**Appendix 1.** Studies on cannabis use in fibromyalgia

| Author, year | Study design | Country | N, age, gender | Disease duration | Cannabis doses (mg/day) | Outcome | Side effects |
|---|---|---|---|---|---|---|---|
| Sagy et al., 2019. [6] | Prospective observational study | Israel | n=367,<br><br>mean age 52.9±15.1 yo,<br><br>82% female | NA | Titration from 1 drop of 15% THC-rich cannabis 2X /Day or<br>one breath every 3–4 h of cigarette contained 0.75 g of cannabis<br><br>until they reached a therapeutic effect | Reduction of pain (VAS of 9→5),<br>Improvement of QoL.<br><br>The 6 months response rate was 70.8% | Mild:<br>• dizziness (7.9%),<br>• dry mouth (6.7%),<br>• gastrointestinal (5.4%). |
| Habib and Avisar 2018. [7] | Internet-based questionnaire | Israel | n=383 (84% consuming cannabis),<br><br>mean age=42.2±14.2 yo,<br><br>85% female | 8.26±7.8 years | Mean=31.4±16.3 g/month | Improvement:<br>• Pain in 94%,<br>• sleep in 93%,<br>• depression in 87%,<br>• anxiety in 62%.<br><br>85% stopped or reduced the dosage of other Meds | Mild- 12%<br>(eye or throat irritation)<br><br>8% reported dependence. |
| Habib et al., 2021. [8] | Retrospective Phone survey | Israel | n=319 (82% with FM)<br>mean age=46±12 yo<br>217 females | 5.6±3.9 years | 31 g/month<br><br>THC-9.3–27%;<br>CBD-0.1–13.9%. | ↓ of pain – 77% (mean level);<br>Improvement of sleep of 78%. | NA |
| Mazza 2021. [9] | Retrospective, open-label case series | Italy | n=38,<br>mean=55 yo,<br>95% female. | 1 to 2 years | THC 200 mg/day or<br>THC: CBD 1:1 400 mg/day. | Improved:<br>• 1 month → NRS, ODI, WPI, SyS.<br>• 3 months → NRS, ODI, WPI;<br>• 12 months → NRS, ODI, SyS. | Interrupted in 17 (48.6%) due to nonserious AEs:<br>• mental confusion → 37%,<br>• dizziness → 14%,<br>• nausea/vomiting → 14%;<br>• agitation/irritation → 14%. |
| Fiz et al., 2011. [10] | Cross-sectional; Questionnaire in users vs non-users | Spain | n=28;<br>mean age =50±11.9 yo;<br>93% females | Median 5 (1–20) years | 54% - smoking;<br>46% - oral;<br>43% combined. | Reduction of<br>• pain (37.1 mm);<br>• stiffness (0.40.7 mm);<br>Enhancement | Present in 96%:<br>• somnolence (n=18),<br>• dry mouth (n=17),<br>• sedation (n=12), |

**Appendix 1 (cont).** Studies on cannabis use in fibromyalgia

| Author, year | Study design | Country | N, age, gender | Disease duration | Cannabis doses (mg/day) | Outcome | Side effects |
|---|---|---|---|---|---|---|---|
| | | | | | Most common dose: 1–2 cigarettes or 1 spoon/each time<br>n=12 → daily use;<br>n=5 → 2–4 days /week;<br>n=3 → < 2x /week;<br>n=8 → occasionally. | • relaxation (0.27.6 mm);<br>• somnolence (20.0 mm);<br>• well-being (40.0mm).<br>Strong improvement:<br>• sleep-81%;<br>• headaches-14%<br>SF-36 was significantly higher | • dizziness (n=10),<br>• high (n=9),<br>• tachycardia<br>• (n=8),<br>• eye irritation (n=7)<br>• hypotension (n=6). |
| van De Donk et al., 2019. [11] | Randomized placebo-controlled 4-way crossover trial | Netherlands | n=20, age=39±13 yo, 100% females | NA | Bedrocan (22.4-mg THC/1 mg CBD);<br>Bediol (13.4-mg THC/17.8 mg CBD);<br>Bedrolite (18.4-mg CBD/1 mg THC);<br>Placebo | Cannabis varieties containing THC caused ↑ in pressure pain threshold. | 1/3 reported sore throat and bad taste, and 2/3 coughed during the 5- to 7-minute inhalation.<br>1/3 had nausea without vomiting.<br>All side effects were mild. |
| Yassin et al., 2019. [12] | Prospective observational cross over study.<br><br>Addition of cannabis to SAT | Israel | n=31 (patients with FM + low back pain);<br><br>Mean age=33.4±12.3 yo;<br><br>90% females. | NA | After 3 months of SAT (5 mg oxycodone + 2,5 mg of naloxone twice/day) + duloxetine 30 mg once/day]<br><br>addition of<br><br>20 g/month of MCT (inhalation)- 6 months<br>(1 THC: 4 CBD). | After 6 months:<br>• Mean pain VAS 8.1 → 3.3;<br>• Mean FIQ R 46.3 → 80.5<br>• Mean ODI 77.5 → 30.7<br>• Mean Schober test 3.7 → 5.3 cm | With MCT;<br>• Red eyes (n=28);<br>• Increased appetite (n=8);<br>• Sore throat (n=3).<br>With SAT:<br>• Depression (n=2);<br>• Loss of appetite (n=8);<br>• Constipation (n=15)<br>• Hemorrhoids (n=4)<br>• Zombie-like feeling (n=5)<br>6 patients stopped treatment by AE |
| Skrabek et al., 2008. [13] | Randomized, double-blind, placebo-controlled. | Canada | n=40;<br>mean age=47.6±9.13 yo;<br>gender – NA | NA | Nabilone (from 0.5 mg PO at bedtime to 1 mg BID) over 4 weeks or placebo | Nabilone group:<br>• ↓ in the VAS pain (-2.04, p<0.02);<br>• FIQ (-12.07, p<0.02);<br>• anxiety (-1.67, p<0.02) | No serious adverse events<br>• drowsiness (7/15)<br>• dry mouth (5/15),<br>• vertigo (4/15),<br>• ataxia (3/15). |
| Sotoodeh et al., 2022. [14] | 12-month prospective cohort study | Canada | n=323;<br><br>mean age= | NA | At baseline: (n=323):<br>• 36.5% → dried flower;<br>• 82.0% → oil | MCT was continued by 74.9%, 58.8%, 40.2%, and 23.5% of patients at the 3, 6, 9, and 12-month respectively. | NA |

**Appendix 1 (cont).** Studies on cannabis use in fibromyalgia

| Author, year | Study design | Country | N, age, gender | Disease duration | Cannabis doses (mg/day) | Outcome | Side effects |
|---|---|---|---|---|---|---|---|
| | | | 52.0±13.0 yo;<br><br>86.7% females. | | • THC-dominant → 16.4%<br>• CBD-dominant → 35.9%<br>• Balanced (1:1) → 52.3%.<br>At 12 months (n=76):<br>• Dried flower → 63.2%<br>• Oil → 76.3%<br>• oil and flower → 42.1%<br>• THC dominant → 26.3%<br>• CBD dominant → 36.8%<br>• Balanced (1:1) → 53.9% | At 12 months:<br>• Mean VAS pain from 6.4 → 5.3<br>• Mean negative affect 4.6 → 3.1<br>• Mean sleep problems 7.0 → 4.9<br>Nabilone was superior o amitriptyline on sleep (Insomnia Severity Index difference =3.2; 95% CI=1.2–5.3). | |
| Ware et al., 2010. [15] | Randomized, double-blind, active-control, equivalency crossover trial | Canada | n=32,<br>mean age= 49.5±11.2 yo;<br>81.2% females | NA | Nabilone (0.5–1.0 mg)<br>or<br>amitriptyline (10–20 mg)<br><br>each drug for 2 wk with a 2-wk washout period | Nabilone was marginally better on restfulness (Leeds Sleep Evaluation Questionnaire difference =0.5 [0.0–1.0]) but not on wakefulness (difference =0.3 [-0.2–0.8]).<br>No effects on pain, mood, or quality of life were observed. | 187 adverse events: 120=mild; 64=moderate; 3 severe (2 with amitriptyline. 1 with nabilone)<br>With nabilone:<br>• Dizziness (n=10)<br>• Nausea (n=9)<br>• Dry mouth (n=7)<br>• Drowsiness (n=6)<br>• Constipation (n=4)<br>• Insomnia (n=4)<br>• Vomiting (n=3). |
| Giorgi et al., 2020. [16] | Prospective observational study | Italy | n=102,<br>mean age= 51.9 yo,<br>91% females | 114.3 months | Bedrocan-(22% THC,<1% CBD)<br>or<br>Bediol-(6.3% THC, 8% CBD).<br>Both diluted 1g/10g oil.<br>Dose 10–30 drops/day (↑ allowed until 120 drops/day) | n=25 (24.5%) lost follow up;<br>n=11 (10.7%) stopped treatment (3 due to lack of benefit; 6 due to side effects)<br>n=66 evaluated:<br>PSQI improved in 44% and FIQ-R in 33%; anxiety and depression in 50% | 33% mild AE:<br>• dizziness → 21%,<br>• sleepiness → 16%,<br>• palpitations → 12%,<br>• nausea → 9%,<br>• xerostomia → 9%. |
| Chaves S et al., 2020. [17] | Randomized, double-blind, placebo-controlled | Brazil | n=17,<br>mean age-51.9 yo,<br>100% females | NA | Mean dose: 4.4 mg of THC + 0.08 mg of CBD) | Reduction of FIQ | Cannabis group:<br>• somnolence → 87.5%,<br>• dizziness → 25%,<br>• mouth dryness → 25%. |

**Appendix 1 (cont).** Studies on cannabis use in fibromyalgia

| Author, year | Study design | Country | N, age, gender | Disease duration | Cannabis doses (mg/day) | Outcome | Side effects |
|---|---|---|---|---|---|---|---|
| | clinical trial | | | | | | |
| Fitzcharles et al., 2021. [18] | Cross-sectional | Canada | n=117 FM (28 using cannabis), mean age=64±14 yo, 73% females | NA | n=13 → inhalation (6 smoking, 7 vaping), n=6 → oral oils, n=5 → (inhalation and oral). When cannabis was inhaled, patients reported 0.5–6 g/day. | Global symptom relief on a VAS (1–10) was 7.0±2.3. n=11 (39.3%) stopped due to lack of effect | 4/28 (mild) |

FM: Fibromyalgia; n: Number; NA: Not available; MCT: Medical cannabis treatment; THC: Tetrahydrocannabinol; CBD: Cannabidiol; SF-36: Short Form (36) Health Survey; NRS: Numerical Rating Scale; ODI: Oswestry Disability Index; Hospital Anxiety and Depression Scale, WPI: Widespread Pain Index; SyS: Severity Score; VAS: Visual Analogic Scale; QoL: Quality of life; PSQI: Pittsburg Sleep Quality Index; FIQR: Fibromyalgia impact questionnaire – revised; SAT: Standardized analgesic treatment.

**Appendix 2.** Studies on cannabis use in rheumatic diseases other than fibromyalgia

| Author, reference | Study design | Country | N, age, gender | Rheumatic disease | Disease duration | CBD dose (mg/day) | Outcome | Side effects |
|---|---|---|---|---|---|---|---|---|
| Blake et al., 2006. [19] | Randomized, double-blind, parallel-group method | UK | n=58 (31 cannabis; 27 placebo) mean age= 47.0±9.4 yo, 79% female | Rheumatoid arthritis | 13.6±11.1 yo | CBD 2.5mg + THC 2.7 mg oromucosal spray | Improved pain on movement (p=0.04) and at rest (p=0.01), quality of sleep (p=0.02), DAS-28, and (p=0.002) SF-MPQ pain at present (p=0.01). | All mild or moderate intensity except for 2 (6%) rated severe (constipation; 'malaise') compared with 6 (22%) in the placebo group. |
| Wang et al., 2021. [20] | Case report | Canada | n=1; 85 yo; female. | Osteoarthritis | ND | maximum dose.: CBD 75 mg/ 2X day THC was used only for 1 week. | Improved pain and functionality. | With THC:<br>• dizziness,<br>• unclear speech,<br>• cognitive impairment. |
| Fader et al. 2023. [21] | Survey on patient's perception of cannabis | USA | n=103 mean age=62±10.3 yo 76% females | Basal thumb joint arthritis | median=64 months | NA | 50% had used marijuana (smoking, vaping, or consuming an edible) 20.6% used topical application. | 14 used for the thumb arthritis and 12 reported to be effective 69% reported to be interested in an oral formulation; 80% interested in topical formulation |
| Maurer et al. 2022. [22] | Case report | USA | n=1; age=72 yo; female | Osteoarthritis and scleroderma | | 1:1 CBD/THC sublingual tincture; ↑ slowly 1 month after- 6 mgTHC/6 mg CBD 3x day. | Improved pain and sleep quality. | When tried ↑ THC dose → dizziness. |
| Renslo et al., 2022. [23] | Open prospective | USA | n=40, median age= 67.9 (46-90) yo; 77.5% females | Osteoarthritis | ND | ND | Opioid dosage ↓; 37.5% reduced to 0.<br>Response - 6 months:<br>• VAS pain ↓ from 6.6–5.4 (p<0.05)<br>• GMH ↑ from 45.2–48 (p=0.42)<br>• GPH ↑ from 37.5–40 (p=0.18) | 9/40 (42.5%) "felt intoxicated," with 3/9 feeling interference in their lives. |
| Vela et al., 2022. [24] | Randomized, double-blind, | Denmark | n=129 (59 with PsA and 77 with | Osteoarthritis and psoriatic | NA | CBD – 20 30 mg/day or placebo | No differences in pain, sleep, anxiety and depression | 2% in each group. CBD had more ear–nose– |

**Appendix 2 (cont).** Studies on cannabis use in rheumatic diseases other than fibromyalgia

| Author, reference | Study design | Country | N, age, gender | Rheumatic disease | Disease duration | CBD dose (mg/day) | Outcome | Side effects |
|---|---|---|---|---|---|---|---|---|
| | placebo-controlled trial | | hand-OA), mean age=61.75 yo, 65% females | arthritis | | 12 weeks | and PCS between CBD and placebo. | throat region and skin side effects than placebo. |
| Rampakakis et al., 2023. [25] | Cross-sectional-collected data from patients and from rheumatologists | Canada | n=799 patients from Ontario Best Practice Research Initiative Mean age; 58.9±15.1 yo; 71.4% females | RA. PsoA, lupus, spondyloarthritis, FM, gout, osteoporosis, polymyalgia rheumatica | NA | | n=163 used cannabis in the last 2 years. n=78 currently using. Users had more • disease activity • pain • Physician global • Patient's global • Diagnosis of Fm and AO • More psychiatric and gastrointestinal comorbidities • Used more opioids and antidepressants. Rheumatologists (n=22/29) felt uncomfortable with the prescription. | NA |
| Frane et al., 2022. [26] | Internet survey | USA | n=604 428 CBD users age- from 18 to >65 yo. Females-63.6% in CBD users; 68.8% in non-users. | RA, osteoarthritis, autoimmune arthritis | | | CBD improved: • pain (83%), • physical function (66%), • sleep quality (66%). OA group had greatest reduction in pain Reduction or cessation of other medication in 60.5% | 41% had at least 1 side effect: • Mild- 84% • Moderate- 14% • Severe- 2% Most common: • Dry mouth- 20% • Somnolence- 17% • ↓ appetite- 9% • Dry eyes- 8.6% • ↓ concentration- 5.4% • Dizziness- 4% • Headache- 4% • Gastrointestinal- 3.5% |

**Appendix 2 (cont).** Studies on cannabis use in rheumatic diseases other than fibromyalgia

| Author, reference | Study design | Country | N, age, gender | Rheumatic disease | Disease duration | CBD dose (mg/day) | Outcome | Side effects |
|---|---|---|---|---|---|---|---|---|
| Wright et al. 2006. [27] | Cross-sectional observational | Canada | n=247<br>mean age- NA<br>sex - NA | Rheumatoid arthritis<br>Osteoarthritis | NA | illicit use | Fell much better – 72%<br>Fell a little better – 28% | NA |
| Spiera et al., 2020. [28] | Randomized, double-blind, placebo-controlled, phase II study | USA | n=32<br>(27 → lenabasum; 15 → placebo)<br>mean age= 49±10.4 yo,<br>60% females | Systemic sclerosis | 34±18 months | Lenabasum 5 mg/day, 20 mg/ day, or 20 mg 2 X /day - 4 weeks, and then by 20 mg twice daily for 8 weeks | Improved CRISS score, skin involvement, and patient-reported function.<br>Gene expression in inflammation and fibrosis pathways was reduced;<br>Inflammation and fibrosis improved on histology. | 63% of the lenabasum group and 60% of the placebo.<br>1 withdrawal because AE in lenabasum group. |
| Spinella et al, 2023. [29] | Prospective randomized placebo controlled | Italy | n=45 (35 limited; 10 diffuse); 25 CBD group; 20 controls.<br>Mean age= 53.0±14.6 yo<br>88.8% females | Systemic sclerosis with digital ulcers | CBD group- 10.6±5.2<br>Control group- 14.3±8.6 | Local use of 10% CBD oil in acidic form and 90% hemp oil,<br>free from THC.<br>4 drops/day for 2 months | Wound related pain scores improved in both groups but more in the CBD group ($p<0.0001$)<br>Complete healing:<br>• 72% CBD group<br>• 30% control group. | 28% of CBD group with itch and perilesional erythema. |
| Nogueira et al., 2019. [30] | Case report | Israel | n=1<br>age= 59 yo, male | Systemic sclerosis | 5 yo | 30 g/day of cannabis sativa leaves (smoke) | Amelioration of all symptoms, complete resolution of Raynaud's phenomenon, and dyspnea.<br>It reduced creatinine levels from 1.7 to 1.1mg/dL.<br>Pulmonary function became normal. | None |
| Ouatah et al., 2023. [31] | Survey on cannabis use by rheumatological patients | France | n=23/501 used cannabis<br>Age- 63.6 yo<br>Sex- NA | RA, PsoA, ankylosing spondylitis | NA | total of 78.3% of current-users reported consuming cannabis daily compared to 60.3% of past-users. | Motivation:<br>• Reduce pain- 26%<br>• To relax- 22%<br>• Help to fall sleep- 21%<br>• Reduce anxiety- 10%<br>Fun-14% | NA |

**Appendix 2 (cont).** Studies on cannabis use in rheumatic diseases other than fibromyalgia

| Author, reference | Study design | Country | N, age, gender | Rheumatic disease | Disease duration | CBD dose (mg/day) | Outcome | Side effects |
|---|---|---|---|---|---|---|---|---|
| Werth et al., 2022. [32] | Single-center, double-blind, randomized, placebo-controlled phase 2 study | USA | n=22, (11 using lenabasum, 11 using placebo); mean age= 53.1±9.31 yo, 90.9% females | Dermatomyositis | NA | 20 mg lenabasum /day for 28 days and then 20 mg 2X/day for 56 days or placebo | Adjusted least-squares mean for CDASI ↓;<br>Significant improvement in:<br>• Physical function<br>• Pain interference.<br>Reduction of IFN-b and IFN-g staining in skin sections;<br>Changes in CD4+ T cells correlated with change in CDASI activity score<br>No significant difference in gene expression of IFNb, IFNg, IL31, or IL4 | No serious or severe AEs<br>• mild dizziness,<br>• mild or moderate fatigue<br>• mild dry mouth<br>• mild diarrhea<br>mild psychiatric AE |
| Tsang et al., 2022. [33] | Survey and blood and urine analysis of patients using or not using cannabis. | Canada | n=151 (100 PsA and 51 PsC ), Mean age= 55 yo, 74% female | Psoriatic arthritis and psoriasis | 28 years | NA | Cannabis users had a shorter PsA duration and poorer mental health as measured by the SF-36.<br>Low IL-23 serum levels in cannabis users. | NA |

N: Number; NA: Not available; RA: Rheumatoid arthritis; PsoA: Psoriatic arthritis; OA: Osteoarthritis; THC: Tetrahydrocannabinol; CBD: Cannabidiol; DAS-28: Disease Activity Score using 28 joints; IFN: Interferon; CDASI: Cutaneous Dermatomyositis Disease Area and Severity Index.