RHEUMATOLOGY

Rheumatology 2012;51:1416–1425
doi:10.1093/rheumatology/kes032
Advance Access publication 24 March 2012

Original article

Multinational evidence-based recommendations for pain management by pharmacotherapy in inflammatory arthritis: integrating systematic literature research and expert opinion of a broad panel of rheumatologists in the 3e Initiative

Samuel L. Whittle[1,*], Alexandra N. Colebatch[2,3,*], Rachelle Buchbinder[4], Christopher J. Edwards[2], Karen Adams[5], Matthias Englbrecht[6], Glen Hazlewood[7], Jonathan L. Marks[2], Helga Radner[8], Sofia Ramiro[9], Bethan L. Richards[10], Ingo H. Tarner[11], Daniel Aletaha[8], Claire Bombardier[7], Robert B. Landewé[9,12], Ulf Müller-Ladner[11], Johannes W. J. Bijlsma[13], Jaime C. Branco[14,15], Vivian P. Bykerk[16,17], Geraldo da Rocha Castelar Pinheiro[18], Anca I. Catrina[19], Pekka Hannonen[20], Patrick Kiely[21], Burkhard Leeb[22], Elisabeth Lie[23], Píndaro Martinez-Osuna[24], Carlomaurizio Montecucco[25], Mikkel Østergaard[26], Rene Westhovens[27], Jane Zochling[28] and Désirée van der Heijde[29]

Abstract

Objective. To develop evidence-based recommendations for pain management by pharmacotherapy in patients with inflammatory arthritis (IA).

Methods. A total of 453 rheumatologists from 17 countries participated in the 2010 3e (Evidence, Expertise, Exchange) Initiative. Using a formal voting process, 89 rheumatologists representing all 17 countries selected 10 clinical questions regarding the use of pain medications in IA. Bibliographic fellows undertook a systematic literature review for each question, using MEDLINE, EMBASE, Cochrane CENTRAL and 2008–09 European League Against Rheumatism (EULAR)/ACR abstracts. Relevant studies were retrieved for data extraction and quality assessment. Rheumatologists from each country used this evidence to develop a set of national recommendations. Multinational recommendations were then formulated and assessed for agreement and the potential impact on clinical practice.

[1]Rheumatology Unit, The Queen Elizabeth Hospital, Adelaide, Australia, [2]Department of Rheumatology, Southampton University Hospitals, Southampton, [3]Yeovil District Hospital, Yeovil, UK, [4]Monash Department of Clinical Epidemiology, Cabrini Institute and Monash University, Melbourne, Australia, [5]Centre Hospitalier de l'Université Laval, Québec, Canada, [6]Department of Internal Medicine 3, University of Erlangen-Nuremberg, Erlangen, Germany, [7]University of Toronto, Toronto, Canada, [8]Division of Rheumatology, Department of Internal Medicine 3, Medical University of Vienna, Vienna, Austria, [9]Academic Medical Centre, Amsterdam, The Netherlands, [10]Institute of Rheumatology and Orthopedics, Royal Prince Alfred Hospital, Camperdown, Australia, [11]Department of Internal Medicine and Rheumatology, Justus Liebig University, Giessen, Germany, [12]Atrium Medical Centre, Heerlen, The Netherlands, [13]Department of Rheumatology and Clinical Immunology, University Medical Center Utrecht, The Netherlands, [14]CEDOC, Faculdade de Ciências Médicas da Universidade Nova de Lisboa, [15]CHLO, EPE - Hospital Egas Moniz, Lisbon, Portugal, [16]Mount Sinai Hospital, Toronto, ON, Canada, [17]Brigham and Women's Hospital, Harvard University, Boston, MA, USA, [18]Department of Rheumatology, Pedro Ernesto University Hospital, Rio de Janeiro, Brazil, [19]Department of Rheumatology, Karolinska University Hospital and Karolinska Institutet, Stockholm, Sweden, [20]Department of Medicine, Central Hospital, Jyväskylä, Finland, [21]Department of Rheumatology, St George's Healthcare NHS Trust, London, UK, [22]Center for Rheumatology, State Hospital Stockerau, Lower Austria, Stockerau, Austria, [23]Department of Rheumatology, Diakonhjemmet Hospital, Oslo, Norway, [24]CIF-Biotec Research Center, Hospital y Fundación Clínica Médica Sur, Mexico City, Mexico, [25]Cattedra di Reumatologia, IRCCS Policlinico S. Matteo, Università di Pavia, Pavia, Italy, [26]Department of Rheumatology, Copenhagen University Hospital at Glostrup, Copenhagen, Denmark, [27]Department of Rheumatology, KU Leuven, Leuven, Belgium, [28]Menzies Research Institute, University of Tasmania, Hobart, Australia and [29]Department of Rheumatology, Leiden University Medical Center, Leiden, The Netherlands.

Submitted 7 October 2011; revised version accepted 25 January 2012.

Correspondence to: Samuel L. Whittle, Rheumatology Unit, The Queen Elizabeth Hospital, Woodville South, South Australia 5011, Adelaide, Australia. E-mail: sam@whit.tl

*Samuel L. Whittle and Alexandra N. Colebatch contributed equally to this study.

CLINICAL SCIENCE

Results. A total of 49 242 references were identified, from which 167 studies were included in the systematic reviews. One clinical question regarding different comorbidities was divided into two separate reviews, resulting in 11 recommendations in total. Oxford levels of evidence were applied to each recommendation. The recommendations related to the efficacy and safety of various analgesic medications, pain measurement scales and pain management in the pre-conception period, pregnancy and lactation. Finally, an algorithm for the pharmacological management of pain in IA was developed. Twenty per cent of rheumatologists reported that the algorithm would change their practice, and 75% felt the algorithm was in accordance with their current practice.

Conclusions. Eleven evidence-based recommendations on the management of pain by pharmacotherapy in IA were developed. They are supported by a large panel of rheumatologists from 17 countries, thus enhancing their utility in clinical practice.

Key words: arthritis, evidence-based medicine, analgesics.

Introduction

Inflammatory arthritis (IA) affects up to 3% of the population [1] and is characterized by pain, stiffness, loss of function and impaired quality of life. Despite recent advances in the management of IA, pain remains a common experience for IA patients, who report pain management to be their highest priority [2–4].

The 3e (Evidence, Expertise, Exchange) Initiative is a multinational collaboration aimed at promoting evidence-based practice in rheumatology by developing practical recommendations that address important clinical problems [5–7]. The objective of the 2010 3e Initiative was to develop recommendations for the use of pharmacotherapy in the management of pain in patients with IA by integrating systematically generated evidence with the expertise of a broad panel of international rheumatologists.

Methods

A total of 453 rheumatologists from 17 countries participated in the 2010 3e Initiative. Participating countries from Europe, Canada, South America and Australasia were represented by 15 scientific committees. The members of each of the national scientific committees formed the panel of experts that attended the multinational meetings. In addition, the bibliographic team comprised 10 multinational fellows (S.L.W., A.N.C., K.A., M.E., G.H., J.L.M., H.R., S.R., B.L.R. and I.H.T.), 6 mentors (D.A., C.B., R.B., C.J.E., R.L. and U.M.-L.) and the scientific chair (D.vdH.).

At the first international meeting, 10 clinically relevant questions regarding pain management in IA were formulated and selected via a modified Delphi voting process by the panel of 89 expert rheumatologists representing all 17 countries. In order to develop a set of recommendations that was sufficiently focused to be of practical value to clinicians, non-pharmacological interventions were not considered in the current project. IA was defined as comprising RA, PsA, AS and SpA.

The multinational fellows undertook a systematic literature review (SLR) for each of the clinical questions. One clinical question regarding the importance of comorbidities was divided into two parts in order to allow a more manageable literature search; this resulted in a total of 11 questions for which an SLR was performed and recommendations were produced. A comprehensive search strategy was formulated for each question in conjunction with an experienced librarian and, where appropriate, the search terms were standardized for each of the SLRs. A search was conducted in MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials (CENTRAL), and hand searches were performed of abstracts presented at the ACR and European League Against Rheumatism (EULAR) scientific meetings in 2008 and 2009. The titles and abstracts of all citations identified by the searches were screened, and potentially relevant articles were reviewed in full text for inclusion according to predetermined inclusion and exclusion criteria. Included articles were restricted to those published in languages in which at least one member of the bibliographic group was fluent. All trials of interventions were assessed for risk of bias according to the methods recommended by the Cochrane Collaboration [8]. Details and results of the SLR for each question will be published separately.

Following presentation of the SLR results, each of the 15 national scientific committees produced recommendations regarding the 11 clinical questions and a provisional algorithm for the pharmacological management of pain in IA. At the final international meeting, the members of each of the scientific committees merged the national recommendations into 11 final recommendations and a treatment algorithm via a process of discussion and a modified Delphi vote.

The participating rheumatologists quantified their agreement with each recommendation and the potential impact of each recommendation on their clinical practice. The level of evidence for each component of the recommendations was appraised, and each recommendation was graded in accordance with the Oxford Centre for Evidence-based Medicine Levels of Evidence [9]. Where there was ambiguity regarding the appropriate grade or level of evidence, a lower grade or level was chosen.

Results

In total, 49 242 references were identified, from which 167 studies were included in the SLRs. The 11 final multinational recommendations are listed in Table 1 with the levels of evidence and grade of recommendation. The level of agreement by the participants with the recommendations ranged from 8.5 to 9.3 (mean 8.9) on a 1–10 point scale, where 10 represents full agreement (Table 1).

Recommendation 1

In patients with IA, pain should be measured routinely using one of the following validated scales: VAS, NRS or VRS; in addition, consider multi-dimensional measures or site-specific tools as needed.

Fifty-one studies were identified that evaluated a total of 20 tools that have been used in the setting of IA (predominantly RA) to measure patient-reported pain. The visual analogue scale (VAS) for overall pain intensity is currently the best evaluated pain measure in RA, but the related single-item measures, numerical rating scale (NRS) and verbal rating scale (VRS) demonstrated comparable clinimetric properties [10].

There was a consensus among the experts that measurement of pain is an important component of routine clinical care in patients with IA. Pain scales that measure overall pain (such as VAS, NRS or VRS) were felt to be most useful. It was recognized that multi-dimensional tools, which measure different characteristics of the phenomenon of pain, and tools limited to specific anatomical sites are also useful in certain clinical or research situations, but are not required in routine practice.

Recommendation 2

Paracetamol is recommended for the treatment of persistent pain in patients with IA.

Data from 12 short-term randomized controlled trials (RCTs) at high risk of bias provided weak evidence for a benefit of paracetamol over placebo and an additive benefit of paracetamol in combination with NSAIDs [11]. Heterogeneity among the trials prevented meta-analysis. No important safety signals were identified in subjects treated with standard doses of paracetamol.

There was consensus among the experts that paracetamol is generally a safe and effective analgesic in IA, both alone and in combination with other pain pharmacotherapies. It was recognized that there is variation between countries in the maximum recommended dose and that clinicians should follow local dosing guidelines. No evidence exists regarding the preferred formulation or dosing interval.

Recommendation 3

Systemic glucocorticoids are not recommended for the routine management of pain in patients with IA in the absence of signs and symptoms of inflammation.

Despite a comprehensive search strategy, no studies were found that addressed the role of systemic glucocorticoids as an analgesic therapy in IA [12]. While a rationale exists for a potential analgesic effect of glucocorticoids [13], there are as yet no clinical data in this setting to support such a notion. The adverse effects of long-term glucocorticoid use are well recognized [14].

Intra-articular glucocorticoids were not considered for this recommendation as they are generally considered to be useful in the management of localized inflammation in IA. While the anti-inflammatory properties of systemic glucocorticoids are recognized to play an important role in the management of IA, the experts strongly agreed that there is no role for steroids in the treatment of IA pain when inflammation is adequately suppressed.

Recommendation 4

In the treatment of pain in IA, tricyclic antidepressants and neuromodulators may be considered for use as adjuvant treatment; muscle relaxants and benzodiazepines cannot be recommended.

There was conflicting evidence regarding the efficacy of tricyclic anti-depressants (TCAs) as analgesics in eight RCTs in patients with RA and a single trial in AS. The majority of the trials were at high risk of bias. Adverse events (AEs) were more common in those treated with TCAs *vs* placebo, but there was no increase in the number of withdrawals due to AEs [15]. The experts agreed that while the evidence regarding TCAs as analgesic agents is unclear, there may be a role for this class of medications in selected patients. There is insufficient evidence regarding the role of newer anti-depressants in patients with IA to warrant a recommendation at this time.

Despite the use of a broad definition of neuromodulators as 'substances that alter nerve transmission' in the initial literature search, data regarding the use of these drugs in this population was scarce. Pooled analysis of two short-term trials of the centrally acting non-opioid analgesic nefopam in RA demonstrated significant reduction in pain at 2 weeks compared with placebo, but the risk of AEs was also significantly increased [16–18]. One study of topical capsaicin for knee pain in RA suggested a benefit at 2 weeks, although local skin irritation was a frequent occurrence [19]. There are no data regarding the use of anti-convulsants as analgesics in IA, although both pregabalin and gabapentin have been shown to reduce pain in patients with FM syndrome [20–22]. The experts agreed that although the evidence regarding neuromodulators in IA is very limited, these drugs, including nefopam and topical capsaicin, and potentially the newer anticonvulsants, may be considered as adjuvant therapies in individual patients.

Benzodiazepines are hypnotic and anxiolytic agents that have some muscle relaxant properties [23]. In six short-term RCTs, no improvement in pain outcomes was seen in those taking muscle relaxants compared with placebo, and both benzodiazepines [24] and non-benzodiazepine muscle relaxants [25] were associated with a significant increase in the risk of AEs [26]. Given this lack of evidence for benefit and the potential for harm (including addiction), the experts recommended against the use of benzodiazepines as analgesics. The paucity of evidence regarding non-benzodiazepine muscle relaxants prevented a specific recommendation

TABLE 1 Multinational recommendations on pain management by pharmacotherapy in IA

Recommendation (with level of evidence and grade of recommendation)	Agreement, mean (S.D.)
(1) In patients with IA, pain should be measured routinely using one of the following validated scales: VAS, NRS or VRS; in addition, consider multi-dimensional measures or site-specific tools as needed. Level of evidence: NA; grade of recommendation: NA	8.6 (1.8)
(2) Paracetamol is recommended for the treatment of persistent pain in patients with IA. RA: Level of evidence: 2b[a]; grade of recommendation: C Other IA: level of evidence 5; grade of recommendation: D	8.8 (1.6)
(3) Systemic glucocorticoids are not recommended for the routine management of pain in patients with IA in the absence of signs and symptoms of inflammation. Level of evidence: 5; grade of recommendation: D	9.2 (1.6)
(4) In the treatment of pain in IA, TCAs and neuromodulators may be considered for use as adjuvant treatment;* muscle relaxants and benzodiazepines cannot be recommended.** *Level of evidence: 5; grade of recommendation: D **Level of evidence: 2b[a] (RA), 5 (other IA); grade of recommendation: C (RA), D (other IA)	9.2 (1.6)
(5) Weak opioids may be used for short-term treatment of pain in patients with IA when other therapies have failed or are contraindicated;* long-term use may be considered and should be regularly reviewed.** Strong opioids should only be used in exceptional cases.** *Level of evidence: 2b[a] (RA), 5 (other IA); grade of recommendation: D (RA), D (other IA) **Level of evidence: 5; grade of recommendation: D	8.5 (1.5)
(6) In patients with an inadequate response to paracetamol or NSAID monotherapy, adding a drug with a different mode of action could be considered; combination of two or more NSAIDs should not be used. Level of evidence: 5; grade of recommendation: D	9.2 (0.9)
(7) NSAIDs should be used at the lowest effective dose, either continuously or on demand, according to clinical circumstances. Level of evidence: 5; grade of recommendation: D	9.1 (1.4)
(8) Existing guidance regarding the safety of pain pharmacotherapies during pre-conception, pregnancy and lactation should be applied. Level of evidence: 5; grade of recommendation: D	8.6 (1.6)
(9) In the management of patients with IA, MTX can be used safely in combination with standard doses of paracetamol and/or NSAIDs (excluding anti-inflammatory doses of aspirin). RA and NSAIDs: level of evidence: 4; grade of recommendation: C Other IA and NSAIDs: level of evidence: 5; grade of recommendation: D All IA and paracetamol: level of evidence: 5; grade of recommendation: D	9.3 (1.0)
(10) In patients with GI comorbidities paracetamol should be considered first;* non-selective NSAIDs in combination with PPI, or COX-2 selective inhibitors ± PPI, may be used with caution.** In the presence of liver disease standard precautions for use of NSAIDs and other analgesics should be applied.* *Level of evidence: 5; grade of recommendation: D **Level of evidence: 3 (RA), 5 (other IA); grade of recommendation: C (RA), D (other IA)	8.8 (1.4)
(11) In patients with IA and pre-existing hypertension,* CV* or renal disease,** paracetamol should be used first; NSAIDs including COX-2 selective inhibitors should be used with caution. *Level of evidence: 2a (RA), 5 (other IA); grade of recommendation: C (RA), D (other IA) **Level of evidence: 5; grade of recommendation: D	8.8 (1.2)

Level of evidence and grade of recommendation according to the Oxford Centre for Evidence-based Medicine Levels of Evidence (http://www.cebm.net/index.aspx?o=1025). [a]Level 1a evidence [Systematic Review with troublesome (and statistically significant) heterogeneity of RCTs] was downgraded to Level 2b to indicate that most included RCTs were at high risk of bias and the results may not apply to IA patients taking anti-rheumatic medication based upon current standards. Agreement relates to the entire statement and was voted on a scale from 1 to 10 (fully disagree to fully agree) by the 76 rheumatologists attending the 3e Multinational Closing Meeting (Brussels, 19–20 November 2010). These attendees were members of the 15 national scientific committees involved in 3e. NA: not available.

regarding these drugs, although it was recognized that most clinicians would not regard them as analgesic agents.

Recommendation 5

Weak opioids may be used for short-term treatment of pain in patients with IA when other therapies have failed or are contraindicated; long-term use may be considered and should be regularly reviewed. Strong opioids should only be used in exceptional cases.

While clinicians and regulatory bodies commonly classify opioids as being 'weak' or 'strong', no consensus classification system exists, and there is no clear pharmacological distinction at the receptor level between drugs to which either of these labels are commonly

applied [27, 28]. Eleven RCTs of opioids in RA were identified: 10 studied opioids that were considered to be weak, including codeine, tilidine, pentazocine, dextropropoxyphene and tramadol [29].

Meta-analysis of pain outcomes up to 6 weeks from three placebo-controlled studies found treatment with weak oral opioids resulted in superior patient-reported global impression of clinical change [30–32]. AEs were significantly more frequent in opioid-treated patients, and after adjustment for AEs there was no difference between opioids and placebo in net efficacy [29, 33].

Although the experts agreed that short-term use of opioids in some patients with IA may have an acceptable risk–benefit profile, caution was advised for long-term use. Given the lack of evidence regarding the use of strong opioids in IA pain and the significant potential for harm, the experts recommended that they should be used only where other treatments have failed, and should be supervised by a clinician experienced in the prescription of strong opioids.

Recommendation 6

In patients with an inadequate response to paracetamol or NSAID monotherapy, adding a drug with a different mode of action could be considered; combination of two or more NSAIDs should not be used.

The use of different analgesic drugs in combination is often recommended to permit the use of lower doses of each analgesic by targeting different pain pathways simultaneously [34]. Twenty-three trials were identified that compared combination analgesic therapy with monotherapy in IA: all were published before 1994 and all were at high risk of bias [35]. There were no trials in IAs other than RA. Heterogeneity of the included trials precluded meta-analysis.

Despite the inconclusive evidence, the experts felt that in patients for whom analgesic monotherapy was insufficient, clinicians could choose to trial an alternative drug from a different class, or a combination of drugs with different modes of action, and that the decision should be made with regard to the individual patient. The use of more than one drug with the same mode of action, in particular NSAIDs and opioids, is likely to disproportionately increase the risk of AEs and should be avoided.

Recommendation 7

NSAIDs should be used at the lowest effective dose, either continuously or on demand, according to clinical circumstances.

It is not known whether there is a difference in the risk–benefit profile of NSAIDs when used as continuous therapy rather than on demand. Only one relevant RCT was identified (in individuals with AS), in which no significant difference was found between the intervention groups for pain measures or AEs [36, 37].

In the absence of strong evidence regarding the optimal method of NSAID use, the experts believed that NSAID therapy should be tailored to the individual patient's clinical circumstances. Given the risk of serious AEs, the experts considered it axiomatic that the lowest effective dose and briefest possible course of NSAID therapy should be sought for all patients in whom these drugs are used.

Recommendation 8

Existing guidance regarding the safety of pain pharmacotherapies during pre-conception, pregnancy and lactation should be applied.

There are few data regarding the safety of analgesics during pregnancy and lactation in women with IA [38]. Pre-conception was excluded from the review, as it significantly complicated the review process.

There was extensive debate among the experts regarding the suitability of specific recommendations for this question. A close vote favoured a general recommendation over specific recommendations regarding individual drug classes. While the experts were mostly of the opinion that paracetamol is generally safe in pregnant women and that NSAIDs may be used with caution before the third trimester, the group wished to emphasize that decisions regarding pharmacotherapy in pregnant and lactating women should be made jointly by the rheumatologist, obstetrician and patient. At present there is no evidence to suggest that women with IA are a sufficiently unique subgroup to warrant recommendations that deviate from existing guidelines regarding the use of drugs in pregnancy. As such, existing guidance regarding these medications should be applied equally to women with IA as to the general population.

Recommendation 9

In the management of patients with IA, MTX can be used safely in combination with standard doses of paracetamol and/or NSAIDs (excluding anti-inflammatory doses of aspirin).

A systematic review of RCTs and non-randomized studies regarding the safety of using NSAIDs and/or paracetamol with MTX in IA identified 17 studies, all in patients with RA [39]. Most of the included studies were of a low to moderate quality. No studies were identified for the combination of MTX and paracetamol, but the experts considered this combination to be generally safe. There was no effect of concurrent NSAID use on the incidence of MTX-related AEs or the rate of MTX withdrawal [40–45].

The use of MTX in addition to anti-inflammatory doses of aspirin has been reported to have an adverse effect on liver [46] and renal [47] function. The evidence regarding low-dose aspirin for the prevention of atherothrombotic disease is less clear, although pharmacokinetic data suggest that aspirin at daily doses of $\geqslant$650 mg has different pharmacokinetic properties and is more likely to increase risk in combination with MTX [39, 48–50].

Recommendation 10

In patients with gastrointestinal comorbidities, paracetamol should be considered first; non-selective NSAIDs in combination with PPI, or COX-2 selective inhibitors ± PPI, may be used with caution. In the presence of liver disease, standard precautions for use of NSAIDs and other analgesics should be applied.

Data regarding the safety and efficacy of analgesic drugs in patients with IA and existing or prior gastrointestinal (GI) or hepatic morbidity could be identified for

NSAIDs only [51]. In RA patients treated with NSAIDs there is an increased risk of GI events in individuals with prior uncomplicated GI events or a history of upper GI symptoms [52]. A meta-analysis of five RCTs involving patients with RA or OA who were receiving NSAIDs also found an increased risk of upper GI events in those with a history of gastro-duodenal ulceration [53].

The experts agreed that paracetamol should be considered as the first-line analgesic in this setting due to the risk of recurrent GI events. Caution should also be exercised in patients with risk factors for significant GI events, including patients without documented prior events, although the magnitude of any increase in risk in these patients cannot be estimated from the literature. Where NSAIDs are required, the experts recommended that either non-selective NSAIDs in combination with proton-pump inhibitors (PPI), or COX-2 selective inhibitors (alone or in combination with PPI) may be used with close surveillance for AEs.

There is little evidence regarding the efficacy and safety of analgesic drugs in patients with IA and co-morbid hepatic disease [51] The experts believed that as the risk associated with the use of analgesics such as paracetamol, NSAIDs and opioids in patients with IA and liver disease is likely to be similar to that seen in other patients with hepatic dysfunction, prescribers should exercise a similar level of caution when using these drugs in IA patients as in other populations.

Recommendation 11

In patients with IA and pre-existing hypertension, cardiovascular or renal disease, paracetamol should be used first; NSAIDs including COX-2 selective inhibitors should be used with caution.

Few studies were found that directly assessed the risk of analgesic drugs in patients with IA and co-morbid renal or cardiovascular (CV) disease [54]. Data from a large RCT comparing diclofenac and etoricoxib in a mixed population of OA and RA were available for patients with pre-existing CV disease [55]. Subjects with CV disease who were treated with either etoricoxib or diclofenac had a 3-fold increase in the risk of thrombotic events compared with those without CV disease. No data was available regarding other IAs and there were no studies that directly assessed the influence of renal disease on the risk–benefit profile of analgesics in IA.

The potential for CV events, renal dysfunction and hypertension in individuals treated with NSAIDs is well recognized [56–58], although the magnitude of this risk in patients with both IA and renal or CV disease remains unclear. Despite preliminary evidence that paracetamol might increase blood pressure in patients with existing coronary artery disease [59], there is as yet no convincing epidemiological evidence to suggest that paracetamol contributes to increased vascular risk in a manner comparable with NSAIDs. Therefore, the experts agreed that the most reasonable approach would be to use paracetamol as the primary analgesic in this setting. There was insufficient data to make specific recommendations about other analgesic drugs.

Algorithm

Based on the recommendations that were developed, the experts proposed an algorithm for the management of pain by pharmacotherapy in patients with IA (Fig. 1). The therapeutic algorithm is predicated on the assumption that the clinician's first goal is to optimally control inflammation with DMARDs according to current practice (including the use of biologic DMARDs and glucocorticoids), although it is recognized that response to DMARDs is often delayed, may vary over time, and that complete suppression of inflammation is not always achievable.

The use of NSAIDs, paracetamol and weak opioids in the algorithm reflects the recommendations above. Due to concerns regarding the risk–benefit profile of strong opioids, these drugs do not form part of the main algorithm, but may be used with caution under exceptional circumstances, as described in Recommendation 5.

As discussed in Recommendation 4, TCAs and neuromodulators are not recommended as analgesic options in isolation, but may be considered as adjuvants in a comprehensive analgesic strategy, at any point in the proposed algorithm. Evidence exists for the use of TCAs only in this population. The experts recognized that data now exist regarding the efficacy of newer antidepressants (such as duloxetine and milnacipran) and the neuromodulators (pregabalin and gabapentin) in FMS, and that while there are no data regarding the use of these drugs in IA, some clinicians may choose to trial them as adjuvants where central sensitization is thought to be contributing to persistent pain [20, 22, 60–62].

Importantly, any analgesic strategy must be tailored to the individual patient, and must reflect the relative risks and benefits in the individual circumstances, as well as the patient's values. The experts included several points to consider at all stages of the therapeutic algorithm, including the type of IA, comorbidities and the preferences of the individual patient. The pain phenotype (e.g. peripheral nociception from joint damage, *vs* diffuse pain associated with central sensitization) was thought to be important in tailoring treatment, and should be assessed at each clinical encounter, in addition to an assessment for the presence of residual (treatable) inflammation.

Impact of recommendations

The recommendations are in accordance with the current clinical practice of the majority of the participating rheumatologists. The proportion of rheumatologists who indicated they would change their practice according to each recommendation is listed in Table 2. Notably, the measurement of pain, the use of anti-depressants, muscle relaxants and neuromodulators, and the final algorithm resulted in modification of clinical practice in 16.7–30% of the rheumatologists.

Discussion

The 2010 3e Initiative developed 11 recommendations and an algorithm for the management of pain by pharmacotherapy in IA. The recommendations, which were

Fig. 1 Algorithm for pain management by pharmacotherapy in IA. The central column of the algorithm contains recommendations for the choice of medications for individuals with IA who experience pain despite optimal management of inflammation. It is recommended that clinicians first select an option from the top row, and move sequentially to lower rows when the options in each row are either ineffective or contraindicated. Adjuvant options may be introduced at any point in the algorithm, where appropriate. Each decision within the algorithm should be made with regard to the individual patient, including the points to consider in the left column. Level of evidence: 5. Grade of recommendation: D. Agreement 8.4/10.

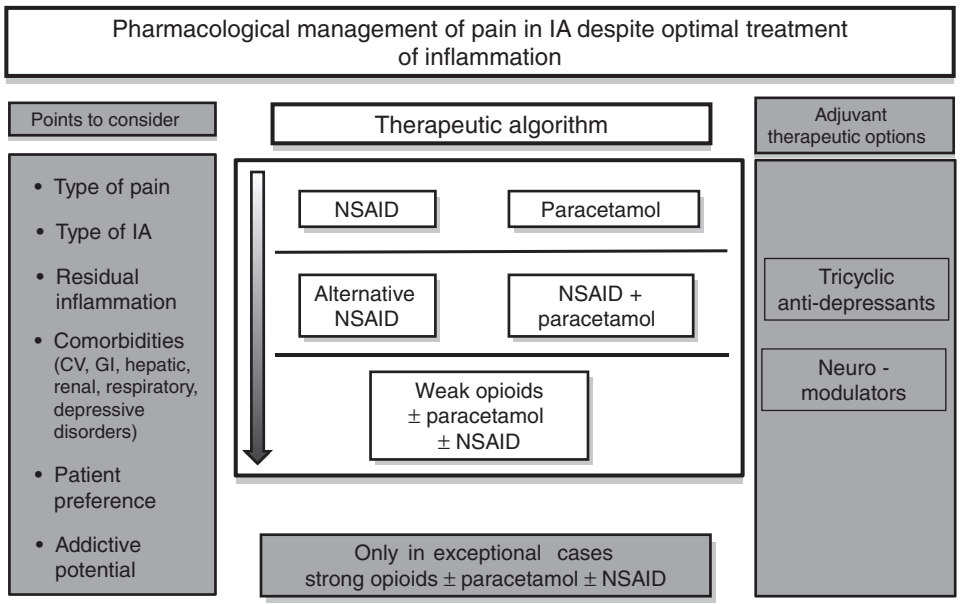

Table 2 Impact of recommendations on the practice of rheumatologists in the 3e Initiative

Recommendation (number and topic)	The recommendation will change my practice, %	The recommendation is in full accordance with my practice, %	I do not want to apply this recommendation in my practice, %
1. Measurement of pain	30.0	63.3	6.7
2. Paracetamol	3.3	85.0	11.7
3. Glucocorticoids	1.7	93.3	5.0
4. Anti-depressants, muscle relaxants, neuromodulators	16.7	70.0	13.3
5. Opioids	8.3	85.0	6.7
6. Combination therapy	1.7	98.3	0.0
7. Continuous *vs* on-demand NSAIDs	5.0	91.7	3.3
8. Pregnancy and lactation	1.7	91.7	6.7
9. MTX + NSAIDs or paracetamol	1.7	96.7	1.7
10. GI and hepatic comorbidity	3.3	91.7	5.0
11. CV and renal comorbidity	6.8	86.4	6.8
12. Algorithm	20.0	75.0	5.0

developed to address clinical questions that are important to practicing rheumatologists, are informed by the current evidence base and are supported by a large panel of international rheumatologists.

This process has a number of strengths. First, the breadth of participation in the 3e Initiative ensures its relevance and promotes the implementation of the recommendations into rheumatology practice worldwide. There was a high level of agreement with the final recommendations, and one in five of the expert rheumatologists reported that the algorithm would change their practice. Second, a rigorous approach was taken to both the systematic appraisal of the evidence base, including a highly sensitive search strategy, and the formal voting process

for the development of the clinical questions and final recommendations.

There was relatively little evidence available for many of the questions in this 3e Initiative, particularly regarding IAs other than RA. Many of the included studies were performed in an era that pre-dates the current practice of early intensive therapy, and the use of novel DMARDs, including the biologic drugs, which may limit applicability to patients in the modern era. This resulted in generally low Oxford levels of evidence within the recommendations, although we took a conservative approach to appraisal and chose to downgrade by one level where there was heterogeneity among the included studies. Nonetheless, the recommendations represent the integration of the best available evidence and multinational clinical expertise, and as such remain a valuable tool for rheumatologists in the clinic. Moreover, our findings highlight the need for further well-designed clinical trials of analgesic drugs in patients with a variety of inflammatory arthropathies, taking into account current immunomodulatory strategies, novel analgesic drugs and modern understanding of the neurobiology of pain.

In summary, 11 multinational recommendations and an algorithm for pain management by pharmacotherapy in IA were developed. They are evidence based and supported by a large panel of rheumatologists from 17 countries, thus enhancing their utility in clinical practice.

Rheumatology key messages

- Good pain management is a high priority for individuals with IA.
- Recommendations for the pharmacological management of pain integrate the best available evidence and international expertise.
- The systematic literature reviews highlight the large research agenda for pain management in IA.

Acknowledgements

The authors acknowledge the work of all members of the 3e scientific committees and all participants in the national meetings, the administrative support from Margaux Orange and, in particular, the work of Louise Falzon in assisting with the development of the literature search strategies.

Funding: This work was supported by Abbott with an unrestricted educational grant.

Disclosure statement: U.M.-L. and R.W. have received honoraria from Abbott for scientific support of the 3e initiative. C.B. is a consultant for Abbott, Amgen, AstraZeneca, Bayer Inc., Biogen Idec, Bristol-Myers Squibb Canada company, Hoffmann-La Roche, Merck (Schering Plough Canada), Pfizer and UCB Canada Inc., is a member of an advisory board for the Janssen (Merck & Company Inc.) National Advisory Board, Combinatorx Incorporated, Schering Plough, Pfizer, Takeda Canada Inc. and holds research grants from Abbott Laboratories, Bristol-Myers Squibb Canada, Janssen, Hoffman La-Roche, Pfizer, Schering Canada and UCB Canada Inc. All other authors have declared no conflicts of interest.

References

1 Bergman MJ. Social and economic impact of inflammatory arthritis. Postgrad Med 2006, Spec No:5–11.

2 Kvien TK. Epidemiology and burden of illness of rheumatoid arthritis. Pharmacoeconomics 2004;22:1–12.

3 Minnock P, FitzGerald O, Bresnihan B. Women with established rheumatoid arthritis perceive pain as the predominant impairment of health status. Rheumatology 2003;42:995–1000.

4 Heiberg T, Kvien TK. Preferences for improved health examined in 1,024 patients with rheumatoid arthritis: pain has highest priority. Arthritis Rheum 2002;47:391–7.

5 Machado P, Castrejon I, Katchamart W *et al*. Multinational evidence-based recommendations on how to investigate and follow-up undifferentiated peripheral inflammatory arthritis: integrating systematic literature research and expert opinion of a broad international panel of rheumatologists in the 3E Initiative. Ann Rheum Dis 2011;70:15–24.

6 Sidiropoulos PI, Hatemi G, Song IH *et al*. Evidence-based recommendations for the management of ankylosing spondylitis: systematic literature search of the 3E Initiative in rheumatology involving a broad panel of experts and practising rheumatologists. Rheumatology 2008;47:355–61.

7 Visser K, Katchamart W, Loza E *et al*. Multinational evidence-based recommendations for the use of methotrexate in rheumatic disorders with a focus on rheumatoid arthritis: integrating systematic literature research and expert opinion of a broad international panel of rheumatologists in the 3E Initiative. Ann Rheum Dis 2009;68:1086–93.

8 Higgins JP, Green S, Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.2 (updated September 2009). The Cochrane Collaboration 2009.

9 Levels of evidence (March 2009). http://www.cebm.net/index.aspx?o=1025 (28 September 2011, date last accessed).

10 Englbrecht M, Tarner IH, Van Der Heijde D *et al*. Measuring pain and efficacy of pain treatment in inflammatory arthritis: a systematic literature review. J Rheumatol in press.

11 Hazlewood G, Van Der Heijde D, Bombardier C. Paracetamol for the management of pain in inflammatory arthritis: a systematic literature review. J Rheumatol in press.

12 Tarner IH, Englbrecht M, Schneider M, Van Der Heijde D, Muller-Ladner U. The role of corticosteroids for pain relief in persistent pain of inflammatory arthritis: a systematic literature review. J Rheumatol in press.

13 Kean WF, Rainsford KD, Kean IR. Management of chronic musculoskeletal pain in the elderly: opinions on oral medication use. Inflammopharmacology 2008;16:53–75.

14 van der Goes MC, Jacobs JW, Boers M *et al*. Monitoring adverse events of low-dose glucocorticoid therapy: EULAR

recommendations for clinical trials and daily practice. Ann Rheum Dis 2010;69:1913–9.

15 Richards BL, Whittle SL, Buchbinder R. Antidepressants for pain management in rheumatoid arthritis. Cochrane Database Syst Rev 2011;11:CD008920.

16 Emery P, Gibson T. A double-blind study of the simple analgesic nefopam in rheumatoid arthritis. Br J Rheumatol 1986;25:72–6.

17 Swinson DR, Booth J, Baker RD. Nefopam in rheumatoid arthritis. Results of a double-blind placebo controlled study. Clin Rheumatol 1988;7:411–2.

18 Richards BL, Whittle SL, Buchbinder R. Neuromodulators for pain management in rheumatoid arthritis. Cochrane Database Syst Rev 2012;1:CD008921.

19 Deal CL, Schnitzer TJ, Lipstein E *et al*. Treatment of arthritis with topical capsaicin: a double-blind trial. Clin Ther 1991;13:383–95.

20 Arnold LM, Goldenberg DL, Stanford SB *et al*. Gabapentin in the treatment of fibromyalgia: a randomized, double-blind, placebo-controlled, multicenter trial. Arthritis Rheum 2007;56:1336–44.

21 Crofford LJ, Mease PJ, Simpson SL *et al*. Fibromyalgia relapse evaluation and efficacy for durability of meaningful relief (FREEDOM): a 6-month, double-blind, placebo-controlled trial with pregabalin. Pain 2008;136: 419–31.

22 Mease PJ, Russell IJ, Arnold LM *et al*. A randomized, double-blind, placebo-controlled, phase III trial of pregabalin in the treatment of patients with fibromyalgia. J Rheumatol 2008;35:502–14.

23 Mohler H, Fritschy JM, Rudolph U. A new benzodiazepine pharmacology. J Pharmacol Exp Ther 2002;300:2–8.

24 Vince JD, Kremer D. Double-blind trial of diazepam in rheumatoid arthritis. Practitioner 1973;210:264–7.

25 Drewes AM, Bjerregard K, Taagholt SJ, Svendsen L, Nielsen KD. Zopiclone as night medication in rheumatoid arthritis. Scand J Rheumatol 1998;27:180–7.

26 Richards BL, Whittle SL, Buchbinder R. Muscle relaxants for pain management in rheumatoid arthritis. Cochrane Database Syst Rev 2012;1:CD008922.

27 Goldman A, Hain R, Liben S. Oxford Textbook of Palliative Care for Children. Oxford: Oxford University Press, 2006.

28 Canadian Guideline for Safe and Effective Use of Opioids for Chronic Non-Cancer Pain, 2010. http://nationalpain centre.mcmaster.ca/documents/opioid_guideline_part_a_ v4_5.pdf (28 September 2011, date last accessed).

29 Whittle Samuel L, Richards Bethan L, Husni E, Buchbinder R. Opioid therapy for treating rheumatoid arthritis pain. Cochrane Database Syst Rev 2011;11: CD003113.

30 Boureau F, Boccard E. Placebo-controlled study of the analgesic efficacy of a combination of paracetamol and codeine in rheumatoid arthritis. Acta Ther 1991;17:123–36.

31 Brunnmuller U, Zeidler H, Alten R, Gromnica Ihle E. [Effective analgesic therapy with tilidine/naloxone for patients with rheumatoid arthritis]. Aktuelle Rheumatologie 2004;29:35–9.

32 Lee EY, Lee EB, Park BJ *et al*. Tramadol 37.5-mg/acetaminophen 325-mg combination tablets added to regular therapy for rheumatoid arthritis pain: a 1-week, randomized, double-blind, placebo-controlled trial. Clin Ther 2006;28:2052–60.

33 Boada JN, Boada C, Garcia-Saiz M *et al*. Net efficacy adjusted for risk (NEAR): a simple procedure for measuring risk:benefit balance. PLoS ONE 2008;3:e3580.

34 Beaver WT. Combination analgesics. Am J Med 1984;77: 38–53.

35 Ramiro S, Radner H, van der Heijde D *et al*. Combination therapy for pain management in inflammatory arthritis (rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, other spondyloarthritis). Cochrane Database Syst Rev 2011;10:CD008886.

36 Wanders A, van der Heijde D, Landewe R *et al*. Nonsteroidal antiinflammatory drugs reduce radiographic progression in patients with ankylosing spondylitis: a randomized clinical trial. Arthritis Rheum 2005;52:1756–65.

37 Adams K, Bombardier C, van der Heijde D. Safety of on-demand versus continuous use of NSAIDs in patients with inflammatory arthritis: a systematic literature review. J Rheumatol in press.

38 Adams K, Bombardier C, van der Heijde D. Safety of pain therapy during pregnancy and lactation in patients with inflammatory arthritis: a systematic literature review. J Rheumatol in press.

39 Colebatch AN, Marks JL, Edwards CJ. Safety of non-steroidal anti-inflammatory drugs, including aspirin and paracetamol (acetaminophen) in people receiving methotrexate for inflammatory arthritis (rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, other spondyloarthritis). Cochrane Database Syst Rev 2011;11: CD008872.

40 Carroll GJ, Thomas R, Phatouros CC *et al*. Incidence, prevalence and possible risk factors for pneumonitis in patients with rheumatoid arthritis receiving methotrexate. J Rheumatol 1994;21:51–4.

41 Carson CW, Cannon GW, Egger MJ, Ward JR, Clegg DO. Pulmonary disease during the treatment of rheumatoid arthritis with low dose pulse methotrexate. Semin Arthritis Rheum 1987;16:186–95.

42 Ideguchi H, Ohno S, Ishigatsubo Y. Risk factors associated with the cumulative survival of low-dose methotrexate in 273 Japanese patients with rheumatoid arthritis. J Clin Rheumatol 2007;13:73–8.

43 Sanchez G, Castro JS, Snih SA *et al*. Durability of treatment with methotrexate in Venezuelan patients with rheumatoid arthritis. Rheumatol Int 2007;27:531–6.

44 Swierkot J, Szechinski J. Side effects of methotrexate treatment in patients with rheumatoid arthritis. Adv Clin Exp Med 2008;17:387–94.

45 McKendry RJ, Dale P. Adverse effects of low dose methotrexate therapy in rheumatoid arthritis. J Rheumatol 1993;20:1850–6.

46 Fries JF, Singh G, Lenert L, Furst DE. Aspirin, hydroxychloroquine, and hepatic enzyme abnormalities with methotrexate in rheumatoid arthritis. Arthritis Rheum 1990;33:1611–9.

47 Seideman P, Muller-Suur R. Renal effects of aspirin and low dose methotrexate in rheumatoid arthritis. Ann Rheum Dis 1993;52:613–5.

48 Tohgi H, Konno S, Tamura K, Kimura B, Kawano K. Effects of low-to-high doses of aspirin on platelet aggregability and metabolites of thromboxane A2 and prostacyclin. Stroke 1992;23:1400–3.

49 Pillinger MH, Capodici C, Rosenthal P *et al*. Modes of action of aspirin-like drugs: salicylates inhibit erk activation and integrin-dependent neutrophil adhesion. Proc Natl Acad Sci USA 1998;95:14540–5.

50 Bourre-Tessier J, Haraoui B. Methotrexate drug interactions in the treatment of rheumatoid arthritis: a systematic review. J Rheumatol 2010;37:1416–21.

51 Radner H, Ramiro S, Buchbinder R *et al*. Pain management for inflammatory arthritis (rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis and other spondylarthritis) and gastrointestinal or liver comorbidity. Cochrane Database Syst Rev 2012;1:CD008951.

52 Laine L, Bombardier C, Hawkey CJ *et al*. Stratifying the risk of NSAID-related upper gastrointestinal clinical events: results of a double-blind outcomes study in patients with rheumatoid arthritis. Gastroenterology 2002; 123:1006–12.

53 Eisen GM, Goldstein JL, Hanna DB, Rublee DA. Meta-analysis: upper gastrointestinal tolerability of valdecoxib, a cyclooxygenase-2-specific inhibitor, compared with nonspecific nonsteroidal anti-inflammatory drugs among patients with osteoarthritis and rheumatoid arthritis. Aliment Pharmacol Ther 2005;21:591–8.

54 Marks JL, Colebatch AN, Buchbinder R, Edwards CJ. Pain management for rheumatoid arthritis and cardiovascular or renal co-morbidity. Cochrane Database Syst Rev 2011; 10:CD008952.

55 Cannon CP, Curtis SP, FitzGerald GA *et al*. Cardiovascular outcomes with etoricoxib and diclofenac in patients with osteoarthritis and rheumatoid arthritis in the Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) programme: a randomised comparison. Lancet 2006;368: 1771–81.

56 Fosbol EL, Kober L, Torp-Pedersen C, Gislason GH. Cardiovascular safety of non-steroidal anti-inflammatory drugs among healthy individuals. Expert Opin Drug Saf 2010;9:893–903.

57 Farkouh ME, Greenberg BP. An evidence-based review of the cardiovascular risks of nonsteroidal anti-inflammatory drugs. Am J Cardiol 2009;103:1227–37.

58 Hermann M. Cardiovascular risk associated with non-steroidal anti-inflammatory drugs. Curr Rheumatol Rep 2009;11:31–5.

59 Sudano I, Flammer AJ, Periat D *et al*. Acetaminophen increases blood pressure in patients with coronary artery disease. Circulation 2010;122:1789–96.

60 Crofford LJ. Pain management in fibromyalgia. Curr Opin Rheumatol 2008;20:246–50.

61 Mease PJ, Clauw DJ, Gendreau RM *et al*. The efficacy and safety of milnacipran for treatment of fibromyalgia. a randomized, double-blind, placebo-controlled trial. J Rheumatol 2009;36:398–409.

62 Russell IJ, Mease PJ, Smith TR *et al*. Efficacy and safety of duloxetine for treatment of fibromyalgia in patients with or without major depressive disorder: results from a 6-month, randomized, double-blind, placebo-controlled, fixed-dose trial. Pain 2008;136:432–44.