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Table 1: Key study design features and results of trials of methotrexate in osteoarthritis

Study	Population	Intervention	Study characteristics (MTX/placebo)	Results	Conclusion
Randomised controlled trials					
Holanda (2007) [41], Brazil	Knee OA with US synovitis <ul style="list-style-type: none"> • Diagnosis of OA for ≥2 years • KL2-3 • Joint effusion confirmed by ultrasound • VAS pain ≥5 • Age ≥40 years 	Intervention: Oral MTX 7.5 mg/week for 4 months Comparator: Placebo Blinding: double-blind.	Sample size: 58 (29 MTX / 29 placebo) Age, mean (sd): 61.86 (8.73) / 60.41 (8.98) Female, n (%): 27 (93.1%) / 21 (72.4%) BMI: 29.56 (5.93) / 27.71 (3.98) KL Grade, n (%): KL2: 2 (6.9%) / 2 (6.9%) KL3: 27 (93.1%) / 27 (93.1%)	Primary endpoint: <ul style="list-style-type: none"> • No significant difference in WOMAC, pain VAS or Lequèsne Algofunctional Index between MTX and placebo groups. Secondary Endpoint: <ul style="list-style-type: none"> • Trend toward less paracetamol in MTX group 	MTX not superior to placebo
PROMOTE Kingsbury (2024) [42], UK	Knee OA <ul style="list-style-type: none"> • ACR KOA criteria • Radiographic tibiofemoral OA • Pain levels ≥40 mm on most days for >3 months • Age>18 years • Inadequate response to current meds 	Intervention: Oral MTX up to 25mg weekly (mean dose at 6-months 20.2mg) for 12 months Comparator: Placebo Blinding: double-blind.	Sample size: 155 (77 MTX / 78 placebo) Age, mean (sd): 61.5 (9.79) / 60.4 (9.59) Female, n (%): 50 (64.9) 49 (62.8) BMI, mean (sd): 31.9 (6.25) 33.7 (6.48) KL Grade, n (%): KL1: 10 (13.0%) / 8 (10.3%) KL2: 32 (41.6%) / 27 (34.6%) KL3: 22 (28.6%) / 27 (34.6%) KL4: 13 (16.9%) / 16 (20.5%)	Primary endpoint: <ul style="list-style-type: none"> • NRS Pain mean between group difference at 6-months: 0.79 NRS points in favour of MTX (95% CI, 0.08 to 1.51; p=0.030). • Effect size: 0.34 Secondary Endpoints: <ul style="list-style-type: none"> • Statistically significant treatment group differences in favour of MTX at 6 months for WOMAC stiffness (0.60 points) and physical function (5.01 points), ICOAP intermittent pain (12.84 points), ICOAP total pain (9.50 points), worst knee pain NRS in the past 7 days (0.81 points), and the OMERACT-OARSI responder index (risk ratio, 1.72) • No differences in imaging outcomes between treatment groups. No differential treatment effects based on degree of baseline synovitis (low vs. high levels, p = 0.57) or K-L grades (1/2 vs. 3/4, p = 0.58). • Significant treatment effect with baseline hsCRP level (p=0.006) 	MTX modestly reduced pain NRS but not WOMAC scores
Enteshari-Moghaddam (2019) [73], Iran	Inflammatory Knee OA <ul style="list-style-type: none"> • Moderate to severe knee OA • KL3-4 • Non-inflammatory joint effusions according to fluid analysis • Pain NRS>5 or total WOMAC>48 • 45-75 years 	Intervention: Oral MTX 15mg weekly for 3 months + glucosamine 1500mg daily Comparator: Placebo + glucosamine 1500mg daily Blinding: double-blind.	Sample size: 60 (30 MTX / 30 placebo) Age, mean (sd): 53.75 (6.59) / 52.42 (7.19) Female, n (%): 26 (63.4) / 31 (62) KL Grade, n (%): KL3: 21 (51.2%) / 31 (62%) KL4: 20 (48.8%) / 19 (38%)	<ul style="list-style-type: none"> • Significant between group difference in pain NRS at 6-months but not at 3-months • Significant between group difference in WOMAC pain and function at 3- and 6-months. • Significant reduction in pain VAS (-18 mm, p<0.01) 	MTX improved pain and synovitis in short-term
MESKO, Zhu (2025) [36], China	Inflammatory Knee OA <ul style="list-style-type: none"> • ACR KOA criteria • Knee pain ≥40 mm on most days for >6 months • KL2-4 • Signs of inflammation (at least 2 of: warmth over the joint area, joint margin tenderness, synovial effusion, and soft tissue swelling around the knee) • MRI-assessed effusion-synovitis grade of ≥ 2 • 45-70 years 	Intervention: Oral MTX 15mg weekly for 12 months Comparator: Placebo Blinding: double-blind.	Sample size: 215 (108 MTX / 107 placebo) Age, mean (sd): 60.6 (6.4) / 60.7 (6.0) Female, n (%): 97 (90.0) / 94 (88.0) BMI: 25.7 (3.5) / 25.7 (4.0) KL Grade, n (%): KL2: 22 (21.0%) / 16 (15.0%) KL3: 39 (37.1%) / 47 (43.9%) KL4: 44 (41.9%) / 44 (41.1%)	Primary endpoints: <ul style="list-style-type: none"> • VAS Pain: Between group difference at 52 weeks (mean) 95%CI: 0.3 (-6.7 to 7.3) p=0.93 • Effusion-synovitis maximal area (cm²): Between group difference: 0.1 (-0.8 to 1.0) p=0.82 Secondary Endpoints: <ul style="list-style-type: none"> • No significant between group difference at 52 weeks for WOMAC pain (2.1 (95% CI, -25.7 to 29.9) p=0.88), stiffness (-6.0 (95% CI, -17.5 to 5.6) p=0.31), and physical function (-12.7 (95% CI, -109.0 to 83.5) p=0.79), or OMERACT-OARSI criteria (59 [54.6%] vs 60 [56.1%]; p=0.83) 	MTX not effective for pain or synovitis in knee OA
Ghosh (2020) [46] India (abstract)	<ul style="list-style-type: none"> • Swelling and pain of both knees for >6 months • KL1-3 	Intervention: Oral MTX 15-20mg weekly for 3 months	Sample size: 137 (78 MTX / 59 glucosamine) Age, mean (sd): 51.56 (7.030)	<ul style="list-style-type: none"> • Significant improvement in WOMAC in MTX group compared to glucosamine group 	Oral MTX shows potential in primary

	<ul style="list-style-type: none"> Systemic inflammation (ESR>30mm/1st hr, CRP>1.5xRef) 40-65 years 	Comparator: Glucosamine Blinding: Information not provided.	Female, n (%): 104 (90.3)	<ul style="list-style-type: none"> Significant reduction in ESR and CRP in MTX group compared to glucosamine group 	knee OA with inflammation
METHODS, Wang (2023 [40]), Australia	Erosive hand OA <ul style="list-style-type: none"> ACR HOA criteria KL≥2 in at least one joint Pain levels >40 mm in last 7 days and for >3 months MRI-detected synovitis of grade 1 or more in at least one joint 40–75 years 	Intervention: Oral MTX 20mg weekly for 6 months Comparator: Placebo Blinding: double-blind.	Sample size: 97 (50 MTX / 47 placebo) Age, mean (sd): 61.4 (6.1) / 61.5 (7.3) Female, n (%): 34 (68%) / 34 (72%) BMI: 29.7 (5.0) / 27.9 (5.0) KL Grade, n (%): KL0: 1/49 (2%) / 1/47 (2%) KL1: 5/49 (10%) / 5/47 (11%) KL2: 18/49 (37%) / 16/47 (34%) KL3: 12/49 (24%) / 13/47 (28%) KL4: 13/49 (27%) / 12/47 (26%)	Primary endpoint: <ul style="list-style-type: none"> VAS Pain mean between group difference at 6-months: –9.9 mm [95% CI –19.3 to –0.6]; p=0.037) in favour of MTX. Effect size: 0.45 (0.03 to 0.87). Secondary Endpoints: <ul style="list-style-type: none"> Greater reduction in mean AUSCAN pain and stiffness at 6 months than the placebo group. The between-group differences in change in mean AUSCAN function, FIHOA, HAQ, MHQ, or grip strength were not clinically meaningful. 	MTX effective in hand OA with synovitis
Ferrero (2021 [43], France & Belgium	Hand OA with MRI-detected synovitis <ul style="list-style-type: none"> ACR HOA At least one joint with erosion on radiography (Verbruggen-Veys stage 'E') Pain>40 mm in last 48hrs and for >3 months 45-85 years 	Intervention: Oral MTX 10mg weekly for 12 months Comparator: Placebo Blinding: double-blind.	Sample size: 64 (32 MTX / 32 placebo) Age, mean (sd): 64.9 (7) / 67.5 (8) Female, n (%): 31 (97%), 29 (91%) BMI: 24.2 ± 4, 24.6 ± 4 Synovitis: 29/1024 joints had synovitis at baseline	Primary endpoint: <ul style="list-style-type: none"> No difference in pain VAS change between groups at 3 months (p = 0.2) Secondary Endpoints: <ul style="list-style-type: none"> No difference in the change in pain VAS score between groups at 12 months (p = 0.6). More joints remodelled (Verbruggen-Veys score) in MTX group compared to placebo at 12 months 	MTX may have structural benefit
Observational studies					
PROM Wenham (2013). [38], UK	Knee OA with US synovitis <ul style="list-style-type: none"> ACR clinical criteria KL ≥1, Synovitis on US (effusion or synovial hypertrophy ≥2mm), Pain VAS ≥40 	Intervention: Oral MTX up to 20 mg/week for 6 months Comparator: None (open-label) Blinding: Not applicable (open-label)	Sample size: 30 Age, mean (range), years: 64.5 (53-85) BMI, mean (sd): 31.4 (5.9) KL Grade, n (%): KL1: 6 (20%) KL2: 20 (67%) KL3: 3 (10%) KL4: 1 (3%)	Pain: <ul style="list-style-type: none"> At 24 weeks, median (IQR) reduction in 48-h pain VAS of 27 mm (4-38) 13/30 participants (43%) achieved >30% reduction in pain VAS, of whom 7 (23%) achieved >50% reduction. 13/30 (43%) participants achieved OARSI responder criteria. Ultrasound: <ul style="list-style-type: none"> Baseline synovitis / effusion not substantively correlated with baseline pain or change in 48-h pain VAS at 24 weeks (r < 0.2) Changes in synovitis / effusion at 24 weeks not substantively correlated with changes in pain (all r < 0.2) 	MTX may have analgesic efficacy in knee OA
Pavelka (2006) [37], Czech Republic (abstract)	Erosive hand OA <ul style="list-style-type: none"> Painful EOA Negative rheumatoid factor ≥1 swollen PIP 	Intervention: Oral MTX 10 mg/week for 2 months Comparator: None (open-label) Blinding: Not applicable (open-label)	Sample size: 21 Age, mean (sd): 60.5 (9.1) Female, n (%): 19 (90.5) Tender joints: 7.9 (3.7) Swollen joints: 3.1 (1.2)	Significant decrease in pain (54.5 ± 17.0 vs 39.7 ± 24.7, p<0.01) and stiffness (28.8 ± 24 min vs 21.8 ± 19.1 min, p<0.01) Non-significant trend for decrease of CRP (3.3mg/l ± 2.0 vs 2.4 ± 1.1mg/l, p=0.08)	MTX shows promise in EOA

Abbreviations: ACR – American College of Rheumatology; AUSCAN – Australian/Canadian Osteoarthritis Hand Index; BMI – Body Mass Index; CI – Confidence Interval; CRP – C-reactive protein; EOA – Erosive Osteoarthritis; ESR – Erythrocyte Sedimentation Rate; FIHOA – Functional Index for Hand Osteoarthritis; HAQ – Health Assessment Questionnaire; HOA – Hand Osteoarthritis; hsCRP – High-sensitivity C-reactive protein; ICOAP – Intermittent and Constant Osteoarthritis Pain; IQR – Interquartile Range; KL – Kellgren-Lawrence; KOA – Knee Osteoarthritis; MHQ – Michigan Hand Outcomes Questionnaire; MRI – Magnetic Resonance Imaging; MTX – Methotrexate; NRS – Numeric Rating Scale; OA – Osteoarthritis; OMERACT – Outcome Measures in Rheumatology; OARSI – Osteoarthritis Research Society International; PIP – Proximal Interphalangeal (joints); SD – Standard Deviation; US – Ultrasound; VAS – Visual Analogue Scale; WOMAC – Western Ontario and McMaster Universities Osteoarthritis Index.