged insoles with neutrally wedged insoles showed no statistical difference between the two groups. However, the group using laterally wedged insoles had a greater reduction in NSAID use together with increased compliance (QS 25). Two controlled studies of insoles (QS 10, 11) demonstrated an improvement over an analgesic control group. A study of cross over within subjects suggested that the pain relief and improvement in function reported might be due in part to the reduced external varus moment and medial compartment load short term (QS 15). No RCTs have examined walking sticks or elastic bandage in the management of knee OA.

Application of an elastic bandage in 68 patients reduced knee pain significantly in a short term study of cross over within subjects (QS 20).

**Table 4** Summary of the effect size versus placebo, quality scores, and number of studies identified

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Number of studies</th>
<th>Positive to placebo</th>
<th>Quality score (range)</th>
<th>Quality score (median)</th>
<th>Effect size versus placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen/paracetamol</td>
<td>5</td>
<td>1/1</td>
<td>17–26</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Opioid analgesic/other</td>
<td>6</td>
<td>2/3</td>
<td>11–24</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>NSAID Conventional NSAID</td>
<td>130</td>
<td>27/31</td>
<td>5–27</td>
<td>17</td>
<td>0.47, 0.50, 0.76, 0.96,</td>
</tr>
<tr>
<td>Coxibs</td>
<td>5</td>
<td>4/4</td>
<td>18–25</td>
<td>23</td>
<td>0.50</td>
</tr>
<tr>
<td>Antidepressant</td>
<td>1</td>
<td>1/0</td>
<td>16</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Topical NSAID</td>
<td>9</td>
<td>5/7</td>
<td>18–26</td>
<td>22</td>
<td>-0.05, 0.16, 0.31, 0.91, 1.03</td>
</tr>
<tr>
<td>Topical capsaicin</td>
<td>2</td>
<td>2/2</td>
<td>21,26</td>
<td></td>
<td>0.41, 0.56</td>
</tr>
<tr>
<td>Sex hormones</td>
<td>2</td>
<td>0/1</td>
<td>15,20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SYSADAA Glucosamine</td>
<td>8</td>
<td>4/6</td>
<td>14–27</td>
<td>24</td>
<td>0.43, 0.53, 1.02</td>
</tr>
<tr>
<td>Chondroitin</td>
<td>5</td>
<td>5/5</td>
<td>20–27</td>
<td>24</td>
<td>1.23, 1.37, 1.44, 1.50</td>
</tr>
<tr>
<td>Diacerein</td>
<td>1</td>
<td>1/1</td>
<td>22</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>ASU</td>
<td>3</td>
<td>3/3</td>
<td>21–24</td>
<td>23</td>
<td>0.32, 1.72</td>
</tr>
<tr>
<td>Nutrients</td>
<td>2</td>
<td>2/2</td>
<td>4.25</td>
<td>-</td>
<td>0.65</td>
</tr>
<tr>
<td>Herbal remedies</td>
<td>5</td>
<td>3/3</td>
<td>14–27</td>
<td>20</td>
<td>0.23, 1.32</td>
</tr>
<tr>
<td>Minerals/vitamins</td>
<td>1</td>
<td>0/1</td>
<td>24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Education</td>
<td>7</td>
<td>3/3</td>
<td>11–15</td>
<td>13</td>
<td>0.28, 0.35</td>
</tr>
<tr>
<td>Exercise</td>
<td>40</td>
<td>8/9</td>
<td>5–26</td>
<td>15</td>
<td>0.57, 0.59, 1.0</td>
</tr>
<tr>
<td>Telephone</td>
<td>3</td>
<td>1/1</td>
<td>16–18</td>
<td>18</td>
<td>1.09</td>
</tr>
<tr>
<td>Acupuncture</td>
<td>6</td>
<td>2/2</td>
<td>11–22</td>
<td>16</td>
<td>0.25, 1.74</td>
</tr>
<tr>
<td>Laser</td>
<td>2</td>
<td>1/1</td>
<td>12,17</td>
<td></td>
<td>0.87</td>
</tr>
<tr>
<td>Pulsed EMF</td>
<td>2</td>
<td>2/2</td>
<td>18,19</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spa</td>
<td>5</td>
<td>3/3</td>
<td>12–17</td>
<td>15</td>
<td>1.0</td>
</tr>
<tr>
<td>TENS</td>
<td>7</td>
<td>6/6</td>
<td>12–22</td>
<td>17</td>
<td>0.76</td>
</tr>
<tr>
<td>Ultrasound</td>
<td>1</td>
<td>0/1</td>
<td>20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight loss</td>
<td>2</td>
<td>1/1</td>
<td>11,15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insoles</td>
<td>5</td>
<td>0/1</td>
<td>3–15</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Orthotic device (knee brace/patella tape/elastic bandage)</td>
<td>9</td>
<td>3/3</td>
<td>7–20</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>IA Hyaluronic acid</td>
<td>35</td>
<td>18/20</td>
<td>9–26</td>
<td>20</td>
<td>0.0, 0.04, 0.48, 0.49, 0.88, 0.9</td>
</tr>
<tr>
<td>IA Corticosteroid</td>
<td>9</td>
<td>6/7</td>
<td>4–22</td>
<td>16</td>
<td>1.27</td>
</tr>
<tr>
<td>Lavage/tidal irrigation</td>
<td>7</td>
<td>1/1</td>
<td>11–25</td>
<td>18</td>
<td>0.84</td>
</tr>
<tr>
<td>Arthroscopy</td>
<td>14</td>
<td>-</td>
<td>6–17</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Osteotomy</td>
<td>26</td>
<td>-</td>
<td>5–15</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Unicompartmental knee replacement</td>
<td>15</td>
<td>-</td>
<td>4–16</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Total knee replacement</td>
<td>35</td>
<td>-</td>
<td>4–23</td>
<td>13</td>
<td></td>
</tr>
</tbody>
</table>

EULAR Recommendations 2003 for management of knee OA 1149

developing symptomatic knee OA in women. A more recent RCT demonstrated that weight loss combined with exercise reduces pain and improves function in older adults for at least six months; unfortunately, no group had weight loss alone17(QS 21).

In summary, there is good evidence that education (1A) and exercise regimens (1B) reduce pain in knee OA and that exercise regimens also improve function. The use of appliances and weight loss seem sensible options in patients with knee OA, but are only supported by relatively weak evidence, with the exception of knee bracing which has level (1B) evidence for reduction in pain and improvement in function.

4. Paracetamol is the oral analgesic to try first and, if successful, the preferred long term oral analgesic

Paracetamol is frequently used as self medication for the treatment of mild to moderate pain. It is the recommended

---

### Table 5
Level of evidence based on the literature search, and strength of recommendation based on both evidence and expert opinion

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Level of evidence</th>
<th>Effect size Range</th>
<th>Strength of recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen/paracetamol</td>
<td>1B</td>
<td></td>
<td>A</td>
</tr>
<tr>
<td>Opioid analgesics</td>
<td>1B</td>
<td></td>
<td>B</td>
</tr>
<tr>
<td>NSAIDs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conventional NSAID</td>
<td>1A</td>
<td>0.47-0.96</td>
<td>A</td>
</tr>
<tr>
<td>Coxibs</td>
<td>1B</td>
<td>0.5</td>
<td>A</td>
</tr>
<tr>
<td>Antidepressant</td>
<td>1B</td>
<td></td>
<td>B</td>
</tr>
<tr>
<td>Topical NSAID</td>
<td>1A</td>
<td>-0.05-1.03</td>
<td>A</td>
</tr>
<tr>
<td>Topical capsaicin</td>
<td>1A</td>
<td>0.41-0.56</td>
<td>A</td>
</tr>
<tr>
<td>Sex hormones</td>
<td>2B</td>
<td></td>
<td>C</td>
</tr>
<tr>
<td>SYSADOA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucosamine</td>
<td>1A</td>
<td>0.43-1.02</td>
<td>A</td>
</tr>
<tr>
<td>Chondroitin</td>
<td>1A</td>
<td>1.23-1.50</td>
<td>A</td>
</tr>
<tr>
<td>Diacerein</td>
<td>1B</td>
<td></td>
<td>B</td>
</tr>
<tr>
<td>ASU</td>
<td>1B</td>
<td>0.32-1.72</td>
<td>B</td>
</tr>
<tr>
<td>Nutrients</td>
<td>1B</td>
<td>0.65</td>
<td>B</td>
</tr>
<tr>
<td>Herbal remedies</td>
<td>1B</td>
<td>0.23-1.32</td>
<td>B</td>
</tr>
<tr>
<td>Minerals/vitamins</td>
<td>1B</td>
<td></td>
<td>C</td>
</tr>
<tr>
<td>Education</td>
<td>1A</td>
<td>0.28-0.35</td>
<td>A</td>
</tr>
<tr>
<td>Exercise</td>
<td>1B</td>
<td>0.57-1.0</td>
<td>A</td>
</tr>
<tr>
<td>Telephone</td>
<td>1B</td>
<td>1.09</td>
<td>B</td>
</tr>
<tr>
<td>Acupuncture</td>
<td>1B</td>
<td>0.25-1.74</td>
<td>B</td>
</tr>
<tr>
<td>Laser</td>
<td>1B</td>
<td>0.87</td>
<td>B</td>
</tr>
<tr>
<td>Pulsed EMF</td>
<td>1B</td>
<td></td>
<td>B</td>
</tr>
<tr>
<td>Spa therapy</td>
<td>1B</td>
<td>1.0</td>
<td>C</td>
</tr>
<tr>
<td>TENS</td>
<td>1B</td>
<td>0.76</td>
<td>B</td>
</tr>
<tr>
<td>Ultrasound</td>
<td>1B</td>
<td></td>
<td>C</td>
</tr>
<tr>
<td>Weight loss</td>
<td>1B</td>
<td></td>
<td>B</td>
</tr>
<tr>
<td>Insoles</td>
<td>1B</td>
<td></td>
<td>B</td>
</tr>
<tr>
<td>Orthotic device (knee brace/patella tape/elastic bandage)</td>
<td>1B</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>IA, Hyaluronic acid</td>
<td>1B</td>
<td>0.0-0.9</td>
<td>B</td>
</tr>
<tr>
<td>IA, Corticosteroid</td>
<td>1B</td>
<td>1.27</td>
<td>A</td>
</tr>
<tr>
<td>Lavage/tidal irrigation</td>
<td>1B</td>
<td>0.84</td>
<td>B</td>
</tr>
<tr>
<td>Arthroscopy + debridement</td>
<td>1B</td>
<td></td>
<td>C</td>
</tr>
<tr>
<td>Osteotomy</td>
<td>3</td>
<td></td>
<td>C</td>
</tr>
<tr>
<td>UKR</td>
<td>3</td>
<td></td>
<td>C</td>
</tr>
<tr>
<td>TKR</td>
<td>3</td>
<td></td>
<td>C</td>
</tr>
</tbody>
</table>

---

### Table 6
Final set of 10 recommendations based on both evidence and expert opinion

1. The optimal management of knee OA requires a combination of non-pharmacological and pharmacological treatment modalities
2. The treatment of knee OA should be tailored according to:
   (a) Knee risk factors (obesity, adverse mechanical factors, physical activity)
   (b) General risk factors (age, comorbidity, polypharmacy)
   (c) Level of pain intensity and disability
   (d) Sign of inflammation—for example, effusion
   (e) Location and degree of structural damage
3. Non-pharmacological treatment of knee OA should include regular education, exercise, appliances (sticks, insoles, knee bracing), and weight reduction
4. Paracetamol is the oral analgesic to try first and, if successful, the preferred long term oral analgesic
5. Topical applications (NSAID, capsaicin) have clinical efficacy and are safe
6. NSAIDs should be considered in patients unresponsive to paracetamol. In patients with an increased gastrointestinal risk, non-selective NSAIDs and effective gastroprotective agents, or selective COX 2 inhibitors should be used
7. Opioid analgesics, with or without paracetamol, are useful alternatives in patients in whom NSAIDs, including COX 2 selective inhibitors, are contraindicated, ineffective, and/or poorly tolerated
8. SYSADOA (glucosamine sulphate, chondroitin sulphate, ASU, diacerein, hyaluronic acid) have symptomatic effects and may modify structure
9. Intra-articular injection of long acting corticosteroid is indicated for flare of knee pain, especially if accompanied by effusion
10. Joint replacement has to be considered in patients with radiographic evidence of knee OA who have refractory pain and disability
Table 7  Research agenda based on expert opinion

1. Clinical predictors of response to pharmacological and non-pharmacological interventions need to be determined.
2. There is a need to establish a set of recommendations for uniform and full reporting of clinical trials in knee OA.
3. Studies should include quality of life and function as well as pain, as outcome measures.
4. New imaging techniques—that is, MRI and ultrasound require validation for the diagnosis and follow up of knee OA.
5. Randomised controlled trials should fully assess non-pharmacological interventions for knee OA.
6. The most efficient and effective exercises need to be determined.
7. What is the effect on tissue, efficacy, and safety of long term COX 2 inhibition?
8. The clinical relevance of structural modification requires evaluation.
9. The indications for joint replacement need to be determined.
10. There is a need to examine the efficacy and cost utility of surgical techniques.

6. NSAIDs should be considered in patients unresponsive to paracetamol. In patients with an increased gastrointestinal risk, non-selective NSAIDs and effective gastroprotective agents, or selective COX 2 inhibitors should be used.

There is good evidence that NSAIDs are more efficacious than paracetamol for some patients, but the statement that they should be used in patients in whom paracetamol has failed, although attractive, does not have an evidence base. Unfortunately, there are no trials using failure of pain relief when treated with paracetamol as entry criteria for the trial. With increasing focus on the low grade inflammatory component of OA, NSAIDs would appear to be logical drugs in patients unresponsive to paracetamol, particularly in the presence of clinically overt synovitis. However, there is no direct evidence base to support this statement. Numerous studies have shown that oral NSAIDs are better than placebo (ES median 0.50, range 0.47–0.96), confirming the efficacy of NSAIDs in the management of knee OA. A Cochrane review examining the relative efficacy of different NSAIDs used in knee OA concluded that despite the large number of publications in this area, many trials were poorly designed, and there was no evidence to distinguish between the efficacy of equivalent recommended doses of conventional NSAIDs.

A few trials have directly compared paracetamol and NSAIDs. They have generally, but not exclusively, found that NSAIDs have better efficacy but increased gastrointestinal side effects. In a two year RCT (QS 23) paracetamol was compared with naproxen in 178 patients. Naproxen led to greater reductions in pain than paracetamol (ES 0.32 after 42 days and 0.45 after 730 days). Patient drop out was high (63%) owing to lack of efficacy in the paracetamol arm and to adverse events in the naproxen arm. A further trial of 382 patients comparing rofecoxib, celecoxib, and paracetamol demonstrated that more patients discontinued treatment early with paracetamol because of lack of efficacy and that significantly more pain relief was obtained with the coxibs than with paracetamol; side effect profiles were similar for all treatment arms (QS 23).
There has been speculation that COX 2 selective agents are more beneficial than conventional NSAIDs, particularly in those at higher risk of adverse gastrointestinal side effects. Large trials comparing COX 2 inhibitors with placebo and conventional NSAIDs have shown their superiority over placebo and a similar efficacy to conventional NSAIDs for pain relief but with a reduction—up to 50% —in perforation, ulcers, and bleeding. An RCT comparing celecoxib, diclofenac, and placebo in 600 patients over six weeks showed that both drugs were better than placebo in improving pain but showed no difference between active treatments. There were more gastrointestinal side effects with diclofenac than celecoxib and the coxib was better tolerated (QS21); there was an ES of 0.5 in comparison with placebo. A further study comparing varying doses of celecoxib with naproxen and placebo in 1003 patients found equal efficacy between the active treatment groups compared with placebo and an increased drop out rate in the placebo group due to lack of efficacy; in this study, however, the incidence of minor gastrointestinal related adverse events was similar for conventional NSAIDs and coxib, but one case of acute gastrointestinal bleeding occurred in the naproxen group (QS25). Current reports show that cardiorenal adverse events occur equally in patients treated with non-selective NSAIDs and coxibs.

A recent Cochrane review, including publications up to July 2002, examined the effectiveness of interventions for the prevention of NSAID induced upper gastrointestinal toxicity. This included 40 RCTs and concluded that all doses of misoprostol significantly reduced the risk of endoscopic ulcers. Standard doses of histamine-2 receptor antagonists effectively reduced the risk of endoscopic duodenal but not gastric ulcers. Double doses of histamine-2 receptor antagonists and protein pump inhibitors effectively reduced the risk of endoscopic duodenal and gastric ulcers, and were better tolerated than misoprostol.

There is therefore (1A) evidence to support the use of NSAIDs in the treatment of knee OA. In those with an increased risk of gastrointestinal complications the evidence supports the use of either a COX 2 selective agent or the addition of a gastroprotective agent to a conventional NSAID.

7. Opioid analgesics, with or without paracetamol, are useful alternatives in patients in whom NSAIDs, including COX 2 selective inhibitors, are contraindicated, ineffective, and/or poorly tolerated

There is little direct evidence to fully support this statement. However, there is indirect evidence and the use of opioid analgesics is widely accepted in everyday clinical practice when other therapeutic options are limited. Indirect evidence would support that there is increased efficacy of pain control in those patients not entirely responsive to paracetamol and/or NSAIDs. It would be prudent, however, to counsel on the increased risk of adverse side effects, particularly in the elderly, and potential dependence when using this group of drugs. An RCT of 90 patients showed that treatment of knee OA with tramadol allowed reduction of the naproxen dose among those patients with naproxen-responsive pain (QS 19). There is therefore (1B) evidence to support this statement.

8. SYSADOA (glucosamine sulphate, chondroitin sulphate, ASU, diclereine, and hyaluronic acid) have symptomatic effects and may modify structure

SYSADOA is a generic term used for symptomatic slow acting drugs for OA, and includes glucosamine sulphate and related compounds, chondroitin sulphate, and diclereine. There is wide variability throughout Europe in the use of these drugs and how they are classified. In the United Kingdom, for instance, they are classified as a health food supplement rather than a prescribable drug, are available only over the counter, and are very widely self administered. Those SYSADOA (for example, glycosaminoglycan polysulphates) that are no longer in use throughout Europe have not been included in this analysis. The other products have been assessed individually.

Both chondroitin sulphate and glucosamine sulphate have been the focus of a meta-analysis, including all studies up to 1999 (QS20). This report concluded that trials of chondroitin and glucosamine compounds demonstrated moderate to large effects on pain and disability in OA compared with placebo; however, these effects may have been exaggerated by publication bias. These products are also safe and associated with few side effects. The ES calculated for chondroitin sulphate was 0.78 and for glucosamine 0.44 in this meta-analysis, where they combined all the studies.

In an RCT assessing the efficacy of chondroitin sulphate compared with diclofenac in 146 patients, a prompter reduction of clinical symptoms was seen in patients treated with the NSAID, but these returned after the end of treatment; chondroitin, however, had a slower onset of action on the therapeutic response, but this lasted for up to three months after the end of treatment (QS20). A more recent RCT (QS 27) demonstrated the benefit of chondroitin over placebo in 130 patients with knee OA and again showed persisting efficacy for up to one month after treatment.

Two RCTs have compared the effect of glucosamine sulphate with ibuprofen. The first, conducted over an eight week period, showed that ibuprofen was more effective at decreasing pain scores within the first two weeks of treatment, but at eight weeks, glucosamine sulphate was significantly better (QS 22). The second, conducted over four weeks, demonstrated that ibuprofen had a faster onset of action, but at four weeks the pain reduction and disability were similar (QS 23). Two other placebo controlled RCTs have been published in addition to those assessed in the meta-analysis. Ninety eight older patients with moderate to severe knee OA showed no difference in pain or function with glucosamine sulphate compared with placebo over a two month period (QS 24). However, 106 patients with mild to moderate knee OA showed delayed progression of joint space loss and improved pain and function scores as compared with placebo over a three year period (QS 26). This had led to the suggestion that glucosamine sulphate could be used as a structure modifying agent in knee OA. Only one RCT has examined the efficacy of glucosamine and chondroitin sulphate in combination; in 93 patients, those with mild to moderate knee OA had significant improvement in the Lequesne index of knee severity score at four and six months; those with severe disease had no improvement over placebo (QS 24). An ES of 0.53–0.87 was calculated for glucosamine sulphate, excluding those used in the meta-analysis.

Only one RCT of dacireine in patients with knee OA was identified. At doses of 100 mg daily, significant differences in pain and handicap scores were seen compared with placebo. At higher doses, a significant number of adverse events were seen (QS 22).

The introduction of hyaluronic acid (HA) has been viewed as an advance in the management of knee OA. Its role in pain reduction, functional improvement, and in disease modification in knee OA has been assessed. Several HA preparations exist, in two main categories: high molecular and low molecular weight. It has been postulated that those preparations with a high molecular weight may have a superior effect. A 12 week RCT comparing a high molecular HA with a
Intra-articular steroid and placebo after one and four weeks. Another RCT involving 98 patients showed a significant one year (QS 22,19,23,14). One study recorded functional improvements on the Lequesne index (ES 0.36) over one year.20

Few trials have directly examined the effect on structure modification. One RCT looked at arthroscopic changes at baseline and after one year; less deterioration was seen over one year when treated with HA, and the HA group also scored higher for quality of life and reduced NSAID use during the period of study.72 Another study demonstrated a reduction in the need for intra-articular steroid injections over a one year follow up period; the authors suggested a possible structure modifying effect by reducing flares.73

Studies examining possible predictors of response are few. Patients over 60 years with important functional impairment as documented by the Lequesne index were associated with the greater efficacy of HA in one study (QS 26). A retrospective study found that the response to HA was statistically influenced by structural severity of the knee OA—those with less severe disease did better, and those with an effusion at baseline did worse (QS 18). It is noteworthy that most trials investigating intra-articular HA exclude severe OA.

In summary, there is evidence to support the efficacy of HA in the management of knee OA both for pain reduction (1B) and functional improvement (1B). However, although pain relief may be obtained for several months, rather than for several weeks as with steroid, this benefit may be offset by its slower onset of action and by the requirement of a course of 3–5 weekly injections with the logistical and cost issues that that entails. There is minimal evidence for a role in disease modification. The term SYScOA covers a range of agents. There is growing evidence to support the use of two of these agents for their symptomatic effects—namely, glucosamine sulphate (1A) and chondroitin sulphate (1A), but for the others the evidence is weak or absent.

9. Intra-articular injection of long acting corticosteroid is indicated for flare of knee pain, especially if accompanied by effusion

Intra-articular corticosteroid injections in knee OA have been used to relieve pain and inflammation for many years. The effects of steroids in knee OA have been assessed in a number of studies. One RCT concluded that steroid was more effective than placebo for pain relief over seven days (ES 0.04, 0.49, 0.88, 0.9) over periods of 60 days to one year (QS 22,19,23,14). One study recorded functional improvements on the Lequesne index (ES 0.36) over one year.20

In conclusion there is evidence (1B) that intra-articular injection of long acting corticosteroid is indicated for flare of knee pain, especially if accompanied by effusion.

10. Joint replacement has to be considered in patients with radiographic evidence of knee OA who have refractory pain and disability

Joint replacement is an irreversible intervention used in those for whom other treatment modalities have failed and who generally have more severe disease. The effectiveness of total knee replacement (TKR) in knee OA has a well established place in those severely incapacitated. A systematic review concluded that TKR was a safe and effective treatment in improving quality of life,21 as well as reducing pain and improving function. The evidence base to support this statement is built wholly on class 3 evidence from observational and retrospective analyses, often using prosthesis survival as the primary outcome measure.

A detailed review of surgery for knee OA identified 154 studies of 37 different tricompartmental prostheses in 9879 people (63% with osteoarthritis OA).22 Good or excellent outcomes for pain and function were reported in 89% of people up to five years after surgery. Unicompartmental and bicompartmental prostheses were also reviewed and showed similar findings. The review concluded that all forms of knee replacement improve quality of life.

The general consensus among orthopaedic surgeons on indications for an operative procedure, carried out by a postal survey, were (a) severe daily pain and (b) x ray evidence of joint space narrowing.23 There are no evidence based guidelines to support this, however.

No RCTs have compared TKR with non-surgical interventions. Although it is acknowledged that difficulties with study design may limit randomised studies on surgical treatments, there are areas that should be explored, including predictors of response, indications for joint replacement, and the effect of differences in surgical technique or joint prosthesis on long term outcomes. Moreover, postoperative outcome assessment should be carried out by an investigator independent of the surgeon who has performed the operation.

DISCUSSION

These clinical recommendations are based on the updated evidence obtained by reviewing the literature up to and including February 2002. The publication also seeks to accommodate all commonly used treatment modalities used in knee OA. The data collected and provided are restricted to the knee only, therefore, and those papers in which summary statistics could not be dissected from the other non-knee data were excluded. Equally, current recommendations cannot be extrapolated to OA at other sites.

The main purpose of the paper is to act as a resource document for secondary care, with the aim that each individual country should use the information generated to produce their own set of management guidelines and algorithms for treatment in primary care. As noted in the 2000 recommendations, there is often discordance between expert opinion and trial evidence, confirming that our own experience and local situations are important in determining individual treatment selection.

Reviewing the literature has reinforced the need to investigate predictors of response to individual treatments as the information relating to this important aspect is limited. Also, there is a lack of information about pooled/combination treatments, which would reflect everyday clinical practice. We still remain ignorant about the difference between efficacy (trial data) and clinical effectiveness (how useful in practice) for many of these treatments.

A heterogeneous array of outcome measures was used which makes comparison between different publications using the same treatment difficult. A more standardised
way of assessing the various treatments needs to be adopted internationally.

The task force attempted to review the evidence for efficacy of individual treatments and to give an additional more subjective summary of expert opinion on the overall safety and usefulness. The task force made no attempt to design a more didactic algorithm for management, even though it was realised that such a simplistic approach might have more immediate impact on the behaviour of health professionals. Many patient centred factors are important in determining the selection of treatments for individual patients with knee OA—for example, psychosocial factors and OA status, comorbid disease and drugs; patient beliefs about their knee OA; patient beliefs and preferences for its management; and previous patient experiences of treatments and health professionals. The costs and logistics of delivering specific interventions (for example, physiotherapy, weekly knee injections of HA) are also important. Therefore the management plan for patients with knee OA has to be individualised, reviewed, and adjusted in the light of the patient’s response and adherence and will vary between patients and between locations. Optimistically, however, the findings of the current EULAR Recommendations show that there is a wide variety of treatments from which to choose for people with knee OA. There is no single right and wrong approach and each health professional must decide with each patient the most appropriate management plan at a particular time and for that location. It is hoped that discussion within healthcare provider groups of the treatment options outlined in this document will improve knowledge and interest in the management of knee OA and result in higher standards of care.

ACKNOWLEDGEMENTS

We thank Bristol Myers Squibb and, in particular, Dr Manuela Le Bars, for financial and logistical support.

MEMBERS OF TASK FORCE

Nigel Arden, Southampton General Hospital, Southampton S016 6YD, UK
Bernard Bannwarth, Laboratoire de Thérapeutique, Université Bordeaux II, 33076 Bordeaux Cedex, France
Johannes Bijlsma, Department of Rheumatology and Immunology, University Hospital Utrecht, 3508 UT Gre, The Netherlands
Paul Dieppe, MRC Health Services Research Collaboration, University of Bristol, Canynge Hall, Whiteladies Road, Bristol BS8 2PR, UK
Michael Doherty, Rheumatology Unit R.U.G., City Hospital, Nottingham NG5 1PB, UK
Maxime Dougdas, Service de Rheumatologie B, Hôpital Cochin, 75014 Paris, France
Klaus-Peter Gunther, Department of Orthopaedic Surgery, University of Dresden, Dresden, Germany
Hans Haußmann, Centre for Rheumatology and Bone Disease, Clinic Im Park, Hirschlanden Group, Bellariastr. 38, CH 8038 Zurich, Switzerland
Gabriel Herrero-Beaumont, Rheumatology Department, Clinique de la Conception, 28040 Madrid, Spain
Kelsey Jordan, Florence Cottage, 17 Dover Street, Southampton SO146GG, UK
Phaedon Kaklamakis, 16 Anaporon Polemon, 11521 Athens, Greece
Burkhard Leeb, NO¨ Zentrum fu ¨r Rheumatology, Stockerau Hospital, A-2000 Stockerau, Austria
Michel Lequesne, 31-33 rue Guillemot, 75014 Paris, France
Stefan Lohmander, Department of Orthopaedics, University Hospital, S-22185 Lund, Sweden
Bernard Mairesse, Service de Rhumatologie, 1 avenue Jean Poulihès, CHU Rangueil, 31054 O, Cedex France
Emilio Martin-Mola, División de Reumatología, Hospital La Paz, 28046 Madrid, Spain
Karel Pavelka, Institute of Rheumatology, 12850 Praha 2, Czech Republic
Adrian Pendleton, 9 Prince Edward Drive, Stranmillis, Belfast BT9 5GB, Northern Ireland
Leonardo Punzi, Universita degli studi di Padova, Policlinico Universitario - VIII Piano, Via Giustinaini, 2, 35128 Padova, Italy
Umberto Semi, Divisione di Reumatologia, Istituto Ortopedico Toscano, Florence, Italy
Burrn Swoboda, Orthopädische Poliklinik der Universität Erlangen-Nürnberg, D-91054 Erlangen, Germany
Gust Verbruggen, Rheumatology Unit, U.Z R.U.G., B-7000 Gent, Belgium
Irena Zimmermann-Gorska, Department of Rheumatology and Rehabilitation, Karol Marcinkowski University of Medical Sciences, 28 Czerwca 1956r, 135/147, 61-545 Poznan, Poland

REFERENCES


