Safety of Nonsteroidal Antiinflammatory Drugs and/or Paracetamol in People Receiving Methotrexate for Inflammatory Arthritis: A Cochrane Systematic Review

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ABSTRACT. ***Objective.*** To systematically review the literature on the safety of using nonsteroidal antiinflammatory drugs (NSAID) and/or paracetamol in people receiving methotrexate (MTX) for inflammatory arthritis (IA), as an evidence base for generating clinical practice recommendations.

Methods. A systematic literature review was performed using the Cochrane Library, Medline, Embase, and conference proceedings for the American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) for 2008-2009. The search aimed to identify studies describing adverse events (AE) with the concurrent use of paracetamol and/or NSAID in people taking MTX for IA. Articles fulfilling our predefined inclusion criteria were systematically reviewed and quality appraised.

Results. Seventeen publications out of 8681 identified studies were included in the review, all of which included people with rheumatoid arthritis (RA) using various NSAID; there were no identified studies for other forms of IA or with paracetamol. Of the studies examining concurrent use of MTX and NSAID, there were no reported adverse effects on lung, liver, or renal function, and no increase in MTX withdrawal or in major toxic reactions. However, transient thrombocytopenia was demonstrated in 1 study. Looking at specific NSAID, there were no clinically significant AE with concomitant piroxicam or etodolac, and only mild AE with celecoxib or etoricoxib. Antiinflammatory dose aspirin was demonstrated to have an adverse effect on liver and renal function.

Conclusion. In the management of RA, concurrent use of NSAID with MTX appears to be safe, provided appropriate monitoring is performed. The use of antiinflammatory doses of aspirin should be avoided. (J Rheumatol Suppl. 2012 Sept;90:62–73; doi:10.3899/jrheum.120345)

Key Indexing Terms:
RHEUMATOID ARTHRITIS PSORIATIC ARTHRITIS ANKYLOSING SPONDYLITIS
METHOTREXATE NONSTEROIDAL ANTIINFLAMMATORY DRUGS ACETAMINOPHEN

The inflammatory arthritides (IA) are a group of chronic, inflammatory joint diseases, including rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriatic arthritis (PsA), and other forms of spondyloarthritis (SpA). The mainstay of treatment of RA and PsA remains with disease-modifying antirheumatic drugs (DMARD) such as methotrexate (MTX), which is often used first-line given its favorable efficacy and toxicity profile, compared with other DMARD[1]. Despite treatment, patients often continue to experience pain and concomitant use of analgesics, including nonsteroidal antiinflammatory drugs (NSAID) and paracetamol, is common.

Patients taking MTX for IA currently receive conflicting advice regarding the safety of using concomitant NSAID and/or paracetamol to help manage their pain. As a result, patients frequently hesitate to use these analgesics, often when their use is clinically indicated. A potential interaction between NSAID and MTX was first described with the use of aspirin during oncological high-dose MTX therapy[2]. Subsequent studies have demonstrated that aspirin appears to decrease the total and renal clearance of MTX, whereas other NSAID have not shown a consistent effect on MTX pharmacokinetics[3].

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As MTX is often used as the first-line DMARD in patients with RA, concerns regarding the safety of using concomitant NSAID or paracetamol with MTX affect a significant proportion of our patients. The advice that patients receive on this issue has the potential to deter them from continuing therapy.

Our review is part of the 3e (Evidence, Expertise, Exchange) Initiative on Pain Management by Pharmacotherapy in Inflammatory Arthritis[4]. The objective of this report was to systematically review the literature concerning one of the 10 selected questions as an evidence base for generating recommendations: "Is it safe to use nonsteroidal anti-inflammatory drugs (NSAID) and/or paracetamol with methotrexate in the management of patients with inflammatory arthritis?". This article is a shortened version of a Cochrane review[5].

METHODS

Our review was performed according to the process outlined for Cochrane systematic reviews[6].

Rephrasing the research question. The clinical question, as formulated by the group of experts, was reconsidered to specify the key components, according to the PICO (Participants, Interventions, Comparisons, and Outcomes) method[6a] (for details see the online Appendix available from www.3epain.com). These components form the basis for the prespecified eligibility criteria for the review. Participants were defined as patients at least 18 years of age with a diagnosis of inflammatory arthritis (RA, AS, PsA, and SpA) receiving treatment with MTX, at any dose, duration, or route. The required intervention was the concurrent use of NSAID and/or paracetamol. There were no restrictions with regard to dose, duration, or route of administration. Studies of valdecoxib, lumiracoxib, and rofecoxib were excluded as they have been withdrawn from use around the world: valdecoxib has been withdrawn from use in the European Union[7], the United States[8], Australia[9], and Canada[10]; lumiracoxib has been withdrawn in many countries worldwide[11]; and rofecoxib has been withdrawn from use worldwide[12].

The primary outcome of interest was any sign of MTX toxicity, as evidenced by hematological, pulmonary, hepatic, or renal adverse events (AE), and withdrawals due to serious AE. Secondary outcomes of all AE including mortality were also included.

Included study designs. The ideal study designs for inclusion in our review are randomized controlled trials (RCT) and quasirandomized studies. However, since we aimed to provide evidence of adverse effects not adequately studied with RCT alone and since we anticipated a low yield from RCT, we also included nonrandomized studies (non-RS) such as controlled before-and-after studies (CBA), interrupted-time-series studies (ITS), cohort and case-control studies, and consecutive and nonconsecutive case series, provided these were reported from large registry databases, but with no restriction on numbers reported.

Systematic literature search. A systematic literature search for published articles was performed in May 2010 with the assistance of experienced librarians, using the following electronic databases: the Cochrane Central Register of Controlled Trials (Central; The Cochrane Library, 2nd Quarter, 2010); Medline, from 1950; and Embase, from 1980, without language restrictions. Specific Medical Subject Headings (MeSH) and additional keywords were used to identify all relevant studies. The complete strategies for the database searches are provided in an online Appendix available from www.3epain.com.

The Cochrane Database of Systematic Reviews (CDSR) and the Database of Abstracts of Reviews of Effects (DARE) were also included to ensure that all potential studies were identified for this systematic review. We also manually searched the bibliographies of all included reports for information on any other relevant studies. We aimed to contact the first authors of any reports if specific data were missing. A hand search was performed of the conference proceedings for the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) for 2008-2009, to identify unpublished studies.

To search the grey literature, the websites of regulatory agencies for reported AE, labels, and warnings were checked, including Current Problems in Pharmacovigilance; Drug Safety Update; the Drug Safety Research Unit (UK); Australian Adverse Drug Reactions Bulletin (Australia); MedWatch, the Food and Drug Administration Safety Information and Adverse Event Reporting Program (USA); the European Public Assessment Reports from the European Medicines Agency; and those agencies recommended by The Canadian Agency for Drugs and Technology in Health manual, "Grey Matters"[13]; as well as the websites of various international rheumatology societies.

Study selection. Two reviewers (ANC, JLM) independently assessed each title and abstract for suitability for inclusion in the review, according to the inclusion criteria described above. Any further information required to establish if the inclusion criteria were met was obtained from the full text of the article. Reasons for excluding any studies were recorded. Disagreement was resolved by consensus after review of the full text article, or after the input of the third author (CJE), who had the final decision. Foreign language studies were excluded unless they were written in one of the languages spoken by 3e International fellows (German, Portuguese, Dutch, and French).

Data extraction and quality appraisal. Relevant data, including publication details, patient characteristics, details of drugs received, and AE recorded, were independently extracted from the included studies by 2 reviewers (ANC, JLM) and entered into standard data extraction forms. If necessary, authors were contacted to provide any required additional information.

Two reviewers (ANC, JLM) assessed the quality of each RCT to be included in the review using risk of bias[14]. Any disagreement between the reviewers was discussed and resolved by consensus meeting. If agreement still could not be reached, a third reviewer (CJE) made the final decision.

As we also included non-RS, the quality of these study types was assessed using the following tools. For CBA and ITS, we used criteria described by the Cochrane Effective Practice and Organisation of Care (EPOC) Group[15]; for cohort studies, the Newcastle-Ottawa Scale (NOS), which assesses quality according to selection, comparability, and outcome; for case-control studies, the NOS, which assesses quality according to selection, comparability and exposure[16]; and for case series, the guidance recommended by the Centre for Reviews and Dissemination[17]. Further quality assessment was made for each included study according to the Oxford Centre for Evidence-based Medicine (CEBM) level of evidence, which gives studies a score for "level of evidence" (1a-5) and a score for "grade of recommendation" (A-D) [18].

Data analysis. AE in each study are reported descriptively in a summary of findings table, with studies grouped by type of AE reported. For AE reported in CBA and cohort studies, frequency and relative risk of the event, and time to event were recorded when data were available. For case-control studies, frequency of the event in cases and controls, and the odds ratio (OR) were recorded when possible. For data extracted from case series, the frequency of each event was recorded.

Since we included non-RS in this review, heterogeneity will be greater than if RCT alone were included. Therefore, it was less likely that we would be able to pool our findings quantitatively. However, we hoped to analyze studies grouped by design (RCT, CBA, ITS, cohort, case-control, and case series), and perform metaanalysis where possible for clinical homogeneous studies with the same design. Data across different study designs would therefore not be pooled.

RESULTS

Results of the search. The search of electronic databases performed in May 2010 resulted in 8681 records, of which 3126 were duplicated records. Of the remaining 5555 records for screening, 5397 records were excluded based on title or abstract, leaving 158 records for detailed, full-text review,

which were all successfully retrieved. This process is illustrated in Figure 1. We excluded 142 articles after reviewing the full text (for details see the online Appendix available from www.3epain.com), leaving 16 articles that met the inclusion criteria[19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34]. Three articles were identified for further review from the hand search of references in articles, but only 1 of these was suitable for inclusion[35]. Hand searching conference abstracts from ACR and EULAR for 2008 and 2009 resulted in 908 further records, none of which were suitable for final inclusion.

Hand search of the grey literature did not reveal any reported AE data, although several sites recommended that use of MTX with NSAID should be avoided. This is described further below in the Discussion.

In summary, 17 references were included in this systematic review.

Characteristics of included studies. The characteristics of the included studies are summarized in Table 1. Of the 17 studies, 3 were RCT[19,20,21], 4 CBA[22,23,24,25], 7 cohort[26,27,28,29,30,31,35], and 3 case-control studies[32,33,34], although few of the studies included primary outcomes that addressed the desired outcomes of our review. Additional information regarding the study design of the study by Fathi, *et al*[19] was obtained from a previous publication[36]. Overall, sample size ranged from 11[24] to 315 subjects[26].

Seventeen studies with a total of 1809 patients were included in this review. The majority of the participants were women, with an average age in the early to mid-50s. All the studies were in RA, mostly classified according to American Rheumatism Association, American College of Rheumatology, or American Rheumatological Society criteria. Five studies did not specify disease duration, and 2 only described including patients with RA for at least 6 months. The mean disease duration was between 2 and 18 years, with the longest disease duration 0–50 years[28]. All studies were on patients on MTX treatment, of variable dose and duration. Although in most studies the route of MTX administration was not specified, in 4 studies MTX was administered orally, in 2 studies intramuscularly[22,23], and in 1 study intravenously[25].

All studies involved NSAID as the intervention; there were no studies with paracetamol. Most studies did not specify type of NSAID used, 3 studies described data for NSAID and aspirin use separately[32,34,35], 4 studies were with aspirin alone[24,25,27,34], and 1 study each with etodolac[22], piroxicam[23], celecoxib[20] and etoricoxib[21]. The majority of these studies did not provide information on route of administration, dose, duration, or frequency of treatment, even when the drug type used was specified.

The majority of studies reported on outcomes relevant to the primary outcome of our review. Evidence of increased MTX toxicity was established according to pulmonary[32,35],

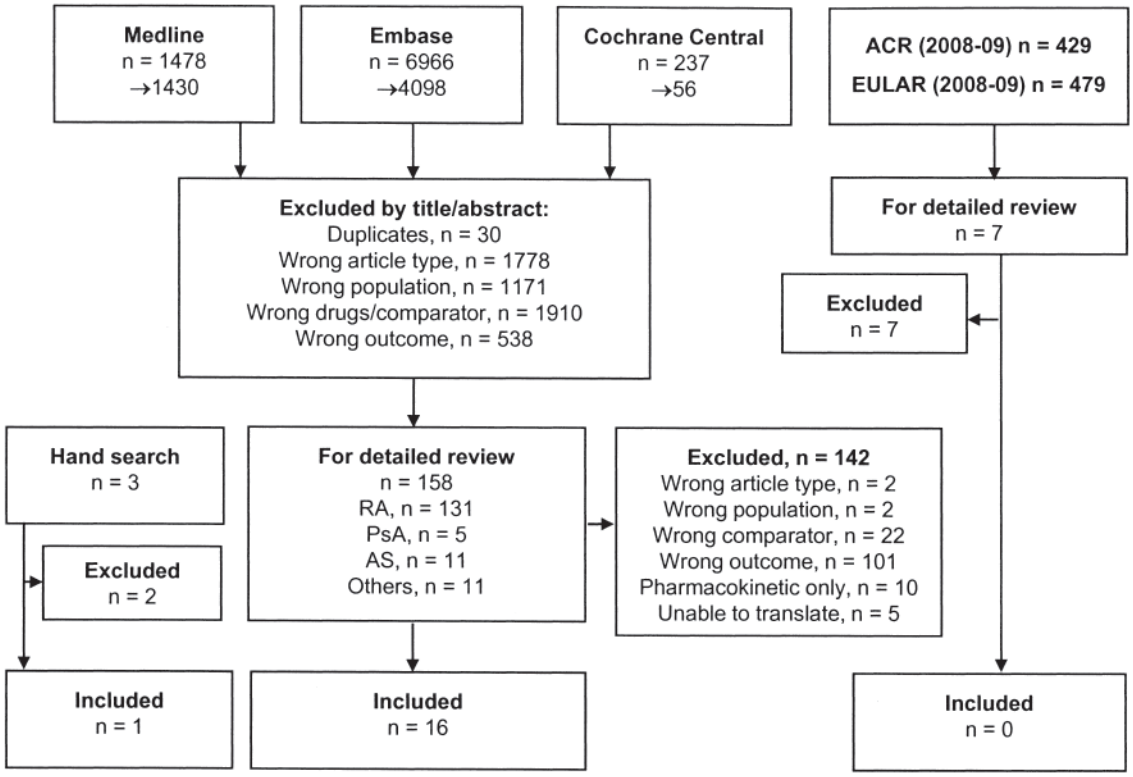

Figure 1. Literature search of 8681 articles, from which 158 articles were selected for detailed review. Seventeen articles met the inclusion criteria.

hepatic[19,27], renal[23,31], and hematological[26] variables; and to withdrawal due to AE reported by 3 studies[28,29,30]. Our review included all AE as a secondary outcome, which was evaluated in 7 studies, although 2 of these studies actually described major toxic reactions not linked to MTX withdrawal[33,34].

Summary of quality assessment. Table 1 provides a summary of the quality assessment for each study by type of design. Of the 3 RCT, one study had a low risk of bias, one a moderate risk of bias, and in the third it was difficult to qualify each statement, making the overall rating unclear. The 4 CBA were judged to have low to moderate quality using the criteria described by the EPOC group; the case-control studies to have a moderate quality; and the cohort studies to have a low to moderate quality, apart from Carson, *et al*[35], which was found to have a high quality, according to the relevant NOS quality assessment scales.

Study results. All studies considered the safety of using NSAID with MTX in patients with RA. No studies in PsA, AS, SpA, or paracetamol were identified for inclusion. The main results are grouped according to evidence of MTX toxicity (pulmonary, hepatic, renal, or hematological AE), withdrawals due to AE, and all AE including mortality, and are presented in Table 2. Unfortunately, as the data from the included studies were significantly heterogeneous, we were unable to pool the data to perform a metaanalysis.

Pulmonary adverse effects. Two studies included pulmonary evidence of MTX toxicity as the primary outcome[32,35], both of which provided separate data for those on NSAID or on aspirin. Neither study identified a significant association between the use of NSAID or aspirin with MTX-induced pulmonary disease when compared with MTX-treated controls. Carroll, *et al* described MTX pneumonitis on aspirin, n = 3 (25%); MTX controls on aspirin, n = 5 (21%); MTX pneumonitis on NSAID, n = 8 (67%); and MTX controls on NSAID, n = 11 (46%), both p values were not significant[32]. In Carson, *et al*, the concurrent use of aspirin or NSAID was not significantly different in those patients with MTX-induced pulmonary disease compared with patients without pulmonary disease ($p > 0.05$), but no other data were given[35].

Hepatic adverse events. Fathi, *et al* and Fries, *et al* described liver damage with concurrent NSAID and aspirin, respectively[19,27]. In Fathi, *et al*, 18 out of 40 patients were taking stable NSAID[19]. No relationship was seen between histological characteristics of liver damage (using Roenigk and Iowa classifications) and NSAID use. Neither multiple linear regression nor logistic regression analysis showed an effect of concurrent NSAID on liver histology, although data were not given separately for MTX versus MTX plus NSAID. In addition, no significant changes in the mean values of biochemical liver function tests occurred.

Fries, *et al* described the effect of concurrent aspirin on hepatic enzyme abnormalities[27]. The combination of MTX with aspirin greatly increased the frequency of abnormal liver enzyme values. Of the 46 patients taking both aspirin and MTX, about one-sixth had abnormal glutamic oxaloacetic transaminase (SGOT) and serum pyruvic transaminase (SGPT) values [mean SGOT for MTX alone (n = 186) 21.79 ± 1.29, 2.69% abnormal; mean SGPT for MTX alone (n = 113) 20.55 ± 1.80, 7.96% abnormal; mean SGOT for MTX with aspirin (n = 46) 32.39 ± 5.45, 15.22% abnormal; mean SGPT for MTX with aspirin (n = 24) 44.79 ± 21.07, 16.67% abnormal]. After adjustment by analysis of covariance for the effects of age, sex, and disease duration, the mean SGOT in those on MTX alone was 21.59 ± 1.67 units/ml compared with 33.20 ± 3.38 units/ml in those on MTX and aspirin ($p = 0.002$); and the mean SGPT was 20.64 ± 4.33 units/ml compared with 45.22 ± 9.54 units/ml ($p = 0.02$) for MTX alone and MTX with aspirin, respectively.

Renal adverse events. Seideman, *et al* investigated the renal effects of MTX with and without combined aspirin, measured by the plasma clearance of EDTA-labelled with chromium-51 (^{51}Cr-EDTA) and dimercatoacetyltriglycerine labelled with technetium-99m (^{99m}Tc-MAG-3), which are measures of glomerular and tubular function, respectively[24]. Clearance of ^{51}Cr-EDTA was reduced from mean 98 (SEM 6) to 87 (SEM 5) ml/min for patients on MTX alone, and further reduced to 76 (SEM 5) ml/min for patients on both MTX and aspirin ($p < 0.001$). This effect was reversible as ^{51}Cr-EDTA increased to 85 (SEM 6) ml/min during continued treatment with MTX alone ($p < 0.01$).

Clearance of ^{99m}Tc-MAG-3 decreased from 366 (SEM 17) ml/min to 315 (SEM 17) ml/min in patients on MTX alone, and to 295 (SEM 17) ml/min during treatment with both MTX and aspirin ($p < 0.01$). Continued treatment with MTX alone resulted in a further decrease in ^{99m}Tc-MAG-3 to 253 (SEM 17) ml/min ($p < 0.001$). These results suggest that MTX affects both glomerular and tubular renal function, particularly when combined with aspirin, and that this effect is only partially reversible on stopping aspirin.

Svendsen, *et al* evaluated the effect of MTX alone or in combination with NSAID on the urinary excretion of α-glutathione S-transferase (α-GST), a marker of renal tubular injury, and on urinary albumin, a marker of glomerular or combined glomerular and tubular injury[31]. No differences were seen in the urinary excretion of α-GST or albumin between patients undergoing concurrent NSAID treatment and patients without NSAID, although the specific data were not given.

Hematological adverse events. Only one study specifically investigated the hematological effect of concurrent NSAID with MTX[26], which evaluated factors contributing to thrombocytopenia (platelet count < 100,000/mm^3). There was a significant correlation between thrombocytopenia on the day of administration of the weekly dosage of MTX with combined NSAID use ($r = 0.6$, $p < 0.05$). A continuously low platelet count was not seen if NSAID were withheld the day of MTX administration.

Table 1. Study and patient characteristics for the included studies.

Study Reference, Design and Quality	Patient Characteristics	Methotrexate Dose/Route	Intervention
Fathi et al 2002[19]; double-blind, parallel RCT; length of followup: 3.5 yrs; risk of bias: unclear; evidence level: 2b (B)	Total: N = 40; diagnosis: ACR RA; mean disease duration (yrs) 12.6 ± 9.0; % female: 67.5; mean age (yrs) ± SD: 54.6 ± 8.8	Oral MTX, randomized to 5 or 10 mg/m^2, then increased according to need (max 35 mg/week)	18/40 patients on stable NSAID; no other data given
Karim, 1999[20]; single-blind, 2-arm, crossover RCT; length of followup: 14 days; risk of bias: moderate; evidence level: 2b (B)	N = 14; diagnosis: ACR RA (minimum duration 6 mo); % female: 100; mean age (yrs): 51.9 (range 31-65)	Weekly dose of MTX, N (%): 5 mg: 1 (7); 7.5 mg: 3 (21); 10 mg: 4 (29); 12.5 mg: 4 (29); 15 mg: 2 (14); route not specified	Crossover study of oral celecoxib 200 mg bd or placebo for 7 days each
Schwartz 2009[21]; double-blind, 2-arm, parallel RCT; length of followup: 15 days; risk of bias: low; evidence level: 1b (A)	Diagnosis: ARS RA. Study 1: N = 12; % female: 71.4; mean age (yrs): 53.0 (range 31-73). Study 2: N = 25; % female: 72.4; mean age (yrs): 54.5 (range 22-72)	Treated for at least 1 mo with a stable weekly dose of MTX, 7.5-20 mg/week (route not given). Study 1: Mean MTX dose: 13.6 mg (range 7.5-20) . Study 2: Mean MTX dose: 15.1 mg (range 7.5-20)	Study 1: etoricoxib 60 mg od days 1-7, 120 mg od days 8-14 Study 2: etoricoxib 90 mg od days 1-7, 120 mg od days 8-14
Anaya, 1994[22]; 2-arm, non-randomized, CBA study (subjects own controls); length of followup: 16 days; quality assessment (EPOC): moderate; evidence level: 3b (C)	N = 19; diagnosis: ACR RA for at least 2 yrs duration; mean disease duration (yrs): 8.7 ± 6.4, range 2-25; % female: 89.5, mean age (yrs) ± SD (range): 48.7 ± 11.8 (23-69)	All subjects on stable dose of IM MTX 10 mg/week for at least 2 mo; mean duration of treatment 7.7 ± 1.6 mo, range 2-48 mo	Arm 1: Patients received no NSAID for a minimum of 8 days. Arm 2: etodolac 3 x 200 mg tablets tds (morning, noon, evening) for 8 days
Combe, 1995[23]; 2-arm, non-randomized, CBA study (subjects own controls); length of followup: 23 days; quality assessment (EPOC): moderate; evidence level: 3b (C)	N = 20; diagnosis: ACR RA; mean disease duration (yrs) ± SD: 8.6 ± 6, range 2-23; % female: 70; mean age (yrs) ± SD: 49.1 ± 13.5	All subjects on stable dose of MTX 10 mg/week for at least 2 mo (or only 1 mo if treated intramuscularly); patients then received 10 mg IM MTX on day 1 and weekly throughout the study	No NSAID for a minimum of 8 days before the study period; piroxicam 20 mg od for 15 days
Seideman, 1993[24]; 2-arm, non-randomized, CBA study (subjects own controls); length of followup: max 24 wks; quality assessment (EPOC): low; evidence level: 3b (C)	N = 11; diagnosis: "classical" or "definite" RA; mean disease duration (yrs): 2 (range 0.5-6); % female: 90.9; mean age (yrs): 55, range 32 -75	Oral MTX 15 mg/week (used alone until the third clearance study, i.e., until a mean of 5 wks)	Aspirin (2 g oral) combined with MTX at the third clearance study until the fourth clearance study (i.e. until mean 20 weeks, range 16-24)
Stewart, 1991 [25]; 2-arm, non-randomized, CBA study (subjects own controls); length of followup: 8 days; quality assessment (EPOC): low; evidence level: 3b (C)	N = 15; diagnosis: ACR RA (for at least 6 mo); % female: 86.7; age range (yrs): 35-63; 86.7% Caucasian, 13.3% black	All subjects on stable dose of MTX (max 20 mg/week) for at least 2 mo; on days 0 and 8, IV MTX (10 mg/week) was given without aspirin	Aspirin 975 mg orally 4 times daily for 1 week

Carroll, 1987 [32]; case-control study; quality assessment (NOS): moderate evidence level: 4 (C)	Cases: N = 12; diagnosis: RA; mean disease duration (yrs) ± SD: 18 ± 13; % female: 58.3; mean age (yrs) ± SD: 68.3 ± 6.3. Controls: N = 24; diagnosis: RA; mean disease duration (yrs) ± SD: 18 ± 8; % female: 58.3; mean age (yrs) ± SD: 69.4 ± 5.8	Route not specified. Cases: Mean dose (mg/week) ± SD (range): 7.3 ± 1.2 (5-10); mean MTX duration (weeks) ± SD (range): 25 ± 20 (5-60). Controls: Mean dose (mg/week) ± SD (range): 7.3 ± 1.8 (2.5-12.5); mean MTX duration (weeks) ± SD (range): 65 ± 62 (1-200)	Aspirin and NSAID, but no data given re drug preparation, dose, duration, route of administration or frequency; No. (%) cases on aspirin: 3 (25); on NSAID: 8 (67); No. (%) controls on aspirin: 5 (21); on NSAID: 11 (46)
McKendry, 1989[33]; case-control study; quality assessment (NOS): moderate; evidence level: 4 (C)	Diagnosis: ARA RA. Cases: N = 29; % female: 76; mean age (yrs) ± SD: 56 ± 11. Controls: N = 29; % female: 76; mean age (yrs) ± SD: 53 ± 13	Mean dose (mg/wk) ± SD: 8.4 ± 3.0, followed for 38 ± 23.3 mo; route not specified	Enteric-coated aspirin; no other data given
McKendry, 1993 [34], case-control study; quality assessment (NOS): moderate; evidence level: 4 (C)	Diagnosis: ARA RA. Cases: N = 50; % female: 82; mean age (yrs) ± SD: 56.7 ± 11.8. Controls: N = 50; % female: 68; mean age (yrs) ± SD: 53.2 ± 12.2	Mean dose (mg/wk), 95% CI (range): 8.2, 7.67-8.73 (2.5-15.0), treated for 39 ± 31 mo (range 2-127 mo); route not specified	NSAID or enteric-coated aspirin; no other data given
Carson, 1987[35]; retrospective cohort study; length of followup: maximum 8 yrs; quality assessment (NOS): high; evidence level: 2b (B)	Diagnosis: definite or classical RA. Cases: N = 9; mean disease duration (yrs); mean ± SD: 9.4 ± 5.1; % female: 66.7; mean age (yrs) ± SD: 55 ± 13. Controls: N = 154; mean disease duration (yrs) mean ± SD: 12.1 ± 9.2; % female: 55.8; mean age (yrs) ± SD: 52 ± 12	Cases: Mean MTX dose (mg/week) ± SD: 10.7 ± 2.9; mean MTX duration (wks) ± SD: 80.0 ± 65.1; route not specified. Controls: Mean MTX dose (mg/week) ± SD: 9.5 ± 2.7; mean MTX duration (wks) ± SD: 73.1 ± 59; route not specified	NSAID or aspirin; no other data given
Franck, 1996 [26]; retrospective cohort study; length of followup: maximum 10 yrs; quality assessment (NOS): moderate; evidence level: 2b (B)	Diagnosis: ACR RA; minimum disease duration: 6 mo; cases: N = 13; % female: not given; mean age (yrs) ± SD: 51 ± 12.6	Weekly dose range 7.5-25 mg; route not specified	NSAID; no other data given
Fries, 1990 [27]; retrospective cohort study; length of followup: maximum 6 yrs; quality assessment (NOS): low; evidence level: 4 (C)	Total: N = 232; subjects on MTX, N = 186; subjects on MTX and aspirin, N = 46, Diagnosis: RA; no other patient demographics given	Mean dose 9.10 mg/week when taking aspirin; 9.41 mg/week when not on aspirin (not statistically significant); route not specified	Aspirin, mean dose 6.84 tablets/day when taking MTX ; no other details, including dose of tablets, given
Ideguchi 2007[28]; retrospective cohort study; length of followup: max 3.75 yrs (437 person-yrs of MTX exposure); quality assessment (NOS): low; evidence level: 2b (B)	N = 273; diagnosis: ACR RA; mean disease duration (yrs) ± SD (range): 9.9 ± 10.6 (0-50); % female: 83.9; mean age at starting MTX (yrs) ± SD (range): 57.6 ± 11.4 (range 21-81)	Mean starting dose 3.8 mg/week (range 2-7.5); mean maximum dose: 5.7 mg/week (range 2-10); mean maintenance dose: 5.5 mg/week ± 1.9 (range 2-10); route not specified	NSAID; no other data given
Sánchez 2007 [29]; retrospective cohort study ; length of followup: maximum 15 yrs; quality assessment (NOS): low; evidence level: 4 (C)	N = 219; diagnosis: ACR RA; mean disease duration (yrs) ± SD: 7.6 ± 7.9 % female: 91.3; mean age (yrs) ± SD: 51.7 ± 13.1 (range 15-84)	Mean weekly dose 7.5 ± 2.1 mg (range 5-25); route not specified	NSAID; no other data given
Svendsen 2005 [31]; prospective cohort study; length of followup: 1 yr; quality assessment (NOS): moderate; evidence level: 4 (C)	N = 19; diagnosis: ACR RA; % female: 69.4; mean age (yrs): 58 (range 32-77)	All were patients starting MTX treatment; median dose at first visit: 7.5 (range 5-10) mg; at week 16: 7.5 (5-15) mg: at week 28: 10 (5-15) mg; at week 52: 10 (5-20) mg; route not specified	NSAID; no other data given
Świerkot 2008[30]; retrospective cohort study; length of followup: max 5 yrs; quality assessment (NOS): low; evidence level: 4 (C)	N = 140; diagnosis: ARA RA; disease duration, range: 0.3-35 yrs; % female: 85 Mean age (yrs) ± SD: 54 yrs ± 13.1	Mean dose (range): 15 mg/wk (10-20 mg/wk); minimum duration (unless developed adverse reactions earlier): 6 mo; route not specified	NSAID; no other details given

RA: rheumatoid arthritis; ACR: American College of Rheumatology; ARS: American Rheumatological Society; ARA: American Rheumatism Association; MTX: methotrexate; od: omne in die; bd: bis die; tds: ter die sumendus; IM: intramuscular; IV: intravenous; RC: , randomized controlled trial; CBA: controlled before and after; EPOC: Cochrane Effective Practice and Organisation of Care; NOS: Newcastle-Ottawa Scale: Evidence level: according to Oxford Centre for Evidence-based medicine (CEBM) level of evidence[18].

Table 2. Summary of findings.

Adverse Event Type, Study Reference	Outcome Measurement Method	Intervention	No. of Participants	Duration of Followup	Outcome
Pulmonary					
Carroll 1987[32]	MTX-related pneumonitis (P-MTX)	Aspirin and NSAID	Cases: N = 12; No. (%) cases on aspirin: 3 (25); on NSAID: 8 (67). Controls: N = 24; No. (%) controls on aspirin: 5 (21); on NSAID: 11 (46)	Case-control	MTX pneumonitis on aspirin; N = 3 (25%); MTX controls on aspirin, N = 5 (21%); MTX pneumonitis on NSAID, N = 8 (67%); MTX controls on NSAID, N = 11, (46%); both P values not significant
Carson 1987[35]	MTX-induced pulmonary disease	Aspirin and NSAID	Cases: N = 9. Controls: N = 154; No. on aspirin and NSAID not given	Max 8 yrs	Use of aspirin or NSAID not significantly different in patients with MTX-induced pulmonary disease versus patients without pulmonary disease (P > 0.05); no other data given
Hepatic					
Fathi 2002[20]	Liver damage according to histology and biochemical liver function tests	NSAID	Total: N = 40; on NSAID, N = 18	3.5 yrs	No effect of concurrent NSAID on liver histology or biochemical liver function tests; data not given
Fries 1990[27]	Hepatic enzyme abnormalities, using SGOT and SGPT	Aspirin; mean dose: 6.84 tablets/day	On MTX, N = 186; on MTX and aspirin, N = 46	Max 6 yrs	1/6 of 46 patients on aspirin and MTX had abnormal SGOT and SGPT values ; adjusted mean SGOT: 21.59 ± 1.67 u/ml vs 33.20 ± 3.38 u/ml (MTX vs MTX + aspirin); P = 0.002; adjusted mean SGPT: 20.64 ± 4.33 u/ml vs. 45.22 ± 9.54 u/ml (MTX vs MTX + aspirin); P = 0.02
Renal					
Seideman1993[24]	Glomerular and tubular function, with plasma clearance of ^{51}Cr-EDTA) and ^{99m}Tc-MAG-3	Aspirin; 2g oral daily for ~ 15 wks	N = 11	24 wks	Clearance of ^{51}Cr-EDTA was reduced on MTX alone, and further reduced on both MTX and aspirin (P < 0.001); this effect was reversible on stopping aspirin (P < 0.01). Clearance of ^{99m}Tc-MAG-3 was reduced on MTX alone, and further reduced with both MTX and aspirin (P < 0.01) This effect was not reversible on stopping aspirin (P < 0.001)
Svendsen 2005[31]	Urinary excretion of α-GST and urinary albumin	NSAID	Total: N = 16; on NSAID; N = 12 (63.2%)	1 yr	No effect of NSAID seen on urinary excretion of α-GST and urinary albumin; data not given

Hematological					
Franck, 1996[26]	Thrombocytopenia (< 150000/m^3)	NSAID	Total: N = 315; with thrombocytopenia (on any drug), N = 13	Max 10 yrs	Significant correlation between thrombocytopenia on the day of administration of weekly dosage of MTX with combined NSAID (r = 0.6, P < 0.05); continuously low platelet count not seen if NSAID withheld on day of MTX
Withdrawal due to adverse events					
Ideguchi 2007[28]	MTX withdrawals	NSAID	Total: N = 273; on NSAID, N = 176 (64.5%)	Max 3.75 yrs	No significant association between concurrent use of NSAID and MTX discontinuation (for any cause)
Sánchez 2007[29]	Discontinuation of MTX	NSAID	Total: N = 219; on NSAID, N = 176 (80.4%)	Max 15 yrs	No significant association between use of NSAID and discontinuation of MTX (for any cause); univariate HR 0.48, 95% CI 0.22-1.05; P = 0.06; multivariate HR 0.59, 95% CI 0.26-1.30; P = 0.19
Świerkot 2008[30]	MTX withdrawals	NSAID	Total: N = 140; on NSAID; N = 59 (56%)	Max 5 yrs	No significant difference between patients on NSAID with and without adverse events (n = 31, 52.5% vs. n = 28, 47.5% . Of those on MTX and NSAID experiencing adverse events, 15 patients (48.4%) withdrew MTX due to the adverse events, whereas 16 patients (51.6%) did not withdraw MTX despite adverse events
All adverse events					
McKendry, 1989 [33]	Major toxic reactions	Enteric-coated aspirin	Cases: N = 29. Controls: N = 29	Case-control	Less patients experienced an MTX-related major toxic reaction on enteric-coated aspirin compared with controls (P = 0.01)
McKendry, 1993[34]	Major toxic reactions	Enteric-coated aspirin and NSAID	Cases: N = 50. Controls: N = 50		No significant association between concurrent use of aspirin or NSAID with major MTX toxicity
Stewart, 1991[25]	All adverse events; laboratory variables	Aspirin; 975 mg orally 4 x daily for 1 wk	N = 15	8 days	No adverse events described; no significant effect of concurrent aspirin on laboratory variables
Combe, 1995[23]	All adverse events; laboratory variables	Piroxicam 20 mg od for 15 days	N = 20	23 days	No adverse events described; a significant decrease seen only in hemoglobin (P < 0.001) and red blood cells (P < 0.01)
Anaya, 1994[22]	All adverse events; laboratory variables	Etodolac 3 x 200 mg tablets tds for 8 days	N = 19	16 days	No adverse events described; a significant decrease seen only in hemoglobin (P = 0.002), means remained in normal range with no clinical significance
Karim, 1999[20]	All adverse events; laboratory variables	Celecoxib 200 mg bd for 7 days	N = 19	14 days	Only mild to moderate adverse events reported; a significant decrease seen only in hematocrit in all patients, no clinical significance
Schwartz 2009[21]	All adverse events	Study 1: etoricoxib 60 mg od days 1-7, 120 mg od days 8-14. Study 2: etoricoxib 90 mg od days 1-7, 120 mg od days 8-14	Study 1: N = 12. Study 2: N = 25	Studies 1 and 2 both 14 days	Study 1: no serious adverse events described; all possible drug related adverse events were mild (nausea and vomiting, headache). Study 2: most adverse events occurred on etoricoxib 120 mg; adverse events all transient and mild

SGOT: serum glutamic oxaloacetic transaminase; SGPT: serum pyruvic transaminase; ^{51}Cr-EDTA: EDTA-labelled with chromium-51; ^{99m}Tc-MAG-3: dimercatoacetyltriglycerine labelled with technetium-99m; α-GST: α-glutathione S-transferase. For other definitions, see Table 1.

Withdrawals due to adverse events. Ideguchi, *et al*[28], Sánchez, *et al*[29], and Swierkot, *et al*[30] described withdrawal of MTX due to AE, although Ideguchi, *et al* did not provide separate information for those patients on NSAID withdrawing MTX due to AE specifically[28]. Univariate analysis showed concurrent use of NSAID (n = 176, 64.5%) to have no significant association with MTX discontinuation (for any cause).

Sánchez, *et al* reported MTX treatment survival in their cohort of Venezuelan patients with RA[29]. Again, this study did not provide the specific reasons for MTX withdrawal in those on concurrent NSAID, but univariate and multivariate analysis hazard ratios (HR) showed no significant association between discontinuation of MTX and use of NSAID (univariate HR 0.48, 95% CI 0.22–1.05, p = 0.06; multivariate HR 0.59, 95% CI 0.26–1.30, p = 0.19).

Swierkot, *et al*[30] evaluated AE and subsequent MTX withdrawals; there were similar percentages of patients on NSAID with and without AE (n = 31, 52.5% vs n = 28, 47.5%). Of those on MTX and NSAID experiencing AE, 15 patients (48.4%) withdrew MTX due to the AE, whereas 16 patients (51.6%) did not withdraw MTX despite AE. No further details regarding the types of AE experienced in this group were given.

All adverse events. Of the included studies, 7 reported nonspecific AE, which are included here. None of the studies described any associated mortality, although 2 of these studies specifically reported major toxic reactions, but these were not associated with drug withdrawal for those on concurrent NSAID[33,34].

McKendry, *et al* 1993 did not identify a significant association between concurrent use of NSAID or aspirin with major MTX toxicity, which was defined as a significant and predefined effect on laboratory variables, or clinical or laboratory AE severe enough to result in MTX discontinuation for at least 3 months[34]. Their earlier study included only data for those on aspirin[33]; fewer patients experiencing an MTX-related major toxic reaction were receiving enteric-coated aspirin compared with their control group (p = 0.01). The types of major toxic reactions in these patients were not further described.

The remaining reports were primarily pharmacokinetic studies, which provided minimal data on the effect of concurrent specified NSAID or coxibs on laboratory variables and AE only. Stewart, *et al* performed a pharmacokinetic study of effects of concurrent aspirin with MTX[25]. All patients completed the study with no adverse effects, and there were no significant differences (p > 0.05, Mann-Whitney test) between MTX alone and MTX with aspirin on laboratory variables. Combe, *et al* looked at the effect of additional piroxicam on MTX pharmacokinetics, laboratory variables, and AE[23]. There were no severe AE resulting in study withdrawal. Laboratory tests performed at baseline and after 15 days of piroxicam treatment showed a significant decrease only for hemoglobin (p < 0.001) and red blood cells (p < 0.01). Anaya, *et al* aimed to determine if the pharmacokinetics of MTX are modified by the coadministration of etodolac[22]. No clinical differences were seen at the end of the study, and all patients completed the study with no adverse effects. No statistical differences were observed between each arm of the study for most laboratory variables, although a statistically significant decrease (p = 0.002) in hemoglobin was noted after addition of etodolac, although the mean values in both arms were in the normal range, and without clinical significance. Karim, *et al* studied the effects of concurrent celecoxib, and identified only mild to moderate AE; no serious events occurred and no patients withdrew due to an AE[20]. The most frequently reported AE (≥ 2 subjects) was a mild headache. The only change of note in laboratory test values during treatment was that all patients experienced a decrease in hematocrit (mean decrease 3.8, range 1.0–6.6). This decrease was attributed to the large volume of blood drawn (500 ml) during the 2-week study period; the changes from baseline hematocrit were not considered clinically significant. No other significant changes in laboratory variables were recorded. Schwartz, *et al* designed 2 parallel RCT to examine the effect of different doses of etoricoxib on MTX pharmacokinetics. In the low-treatment arm, there were no reported AE that were serious or resulted in discontinuation[21]. Of the AE reported, those considered by the investigator to be drug-related were all mild (nausea and vomiting, headache). In the higher-dose etoricoxib arm, the majority of adverse experiences occurred during the etoricoxib 120 mg treatment phase, and the adverse experiences were all transient and mild in intensity.

DISCUSSION

Our systematic review provides a summary and evaluation of the available literature on the safety of using concurrent NSAID and/or paracetamol in patients receiving MTX for IA. These results form the basis for generating one of the 10 clinical recommendations on pain management by pharmacotherapy in IA. A detailed description of all these final recommendations can be found elsewhere[4].

These results describe the use of various NSAID in patients receiving MTX for RA; no data were identified describing the adverse effects of concurrent paracetamol, or in patients with other forms of IA, such as AS, PsA, or SpA. Although the data identified are sparse, and most collected data were secondary reported outcomes of included studies and therefore not reported fully, the available evidence suggests that MTX can be used safely with concurrent NSAID in patients with RA.

Of the included studies using concurrent NSAID, there were no reported AE on MTX-induced pulmonary disease[32,35], liver function[20], renal function[31], increase in MTX withdrawal[28,29,30], or major toxic reactions[34]. One study did demonstrate the concurrent use of NSAID to be associated with transient thrombocytopenia on the day of administration of the weekly dose of MTX[26].

Several included studies used named NSAID or coxibs, but these were all primarily designed as studies of MTX pharmacokinetics, with safety data as secondary outcomes only. One study each of piroxicam[23] and etodolac[22] reported no AE; but a reduction was seen in hemoglobin, and hemoglobin and red blood count, respectively, which did not have any particular clinical significance. Two studies using concurrent coxibs were included, 1 using celecoxib[20] and the other etoricoxib[21]. In these studies, only mild to moderate AE were recorded, such as nausea and vomiting, and headaches.

Of significant AE reported, a number were in studies using antiinflammatory doses of aspirin. The studies demonstrated concurrent aspirin to adversely affect liver function at a mean dose of 6.84 tablets of aspirin per day[27], which is a possible daily dose of 2.1 g, presuming that 300 mg aspirin tablets were given, and to cause a partially reversible decline in renal function with 2 g daily of aspirin[24]. However, no increase in MTX-induced pulmonary disease or major toxic reactions was seen in those on aspirin[32,33], although these studies do not specify the dose of aspirin patients received. One study also reported no increase in AE or effect on laboratory variables in those taking 975 mg aspirin 4 times per day, but the duration of this study was only 1 week[25].

Our review did not include those studies in which patients were using low-dose aspirin for prevention of atherothrombotic disease. This action of low-dose aspirin (less than 100 mg/day) is through inhibition of cyclooxygenase (COX)-1, which causes significant reduction in thromboxane A_2 in platelets without inhibition of prostaglandin I_2, resulting in inhibition of platelet function[37]. Aspirin doses of 650 mg to 4 g/day inhibit both COX-1 and COX-2, resulting in an analgesic and antipyretic effect, with even higher doses (> 4 g daily) causing prostaglandin-dependent and independent effects[38].

It appears that the antiinflammatory effect of higher-dose aspirin can cause AE when combined with MTX, with data from pharmacokinetic studies supporting this. The search performed for our review identified 15 articles that dealt with the effect of concurrent NSAID on MTX pharmacokinetics, as assessed by area under the concentration-time curve (AUC) and the maximum concentration of MTX observed in plasma, with some studies also looking at the MTX metabolite, 7-hydroxymethotrexate (7-OH-MTX). However, only 5 of these reports were included in the results of our review as they included some safety outcome data[20,21,22,23,25], whereas the 10 excluded studies considered MTX pharmacokinetics alone[39,40,41,42,43,44,45,46,47,48].

Of these 15 studies, 5 showed an increase in MTX or 7-OH-MTX, but the results were inconsistent. Aspirin seemed to be most consistently associated with this effect. However, one study each with etodolac or piroxicam showed a reduction in C_{max} with no change in the AUC, suggesting a possible reduction in MTX exposure. These results are summarized in an online Appendix available from www.3epain.com, as adapted from Bourré-Tessier and Haraoui[49].

Searching the grey literature identified several resources that advise against concurrent use of NSAID and MTX. In the United Kingdom, the MTX summary of product characteristics and package leaflet that are provided by Goldshield PLC and Hospira UK Limited, respectively, both state that care is needed if taking NSAID or aspirin with MTX due to the risk of interaction[50,51]. Similar advice is given by health agencies across the world, including France[52], Australia[53,54], New Zealand[55], and the United States[56,57,58].

Evidence for a potential interaction between NSAID and MTX first emerged when the use of aspirin during oncological high-dose MTX therapy resulted in a 54% decrease in white cell count, where 50 mg per day of MTX was given for 10 days[2]. As the oncological dose of MTX far exceeds the dose ordinarily used in the management of IA, it is reasonable to conclude that although the use of NSAID appears to be safe in patients taking MTX for IA, this may not be the case with the use of NSAID and MTX in oncological conditions. In all cases, it remains important to follow general recommendations of periodic monitoring of liver function and blood count on those taking longterm MTX, in order to detect liver and bone marrow toxicity at the earliest opportunity[59].

In our systematic review, we aimed to identify all available evidence on the safety of using NSAID and/or paracetamol in people receiving MTX for IA using a meticulous search and selection process[6]. We included both RCT and non-RS as we aimed to provide evidence of adverse effects that would not be adequately studied with RCT alone, and we anticipated a low yield from RCT. Unfortunately, this reduces the quality of the included studies, particularly as in many of these studies the relevant reported data were secondary outcomes only, and therefore little detail was often provided.

In conclusion, no studies were identified for the concurrent use of paracetamol and MTX, and all of the 17 included studies were in people with RA only, with quality assessment of 4 (C) in most studies. The majority of these studies showed no adverse effect of using NSAID with MTX in people with RA; only 3 studies provided any convincing data for a clinically significant adverse effect. On this basis, we conclude that MTX can safely be used in combination with NSAID, excluding antiinflammatory doses of aspirin, in the management of patients with IA.

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