The Efficacy and Safety of Treatments for Acute Gout: Results from a Series of Systematic Literature Reviews Including Cochrane Reviews on Intraarticular Glucocorticoids, Colchicine, Nonsteroidal Antiinflammatory Drugs, and Interleukin-1 Inhibitors

Mihir D. Wechalekar, Ophir Vinik, John H.Y. Moi, Francisca Sivera, Irene A.A.M. van Echteld, Caroline van Durme, Louise Falzon, Claire Bombardier, Loreto Carmona, Daniel Aletaha, Robert B. Landewé, Désirée M.F.M. van der Heijde, and Rachelle Buchbinder

ABSTRACT. ***Objective.*** To determine the efficacy and safety of glucocorticoids (GC), colchicine, nonsteroidal antiinflammatory drugs (NSAID), interleukin-1 (IL-1) inhibitors, and paracetamol to treat acute gout.

Methods. We searched MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials to September 2011. Randomized controlled trials (RCT) or quasi-RCT in adults with acute gout that compared GC, colchicine, NSAID, IL-1 inhibitors, and paracetamol to no treatment, placebo, another intervention, or combination therapy were included. Two authors independently extracted data and assessed risk of bias. Primary endpoints were pain and adverse events. Data were pooled where appropriate.

Results. Twenty-six trials evaluating GC (N = 5), NSAID (N = 21), colchicine (N = 2), and canakinumab (N = 1) were included. No RCT assessed paracetamol or intraarticular (IA) GC. No RCT compared systemic GC with placebo. Moderate quality evidence (3 trials) concluded that systemic GC were as effective as NSAID but safer. Low quality evidence (1 trial) showed that both high- and low-dose colchicine were more effective than placebo, and low-dose colchicine was no different to placebo with respect to safety but safer than high-dose colchicine. Low quality evidence (1 trial) showed no difference between NSAID and placebo with regard to pain or inflammation. No NSAID was superior to another. Moderate quality evidence (1 trial) found that 150 mg canakinumab was more effective than a single dose of intramuscular GC (40 mg triamcinolone) and equally safe.

Conclusion. GC, NSAID, low-dose colchicine, and canakinumab all effectively treat acute gout. There was insufficient evidence to rank them. Systemic GC appeared safer than NSAID and lower-dose colchicine was safer than higher-dose colchicine. (J Rheumatol Suppl. 2014 Sept; 92:15–25; doi:10.3899/jrheum.140458)

Key Indexing Terms:
GOUTY ARTHRITIS GLUCOCORTICOIDS COLCHICINE
NSAID PARACETAMOL INTERLEUKIN-1 INHIBITORS

From the Rheumatology Research Unit, Repatriation General Hospital, Daw Park, South Australia; and Flinders University, Bedford Park, South Australia, Australia; Division of Rheumatology, University of Toronto, Toronto, Ontario, Canada; Department of Rheumatology, The Royal Melbourne Hospital, Melbourne, Australia; Department of Rheumatology, Hospital General Universitario Elda, Alicante, Spain; Rheumatology Department, St. Elisabeth Hospital, Tilburg, The Netherlands; Rheumatology Department, Maastricht University Medical Centre, Maastricht, The Netherlands; and Rheumatology Department, Centre Hospitalier Universitaire, Liège, Belgium; Center for Behavioral Cardiovascular Health, Columbia University Medical Center, New York, NY, USA; Division of Rheumatology and Institute of Health Policy, Management, and Evaluation, University of Toronto; and Toronto General Research Institute, University Health Network; Institute for Work and Health, Mount Sinai Hospital, Toronto, Ontario, Canada; Facultad de Ciencias de la Salud, Universidad Camilo Jose Cela, Madrid, Spain; Internal Medicine, Rheumatology Department, Medical University of Vienna, Vienna, Austria; Department of Clinical Immunology and Rheumatology, Academic Medical Center, Amsterdam, The Netherlands; and Atrium Medical Center; Rheumatology Department, Leiden University Medical Center, Leiden, The Netherlands; Monash Department of Clinical Epidemiology, Cabrini Hospital, Malvern, Victoria, Australia; and Department of Epidemiology and Preventive Medicine, School of Public Health and Preventive Medicine, Monash University, Malvern, Victoria, Australia.

The authors acknowledge the work of all members of the 3e scientific committees and all participants in the national meetings. This article is derived from the 3e Gout program, which was sponsored by AbbVie Inc. Margaux Orange, Paris, France, provided logistical and administrative support for the 3e Gout meetings; this work was funded by AbbVie Inc. AbbVie employees were present during the 3e meetings, but did not influence the scientific discussions. AbbVie did not review the content or have influence on this manuscript. In addition to systematic literature reviews on systemic glucocorticoids and paracetamol, this article is based on four Cochrane reviews, and was submitted to the Cochrane Database of Systematic Reviews (CDSR) (see the www.cochranelibrary.com for

information). Cochrane reviews are regularly updated as new evidence emerges and in response to feedback, and the CDSR should be consulted for the most recent version of the review.

M.D. Wechalekar, MD, FRACP, Rheumatology Unit, Repatriation General Hospital, Daw Park, South Australia, Australia; and Flinders University; O. Vinik, MD, FRCPC, Division of Rheumatology, University of Toronto; J.H.Y. Moi, BPhysio (Hons), MBBS (Hons), FRACP, Rheumatologist, Department of Rheumatology, The Royal Melbourne Hospital, Melbourne, Australia; F. Sivera, MD, Department of Rheumatology, Hospital General Universitario Elda; I.A.A.M. van Echteld, MD, Rheumatology Department, St Elisabeth Hospital; C. van Durme, MD, Rheumatology Department, Maastricht University Medical Centre; and Rheumatology Department, Centre Hospitalier Universitaire; L. Falzon, PGDipInf, Center for Behavioral Cardiovascular Health, Columbia University Medical Center;
C. Bombardier, MD, FRCPC, Professor, Division of Rheumatology and Institute of Health Policy, Management, and Evaluation, University of Toronto; and Toronto General Research Institute, University Health Network; Institute for Work and Health, Mount Sinai Hospital;
L. Carmona, MD, PhD, Facultad de Ciencias de la Salud, Universidad Camilo Jose Cela; D. Aletaha, MD, MSc, Internal Medicine, Rheumatology Department, Medical University of Vienna; R.B. Landewé, MD, PhD, Professor, Department of Clinical Immunology and Rheumatology, Academic Medical Center, Amsterdam, The Netherlands; and Atrium Medical Center; D.M.F.M. van der Heijde, MD, PhD, Professor of Rheumatology, Rheumatology Department, Leiden University Medical Center; R. Buchbinder, MBBS (Hons), MSc, PhD, FRACP, Director, Monash Department of Clinical Epidemiology, Cabrini Hospital, Malvern, Victoria, Australia; and Professor, Department of Epidemiology and Preventive Medicine, School of Public Health and Preventive Medicine, Monash.

Address correspondence to Dr. M.D. Wechalekar, Rheumatology Unit, Repatriation General Hospital, Daws Road, Daw Park SA 5041, Australia. E-mail: mihir.w@gmail.com

The natural history of gout is composed of 3 periods: asymptomatic hyperuricemia, episodes of acute gout, and chronic gouty arthritis[1]. Hyperuricemia results from either urate overproduction or more commonly urate underexcretion, or a combination of these[2]. Gout heralds its presence by an exquisitely painful, acute monoarthritic attack of sudden onset; polyarticular initial attacks although less common (3%–14%) are well recognized[2]. Initial attacks are usually monoarticular, affecting lower limb joints, most commonly big toe; subsequent attacks tend to be longer lasting, polyarticular, and tend to affect upper limb joints as well[1].

Pharmacologic treatment options to treat gout include glucocorticoids (GC), colchicine, nonsteroidal antiinflammatory drugs (NSAID), paracetamol, and more recently, interleukin 1 (IL-1) inhibitors, alone or in combination. Preference and usage of these drugs differ across regions. Despite the common occurrence of acute gout, few guidelines have a multinational, in contrast to a more regional[3,4,5], perspective. It is in this context that a series of systematic reviews were conducted to address this question as an evidence base for developing multinational clinical practice recommendations.

This article is part of the 3e (Evidence, Expertise, Exchange) Initiative on Diagnosis and Management of Gout[6]. Its objective was to systematically review the available evidence for the question, "What is the role of glucocorticoids, colchicine, nonsteroidal antiinflammatory drugs, anti-interleukin 1 drugs, and paracetamol in the management of acute gout?", as an evidence base for generating recommendations. This article includes systematic literature reviews (SLR) on systemic GC and paracetamol in acute gout and modified versions of Cochrane reviews of intra-articular (IA) GC[7,8], colchicine[9], NSAID[10], and IL-1 inhibitors[11,12] for the treatment of acute gout.

MATERIALS AND METHODS

The systematic reviews were carried out in several steps in accord with the methods recommended by the Cochrane Collaboration[7,11,13].

Rephrasing the research question. The clinical question posed by the experts was rephrased to enable epidemiological enquiry using the PICO (Patient, Intervention, Comparator, Outcome) approach[14]. Patients were defined as adults (age ≥ 18 yrs) with acute gout as defined by study authors, identification of monosodium urate crystals, or fulfilling the 1977 American College of Rheumatology (ACR), Rome, or New York criteria for gout[15,16]. The interventions included GC by any route, colchicine, NSAID, IL-1 inhibitors, and paracetamol. Comparators were defined as placebo or no treatment, nonpharmacologic treatment (e.g., rest, ice), different modes of therapy, and combination therapy (of any of the interventions). In accord with outcomes recommended by OMERACT (Outcome Measures in Rheumatology Clinical Trials)[17], the major outcomes were pain, withdrawals due to adverse events (AE) or serious adverse events (SAE), inflammation (joint swelling, tenderness, and erythema), patient global assessment (PGA), function of target joint, health-related quality of life (HRQOL), and number of participants with AE.

Included study types were randomized controlled studies (RCT) or quasi-RCT; in addition, for safety, US Food and Drug Administration (FDA)/blackbox warnings were noted. Studies that compared different drugs in the same class (e.g., one NSAID versus another), or the same drug administered by a different route or dosing strategy, were also included. Studies were excluded if there was a mixed population, and data for people with acute gout could not be extracted separately. Trials of drugs no longer licensed were also excluded. Studies in a language other than English were excluded unless in a language in which at least 1 member of the 3e bibliographic group was fluent (Dutch, German, French, and Spanish); the Cochrane reviews were unrestricted by language.

Systematic literature search. A systematic search of the Cochrane Central Register of Controlled Trials (CENTRAL) (via the Cochrane Library, to Issue 9, 2011), MEDLINE (via OVID 1948 to September 2011), and EMBASE (via OVID 1980 to September 2011) was conducted using a search strategy devised with the help of an experienced librarian (LF) (for complete search strategy see online appendix available from the authors). Abstracts from the ACR and European League Against Rheumatism meetings (EULAR) (2010–2011), were also searched. Prior to publication of the Cochrane reviews, searches were updated (NSAID April 2013[10], IL-1 inhibitors June 2013[12], colchicine July 2013[9]), and in some instances additional studies were identified. This is indicated in the relevant section of the individual therapies.

Selection of studies. Search results were independently reviewed by 2 reviewers (MW, OV for IA GC; MW, JM for systemic GC; MW, IvE for colchicine; MW, CvD for NSAID and MW, FS for IL-1 inhibitors).

Data extraction and risk of bias. Raw data (including study design, characteristics of study population, treatment regimen and duration, outcomes and timing of outcome assessment) were extracted from the included studies by 2 reviewers (as above), or in the case of non-English publications, by a member of the 3e multinational panel fluent in the publication language. Risk of bias was assessed by the 2 authors independently using methods recommended by the Cochrane Collaboration[13].

Data analysis. For continuous data, results were analyzed as mean differ-

ences (MD) between the intervention and comparator groups, with corresponding 95% confidence intervals (95% CI). For dichotomous data, a risk ratio (RR) with corresponding 95% CI was calculated. We assessed studies for clinical homogeneity with respect to type of therapy, control group, and outcomes, and only studies judged to be clinically homogeneous were pooled. Statistical heterogeneity was assessed using the I^2 statistic[18].

RESULTS

A total of 564 potentially relevant articles were identified: 153 for IA and systemic GC, 308 for colchicine, 410 for NSAID, 42 for IL-1 inhibitors, and 20 for paracetamol (Figures 1A-1F). Of these, 5 trials for systemic GC, 2 for colchicine, 21 for NSAID, and 1 for IL-1 inhibitors met our inclusion criteria. No trials of IA GC or paracetamol met our inclusion criteria. Of 9 ACR and EULAR abstracts of potential relevance, none were suitable for inclusion. The characteristics of studies included in the final review are summarized in Table 1. A list of excluded studies and reasons for exclusion are included in the online Appendix available from the authors.

Systemic Glucocorticoids

All 5 included trials[19-23,24] that met our inclusion criteria

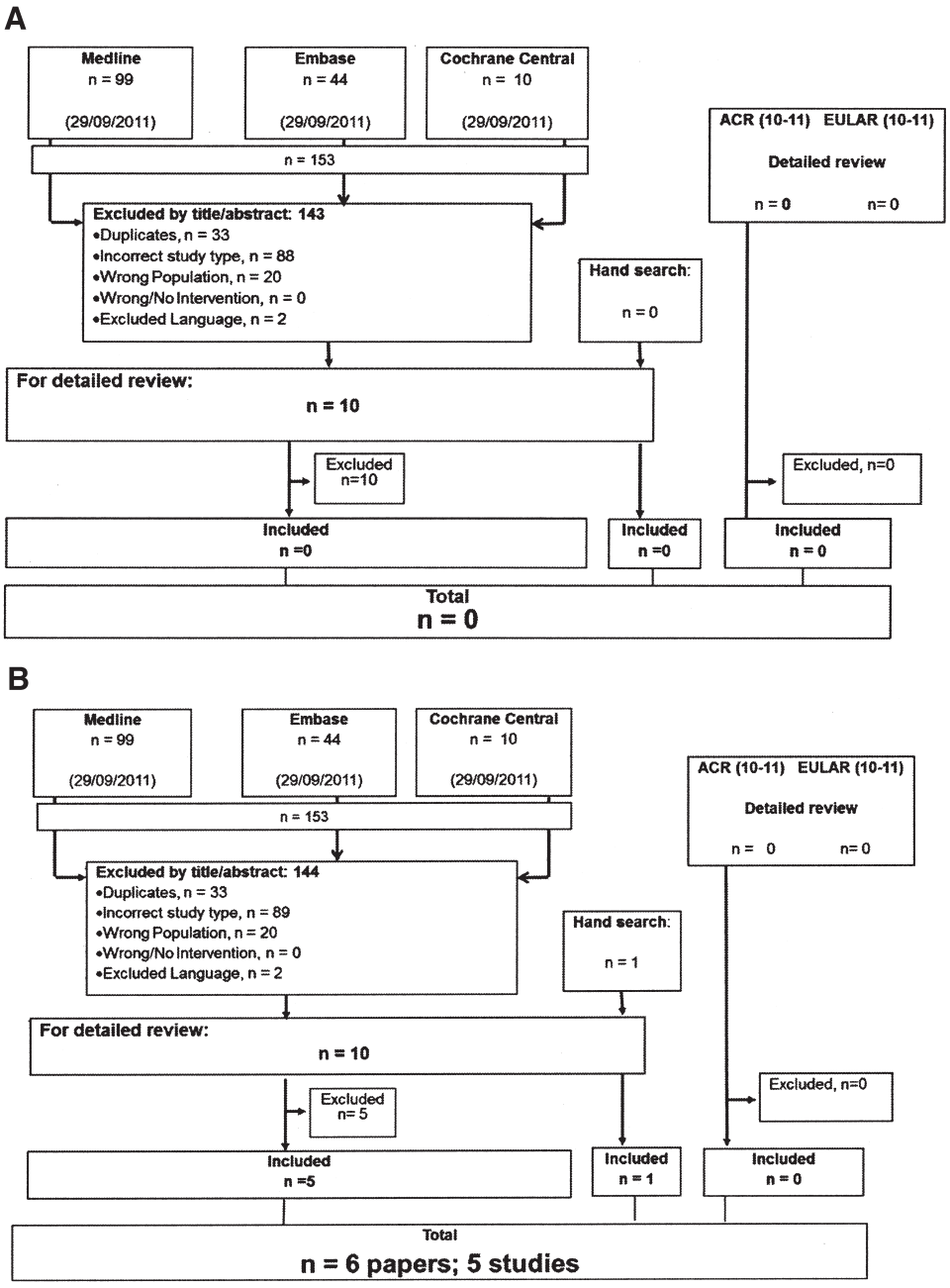

Figure 1. A. Results of the search strategy. Literature search for intraarticular glucocorticoids in acute gout. A total of 153 studies were identified by the initial search; of these, 10 studies were retrieved in full text for detailed review. None met the criteria for inclusion in the final review. B. Results of the search strategy. Literature search for systemic glucocorticoids in acute gout. A total of 153 studies were identified by the initial search; of these 5 studies (1 study was published in 2 articles; 1 found on hand search) met the criteria for inclusion in the final review.

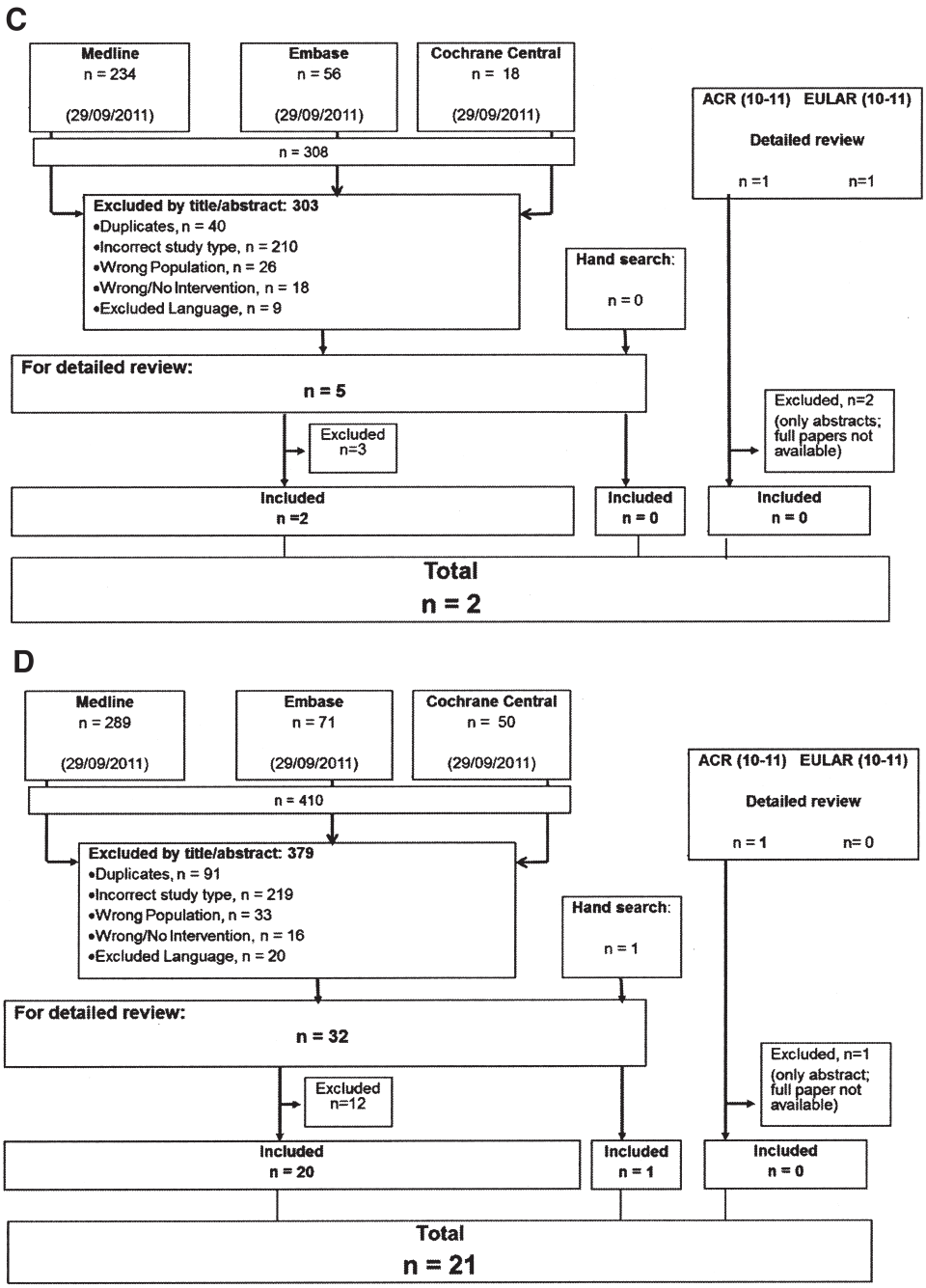

Figure 1. C. Results of the search strategy. Literature search for colchicine in acute gout. A total of 308 studies were identified by the initial search; of these, 2 studies met the criteria for inclusion in the final review. D. Literature search for NSAID in acute gout. A total of 410 studies were identified by the initial search; of these, 21 studies met the criteria for inclusion in the final review.

were parallel RCT; no trials compared systemic GC to placebo. Three trials compared systemic GC to NSAID[19,20,21], one compared 1 systemic GC to another[23], and 1 (reported in 2 articles) compared systemic GC to canakinumab, an IL-1 inhibitor[22,24]. Risk of bias of included trials is shown in supplementary Figure 2A in the Appendix available from the authors.

Systemic GC versus NSAID. Of the 3 trials that compared systemic GC to NSAID, one[21] (n = 90; low risk of bias) compared oral prednisolone (35 mg daily for 5 days) to indomethacin (indomethacin 50 mg and diclofenac 75 mg on day 1 followed by indomethacin 150 mg for 2 days and 75 mg for 3 days). Outcomes (pain reduction in mm/h and AE) were evaluated every 30 min for 2 h, at 24 h, and on day

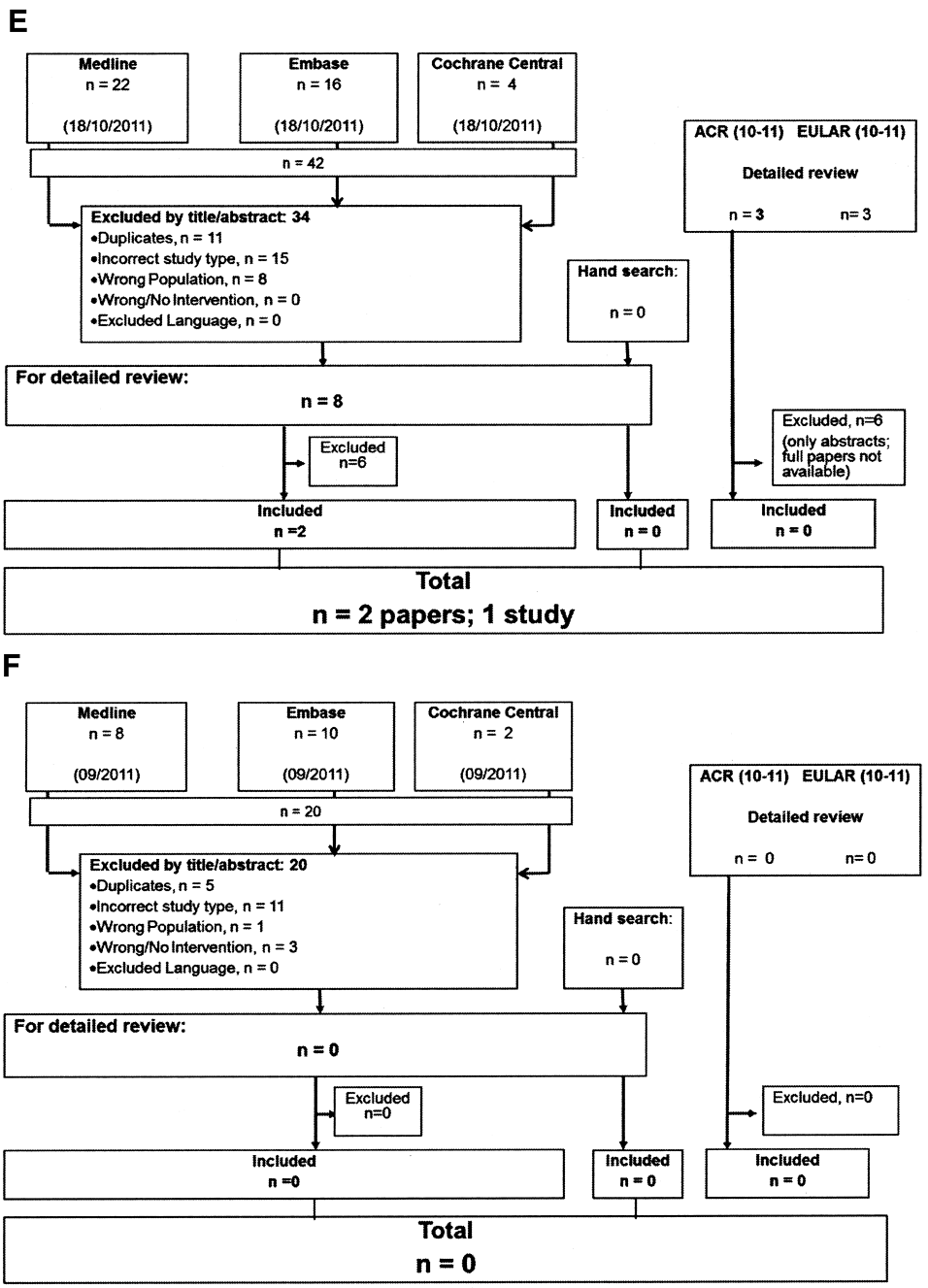

Figure 1. E. Results of the search strategy. Literature search for anti-interleukin 1 drugs in acute gout. A total of 42 studies were identified by the initial search; of these, 1 study (published in 2 articles) met the criteria for inclusion in the final review. F. Results of the search strategy. Literature search for paracetamol in acute gout. A total of 20 studies were identified by the initial search; no study met the criteria for inclusion in the final review.

5 and 14. Another low risk of bias trial (n = 120)[20] compared oral prednisolone (35 mg daily for 5 days) to naproxen (1 g daily for 5 days). Outcomes measured (on a 100 mm VAS) over 90 h were pain, general disability and walking disability, and AE. The third trial (n = 100)[19] (high risk of bias) compared 40 IU intramuscular (IM) adrenocorticotropic hormone (ACTH) to indomethacin (up to 200 mg daily till pain relief). Outcomes were evaluated at 0–5 h and at 5–7 days; followup was for 1 year. Primary outcome was time to complete pain relief on ambulation; other outcomes were time to complete pain relief, intervals between attacks during trial period, and AE.

One systemic GC versus another. A single trial[23] (n = 31; high risk of bias) compared a single IM dose of 40 IU of

Table 1. Characteristics of studies included in the final review.

Study, Country	Gout Diagnosis; No. Joints Involved	Total No. (dropouts)	Duration	Design	Intervention	Comparator	Overall Risk of Bias
Systemic glucocorticoids	No studies of systemic glucocorticoids vs placebo						
Systemic glucocorticoids vs NSAID							
Axelrod 1988[19], USA	Expert opinion, MSU crystals; mono/oligo	100 (24)	7 days (1 yr)	Parallel RCT	ACTH 40 IU	Indomethacin 50 mg × 4/d, till pain relief	High
Janssens 2008[20], Netherlands	MSU crystals; mono	120 (2)	3 weeks	Parallel RCT	Prednisolone 35 mg/d × 5 days	Naproxen 1g × 5 days	Low
Man 2007[21], China	MSU crystals/ study predefined clinical criteria; mono in 85	90 (0)	14 days	Parallel RCT	Prednisolone 30 mg/ paracetamol 1 g × 5 days	Indomethacin 50 mg/diclofenac IM 75 mg/paracetamol 1 g, then indomethacin 150 mg/d × 2 days, then 75 mg/d × 3 days	Low
Systemic glucocorticoids vs canakinumab							
So 2010[24], Switzerland, USA	ACR 1977; 126 mono, 56 oligo, 18 poly	200 (9)	8 weeks	Parallel RCT	Triamcinolone 40 mg IM	Canakinumab 10-150 mg S/C	Unclear
Systemic glucocorticoids vs systemic glucocorticoids							
Siegel 1994[23], USA	MSU crystals; mono/oligo	31 (1)	30 days	Parallel RCT	ACTH 40 IU IM	Triamcinolone 60 mg IM	High
Colchicine							
Ahern 1987[27], Australia	MSU crystals; mono in 42/43	43 (2)	48 h	Parallel RCT	Oral colchicine 1 mg, then 0.5 mg 2 hourly till symptom relief or GI toxicity	Placebo	Low
Terkeltaub 2010[28], USA	ACR 1977; mono/ oligo/ poly	575 (1)	72 hours	Parallel RCT	High dose colchicine 1.2 mg, then 0.6 mg q 1h for 6 h (total 4.8 mg)	Placebo; low dose colchicine 1.2 mg, then 0.6 mg in 1 h	Unclear
NSAID							
NSAID vs placebo							
Garcia de la Torre, 1987[34], Mexico	MSU crystals/ clinical criteria; n/a	30 (1)	4 days	Parallel CCT	Tenoxicam 40 mg × 4 d	Placebo	High
NSAID vs alternate NSAID (for NSAID vs systemic glucocorticoids, please see above)							
Altman 1988[29], USA	MSU crystals/ clinical / ACR 1977; n/a	59 (7)	15 days	Parallel CCT	Ketoprofen, 150 mg, then up to 100 mg × 3 doses	Indomethacin, 75 mg, then up to 50 mg × 3 doses	Low
Butler 1985[30], UK	MSU crystals/ clinical; n/a	33 (7)	10 days	Parallel CCT	Flurbiprofen, 400 mg/ d × 2 days, then 200 mg/d × 10 days	Phenylbutazone 800 mg/d × 2 days, then 400 mg/d × 10 days	Unclear
Cheng 2004[31], China	ACR 1977; Mono/oligo	62 (n/a)	8 days	Parallel RCT	Diclofenac SR, 75 mg/d × 7 days	Meloxicam 7.5 mg/d × 7 days, Rofecoxib arm 50 mg/d × 7 days	High
Douglas 1970[32], UK	Clinical criteria; n/a	25 (1)	14 days	Parallel RCT	Phenylbutazone, 800 mg × 2 days, then 400 mg till resolution of attack	Flufenamic acid, 800 mg × 2 days, then 400 mg till resolution of attack	Low
Eberl 1993[33], Austria	MSU crystals/ NY criteria; n/a	20 (n/a)	14 days	Parallel CCT	Meclofenamate, 200 mg then 600 mg × 1 day, then 300 mg/d × 6 days	Indomethacin, 25 mg then 150 mg for 1d, then 75 mg/d x 6 days	High
Lederman 1980[35] Brazil	MSU crystals/ NY criteria; n/a	60 (0)	7 days	Parallel CCT	Etodolac 600 mg/d × 7 days	Naproxen 1.5 g/d × 7 days	High
Lomen 1986[36], USA	MSU crystals/ NY criteria; mono	29 (3)	5 days	Parallel RCT	Flurbiprofen 400 mg/d, then 200 mg/d × 5 days	Indomethacin, 200 mg/d, then 100 mg/d × 5 days	Low

Table 1. Continued.

Study, Country	Gout Diagnosis; No. Joints Involved	Total No. (dropouts)	Duration	Design	Intervention	Comparator	Overall Risk of Bias
Maccagno 1991[37], Argentina	MSU crystals/ NY criteria; n/a	61 (0)	7 days	Parallel CCT	Etodolac 600 mg/d × 7 days	Naproxen 1 g/d × 7 days	High
Rubin 2004[38], USA	ACR 1977; mono 144, poly 49	189 (25)	8 days	Parallel RCT	Etoricoxib, 120 mg/d × 8 days	Indomethacin, 150 mg/d × 8 days	Low
Schumacher 2002[39], USA	ACR 1977; mono/ oligo	150 (23)	8 days	Parallel RCT	Etoricoxib, 120 mg/d × 8 days	Indomethacin, 150 mg/d × 8 days	Low
Shrestha 1995[40], USA	ACR 1977; n/a	20 (0)	1 day	Parallel RCT	Ketorolac, 60 mg IM, then indomethacin 150 mg/d × 2 days, then 100 mg/d × 5 days	Indomethacin, 50 mg, then 150 mg/d × 2 days, then 100 mg/d × 5 days	Low
Smyth 1973[42], Canada	Expert opinion; mono/ oligo	28 (n/a)	Not described	Parallel RCT	Phenylbutazone 800 mg/d, then 600 mg × 1 day, then 400 mg/d	Indomethacin, 200 mg/d, then 150 mg × 1 day, then 100 mg/d	Low
Sturge 1977[43], UK	Expert opinion; n/a	41 (n/a)	7 days	Parallel CCT	Naproxen, 750 mg, then 500 mg/d	Phenylbutazone, 800 mg, then 600 mg/d	High
Tumravasin 1985[44], Thailand	MSU crystals; Mono/ oligo/ poly	34 (n/a)	7 days	Parallel CCT	Piroxicam, 40 mg/d × 7 days	Piroxicam, 40 mg/d × 1 day then 20 mg/d × 6 days	High
Valdes 1987[45], Argentina	MSU crystals/ clinical criteria; n/a	10 (n/a)	6 days	Parallel CCT	Tenoxicam, 20 mg/d × 6 days	Tenoxicam, 40 mg/d × 6 days	High
Weiner 1979[46], USA	MSU crystals; n/a	30 (n/a)	4 days	Parallel CCT	Phenylbutazone, 700 mg, then 400 mg × 3 days	Fenoprofen, 3.6 g, then 3 g × 3 days	Low
Willburger 2007[47], Germany	ACR 1977; Mono 187, poly 48	235 (12)	7 days	Parallel RCT	Lumiracoxib, 400 mg/d × 7 days	Indomethacin, 150 mg/d × 7 days	Low
IL-1 inhibitors							
So 2010[24], Switzerland USA	ACR 1977; 126 mono, 56 oligo, 18 poly	200 (9)	8 weeks	Parallel RCT	Triamcinolone, 40 mg IM	Canakinumab, 10–150 mg S/C	Unclear

Mono: monoarticular (1 joint); oligo: oligoarticular (≤ 4 joints); poly: polyarticular (> 4 joints) involvement.

ACTH to a single dose of 60 mg IM triamcinolone; outcomes (grading of pain, swelling, function and mobility as improved by < or > 50%, unchanged, or worse) were assessed at days 1–2, 3–4, 10–14, and 30.

Systemic GC versus IL-1 inhibitors. One trial (n = 200; unclear risk of bias)[22,24] compared systemic GC to canakinumab; patients received either a single IM dose of 40 mg triamcinolone (n = 57) or canakinumab [10–150 mg subcutaneously (SC) at differing doses; n = 143]. Outcomes were assessed at 72 h, 7 days, 4 weeks, and 8 weeks post-dose. Primary outcome was determination of the canakinumab dose that produced equivalent efficacy to that achieved with triamcinolone acetonide 40 mg 72 h after treatment, according to patient assessment of pain on a 100 mm visual analog scale; other outcomes were time to 50% reduction in pain, time to recurrence of flare, reductions in C-reactive protein and serum amyloid A protein levels, use of rescue medication, physician and patient global assessments, and HRQOL. An updated literature search for the related Cochrane review identified 2 more articles [reporting 3 studies; 2 comparing 150 mg canakinumab with 40 mg triamcinolone, and one comparing 320 mg of rilonacept (an IL-1 inhibitor) with indomethacin][25,26].

Effects of systemic GC. Systemic GC versus NSAID. There was moderate quality evidence based on 2 trials of no between-group difference in pain reduction over 2–6 hours [mean difference –1.77 (95% CI –4.80 to 1.26)][20,21]. One of these trials also found no between-group difference in terms of general and walking disability[20]. The third trial reported faster pain relief in the ACTH group compared with the indomethacin group[19], although it was not possible to extract and independently verify the presented data. Gastrointestinal (GI) and non-GI AE were more common with NSAID than systemic GC in 1 trial (22/40 vs 1/36 for GI and 27/40 vs 1/36 for non-GI AE)[19]. SAE were also more common with NSAID than systemic GC in another trial (7/40 vs 0/40)[21]; 5 SAE in the NSAID group were related to GI bleeding.

One systemic GC versus another. There was low quality evidence, based upon 1 trial, of no difference between ACTH and triamcinolone in time to average resolution of symptoms (8 days in both groups)[23].

Systemic GC versus IL-1 inhibitors. Canakinumab at the highest dose used (150 mg) was significantly better than triamcinolone for reduction in pain at 72 h [24/27 vs 6/11 (numbers in the triamcinolone group have been adjusted to account for multiple comparisons); mean difference 26.80 (95% CI 2.35 to 51.25)]; there were no between-group differences in efficacy outcomes between triamcinolone and the lower doses of canakinumab (10 mg, 25 mg, 50 mg, and 90 mg) and no between-group differences in AE comparing triamcinolone to any dose of canakinumab[24].

Colchicine

Both included colchicine trials were parallel RCT: 1 with low[27] and the other with unclear[28] risk of bias (see supplementary Figure 2B in the Appendix available from the authors). One trial (n = 43) randomized partici-pants to either high-dose colchicine (n = 22) or placebo (n = 21)[27]. The other (n = 575) randomized participants to either low- (n = 192) or high-dose colchicine (n = 193) or placebo (n = 190)[28]. Both trials converted pain to a dichotomous measure of success (proportion who improved by ≥ 50%); pain reduction measurements were taken at 12, 24, 36, and 48 h in the first[27] trial and at 24 and 32 h in the second[28]. Secondary outcomes in the first trial were 50% reduction in a compounded score comprising pain, joint tenderness, swelling, redness, and AE; for the second study, secondary outcomes were treatment response based on at least a 2-unit reduction in target joint pain score at 24 and 32 h and AE.

Effects of colchicine. There was low quality evidence based upon 2 trials that showed significantly more people taking high-dose colchicine compared with those taking placebo obtained pain relief at 24 h [26/74 vs 6/50, RR 2.88 (95% CI 1.28 to 6.48)] and 36 hours [35/74 vs 12/50, RR 2.16 (95% CI 1.28 to 3.65)][27,28]. There was low quality evidence based upon 1 trial that low-dose colchicine was also significantly more effective than placebo for pain relief at 24 h [28/74 vs 4/29, RR 2.74 (95% CI 1.05 to 7.13)] and 36 h [31/74 vs 5/29, RR 2.43 (95% CI 1.05 to 5.64)] in 1 trial, but there was no between-group difference in pain relief at 24 h or 36 h for those taking high- versus low-dose colchicine[28].

High-dose colchicine was associated with significantly more GI AE than placebo in both trials: 22/22 versus 5/51 [RR 3.91 (95% CI 1.89 to 8.09)] in 1 trial[27] and 40/52 versus 8/29 [RR 3.72 (95% CI 1.80 to 7.70)] in the other trial[28]. However, participants were instructed to continue taking colchicine until either pain relief or toxicity in the first trial. This may have inflated the risk of GI AE because all partici-pants in this trial developed diarrhea and/or vomiting with median time to onset of toxicity being 24 h or after a mean dose of 6.7 mg of colchicine[27]. High-dose colchicine was associated with significantly more GI AE than low-dose colchicine [40/52 vs 19/74, RR 3.00 (95% CI 1.98 to 4.54)]; with regard to GI AE, low-dose colchicine was no different from placebo [19/74 vs 6/29, RR 1.24 (95% CI 0.55 to 2.79)][28]. For colchicine, we found a FDA warning of the association of potentially fatal AE with IV colchicine (including bone marrow, renal, and cardiac toxicity) and a significant drug interaction between drugs metabolized with CYP3A4 and P-glycoprotein enzyme systems (such as clarithromycin, erythromycin, ketoconazole, ritonavir, vera-pamil, and diltiazem), particularly in the presence of hepatic or renal dysfunction.

NSAID

Trial duration of the 21 NSAID trials (n = 1621) that met our inclusion criteria varied between 90 h and 14 days[19,20,29-33,34-38,39-43,44,45,46,47]. Risk of bias of the included trials is shown in supplementary Figure 2C in the Appendix available from the authors. Only 1 trial (high risk of bias) compared an NSAID (tenoxicam) to placebo[34]; the primary outcomes were time to improvement and resolution of symptoms; secondary outcomes were pain and inflammation. Seventeen trials compared 1 NSAID to another[29-33,35-39,40,42-46,47]. There were 3 trials, all judged to be at low risk of bias, that compared a conventional NSAID (indomethacin) to a selective COX-2 inhibitor (etoricoxib[38], celecoxib[39], or lumiracoxib[47]. The duration of treatment ranged from 5 to 10 days, and followup from 24 h to 14 days. The primary efficacy endpoint in 3 trials was the proportion of participants improved by ≥ 50%[33,34,36] (pain reported on ordinal scales) and the primary safety endpoint of withdrawals due to AE in 13/18 trials[29-33,34-38,39,40,47]. Other endpoints were variably reported. Seven trials[31,32,33,35,36,37,42] variably assessed inflammation as an outcome. Function was assessed in 5 trials[29,31,33,35,37]; of these, two[29,31] assessed function as part of a total inflam-matory score while the other three[33,35,37] trials reported whether there was a limitation of motion of the index joint. Five trials[29,31,35,36,37] included a measure of the patient global assessment; no trials included a measure of HRQOL. Eleven trials[29-33,35,36,37,40,42,43] included the number of participants with AE and provided a description of these. All 3 trials of NSAID versus cyclooxygenase-2 selective drugs measured pain as a primary outcome using a Likert scale[38,47] or 5-point ordinal scale[39] and measured inflam-mation, PGA, and AE as secondary outcomes; function was not assessed in any of the trials and only 1 trial[47] measured HRQOL as a secondary outcome. The description of the 3 trials[20,21,48] that compared an NSAID to GC (oral or systemic) is given above. An updated literature search for the related Cochrane review identified 1 more study[49] (n = 86, low risk of bias) comparing celecoxib to indomethacin.

Effects of NSAID. There was low quality evidence based upon 1 trial (n = 50) that NSAID (tenoxicam) was no different from placebo with respect to ≥ 50% reduction in pain and joint swelling at 24 h and at day 4[34]. Only 2 trials that compared etodolac to naproxen (n = 121) could be pooled; and there were no between-group differences with

respect to proportion who considered themselves markedly improved at the end of treatment [etodolac 53/60 vs naproxen 53/61, RR 1.01 (95% CI 0.89 to 1.15)][35,37]. In the 3 trials (n = 108) that compared indomethacin to another NSAID (flurbiprofen[36], meclofenamate[33], or ketoprofen[29]), there were no between-group differences in efficacy. There was moderate quality evidence, based upon 3 trials (n = 574), of no between-group differences between indomethacin and coxibs with respect to pain [MD 0.02 (95% CI –0.10 to 0.13)], inflammation [MD 0.02 (95% CI –0.08 to 0.11)], or global assessment of treatment success [MD –0.02 (95% CI –0.15 to 0.12)], while 1 trial reported no between-group differences with respect to HRQOL (data not provided)[47].

There was no between-group difference in number of AE in the trial that compared NSAID to placebo[34], or in the trials that compared 1 conventional NSAID to another. There were no withdrawals due to AE in either arm of the placebo-controlled NSAID trial. There was moderate quality evidence, based upon pooled data from 3 trials[38,39,47], that coxibs are associated with significantly fewer GI events [20/296 (coxibs) vs 44/278 (NSAID), RR 0.42 (95% CI 0.26 to 0.70)], and fewer total AE [74/296 (coxibs) vs 110/278 (NSAID), RR 0.57 (95% CI 0.44 to 0.74)].

IL-1 inhibitors

The one trial (n = 200) that met our inclusion criteria was a parallel RCT judged to be at unclear risk of bias [see supplementary data (Fig. 2D) in the online Appendix available from the authors upon request[22,24]]. This trial compared canakinumab to systemic GC and is described in the systemic GC section above.

DISCUSSION

This article synthesizes the existing evidence on various treatments for acute gout. These results were combined with expert opinion from the panel of rheumatologists taking part in the 3e Initiative to generate 1 of the 10 clinical recommendations on the management of gout. A detailed description of all the final recommendations can be found elsewhere[6].

Our review highlights the paucity of high-quality evidence regarding efficacy of commonly used treatments for acute gout. Despite their perceived effectiveness[1] and endorsement by various guidelines and literature reviews[3,4,5,8,50], there are no published RCT or quasi-RCT that have assessed the efficacy and safety of either IA GC therapy or paracetamol (vs placebo or other interventions) in people with acute gout, and we identified only a single placebo-controlled trial of NSAID[34], one placebo-controlled trial of low-dose colchicine[28], and no placebo-controlled trials of systemic GC. We found moderate quality evidence from 3 trials that systemic GC were as effective as NSAID but had a better safety profile. Low-dose colchicine was as effective as high-dose colchicine (1 trial) but had a better safety profile. No NSAID was more effective than another. While the coxibs were as effective as conventional NSAID (based on 3 trials), they had a safer GI profile. Based on 1 trial, 150 mg canakinumab was more effective than a dose of 40 mg triamcinolone, with a similar safety profile.

Several systematic reviews and guidelines on the management of acute gout have been published over the last few years including those by the EULAR[5], by Hamburger, *et al*[3], and more recently by the ACR[4]. The ACR guidelines differed methodologically from the others in using the RAND/UCLA (University of California at Los Angeles) Appropriateness Method, rather than the Delphi approach. The EULAR guidelines recommended oral colchicine and/or NSAID as first-line agents, and IA GC (on the basis of 1 uncontrolled trial) in patients with a severe monoarticular attack and in those with contraindications to NSAID and colchicine. The conclusions of the reviews by Hamburger, *et al* and the ACR are broadly consistent with our review, and recommend oral colchicine, NSAID, or GC as appropriate first-line therapeutic options.

Following presentation of the evidence for the use of the above treatments in acute gout, notwithstanding the variable quality of the evidence, the consensus opinion from the multinational experts from the 3e Initiative gout project was that equal weight be given to NSAID, low-dose colchicine, and GC (given as IA, oral, or IM therapy), as there was insufficient evidence to prioritize them. Although there was early evidence that canakinumab may be useful in the treatment of acute gout, further evidence was required prior to making a formal recommendation. Paracetamol, although not recommended as first-line therapy, could be a useful analgesic adjunct. Individual treatment decisions should be made on the basis of an individual's comorbidities and in consideration of each drug's safety profile.

ACKNOWLEDGMENT

The authors acknowledge the work of all members of the 3e scientific committees and all participants in the national meetings.

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