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PAIN IN PSORIATIC ARTHRITIS AND HAND OSTEOARTHRITIS

BY
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Pain in Psoriatic Arthritis and Hand Osteoarthritis

By

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Preface

This thesis and the studies within have been a collaborative effort between The Department of Rheumatology, Aalborg University Hospital, and the Centre for Sensory-Motor Interaction, Department of Health Science and Technology, Faculty of Medicine, Aalborg University.
The thesis consists of an introductory backgrounds section, hypotheses and aims, description of the studies and methods, presentation of the results and concluded with a discussion and perspective for future trials section.
This work is original except where acknowledgement and references are made.
This thesis is based on four papers listed below.

Study 1
Jonathan Vela, Rene Lindholm Cordtz, Salome Kristensen, Christian Torp-Pedersen, Kristian Kjær Petersen, Lars Arendt-Nielsen, Lene Dreyer.
Is pain associated with premature mortality in patients with psoriatic arthritis? A nested case-control study using the DANBIO Register.
Published in Rheumatology 2021

Study 2
Jonathan Vela, Lene Dreyer, Kristian Kjær Petersen, Lars Arendt-Nielsen, Salome Kristensen.
Pain mechanisms in patients with psoriatic arthritis and hand osteoarthritis. Manuscript ready for submission.

Study 3
Jonathan Vela, Lene Dreyer, Kristian Kjær Petersen, Lars Arendt-Nielsen, Kirsten Skjærbæk Duch, Salome Kristensen.
Cannabidiol treatment in hand osteoarthritis and psoriatic arthritis – A randomized, double-blind placebo-controlled trial. Published in Pain. 2021

Study 4
Jonathan Vela, Salome Kristensen, Lene Dreyer, Lars Arendt-Nielsen, Kristian Kjær Petersen.
Mechanistic pain profiling in patients with hand osteoarthritis and psoriatic arthritis treated with cannabidiol for 12 weeks.
Manuscript ready for submission.

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Thank you to the patients and controls who participated in my research. I spent a lot of time talking about pain and politics with you guys and your help has been greatly appreciated.
Thank you to Psoriasisforeningen, Gigtforeningen, Aalborg University and

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*And lastly my wife **Maja**, my two sons **Mateo** and **Emillio** and my cats **Stormy** (RIP) and **Windy**. I hope to spend more quality time with you now that this project has come to completion.*

Jonathan Vela 2021

List of abbreviations

5-HT_{1A}: Serotonin 1A receptor
A_{2a}: Adenosine 2a receptor
ACR: American College of Rheumatology
AE: Adverse event
BPS: Biopsychosocial
CASPAR: Classification Criteria for Psoriatic Arthritis
CBD: Cannabidiol
CI: Confidence interval
CMC: Carpometacarpal
COPD: Chronic obstructive pulmonary disease
CPM: Conditioned pain modulation
CRP: C-reactive protein
CVD: Cardiovascular disease
DM: Diabetes mellitus
DMARD: Disease modifying antirheumatic drug.
EULAR: European Alliance of Associations for Rheumatology
GPR55: G protein-coupled receptor 55
Hand-OA: Hand osteoarthritis
HAQ: Health assessment questionnaire
IASP: International Association for the Study of Pain
IMMPACT: Initiative on Methods, Measurement and Pain Assessment in Clinical Trials
NRS: Numeric rank scale
NSAID: Nonsteroidal anti-inflammatory drug
PCS: Pain catastrophizing scale
PDT: Pain detection threshold
PPT: Pressure pain threshold
PRO: Patient reported outcome
PsA: Psoriatic arthritis
PSQI: Pittsburgh sleep quality index
PTT: Pain tolerance threshold
QST: Quantitative sensory testing
RA: Rheumatoid arthritis
RCT: Randomized controlled trial
SAE: Serious adverse event
SETS: Stanford expectations of treatment scale
SMD: Standardized mean difference
SMM: Superficial masseter muscle

SpA: Spondylarthritis
SSS: Symptom severity scale
THC: Δ^9-tetrahydrocannabinol
TMJ: Temporomandibular joint
TRPV: Transient receptor potential vanilloid
TSP: Temporal summation of pain
VAS: Visual analogues scale
WPI: Widespread pain index

English summary

Chronic pain occurs in 20% of the world's population and musculoskeletal pain is the most common reason for referral to a rheumatology outpatient clinic. Chronic pain has also been linked to premature death, but whether the degree of pain intensity plays a role in excess mortality is not known. The cause of chronic pain is multifactorial and contributors to the pain experience can be psychosocial factors (anxiety, depression, catastrophizing and sleep quality, etc.) or changes in various pain processing mechanisms. These are expressed as pressure hypersensitivity distal to an injured joint, increased temporal summation of pain and decreased conditioned pain modulation. Two joint diseases that can cause chronic pain are hand osteoarthritis and psoriatic arthritis. Osteoarthritis of the hand is a degenerative arthritis where the core symptoms are pain, stiffness and reduced mobility and there is currently no effective treatment. Previous studies have indicated that these patients may experience altered pain processing, but this has not been fully established. Psoriatic arthritis is an inflammatory arthritis that can also affect the skin, entheses, nails and spine. There are medications that effectively alleviate the inflammation, but many patients continue to experience chronic pain despite being treated with anti-inflammatory and disease modifying drugs.
Currently, there is no effective treatment for chronic pain and patients have begun to inquire about and try treatment with medical cannabis. Cannabidiol (part of the cannabis sativa plant) is frequently used by patients with chronic joint pain as cannabidiol does not produce euphoria. But, despite its popularity, no randomized placebo-controlled studies have been performed demonstrating its analgesic effect.

This dissertation is based on four studies on pain in patients with psoriatic arthritis and hand osteoarthritis.
In study 1, the relationship between pain intensity and the risk of excess mortality in patients with psoriatic arthritis registered in the DANBIO database was investigated. The study showed an association between higher pain intensity and excess mortality, but this association disappeared when adjusting for confounders. Comorbidity (chronic obstructive pulmonary disease, diabetes, cardiovascular disease, and cancer) was associated with excess mortality and the same was true for patients who had redeemed a prescription for glucocorticoids within a year.

In Study 2, the presence of abnormal pain processing was examined in patients with hand osteoarthritis and psoriatic arthritis who had moderate to severe chronic pain. In a cross-sectional study, patients showed greater degree of pressure hypersensitivity distal to an arthritis-affected joint, increased temporal summation of pain, and inhibited conditioned pain modulation compared with healthy controls. Patients also reported more anxiety and depression, more catastrophizing, poorer sleep quality, and increased disability. Patients who simultaneously met the criteria for fibromyalgia had a greater degree of abnormal pain processing than patients who did not, and they also had greater scores of anxiety, depression and catastrophizing, worse sleep quality, and an even greater degree of disability.
In Study 3, the analgesic effect of 20 mg to 30 mg cannabidiol given for 12 weeks to patients with hand osteoarthritis and psoriatic arthritis was examined. The study was conducted as a randomized trial with a placebo control group and both patients, the treating physician and data processor were blinded. One hundred and thirty-six patients participated in the trial and 129 (95%) completed and were included in the final analysis. Twelve weeks of cannabidiol treatment did not result in a significant decrease in pain intensity compared to treatment with an inactive placebo. There was no significant difference in the number of patients who experienced a decrease in pain intensity of more than 30% and there was no significant difference in self-reported anxiety and depression, catastrophizing, sleep quality or functioning. No patients experienced serious adverse reactions attributable to cannabidiol.
In study 4, it was investigated whether cannabidiol could modify patients' pain processing mechanisms and whether baseline differences could be identified between patients who had responded to cannabidiol treatment (≥ 30% pain reduction) compared to those who did not. The same data collected in Study 3 were used. Cannabidiol did not affect the pain processing mechanisms when compared to patients receiving placebo and there was no difference in measured values at the start of the trial in patients responding to CBD and those who did not. In a statistical model designed to identify variables that affected the variance of pain reduction after treatment (CBD or placebo), pain intensity was the only consistently significant variable and the models generally had little ability to predict who benefited from treatment.

In summary, this dissertation showed that pain intensity did not affect excess mortality in patients with psoriatic arthritis when other factors such as

comorbidity and medication use were considered. However, patients with hand osteoarthritis and psoriatic arthritis with moderate to severe pain could have changes in pain processing mechanisms and psychological factors compared to healthy controls which could potentially contribute to the pain experience. At the same time, a large proportion of these patients meet the criteria for fibromyalgia and represent a group that has a greater degree of affected pain processing and further impaired functioning. Treatment with 20 mg to 30 mg cannabidiol for 12 weeks for patients with hand osteoarthritis and psoriatic arthritis was no better than placebo to relieve pain, change pain processing mechanisms, psychological factors, sleep quality or disability. Finally, it was not possible construct models that could predict who would benefit from the treatment.

Dansk resume

Kroniske smerter forekommer hos 20% af verdens befolkning og smerter i bevægeapparatet er den hyppigste årsag til henvisning til et reumatologisk ambulatorium. Kroniske smerter er også sat i forbindelse med tidlig død, men om graden af oplevet smerteintensitet spiller en rolle i overdødelighed vides ikke.
Årsagen til kroniske smerter er multifaktoriel og bidrag til smerteoplevelsen kan være psykosociale faktorer (angst, depression, katastrofetankegang og søvn kvalitet m.fl.) eller ændringer i forskellige smertebearbejdelsesmekanismer. Disse kommer til udtryk som trykoverfølsomhed distalt for et skadet led, øget tidsmæssig smertesummering og nedsat betinget smertemodulation. To artrit sygdomme som kan give kroniske smerter, er håndartrose og psoriasisartrit.
Håndartrose er en degenerativ artrit hvor kernesymptomerne er smerte, stivhed samt nedsat bevægelighed og der findes aktuelt ikke en effektiv behandling. Tidligere studier har indikeret at disse patienter kan opleve ændring i smerteforarbejdelsen, men der mangler studier som fastslår at dette er tilfældet.
Psoriasis gigt er en inflammatorisk artrit som også kan påvirke hud, enteser, negle og rygsøjlen. Der findes medicin som effektivt dæmper inflammationen, men mange patienter oplever fortsat kroniske smerter trods de er i behandling med anti-inflammatorisk medicin.
Aktuelt findes der ikke effektiv behandling af kroniske smerter og flere patienter er begyndt at efterspørge og selv afprøve behandling med medicinsk cannabis.
Cannabidiol (en del af cannabisplanten) anvendes hyppigt af patienter med kroniske ledsmerter da Cannabidiol ikke anses for at være euforiserende. Trods cannabidiols popularitet er der ikke er udført randomiserede placebokontrollerede studier, som påviser en smertestillende effekt.
Denne afhandling er baseret på fire studier omhandlende smerter hos patienter med psoriasisgigt og slidgigt i hænderne.
I studie 1 blev sammenhængen mellem smerteintensitet og risikoen for overdødelighed hos patienter med psoriasisgigt registreret i DANBIO databasen undersøgt. Studiet viste en sammenhæng mellem højere smerteintensitet og overdødelighed men denne forsvandt når der samtidigt blev justeret for confoundere. Komorbiditet (kronisk obstruktiv lungesygdom, diabetes, hjertekar sygdom og kræft) var forbundet med overdødelighed og det samme gjaldt for patienter der indenfor et år havde indløst recept på binyrebarkhormon.

I studie 2 blev forekomsten af abnorm smertebearbejdelse undersøgt hos patienter med håndartrose og psoriasisgigt som havde moderate til svære kroniske smerter. I et tværsnitsstudie udviste patienterne større grad af trykoverfølsomhed distalt for et artrit afficeret led, øget tidsmæssig smertesummering og nedsat betinget modulation sammenlignet med raske kontroller. Patienterne rapporterede også om mere angst og depressionsfornemmelse, mere katastrofe tankegang, dårligere søvnkvalitet og nedsat funktionsevne. Patienter der samtidigt opfyldte kriterierne for fibromyalgi havde større grad af abnorm smerteforarbejdelse end dem der ikke opfyldte kriterierne og de havde også større mental påvirkning og funktionsevnen var yderligere nedsat.
I studie 3 blev den smertestillende effekt af 20 mg til 30 mg cannabidiol givet i 12 uger til patienter med håndartrose og psoriasis gigt undersøgt. Studiet blev udført som et lodtrækningsforsøg med en placebo kontrol gruppe og både patienter, behandler og databehandler var blindet. Et hundrede og seksogtredive patienter deltog i forsøget og 129 (95 %) gennemførte og blev inkluderet i den endelige analyse. Tolv ugers cannabidiol behandling medførte ikke et signifikant fald i smerteintensitet sammenlignet med behandling med en inaktiv placebo. Der var ikke signifikant forskel i antallet af patienter der oplevede et fald i smerteintensitet på mere end 30 % og der var ikke signifikant forskel i selvrapporteret angst og depressionsfornemmelse, katastrofe tankegang, søvn kvalitet eller funktionsevne. Ingen patienter oplevede alvorlige bivirkninger som kunne tilskrives cannabidiol.
I studie 4 undersøgte blev det undersøgt om cannabidiol kunne modificere patienternes smertebearbejdelsesmekanismer og om man kunne identificere forskelle mellem patienter der havde responderede på cannabidiol behandlingen (≥ 30 % smertereduktion) sammenlignet med dem der ikke havde. Samme data som blev indsamlet i studie 3, blev anvendt. Cannabidiol påvirkede ikke smerteforarbejdelsesmekanismerne når man sammenlignede med patienter der fik placebo og der var ingen forskel i målte værdier ved forsøgets start på patienter der responderede på CBD og dem der ikke gjorde. I en statistisk model konstrueret til at identificere variabler der påvirkede variansen af smertereduktion efter behandling (CBD eller placebo), var smerteintensitet den eneste gennemgående signifikante variabel og modellerne havde overordnet ringe evne til at forudsige hvem der havde gavn af behandlingen.

Sammenfattende viste denne afhandling at smerteintensitet ikke havde indflydelse på overdødelighed hos patienter med psoriasis gigt, når man

tager højde for andre faktorer så som komorbiditet og medicinforbrug. Patienter med håndartrose og psoriasis gigt med moderate til svære smerter kunne dog have ændringer i smerteforarbejdelsesmekanismer og psykologiske faktorer sammenlignet med raske hvilket potentiel kan bidrage til smerteoplevelsen. En stor del af disse patienter opfylder samtidigt kriterierne for fibromyalgi og repræsenterer en gruppe der har større grad af påvirket smerteforarbejdelse og yderligere nedsat funktionsevne. Behandling med 20 mg til 30 mg cannabidiol i 12 uger til patienter med hånd artrose og psoriasis gigt var ikke bedre end placebo til at lindre smerter, ændre på smerteforarbejdelsesmekanismer, psykologiske faktorer, søvnkvalitet eller funktionsevne. Slutteligt var det ikke muligt at opstille gode modeller som kunne forudsige hvem der ville have gavn af behandlingen.

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Chapter 1. Background

1. Pain

1.1 Chronic pain

Chronic pain is a prevalent condition affecting 20% of the world's population[106]. Pain experienced in the musculoskeletal system is the predominant reason for referral to rheumatology outpatient clinics[107] and inadequate pain control is the chief complaint among many patients with rheumatic disorders[177]. The International Association for the Study of Pain (IASP) definition of pain describes pain as both a sensory and an emotional experience associated with tissue damage - actual or potential[221].
Pain would Ideally subside once tissue damage has healed but sometimes pain remains. The IASP defines chronic pain as persistent or recurrent pain lasting longer than three months and in the IASP revision for ICD-11 chronic pain has been subdivided into seven different syndromes where the underlying cause of pain is not completely understood[256].
Chronic pain represents a challenge to the rheumatologist because of a frequent discrepancy between the pain experienced by the patient and findings indicating tissue damage or inflammation including serological markers[257] and medical imaging as is seen in the low back pain[164] shoulder[207] and knee[127].

1.2 Pain and mortality

The association between pain and mortality has been extensively studied in different cohorts. But, determining if an association between pain and mortality exists, is difficult due to the multifaceted and subjective nature of pain and the many ways in which pain can be categorized and quantified. One of the largest studies done to date, in terms of sample size, is a meta-analysis performed by Smith and colleagues exploring the association

between chronic pain (duration >3 months or widespread pain) and excess mortality[240]. They found an overall small and not statistically significant mortality rate ratio of 1.14 (95 % CI 0.95 to 1.37). The effect size was similar when limiting the analysis to studies examining widespread pain with a mortality rate ratio of 1.22 (95% CI 0.93 to 1.60). Macfarlane and colleagues later performed a study with data added from the UK Biobank and found a greater mortality rate ratio among patients with chronic widespread pain 1.57 (95% CI 1.06 to 2.33)[163] but in contrast to Smith et al. decided to use a crude model thus omitting confounders.

1.3 Pain and inflammation

Inflammation is a broad term encompassing the physiological processes involved in a response to harmful stimuli (invading pathogens, tissue damage etc.)[228]. Pain is considered a cardinal sign of inflammation and many inflammatory mediators i.e., pro-inflammatory cytokines (IL-1B, IL-6 and TNF-a)[287], chemokines and classical mediators (bradykinin, prostaglandins, protons, nerve growth factor) contribute to nociceptive signalling by activating nociceptors directly and by increasing neuronal excitability of the primary afferent neurons[105]. This increased responsiveness and reduced threshold is termed peripheral sensitisation and is expressed clinically as hyperalgesia[105].
Nociception and inflammation serve as protective measures in acute pain by activating withdrawal reflexes and eliciting unpleasant sensation leading to both present and future protective behaviour[279].

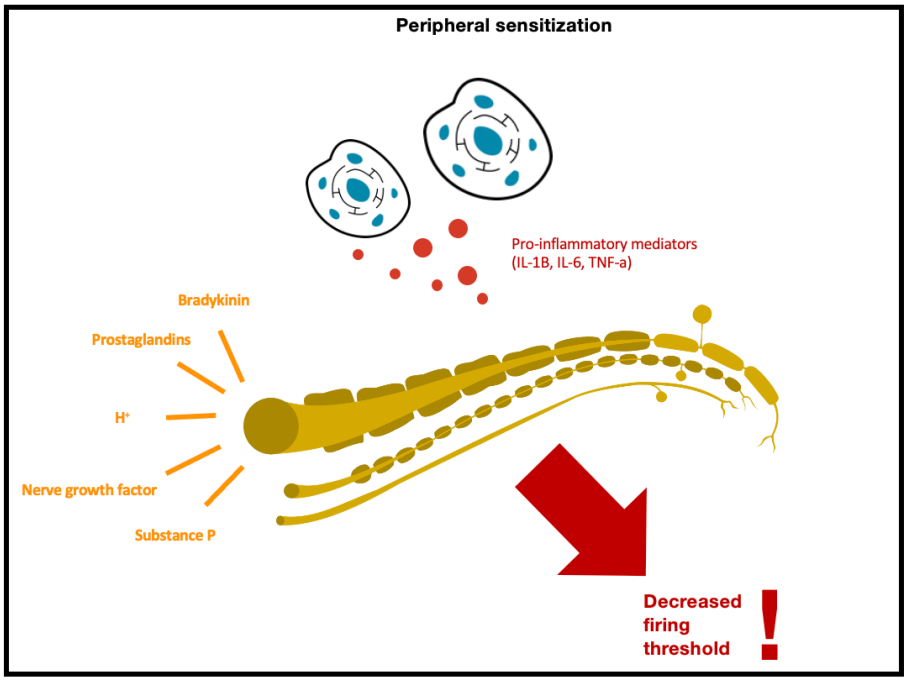

Figure 1-1 Peripheral sensitization.

Inflammation could be a key driver of chronic pain as persistent pathological inflammation plays a key role in autoimmune and autoinflammatory disorders and according to a review by Mifflin and Kerr 19 out of 24 (79%) autoimmune disorders on the National institute of Health's National Institute of Arthritis and Musculoskeletal and Skin Diseases list are associated with chronic pain[180].

1.4 Pain in a psychosocial context

In the last 40 years it has been repeatedly demonstrated that cognitive factors contribute to the pain experience[78,100,176]. This understanding of pain, is termed the biopsychosocial model of pain (BPS) and has its origin in

the BPS model of disease proposed by Engel in 1977[85] . In the BPS model the pain experience is portrayed as an interaction between physiological, psychological and social phenomenon, and psychosocial factors are now thought to cause some of the variance in prognosis and treatment response related to chronic pain[78]. To minimize inter-patient variability in RCT's (randomized controlled trial) due to patient heterogeneity the Initiative on Methods, Measurement and Pain Assessment in Clinical Trials (IMMPACT) has proposed a set of measures to assess psychosocial factors[79].

1.4.1 Negative affect including anxiety and depression

Depression is prevalent among patients with chronic pain ranging from 5% to 85% depending on study design, case criteria and population[18]. Depression in patients with chronic pain has been linked to different deleterious outcomes including increased self-reported disability[80,145] and increased pain intensity[19]. Another aspect of negative affect is anxiety. According to Asmundson and colleagues 25% to 29% of patients with chronic pain experience anxiety compared with 18% in the general population though this differs based on study design, population, geography and concomitant morbidity[13]. IMMPACT recommends the hospital anxiety and depression scale (HADS)[289] as a tool to assess anxiety and depression. The HADS is a 14-item questionnaire with seven items related to an anxiety domain and seven to a depression domain. Each item is scored from 0 to 3 yielding a range of 0 to 21, where a higher score equals greater involvement of either anxiety or depression.
The scale is reliable (22 day test-retest Pearson correlation of 0.89 for anxiety and 0.86 for depression) [245] and shows good internal consistency (Cronbachs alpha 0.83 for anxiety and 0.84 for depression) [202]. The validity of the scale has been questioned regarding the ability to distinguish between anxiety and depression, but a metanalysis concluded that the use of a bifactor model was acceptable for research purposes[193].

1.4.2 Catastrophizing

Catastrophizing is a multidimensional construct consisting of magnification of pain, rumination and a feeling of helplessness[169].
It is associated with increased pain intensity and according to Sullivan and colleagues could account for 7% to 31% of the variance in pain ratings[249]. Increased levels of catastrophizing (quantified using the Pain Catastrophizing Scale) is associated with a worse outcome in treatment of back pain[270] and after total knee arthroplasty[41]. A metanalysis performed by Martinez-Calderon and colleagues found a positive association between catastrophizing and disability, and catastrophizing and pain intensity in patients with RA, low back pain, knee pain, neck pain and widespread pain[169].
IMMPACT recommends the Pain Catastrophizing Scale (PCS) as a tool to assess catastrophizing[79]. The questionnaire consists of 13 items each score on a five-point scale (0 to 4). A global score can be calculated ranging from 0 to 52 and individual scores can be calculated for each domain (magnification, rumination and helplessness)[250]. The scale has good test retest reliability (0.88; 95% CI 0.83 to 0.93) and shows good internal consistency (Cronbachs alpha = 0.92; 95%CI 0.91 to 0.93) [271].

1.4.3 Expectation

Expectations of treatment both positive and negative potentially influences treatment outcome though studies supporting this is conflicting possibly owing to multiple measurement tools[184]. IMMPACT recommends the Stanford expectations of treatment scale (SETS) a questionnaire consisting of six items scored on a seven-point Likert scale[285]. Three items represent a positive expectations subscale while the remaining three represents a negative expectations subscale. Each subscale is scored from 0 to 21 with a higher score representing a stronger expectation. The scale shows good internal consistency (Cronbachs alpha = 0.81 to 0.88 for positive expectancy and 0.81 to 0.86 for negative expectancy)[285]. But its ability to predict outcome variance (change in Patient Global impression of Change scale) is modest (12% to 16%)[285].

1.4.4 Sleep quality

Insomnia is prevalent among patient with chronic pain occurring in 24% to 32% while the prevalence in the general population is estimated to be 10% to 15%[128]. Sleep disturbance is seen even more frequently in patients with chronic pain ranging from 50% to 80%[51] and a bidirectional relationship between sleep disturbances and pain seems to exist[76,149]. Furthermore, multiple studies have correlated sleep disturbances with greater pain intensity and risk of developing chronic pain[91].
IMMPACT recommends the Pittsburgh sleep quality index (PQSI) as a tool to assess sleep quality[79]. The PSQI is composed of 19 items assessing seven domains (subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication and daytime dysfunction). Each domain is scored from 0-3 based on the answers to each item[43]. A global score is calculated via a formula giving a score ranging from 0-21 where 21 indicates severe difficulties in all sleep related areas. The PSQI is the most used measure of sleep quality and it is considered reliable with an ICC of 0.70 to 0.86[186]. The PSQI total score is associated with other scales measuring insomnia and sleep quality and actigraphy[186].

In summery it is generally accepted that a range of psychosocial factors modulate pain and endorsements from pain research networks exist advocating that affective state, catastrophizing thoughts, sleep quality and treatment expectations should be assessed when classifying and studying pain[79].

1.5 Central Sensitization

Central sensitization is defined as: “Increased responsiveness of nociceptive neurons in the central nervous system to their normal or subthreshold afferent input”[12].
Central sensitization is thought to encompass different alterations in the central nervous system causing altered processing of nociceptive and sensory stimuli which can be expressed clinically as local and widespread hyperalgesia, and allodynia[278]. The molecular mechanisms behind persistent sensitization are many and at present no treatment has provided

a consistent effective reversal[152]. Signs of central sensitization are found in patients with different musculoskeletal pain conditions including chronic low back pain[230] and knee osteoarthritis[92] and in conditions often seen by rheumatologists including fibromyalgia[174] and rheumatoid arthritis (RA)[175].

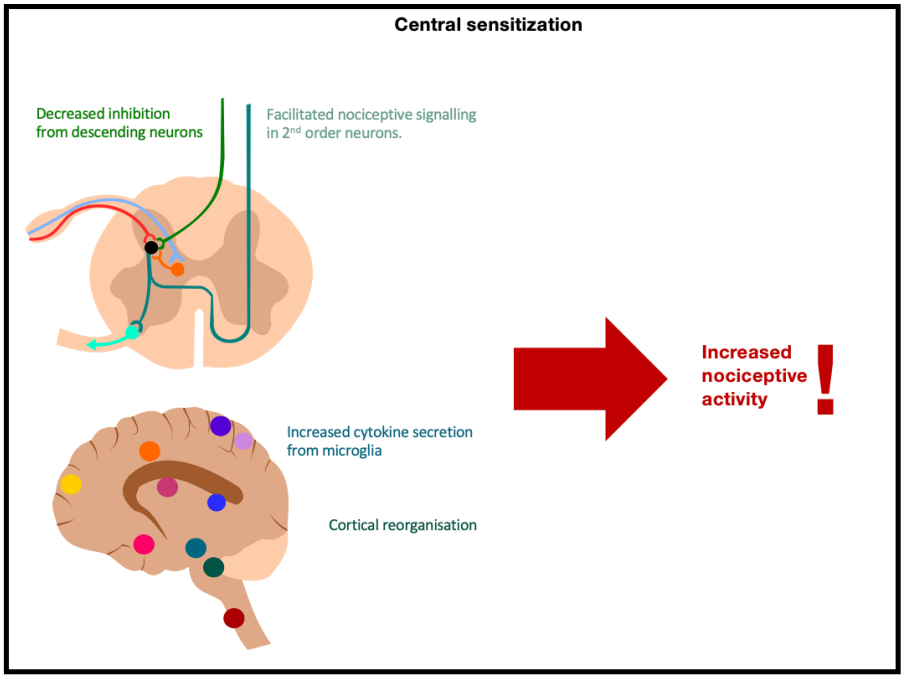

Figure 1-2 Central sensitization

Further evidence for the manifestation of central sensitization can be obtained by examining pain processing mechanisms like temporal summation of pain (TSP) and conditioned pain modulation (CPM)[12]. TSP refers to increased pain occurring when a noxious stimulus is applied repeatedly with the same intensity, for a short duration of time. TSP mimics the wind-up process assessed in preclinical trials, which reflects excitability of dorsal horn neurons and therefore central sensitization at the dorsal horn level[12].

CPM is a measure of the net effect of descending facilitation and the inhibitory system[219] and can be assessed using one painful stimulus, which inhibits another painful stimulus. CPM is impaired in a range of different chronic pain conditions[155].

2. Pain measurement and quantitative sensory testing

Pain intensity is a widely measured pain quality and can be quantified using different instruments[144]. The visual analogue scale (VAS) is frequently used in patients with rheumatic diseases[86,120]. It is a single item scale consisting of a horizontal line usually with a length of 100 mm anchored by a verbal descriptor at each extreme[130]. Recall period is often “current” or “in the last 24 hours”[120].It has good test-retest reliability in the literate (Pearson’s correlation coefficient = 0.94 between first and second assessment)[90] and correlates well with the numeric rank scale (NRS)[144]. The minimal clinically important difference in pain intensity in chronic pain (reduction in mm on a 100 mm scale) was estimated at 20 mm in a metanalysis performed by Olsen and colleagues[199].
As established in previous chapters, pain is an emergent phenomenon made even more complex by its subjectivity, but pain is also a clinical phenomenon worth quantifying to evaluate treatment response, prognosis, and other clinical variables. Quantitative sensory testing (QST) represents an attempt to measure perception (subjective sensation e.g., pain) by applying a quantifiable stimulus[108].
QST encompasses a range of methods used to evaluate sensory function and specific pain mechanisms usually be measuring thresholds or response curves[8].

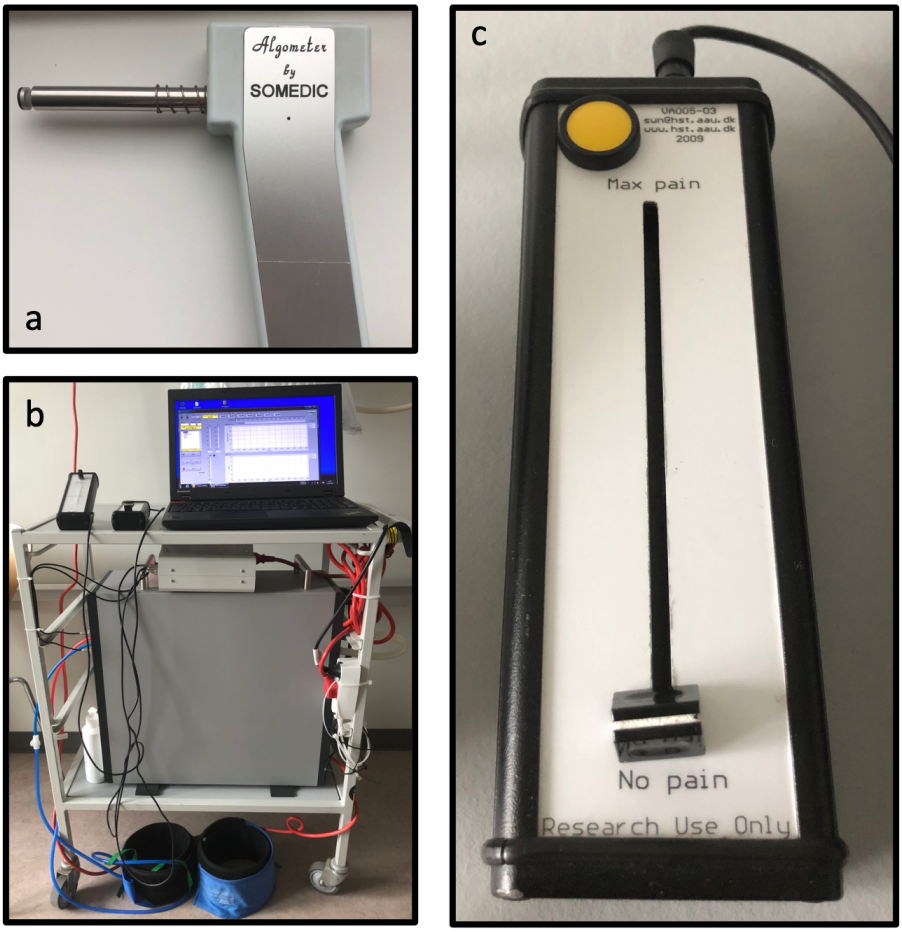

Figure 1-3 Quantitative sensory testing equipment. a: Hand-held algometer, b: Computer controlled cuff algometer setup, c: electronic visual analogue scale with slider.

2.1 Static measures

Static measures assess sensitivity including hyperalgesia and allodynia. These measures can be applied locally (e.g., a joint affected by arthritis) or distally at a non-segmental area (e.g., the arm in patients with low back pain) to determine widespread altered sensitivity.
Assessing the sensitivity of deep somatic tissue (muscle and joints) can be done with a handheld pressure algometer[255] or with a computer-controlled cuff algometer[218]. The pressure algometer is usually fitted with a rounded padded head of a large diameter (1 cm) to avoid stimulating nerve endings in cutaneous tissue [255] and pressure is applied slowly and increased at a constant rate (30 kPa/sec) to ensure reliability[10].
Typical measures include a pain detection threshold (PDT) also called pressure pain threshold (PPT) when relating to a pressure stimulus. The PPT is defined as the minimum pressure that is perceived as painful[11] while the pain tolerance threshold (PTT) is defined as the maximum pressure that a patient is willing to accept[123].
Hand-held algometry has shown good inter and intratester reliability of PPT measurements in patients with knee-OA with (intra class correlation coefficients (ICC) of > 0.6 for both[135].
An alternative to hand-held pressure algometry is using torniquets or “cuffs” so-called cuff pressure algometry where pressure can be regulated by a computer thus eliminating examiner dependence[218].
Local hypersensitivity is assessed by measuring PPT at an injured joint or area and comparing it with PPT of the same joint in an asymptomatic individual. Decreased PPT indicates local hypersensitivity[8].
Widespread hypersensitivity can be inferred by measuring PPT a distal extra segmental site (e.g. the shin in people with backpain) and comparing with the same measurement in a healthy control[8].

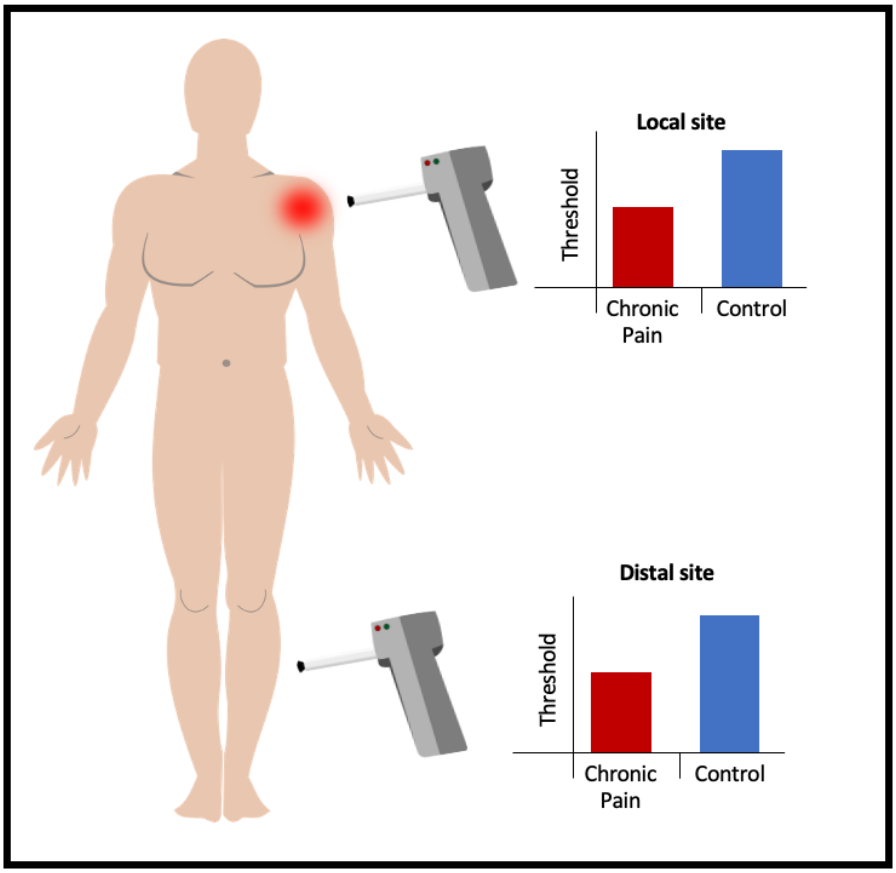

Figure 1-4 Assessing local and widespread hypersensitivity

2.2 Dynamic measures

Dynamic measures are used to assess pain modulation both inhibitory and faciliatory and cuff pressure algometry is also a reliable method for indirectly assessing both CPM and TSP.

When assessing TSP the cuff is placed in a specific area (usually around the gastrocnemius muscle) and repeatedly inflated five to ten times with the stimuli lasting one to two seconds each interspersed with a one second break[238]. The patient continually rates the pain intensity preferably with an electronic VAS and TSP is defined as the pain intensity as the difference in pain intensity between the 1st and 10th stimulus[208]. Greater difference equals more facilitated TSP This method of assessing TSP has shown good reliability with an ICC of > 60 when the cuff is placed at the calf[110].

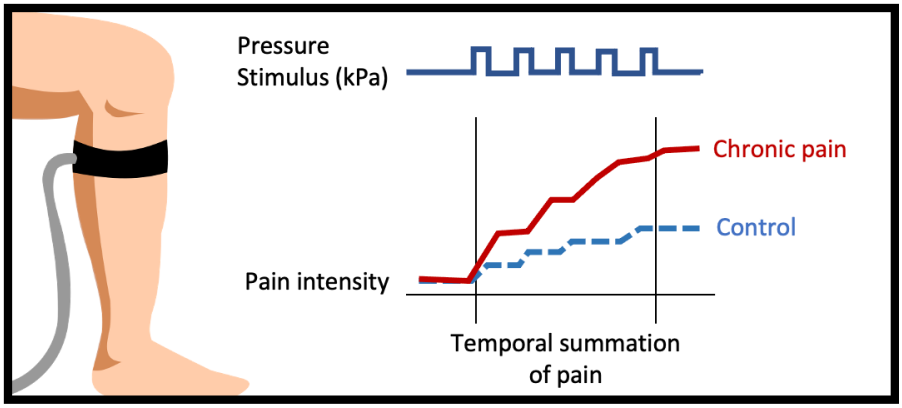

Figure 1-5 Assessing temporal summation of pain

When assessing CPM two cuffs are used and fitted to the left and right gastrocnemius muscle or similar anatomical location. The PPT is measured at an index site and then measured again at the index site but with simultaneous pressure in the second cuff (conditioning stimulus). The CPM effect is the difference between PPT without and PPT with a conditioning stimulus. Less difference equalling greater inhibition of CPM[209][212]. Measuring CPM with cuff algometry has moderate reliability with an ICC of > 50[109].

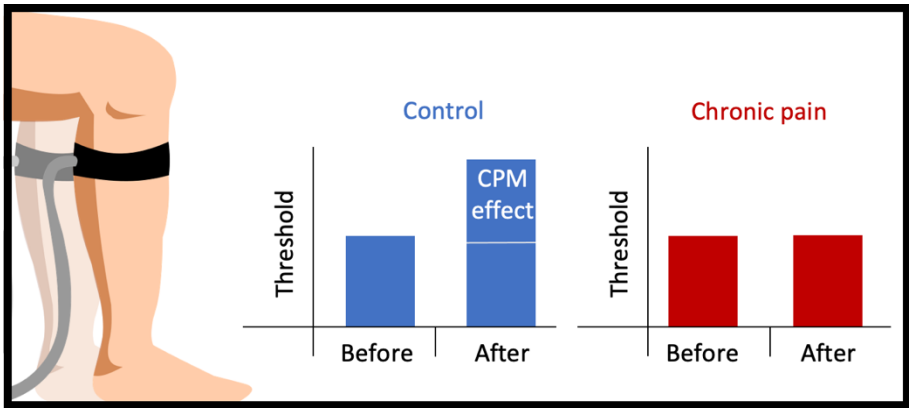

Figure 1-6 Assessing conditioned pain modulation

2.3 Quantitative sensory testing as a predictor of analgesic effect in pharmacological studies on joint pain.

Facilitated pain processing indirectly assessed with QST has shown predictive capabilities in patients with knee osteoarthritis, has been correlated with lack of pain relief after physiotherapy[201] and persistent pain after total knee replacement[209,211]. QST has also been used to predict the effect of analgesics in neuropathic pain[213] and with NSAIDS in joint pain.

The first trials examining the predictive capabilities of QST on the analgesic effect of NSAID's were performed on patients with knee osteoarthritis in 2016.

Arendt-Nielsen and colleagues performed cuff algometry and found that TSP at baseline was negatively correlated (Pearson's r = - 0.64 and – 0.42) in non-responders to Celecoxib (< 30% and < 50% pain alleviation) but not in responders[11]. They also tested CPM and PPT at baseline but found no significant correlation.

Edwards and colleagues used noxious cold and pressure to examine the predictive capabilities of QST in patients with knee osteoarthritis treated with diclofenac gel. They found an inverse association between the magnitude of CPM assessed via cold pressor tasks and pain intensity after treatment (Pearson's r = - 0.38), but no significant correlation between TSP or PPT measured with a handheld pressure algometer[77].

Petersen and colleagues used multiple linear regression to establish predictive models for pain alleviation in patients with knee osteoarthritis treated with a combination of paracetamol and ibuprofen[210]. They found that a model using TSP (Standardized Beta = -0.22) and pain intensity before treatment (Standardized Beta = 0.47) had a predictive value of 24% (R^2 = 0.24) when using worst pain within 24 hours after treatment as the independent variable. Similar results were seen when using pain during activity after treatment as the independent variable. Indicating that patients with greater TSP had greater pain intensity after treatment.
Petersen and colleagues conducted another trial with knee osteoarthritis patients treated with ibuprofen and paracetamol[212] and they found that magnitude of CPM, assessed with cuff algometry, was positively correlated with analgesic effect (Pearson's r = 0.39). Using linear regression, they found a predictive value of 18% (R^2 = 0.18) in a model including CPM at baseline.

3. Hand osteoarthritis

Hand-OA is considered a common condition though prevalence and incidence varies depending on the study method and country[206]. The prevalence of radiographic OA of the first MCP joint was 4% in a randomly selected sample from Denmark with increasing frequency at greater age[244]. These data match a Norwegian survey of self-reported Hand-OA with a prevalence of 4.3 (95% CI 3.6-5.0)[112]. Cardinal symptoms of Hand-OA are pain in the distal and proximal interphalangeal joints and around the base of the thumb, stiffness, and loss of hand function while common clinical signs include bony enlargement, nodules and deformity of the finger joints[168]. Hand-OA is a heterogenous disorder and can be grouped into different subsets with different prevalence, risk factors and prognosis[148]. The pain and disability experienced by patients with Hand-OA is on par with that of patients with RA[56] yet in contrast to RA no disease modifying treatment for OA exists and thus symptom management is the only option. The American College of Rheumatology (ACR) recommends exercise, self-management programs and orthosis for the first carpometacarpal OA as treatment options and NSAID's as analgesic treatment for Hand-OA[150]. These recommendations are in-line with the European Alliance of Associations for Rheumatology (EULAR) who also emphasises patient education and limitation on the duration of NSAID use[147].

Though both societies recommend exercise and NSAID's the analgesic effects are small. A Cochrane metanalysis of five RCT's found a standardized mean difference (SMD) of -0.27 (95% CI-0.47 to -0.07) in favour of exercise when compared to placebo for short-term pain relief, but the same review found uncertain effect of exercise at medium- long-term follow-up[200]. The EULAR recommendations for NSAID's are based on two studies with 2-4weeks follow up and a pooled standardized effect size of 0.40 (95% CI 0.20 to 0.60)[288].

In summary Hand-OA is a prevalent disease which affects quality of life significantly. At present no effective treatments exist and new options must be explored.

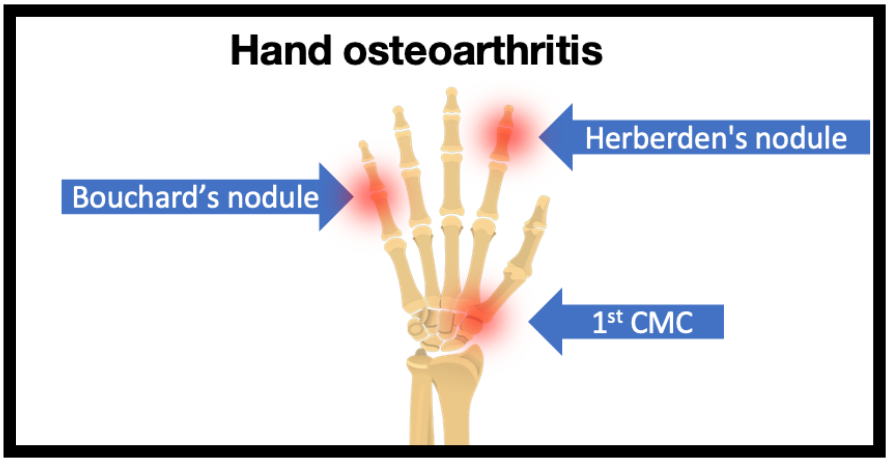

Figure 1-7 Typical features of hand osteoarthritis

3.1 Pain and sensitization in Hand-OA

The role of central pain mechanisms has been studied extensively in OA; especially OA of the knee[198] where the presence of wide-spread hyperalgesia and TSP is associated with increased patient reported pain intensity and disease duration[9], and CPM.

Farrell and colleagues were the first to examine sensitization in patients with Hand-OA[89]. They assessed PDT/PPT with a CO2laser, von Frey filament and percussion in patients with Hand-OA (n = 65) and controls (n = 15). Hand-OA patients were subdivided based on a pain profile (continual pain, pain with movement, both forementioned, spontaneous pain and no pain). Threshold tests were done at the 1st CMC joint affected by OA, and at the forearm and they found lower thresholds at the CMC joint compared with the forearm in the continual pain, pain with movement and "both forementioned" groups indicating local cutaneious, heat and mechanical hypersensitivity in some patients with hand-OA.

Wajed and colleagues performed the first pressure algometer examination in a small sample of patients with hand-OA (n = 13) and compared them with controls (n = 13) [265]. They determined PPT for finger joints and wrists bilaterally and found that hand-OA patients scored significantly lower than controls (mean 23.5N/cm^2 vs. 34.1N/cm^2 They also found that joints not affected by OA showed reduced PPT, possibly indicating wide-spread hyperalgesia, but did not compare these sites with the control group.

Chiarotto and colleagues have compared algometer assessed PPTs at extra segmental pain-free sites in patients with hand-OA and pain free controls[54,55]. In one study they examined PPTs at a local painful site, a contralateral pain-free site and an extra-segmental pain-free site (lateral epicondyle) in 32 patients with Hand-OA and 32 controls[55]. As in previous trials they found a significant between group difference in PPT at the local painful site and contralaterally but no statistically significant difference at the extra-segmental pain-free site. In a second study Chiarotto and colleagues examined 16 patients with Hand-OA and 16 controls and found significantly lower PPTs at different extra segmental pain-free sites (C5-C6 facet joint, the tibialis anterior, and over the median, ulnar and radial nerve)[54].

Pedersini and colleagues[205] performed a similar study where PPT was assessed at an extra segmental pain-free site (C5-C6 facet joint) in 20 participants with Hand-OA and 20 healthy controls and found no significant difference between groups.

The largest study done to date is by Pettersen and colleagues[248] with 282 participants with CMC OA. Their aim was to examine the relation between patient reported hand pain and peripheral and central pain mechanisms. They assessed PPT at a local painful site, local non-painful site plus different extra segmental non-painful sites and assessed TSP which had not been done before in patients with Hand-OA. They reported that 42% of patients had facilitated TSP (Calculated based on "Smallest detectable change") and higher TSP was associated with higher self-reported pain.

In summary studies are conflicting with regards to the presence of wide-spread hyperalgesia in patients with hand-OA which could indicate heterogeneity in pain mechanisms which is supported by Pettersen and colleagues who found facilitated TSP in 42% of patients. Further studies are needed to assess the presence of CPM and to assess whether difference in pain mechanisms relate to prognosis.

Table 1-1 Characteristics of studies examining pain mechanisms in hand-OA

Study	Subjects	Test modality	QST	PRO	Main findings
Farrell et al., 2000[89]	Hand-OA (1st CMC) =50 Hand-OA (no pain) = 15 Controls = 15	CO2laser, Von Frey filament, Percussive stimulator. 1st CMC Dorsal forearm.	PDT PPT	None	Patients with persistent pain had statistically lower mechanical and thermal pain thresholds over CMC vs forearm. Data supplied as figures.
Wajed et al., 2012[265]	Hand-OA = 13 Controls = 13	P. algometer DIP, PIP, MCP, Wrists.	PPT	VAS pain 1wk (100 mm) HADS, HAQ	Summed algometer scores: Hand-OA 23.5 ± 11.9 Newtons, Controls 34,1 ± 13.8 Newtons. Patients with hand-Oa had lower summed PPT compared with controls.

Chiarotto et al., 2013a[55]	Hand-OA (CMC joint) =32 Controls = 32	P.Algometer: CMC, Os. Hamate, Lateral epicondyle.	PPT	None	CMC: hand-OA 3.2 ± 1.0, controls 4.0 ± 1.4; $p < 0.01$ Hamate: hand-PA 5.4 ± 1.7, controls 6.8 ± 2.0; $p = 0.002$ Patients with hand-OA had lower PPT than controls.
Chiarotto et al., 2013b[54]	Hand-OA (CMC joint) = 16 Controls = 16	P.Algometer: 1st CMC, N. medianus,, N. Ulnaris, N. Radialis, C5 facet- C6 facet, Tibialis ant.	PPT	NRS-11 pain at pinchgrip. NRS-11 pain avg. pain 24 hours NRS-11 pain 1wk QuickDASH	CMC: Hand-OA 272.0 ± 90.0, controls 432.2 ± 118.7 $p < 0.001$ C5-C6: Hand-OA 270.0 ± 81.0, controls 359.0 ± 80.1; $p < 0.001$ Tibialis ant.: Hand-OA 290.8 ± 96.9, controls 506.4 ± 121.6; $p < 0.001$ Median nerve: Hand-OA 252.2 ± 109.8, controls 399.6 ± 85.1; $p < 0.001$ Ulnar nerve: Hand-OA 329.3 ± 85.1, controls 423.3 ± 119.9; $p = 0.39$ Radial nerve: Hand-OA 295.7 ± 91.0, controls 441.1 ± 92.0; $p < 0.001$ Patients with CMC osteoarthritis had lower PPT in both 1st CMC joints, C5-C6 joints, tibialis anterior muscle and peripheral nerves.

Pettersen et al., 2019[248]	Hand-OA n =282	P. Algometer: Painful phalanx, non painful phalanx, Distal radioulnar joint, Trapezius Tibialis ant.	PPT TSP	NRS-11 24 hours, PCT, HADS, Sleep disturbance scale (0-4 worst), AUSCAN,	TSP was associated with greater NRS pain (adjusted B = 0.6 95% CI 0.2 to 1.1)
Pedersini et al., 2020[205]	Hand-OA = 20 Controls = 20	P.Algometer: CMC, C5-C6 facet, N. Radialis, N. Medianus, N. Ulnaris,	PPT	VAS-24h and VAS-grip	Algometry: Between group difference in CMC joint 1.6 (95 % CI -0.9 to 2.2) p < 0.5 right side, 1.6 (95 % CI 1.0 to 2.2) p < 0.5 C5-C6 data not reported numerically

Abbreviations: AUSCAN, Australian Canadian Osteoarthritis Hand Index, CMC, Carpometacarpal joint; DIP, Distal interphalangeal joint; HADS, Hospital anxiety and depression scale; Hand-OA, Hand osteoarthritis; NRS, Numeric rank scale; PCT, Pain catastrophizing scale; PDT, Pain detection threshold; PPT, Pressure pain threshold; PRO, Patient reported outcome; PTT, Pain tolerance threshold; QuickDASH, Quick Disabilities of Arm, Shoulder and Hand; QST, Quantitative sensory testing; TSP, Temporal summation of pain; VAS, Visual analogue scale.

4. Psoriatic arthritis

Psoriatic arthritis (PsA) is a chronic systemic inflammatory arthritis occurring in up to 30% of patients with psoriasis[225]. It was recognized as a separate disease from RA in 1964 and now categorized in the seronegative spondylarthritis group[87]. PsA has a prevalence of 0.15 %[81,204] in

Denmark and an incidence of 27.3 pr. 100.000 [81]. The currently endorsed classification criteria are the Classification Criteria for Psoriatic Arthritis (CASPAR)[252] which are fulfilled if the patient has an inflammatory articular disease (peripheral joint, axial or entheseal) and ≥3 of the following: Current or previous psoriasis or near relatives with psoriasis, current psoriatic nail dystrophy, absence of rheumatoid factor, present or previous of dactylitis, radiograph of the hands or feet with presence of juxta articular ossification. The presence of psoriasis at the examination counts for two manifestations for the CASPAR criteria.
Besides the skin manifestations the cardinal symptoms are described as tender and swollen peripheral joints combined with general fatigue, but 38% of patients with PsA also experience inflammatory back pain[281] and 35% experience painful enthesitis[217]; conditions which are both hard to diagnose and treat.

Preferred treatments for PsA are drugs which can slow the disease course termed disease modifying antirheumatic drugs (DMARDs). Methotrexate, considered a conventional synthetic DMARD (csDMARD), is the primary option for most patients with peripheral arthritis. Antibodies against TNF-a or IL-17 are termed biologics (bDMARD). In Denmark bDMARDs are initiated if a patient has severe disease activity, fails to reach disease remission on csDMARDs, or has axial disease in which case bDMARDS are the primary treatment option if NSAIDs fail[192].

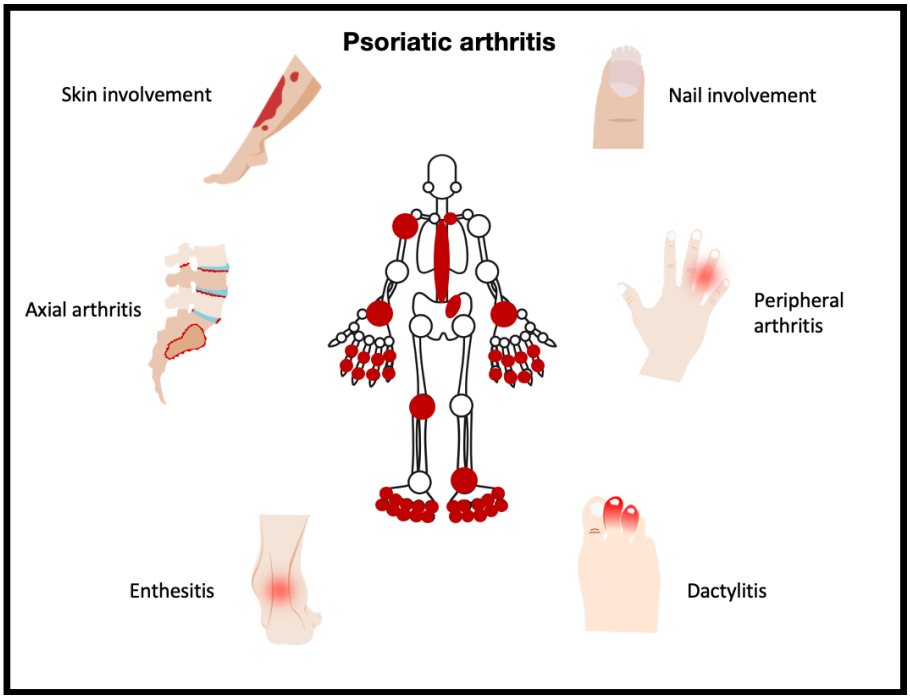

Figure 1-8 Typical features of psoriatic arthritis

4.1 Pain and sensitization in PsA

Even though treatment options exist real-world data show that one third or less of patients with PsA achieve disease remission[32,179]. Furthermore, more than 30% of patients with PsA in remission or with low disease activity according to the Disease Activity Score 28 using CRP may still be experiencing pain with VAS scores for pain intensity above 4[146]. Pain is a dominant and persistent symptom in PsA and is not uniformly correlated to routine measures of inflammatory activity[129,151,178,220] indicating that central pain mechanisms could play a role. Furthermore, several studies report that widespread pain is prevalent (23% to 35%) among patients with PsA [20,126].

The first pressure algometry study assessing patients with PsA was performed by Bagnato and colleagues [17]. They compared PPTs over the dorsal surface of the middle phalanx (a non-painful site) in patients with PsA (n = 23), RA (n = 50), AS (n = 23) and healthy controls (n = 28). Patients with PsA and RA had significantly lower PPT when compared with controls while AS patients did not. Patients were treated with either csDMARDs or bDMARDS but the authors do not disclose if the patients had active arthritis which could affect sensibility in a broad anatomical area. A trial by Giudice and colleagues[103] found lower mean PPT in patients with PsA (n = 30) over the temporomandibular joint and masseter muscles, bilaterally when compared with healthy controls (n = 30) while patients with systemic sclerosis (n = 30) had lower PPT over the previously mentioned areas when compared with patients with PsA. It was, however, not stated whether the patients with PsA had joint involvement of the temporomandibular joint.

Due to methodological uncertainties, it is unclear whether hypersensitivity is present at a distal site in patients with PsA.
While no QST studies have examined PPT at a “non-joint” site in patients with PsA nor examined the presence of facilitated TSP or inhibited CPM, several studies have found that a proportion of patients (around 27%) with PsA have high PDQ scores[222,224]. Some researchers suggest that higher PDQ scores could be associated with signs of central sensitization measured via QST [6,113,125].

Table 1-2 Characteristics of studies examining pain mechanisms in PsA

Study	Subjects	Test modality	QST	PRO outcomes	Main findings
Bagnato et al., 2013[17]	PsA n=23 RA n=50 AS n=23 Controls n=28	Algometer on the dorsal surface of the middle phalanx.	PPT	Hamilton Depression Rating Scale, VAS 0-10	PPT for RA 3.1±2.9, PsA 2.9±1.4, AS 4.0±1.7, controls 4.3±1.1 PsA and RA had lower PPT when compared with controls p<0.0001

Giudice et al., 2018[103]	PsA n=30 SS n=30 Controls n=30	Algometer - TMJ (bilateral), SMM	PPT	VASpain TMJ VASpain SMM	PPT TMJ: PsA 2.83 ± 1.18, control 4.65 ± 1.18 p < 0.001 PPT MSS: PsA2.67 ± 0.98, control 4.31 ± 1.29 p < 0 001 PPT was overall significantly lower in the SS group compared with PsA and controls.

Abbreviations: AS, Ankylosing Spondylitis; PPT, Pressure pain threshold; PRO, Patient reported outcome; PsA, Psoriatic Arthritis; QST, Quantitative sensory testing; RA, Rheumatoid arthritis; TMJ, Temporomandibular joint; SMM, Superior masseter muscle; SS, Systemic sclerosis; VAS, Visual analogue scale.

5. Cannabidiol

5.1 The endocannabinoid system

The idea of an endogenous cannabinoid system or endocannabinoid system (ECS) was proposed after the discovery of an in vivo receptor, isolated in 1990, with high affinity for phytocannabinoids (plant derived cannabinoids)[171]. The ECS is composed of ligands called endocannabinoids, cannabinoid receptors and the enzymes involved with endocannabinoid metabolism[64].
The receptors of the ECS consists are called CB1 and CB2 initially thought to be located in the plasma membranes of cells of the CNS (CB1) and different immune cells (CB2); however emerging evidence show diverse intracellular and tissue distribution[139].
Our understanding of the significance of the ECS in different physiological processes is still vague. At present the system has been shown to be implicated in modulating a range of mechanisms including nociceptive processing[277], energy homeostasis[236], inflammation/immunity[44] and neurotransmission[50] to name a few.

5.2 Pharmacodynamics of CBD

Cannabidiol (CBD) is one of more than 100 phytocannabinoids (plant-derived cannabinoids) of the cannabis sativa plant and together with Δ^9-tetrahydrocannabinol (THC) is among the most abundant phytocannabinoids present [7]. CBD was isolated in 1940 by Roger Adams[1] but the chemical structure was first determined in 1963 by Raphael Mechoulam[173]. Sativex a 1:1 CBD: THC was the first marketed drug containing CBD (plant material) and was approved in 2006 in Canada as treatment add-on for spasticity and neuropathic pain in MS and for cancer pain. Epidiolex is the first CBD product approved by the FDA (2018) and is an oral solution used as add on therapy for childhood epilepsy disorders (Dravet and Lennox-Gastaut Syndromes)[272]. CBD is also being assessed for therapeutic use in a broad range of diseases including anxiety and depression[21], a range of neurodegenerative disorders[49], different cancers[167], infections[162], inflammatory and immune disorders[122], cardiovascular disease[246] and more.

CBD has low bioavailability when ingested orally owing to considerable first pass metabolism by the liver enzymes CYP3A4 and CYP2C19[137]. When given orally (e.g., capsule) peak serum concentration is reached after 1.5 hours to 3 hours depending on the dose. The half-life is estimated to be 1 to 3.5 hours[182]. Different methods of administration e.g. intravenous or inhalation result in larger peak serum concentrations[182]. Ingesting CBD with food (especially lipids) can increase plasma levels fourfold[25,65,251] possibly due to increased bioavailability as CBD is a highly lipophilic molecule[189].
CBDs interaction with the traditional cannabinoid receptors is complicated and not completely understood. It can act as a negative allosteric modulator (binds to a site different from the agonist and decreases agonist efficacy) at CB1[254] and CB2[170] and as an agonist with reduced efficacy (partial agonist) at CB2[254].

5.3 CBD as an analgesic

Several mechanisms are in play regarding CBD's analgesic properties[183]. The Transient receptor potential vanilloid (TRPV1) is mainly expressed on C-fibres and can be activated by different stimuli including vanilloids (most know capsaicin), protons and noxious heat. TRPV1 is also sensitized by different pro-inflammatory mediators including neuropeptides, histamine, cytokines, leukotrienes, and nerve growth factor lowering the threshold for activation. In vitro[214] and in vivo[59,63,111] studies show that CBD acts as an agonist of the TRPV1 but like capsaicin it causes a desensitization of the channel[214] leading to decreased activity. CBD also acts as an agonist of the serotonin 1A receptor (5-HT_{1A}) [136,268]. The 5-HT_{1A} receptor is located post synoptically in 2nd order neurons of the dorsal horn of the spinal cord. Activation of 5-HT_{1A} leads to inhibition of further neurotransmitter release thus blunting nociceptive signalling)[114].

5.4 CBD as an anti-inflammatory drug

In vitro and in vivo studies have shown that CBD acts as an agonist to the adenosine 2a receptor (A_{2a}) present on lymphocytes and monocytes. Adenosine based signalling plays an important role in the pathogenesis of inflammatory arthritis, including psoriatic arthritis[223] and activation of the A_{2a} receptor leads to a decrease in cytokine expression from macrophages and inhibits certain T-cell functions [67].Increased activation of the A_{2a} receptor due to an increase in extracellular levels of adenosine is also thought to be how Methotrexate[66] and Sulfasalazine[133] mediate some of their anti-inflammatory effects. CBD also acts as an antagonist to the G protein-coupled receptor 55 (GPR55) sometimes referred to as the third cannabinoid receptor[280]. Although little is known about GPR55's role in general, GPR55 knockout mice show less severe colitis in experimental models of colitis[156], but studies using GPR55 knockout mice in models of neuropathic pain and inflammation induced by complete Freunds adjuvant are inconsistent[46,247].

5.5 Preclinical trials

CBD has been tested extensively in different models of pain[243] with nerve injury and neuropathy models being the most frequently studied showing overall reduction in signs allodynia and hyperalgesia[48,59,63,111,118,267,269].

CBD has also been tested in inflammatory models of pain. Carrageenan injection induces an acute local nonimmune mediated inflammatory response leading to hypersensitive behaviour in the model. It has been used as a model for testing NSAID, IL-1R antagonist and anti-IL-6[187] treatment. CBD has been tested extensively in different carrageenan models with studies showing statistically significant decrease in rat and mouse paw oedema when CBD is given orally or applied to the dermis after carrageenan injection[61,159,284] but not before[226]. Carrageenan induced hypersensitivity has been shown to decrease or disappear in mouse and rat models after CBD treatment orally[61,62,226,235] or applied dermally[159,284] with a greater effect seen at larger oral doses.
Injection of inactivated mycobacterium tuberculosis in a mineral oil solution also induces inflammation and arthritis with wearying degrees of systemic affection[30]. In this inflammatory model oral treatment with CBD has yielded diverging results with one study showing a reduction of hyperalgesia[63] in rats treated with oral CBD and rats treated with application of a CBD gel[116] while another found no effect in rats receiving intraplantar injections[36].
Immunizing mice with type 2 collagen in Freund's adjuvant creates a milieu akin to polyarticular arthritis (collagen induced arthritis) with synovial hypertrophy, monocyte infiltration and cartilage degradation[33]. Malfait and colleagues conducted a number of trials in mice with collagen induced arthritis[166] and found that mice given CBD orally (25 to 50mg/kg) had better clinical scores than mice given placebo in both an acute (first sign of arthritis) and chronic (five weeks after arthritis started) setting. They also observed less joint damage in mice given CBD.
Lastly, Philpott and colleagues[215] tested the effects of intraarticular CBD injections in a sodium monoiodoacetate induced osteoarthritis rat model[253] and found that rats treated with the highest dose had a decrease in mechanical allodynia tested with von Frey hair.
In summary CBD treatment leads to reduced hypersensitivity and

inflammation in different preclinical models of arthritis[94].

5.6 Clinical trials

At present different cannabinoids have been proposed as treatment or add-on's to existing regimens for patients with degenerative or inflammatory joint diseases[160] and due to possible analgesic and anti-inflammatory effects CBD has caught the interest of rheumatologists and patients with rheumatic disease[97]. However, few human trials (no longitudinal RCT's) have explored the analgesic properties of CBD without the addition of THC and early trials have small sample size (≤ 24 patients) making it hard to interpret their results.

In an industry funded trial Wade and colleagues conducted a randomized placebo-controlled cross-over trial in 24 patients with various neurological conditions of which 13 patients had pain as their target symptom[264]. The trial consisted of an unblinded phase where participants received a 1:1 THC:CBD blend for two weeks and a cross-over phase where the intervention was two weeks with each of the following a THC-rich, CBD-rich, 1:1 THC:CBD cannabis extract or a placebo given as a sublingual spray. One spray with the CBD-rich strain delivered 2.5 mg CBD and the mean number of sprays used were 8.9 (+-7.2) which translates to a mean dose of 22.25mg CBD daily. A significant reduction in pain was observed in the CBD group compared with placebo when assessing mean pain scores over the last seven days of the two-week treatment period 54.8 vs 44.5 on a 0-100 scale where 100 equals best possible. But the authors did not report the THC concentration of their CBD rich plant extract and patients had access to open-label rescue medication containing 1:1 THC:CBD during the blinded CBD portion of the trial.

Palmieri and colleagues conducted a small interventional case series study without randomization, blinding or control group[203]. Twelve patients with a post vaccination fatigue syndrome received an unknown dose of CBD for twelve weeks. The authors reported a significant analgesic effect but did not report the numbers and statistics to support this finding. They also failed to disclose the THC content of the CBD blend.

Cunetti and colleagues conducted a small interventional case series without randomization, blinding or control group[68]. They assessed the analgesic effects of CBD in seven kidney transplant patients with different pain complaints (two with fibromyalgia, four with osteoarticular and one with

neuropathic). Patients received a cannabis extract with a CBD to THC ratio of 30:1 and doses up to 300mg CBD per day for three weeks. The authors reported optimal analgesic effect in two patients, partial response in four patients and no response in one patient but did not disclose the conditions for response, how pain was quantified and did not perform statistics. Furthermore, patients received a substantial amount of THC (10mg) making it hard to classify this as a CBD only study.

Table 1-3 Characteristics of prospective studies examining CBDs analgesic effect

Study	Population	Design	Intervention	Outcome	Results
Wade 2003[264]	Patients with a range of neurological diseases n = 24 (13 with pain complaints)	RCT Blinded Crossover	Whole plant CBD extract two weeks	VAS (0-100) with 100 indicating best outcome Numerical symptom scale PAIN (0-10) 10 indicating worse score	VAS: CBD 54.8± 22.6 vs Placebo 44.5 ± 22.7 Significant difference in favour of CBD Pain symptom scale: CBD 3.8 ± 2.0 vs placebo 4.4 ± 3.2 No statistically significant difference

Palmieri 2017[203]	Patients with post vaccination fatigue syndrome n = 21	Case series	CBD-enriched hemp oil twelve weeks	SF-36 pain component	No statistics stated regarding the pain outcome
Cunetti 2018[68]	Kidney transplant patients with chronic pain condition n = 7	Case series	Whole plant CBD extract 21 days 50-300mg/day	Likert like pain-rating scale	No statistics stated regarding the pain outcome

Abbreviations: CBD, Cannabidiol; RCT, Randomized controlled trial; SF-36, Short form (36) Health Survey; VAS, Visual analogue scale.

Three trials have been conducted exploring the acute effects (two to three hours) of a single dose of CBD [22,73].
Van det Donk and colleagues conducted the first RCT of CBD treatment which was published in 2019[73]. They tested four different medicinal cannabis products in a crossover design of which one was a plant extract containing 18.4 mg CBD and less than one mg THC delivered in an inhalation device. Twenty-five patients diagnosed with fibromyalgia received the treatment but no statistically significant difference in spontaneous pain relief, their primary outcome, was observed between CBD and placebo (data was not reported numerically).
Schneider and colleagues conducted an RCT using a crossover design with (800 mg in an 8 mL oil based solution)[231]. Participants where 20 healthy volunteers and an intradermal electrical currant was used to simulate acute pain. There were no differences between groups in pain response measured via NRS-11 (mean of 5.2 vs 5.3 p=0.9) nor in average area of hyperalgesia or average area of allodynia.
Bebee and colleagues published the first RCT with synthetic CBD (400 mg in a 4 mL medium chain triglyceride oil) in 2021[22]. The study was performed in an emergency department and 100 patients presenting with acute low back pain were included. Primary outcome was a verbal NRS-11 after two hours and the difference between groups were -0.3 (95% CI -1.3 to 0.6).

Table 1-4 Characteristics of single-dose studies examining CBDs analgesic effect

Study	Population	Design	Intervention	Outcome	Results
Donk T 2019[73]	Fibromyalgia (female only) n = 25	RCT Double blinded Placebo-controlled Crossover	Plant material 18.4mg CBD < 1mg THC vaporized	NRS-11	-1.53(+-1.6) for CBD and -1.53(+-1.6) for placebo No statistically significant difference between CBD and placebo group
Schneider 2021[231]	Healthy subjects n = 20	RCT Double blinded Placebo-controlled Crossover	CBD isolate 800mg in oil	NRS-11, Area of allodynia, Area of hyperalgesia	Mean of 5.2(+-0.7) for CBD and 5.3(+-0.7) for placebo No statistically significant difference between CBD and placebo group

Bebee 2021[22]	Acute low back pain n = 100	RCT Double blinded Placebo-controlled	Synthetic CBD 400mg in oil.	Verbal numeric pain scale 0-10	-0.3 difference (95% CI -1.3 to 0.6) No statistically significant difference between CBD and placebo group

Abbreviations: CBD, Cannabidiol; NRS, Numeric rank scale; RCT, Randomized controlled trial; THC, Δ^9-tetrahydrocannabinol.

A single RCT study has been published examining the effects of medical cannabis (Sativex) as treatment for RA[27]. In this industry sponsored trial 58 patients with RA were randomized to Sativex (almost 1:1 CBD:THC) or placebo for five weeks. Primary outcome was NRS-11 “Morning pain on movement” with a mean difference in pain reduction favoring Sativex (-0.95; 95% CI -1.83 to -0.02; p= 0.044) with similar results for “Morning pain at rest” (-1.04; 95% CI -1.90 to -0.18; p=0.018). Although the difference between the placebo group was statistically significant the difference in effect was small especially taking the confidens intervals into consideration.

5.7 The entourage effect

The term entourage effect was popularized by Russo in 2011[227] though first appearing in a paper by Ben-Shabat and colleagues in 1998[23]. The entourage effect refers to a synergistic interaction between different constituents of the cannabis plant[227] and can refer to a cumulative effect obtained by mixing active cannabinoids (e.g. THC and CBD) or by mixing other plant constituents with cannabinoids (e.g. CBD and terpenes and flavanols). A narrative review by Cogan[57] concluded that evidence for an entourage effect in animal models of pain was

inconsistent[29,37,93,117,260,290] and that proper clinical trials were lacking.

5.8 CBD and pain mechanisms

Studies examining the effects of cannabinoids for pain modulation have mostly been conducted with THC or whole plant cannabis[190].
Two trials performed in patients with neuropathic pain and allodynia (postherpetic neuralgia, peripheral neuropathy, radiculopathy and chronic regional pain syndrome type 2) examined the effects of Sativex on allodynia by assessing pain intensity during a brush examination and at the point of PPT during pressure algometry[194,232]. But results were conflicting with a statistically significant difference for both measures reported by Nurmikko and colleagues[194] but not by Serpell and colleagues[232].
The only trial to examine the effect of CBD on QST is by Van de Donk and colleagues[73] described in chapter (XX). Using a pressure algometer they found no change in PPT when assessing a high CBD low THC blend (18.4 mg CBD and ≤ 1 mg THC) but did see an increase in PPT when using blends with greater THC amount (≥ 13.4 mg).
Conclusively, these studies report conflicting evidence on the modulatory effect of cannabinoids on pain mechanisms assessed using QST.

5.9 Adverse events of CBD

CBD has been tested in humans in doses up to 6000 mg (single dose) in healthy volunteers with side-effects consisting of diarrhea, somnolence, headache and dizziness[251]. These adverse effects are in-line with a systematic review of twelve trials conducted by Chesney and colleagues. They found that CBD was associated with greater odds of decreased appetite (OR = 3.56; 95% CI 1.94 to 6.53), diarrhoea (OR 2.61; 95% CI 1.46 to 4.67) and somnolence (OR = 2.23; 95% CI 1.07 to 4.64) when compared with placebo [53]. The median dose used in the trials was 1200 mg daily. These findings are in-line with a systematic review, with slightly different inclusion criteria, conducted by Dos Santos and colleagues[229]. A metanalysis performed by Aviram and colleagues including RCT's with THC,

Nabiximols or other plant formulations found the most frequent AE's where dizziness, drowsiness, nausea, vomiting, blurred vision and a range of psychological AE (anxiety, confusion, euphoria, forgetfulness and paranoia)[14].
Lastly, due to CBDs ability to inhibit CYP3A4 and CYP2C19 Brown and colleagues raised concern regarding drug to drug interactions with CBD[38]. Commonly used CYP3A4 substrates with a narrow therapeutic index in rheumatology include Cyclosporine[58] Baricitinib[266] and Tofacitinib[263].
In summary while CBD is relatively well tolerated in clinical trials higher doses lead to more adverse effects. At present it is unknown at which doses CBD has analgesic or anti-inflammatory properties in humans and how well CBD will be tolerated in multimorbid patients with concomitant inflammatory disease.

Chapter 2. Hypothesis and aims

The hypotheses of this thesis were

- Patients with PsA reporting higher levels of pain intensity are at risk of excess mortality.
- Patients with PsA or Hand-OA with a pain intensity of at least 30 mm on a 100 mm VAS scale will have altered pain processing when compared with pain-free controls. Furthermore, these patients will also experience a greater degree of self-reported sleep disturbance, anxiety, depression, and pain catastrophizing.
- In patients with PsA or Hand-OA with a pain intensity of at least 30 mm on a 100 mm VAS scale, 20mg to 30mg of CBD daily improves self-reported levels of pain intensity more than placebo.
- In patients with PsA or Hand-OA with a pain intensity of at least 30 mm on a 100 mm VAS scale, 20mg to 30mg of CBD daily improves PPT, TSP and CPM values more than placebo.
- Baseline QST values will predict the variability in % reduction in pain intensity in patients treated with CBD for 12 weeks.

The aims of this thesis were

- To examine if higher self-reported pain intensity is correlated with greater excess mortality. (Study 1)
- Assess the presence of altered pain mechanisms in patients with PsA and Hand-OA compared with healthy controls. (Study 2)
- Investigate whether CBD 20 mg to 30 mg daily for 12 weeks decreases self-reported pain intensity on a VAS scale 0-100mm more than placebo for patients with PsA and Hand-OA. (Study 3)
- Investigate whether CBD 20 to 30 mg daily for 12 weeks modify pain mechanisms (PPT, TSP and CPM) for patients with PsA and Hand-OA. (Study 4)
- Investigate whether baseline QST values can predict who benefits from CBD. (Study 4)

Chapter 3. Presentation of studies

Study 1

Study objectives

The objective of this study was to investigate the impact of cumulative pain experienced on mortality in patients with PsA.

Study design, population, and methods

The study was designed as a nested case-control study based on the nationwide DANBIO rheumatology register[131] and Danish nationwide administrative health care registers. DANBIO includes a range of patient and physician reported measures recorded at each visit to a rheumatological outpatient clinic including a patient reported pain intensity (0-100) measurement.
Each patient in DANBIO is identified by their unique Civil Personal Register (CPR) number making linkage with other Danish registers possible. For this study we used the Danish National Patient Register[161] to obtain information regarding comorbidities, The Danish Register of Causes of Death to identify cases[121], The Danish Income Statistics register to determine socioeconomic status[15] and the Danish National Database of Reimbursed Prescription[138] to obtain data regarding glucocorticoid prescription. For a more detailed description of the different registers see Appendix A (Manuscript 1)
The study population were patients with a PsA diagnosis identified from the year 2006 to 2018. The exposure of interest was patient reported pain intensity averaged during the entire observational period and cases were patients who died during the observational period[261].
Odds ratios for mortality and 95% confidence intervals were calculated using conditional logistic regression. Besides a crude model (adjusting only for age) we performed two additional models. Model 1 adjusted for age,

average CRP, average HAQ, average swollen joint count, use of classical and biological DMARDs and having glucocorticoids prescribed during the last year. Model 2 adjusted for all the variables from model 1 but with the addition of comorbidities chronic obstructive pulmonary disease (COPD), cancer, diabetes (DM) and cardiovascular disease (CVD). We also performed different secondary analysis and sensitivity analysis which can be found in the original article along with a more detailed description of the statistical analysis.

Results

We identified 276 cases among 8019 patients with a PsA diagnosis and matched them with 1187 controls (4.3 controls per case). Median age was 72.2 for cases and 55.1% were women.
In general, cases had a lower income and lower education level than their matched controls (see published paper for data). More cases were prescribed glucocorticoids during the last year (49.6% for cases vs. 13.2% for controls) and had comorbidities (DM 25.7% vs 10.6%, COPD 24.3% vs. 9 %, CVD 51.8% vs. 25.3%, Cancer 45.7% vs. 9.9%). Objective markers of inflammation i.e., CRP and swollen joint count were equal among the groups.

Association between pain and mortality

In the crude analysis odds ratio for mortality increased by 1.06 (95% CI 1.02 to 1.10) for every 5 unit increase in average pain but this association disappeared when adjusting for the variables included in Model 1 OR = 0.99 (95% CI 0.94 to 1.03) and model 2 OR = 0.99 (95% CI 0.95 to 1.04). Results from the secondary analyses and sensitivity analyses where similar to the primary analysis (see table 3.1)

Table 3.1 Odds ratios per 5 unit increase in pain for secondary analyses and sensitivity analyses.

	Model OR (95% CI)		
Analysis	Crude	Model 1	Model 2
Mean pain (recent year)	1.06 (1.02 to 1.09)	0.99 (0.95 to 1.04)	0.98 (0.94 to 1.04)
Mean pain (last five years)	1.06 (1.02 to 1.09)	0.99 (0.94 to 1.03)	0.99 (0.94 to 1.04)
Omission of HAQ	-	1.03 (0.99 to 1.07)	1.00 (0.96 to 1.05)
VAS pain 34 to 66 mm	1.13 (0.90 to 1.42)	-	-
VAS pain 67 to 100 mm	1.84 (1.36 to 2.47)	1.15 (0.89 to 1.49)	1.10 (0.74 to 1.65)
Complete case analysis	1.07 (1.03 to 1.11)	0.97 (0.92 to 1.02)	0.96 (0.91 to 1.02)

HAQ, Health assessment questionnaire; VAS, Visual analogue scale.

Association between other covariates and mortality

The following variables were associated with increased risk of mortality: Recently prescribed oral glucocorticoids OR of 5.60 (95%CI 3.71 to 8.45), Diabetes mellitus OR of 1.86 (95%CI 1.19 to 2.90), Cardiovascular disease OR of 3.04 (95%CI 2.06 to 4.49) and Cancer OR 7.17 (95%CI 4.70 to 10.94). Use of csDMARDs was associated with decreased mortality OR of 0.56 (95%CI 0.39 to 0.82).

Methodological considerations

A 100 mm horizontal VAS is a simple and reliable way to measure pain intensity[143,144] and is frequently used in rheumatological research and in outpatient clinics[86,241]. However the VAS can be difficult to fill out correctly for patients with increased age and opioid intake[74] a subgroup at risk of excess mortality. In the present trial pain intensity was evaluated at each visit to an outpatient clinic but pain intensity could vary in-between visits. Furthermore, patients with absence of active arthritis (swollen joints,

radiographic signs of axial psoriatic arthritis, absence of inflammatory markers in biochemistry results) are discontinued from outpatient clinics and could represent a subgroup with high levels of pain intensity related to arthritis sequalae and a different risk of excess mortality.

Missing data was minimal in the present study, but a large proportion of the data on body mass index (BMI) and smoking were missing and could not be included in the analysis. Smoking is related to excess mortality[47] and excess pain[234] and so is BMI[98,191] and thus could be considered relevant confounders. However, the way in which smoking, and obesity leads to excess mortality is in large part due to increased risk of developing comorbidities included in our analysis. Juneblad and colleagues included smoking and BMI in their analysis of excess cardiovascular death among patients with PsA but found no effect of smoking (odds ratio 1.25; 95% CI 0.65 to 2.43) or BMI (odds ratio 0.98; 95% CI 0.91 to 1.06)[140]. No data on alcohol intake and sedentary behaviour (physical activity) were available both of which are associated with excess mortality[26,101] but the relationship to pain is less well known[237,286].
Misclassification bias cannot be ruled out in the present study as validity and completeness have not been evaluated for the PsA diagnosis in DANBIO. These parameters have been examined for RA where the number of true RA cases were 96 % and completeness of cases was 90%[132].
Though a prospective cohort would usually have been the optimal design to explore the association between pain and mortality a nested case control was chosen for two reasons. Nested case control design was chosen because of the low number of cases relative to the number of variables we would have to adjust for. Matching on year of birth (age) and sex within the PsA cohort ensured confounder adjustments for these important factors, thus, avoiding the need to adjust for these variables in the conditional logistic regression analysis. The main objective was to explore the effect of pain intensity as a continuous variable over time. The nested case control design allowed us to estimate the average cumulative pain in one variable, whereas this would have required a more advanced and perhaps a more difficult to interpret exposure variable in a cohort study setting.

Conclusion

In conclusion we demonstrated that pain intensity was associated with excess mortality in patients with PsA, but the effect disappeared after adjustment for potential confounders. This indicates that pain intensity in and of itself has limited predictive value with regards to mortality. Glucocorticoid use and comorbidities (COPD, diabetes, CVD, and cancer) were all associated with increased risk of early death.

Study 2

Study objectives

The objective of study 2 was to assess altered pain mechanisms and patient reported outcomes (PRO) related to pain in patients with Hand-OA and PsA compared with healthy controls by measuring pressure pain thresholds, temporal summation, and conditioned pain modulation.

Study design, population, and methods

The study was designed as a cross-sectional study with a healthy control group. Patients were part of the NordCAN study cohort[262] and encompassed patients diagnosed with PsA or Hand-OA and chronic pain of at least moderate intensity (≥ 30 mm on a 100 mm VAS). Healthy controls were recruited from the Department of Rheumatology staff and were eligible for inclusion if they were at least 18 years of age, had no pain equal to or exceeding 10 mm on a 100 mm VAS during the last 24 hours and reported no known chronic pain conditions. The study was approved by the regional ethics committee (N-20170074) and was preregistered on clinical trials.gov (NTC03703934). Written consent was given before participants were enrolled in the study.

Quantitative sensory testing procedures

PPT was assessed using a pressure algometer fitted with a $1cm^2$ flat probe. PPT was determined at the two most painful finger joints and the shin of the right leg (pain-free non-segmental site). The second and third proximal interphalangeal joint on the dominant hand were used for healthy controls. TSP and CPM was assessed using a computer-controlled cuff algometer. A torniquet was fitted to the right lower leg and TSP was assessed by applying ten cuff pressure stimuli (1-second duration and 2-second interstimulus

intervals) while the participant continually rated pain intensity on an electronic VAS. TSP was defined as the difference between measured pain intensity at the first and tenth stimulus. CPM was assessed by first performing a measurement of PPT on the index leg (right) and then fitting a second torniquet on the contralateral leg. A conditioning stimulus of 60 kPa was delivered through the second torniquet while a measurement of PPT and PTT was performed on the index leg. The CPM effect was defined as the difference between PPT with and without the conditioning stimulus.

Patient reported outcomes

Patients rated their pain intensity during the last 24 hours using a 100 mm VAS where greater score equalled greater pain intensity. Healthy controls and patients filled out the HADS[289] to assess anxiety and depression, the PCS[250] to assess catastrophizing and the PSQI[42] to assess sleep quality. Disability was quantified using the HAQ consisting of 20 questions related to eight categories of function[39]. The HAQ is rated from 0 to 3 with a higher score equalling greater patient reported disability. Patients also answered the painDETECT questionnaire originally designed to “screen” for neuropathic pain in patients with musculoskeletal pain conditions rated from -1 to 38 were a score of > 18 indicates a neuropathic component[99].

Fibromyalgia status was determined using the 2016 ACR criteria for Fibromyalgia[274]. Patients fulfilled the criteria if they reported pain in four out of five body regions, if symptoms had been present for at least three months and if they reported a widespread pain index (WPI)[275] score ≥ 7 and symptom severity scale (SSS)[275] score of ≥ 5 OR WPI score of 4–6 and SSS score of ≥ 9.

Comparisons between patients with PsA, patients with hand-OA and healthy controls were done using a one-way analysis of variance with a post hoc Tukey’s test performed for pairwise comparisons. Difference in continuous outcomes between groups were compared using an independent two-sided t-test. For a more detailed description of the statistical analysis see Appendix B (Manuscript 2).

Results

Seventy-five patients with Hand-OA, 58 patients with PsA and 20 healthy controls were included in the analysis. Patients with hand-OA were significantly older than patients with PsA and controls (Mean age for Hand-OA 66 years, PsA 53 years and controls 58 years). A larger proportion of controls where female than patients with hand-OA and PsA (69% for hand-OA, 75% for PsA and 90% for controls). There were no significant differences in analgesics used by patients with hand-OA and PsA.
Patients with hand-OA and PsA had significantly lower PPT's at a painful joint and a distal non-painful site when compared with healthy controls. Patients with hand-OA and PsA also had significantly more facilitated TSP and inhibited CPM when compared with healthy controls. There was no significant difference in QST parameters observed between patients with hand-OA and PsA.
Patients with hand-OA and PsA had significantly greater scores of depression, anxiety and catastrophizing when compared with healthy controls. Furthermore, patients with hand-OA and PsA reported significantly greater disability and reduced sleep quality when compared with controls. Furthermore, a significantly greater depression score (difference of 1.33; 95% CI 0.39 to 2.28; p = 0.004) was found in patients with PsA when compared to patients with OA. No differences in PROMs were observed (see table 3.2).

Table 3.2 Baseline values

	Hand-OA	PsA	Controls
PROM			
Pain baseline, mm	56.6 (18.3)	58.6 (18.0)	-
HADS depression	2.09 (2.16) *	3.43 (2.68) *	0.50 (0.95)
HADS anxiety	4.34 (3.37) *	5.55 (3.32) *	1.79 (2.82)
PCS	16.52 (9.26) *	16.95 (7.80) *	3.75 (5.23)
PSQI	8.23 (3.84) *	9.02 (4.18) *	4.42 (2.41)
HAQ	0.77 (0.56) *	0.86 (0.61) *	0.01 (0.04)
QST			
PPT finger, kPa	214.60 (127.27) *	260.60 (178.24) *	369.85 (180.74)

PPT shin, kPa	284.40 (152.18) *	281.36 (154.18) *	446.25 (180.40)
TSP	2.68 (2.35) *	2.51 (1.91) *	1.13 (1.34)
CPM, kPa	3.13 (15.78) *	7.70 (18.02) *	19.03 (14.35)

* $p < 0.05$ when compared with controls
Abbreviations: CPM, Conditioned pain modulation; HADS, Hospital anxiety and depression scale; hand-OA, hand osteoarthritis; HAQ, Health Assessment Questionnaire; PCS, Pain catastrophizing scale; PPT, Pressure pain threshold; PROM, Patient reported outcome measure; PsA, Psoriatic arthritis; PSQI, Pittsburgh sleep quality index; TSP, Temporal summation of pain.

Twenty-nine patients with hand-OA (39%) and 30 patients with PsA (52%) fulfilled the criteria for fibromyalgia. Patients with concomitant fibromyalgia had greater TSP (3.07±2.53 for fibromyalgia vs 3.07 ±2.53 for patients without; $p = 0.027$) but no significant difference was observed for the other QST measures when compared to patients without fibromyalgia. Patients with concomitant fibromyalgia had significantly greater scores of depression (3.43 ± 2.68 vs 2.09 ± 2.16; $p = 0.005$), anxiety (5.83±3.57 vs 4.13±3.07; $p = 0.004$) and catastrophizing (18.88 ± 8.44 vs 15.03 ± 8.42; $p = 0.012$) when compared to patients without concomitant fibromyalgia. Patients with fibromyalgia also reported a significantly higher disability score (1.00 ± 0.59 vs 0.65 ± 0.53; $p < 0.001$) and painDETECT score (20.22 ± 5.52 vs 16.67 ± 5.58; $p = < 0.001$) but there was no difference in reported pain intensity measured with VAS (60.00 ± 1.84 vs 55.42 ± 1.78; $p = 0.149$).
When examining subgroups based on diagnosis (hand-OA only or PsA only) and comparing patients with and without concomitant fibromyalgia the only significant differences seen between groups were a greater HAQ and PDQ score among patients with fibromyalgia. This was the same for patients with PsA and hand-OA.

When comparing the 74 patients without fibromyalgia with healthy controls the patients with chronic pain had significantly lower PPT at a painful joint (226.61 ± 125.92 for hand-OA, 278.68 ± 177.41 for PsA, 369.85 ± 180.74 for controls) and a distal nonpainful site (307.09 ± 167.08 for hand-OA, 307.00 ± 150.41 for PsA, 446.25 ± 180.40 for controls), had facilitated TSP (2.31 ± 1.78 for hand-OA, 2.11 ± 1.70 for PsA, 1.13 ± 1.34 for controls) and inhibited CPM when compared with healthy controls (2.52 ± 16.42 for hand-OA, 2.11

± 1.70 for PsA, 19.03 ± 14.35 for controls). Moreover, patients with chronic pain reported significantly greater scores of depression (5.46 ± 1.70 for hand-OA, 3.11 ± 3.08 for PsA, 0.50 ± 0.95 for controls), anxiety (1.53 ± 1.98 for hand-OA, 3.11 ± 3.08 for PsA, 1.79 ± 2.82 for controls) and catastrophizing (14.57 ± 8.95 for hand-OA, 15.75 ± 7.60 for PsA, 3.75 ± 5.23) when compared with healthy controls and significantly greater disability (0.61 ± 0.51 for hand-OA, 0.71 ± 0.58 for PsA, 0.01 ± 0.04 for controls) and reduced sleep quality (7.67 ± 3.91 for hand-OA, 8.14 ± 3.85 for PsA, 4.42 ± 2.41 for controls).

Methodological considerations

External validity of the results should be considered due to potential selection bias as patients in the present study were recruited as part of an RCT and thus might not represent an unselected patient cohort with PsA or Hand-OA. Patients with PsA did not display signs of active peripheral joint disease (no swollen joints).

Patients in study 2 did not abstain from using their usual analgesics. Previous studies have reported inhibition of central pain mechanisms due to pharmacological treatment[11,282] and it can be hypothesised that the observed differences between patients and controls would be greater if patients had abstained from using analgesics.

Study 2 used a cross-sectional design and thus causality cannot be inferred from the results only association.

The study could be underpowered when it comes to subgroup analysis due to the low number of participants and prone to type 2 errors. Results from the subgroups analysis should be interpreted with caution.

The PROMs used in the present study have previously been used in studies assessing patients with inflammatory and degenerative joint pain conditions including PsA and hand-OA[16,102,158] and although their use is recommended in patients with a range of pain conditions[79], they have not been validated specifically for PsA and hand-OA. This could introduce measurement error into the results and interpretations of these results should be done with this in mind.

Conclusion

Patients with hand-OA and PsA experienced lower PPTs, facilitated TSP and inhibited CPM when compared with healthy controls. A large proportion of patients with hand-OA and PsA fulfilled the fibromyalgia criteria. A continuum was established were patients with concomitant fibromyalgia reported significantly greater scores in PROMs related to depression, anxiety, catastrophizing, sleep quality and disability than patients without, who in turn reported greater scores than healthy controls. A similar continuum was seen for TSP but not for other QST parameters.

Study 3

Study objectives

The objectives of this study were to examine the effects of 20-30 mg synthetic CBD on self-reported pain intensity measured with a 100 mm VAS in patients with PsA and Hand-OA with moderate pain intensity. Secondarily, to examine the effects on PROMs related to anxiety, depression, sleep quality and pain catastrophizing. Furthermore, to quantify adverse events related to low dose CBD treatment.

Study design, population, and methods

The study (NordCAN) was designed as a randomised, double-blind, placebo-controlled trial. Patients were randomised to receive tablets with either CBD or Placebo for 12 weeks [262]. The study was approved by the regional ethics committee (N-20170074), by the Danish Data Protection Agency (2017-245) and by the Danish Medicines Agency (2017091784). It was preregistered on clinical trials.gov (NTC03693833). The study was monitored by the good clinical practice unit of the North Denmark Region and by the Danish Medicines Agency. Written consent was given before patients were enrolled in the study.

Patients aged ≥ 18 years with pain intensity ≥ 30 mm and fulfilling either the Criteria for Psoriatic Arthritis[252] or the 1990 American College of Rheumatology criteria[5] for hand osteoarthritis were eligible for inclusion. Exclusion criteria included concurrent diagnosis with another inflammatory joint disease, treatment with systemic corticosteroids, active malignant disease, planned pregnancy or breastfeeding, previous abuse of pharmaceutical drugs or cannabis, severely decreased liver or kidney function, heart failure and a history of epilepsy.

The intervention was synthetic CBD tablets produced by Glostrup Pharmacy (Glostrup, Denmark). Patients received identical looking odourless tablets containing either 10 mg CBD or an inactive placebo.

Table 3.3 Dose regimen

Week 1+2	**Week 3+4**	W**eek 5-12**
10 mg once daily	10 mg twice daily	10 mg thrice daily* or 10 mg twice daily

Preferably study medication is taken with a meal rich in fat
*If adequate analgesic effect is NOT attained by week 5 then the dose is increased to 10 mg thrice daily. Adequate analgesic effect was defined as a decrease in pain intensity of ≥ 20 mm.

This trial consisted of three "visits" excluding the screening: A baseline visit where medical history was obtained, study related outcomes were assessed, patients were randomized and received study medication; a telephone visit at four weeks were patients not experiencing a decrease in pain intensity of ≥ 20 mm or more had their dose increased to 10 mg thrice daily (see table 3.3 for regimen); an end of trial visit at 12 weeks where pain intensity and other study related outcomes and blinding were recorded. Adverse events were assessed at the phone visit, end of trial visit and if the patient contacted the primary investigator at any time during the study period.

The primary outcome was change in pain intensity between the baseline and end of trial visit in patients receiving CBD compared to patients receiving placebo. Pain intensity was quantified using a 100 mm VAS representing mean pain intensity during the last 24 hours. A higher score meant greater pain intensity. Exploratory outcomes included between group differences in the HADS anxiety and HADS depression scores, PSQI score, HAQ-DI score, and PCS score. A characterisation of serious adverse events (SAE) and percentage of patients reporting an adverse event (AE) were included as safety outcomes.

Between group comparisons were done using an independent two-sided t-test for normally distributed variables. A bootstrapped t-test with 10000 replicates was used for non-normally distributed variables. Chi^2 test was used when comparing discrete variables.
For a more detailed description of methods and statistical analysis, see Appendix C (Manuscript 3).

Results

One-hundred-and-thirty-six patients were included in the study (PsA = 59 and hand-OA = 77).
Difference in effect of treatment (pain intensity measured by VAS) between CBD and placebo was ΔVAS 0.23 mm (95% CI -9.41 mm to 9.90 mm; p = 0.96) rated on a 0 – 100 mm scale. Same results were seen when stratifying by disease; PsA ΔVAS 4.48 mm (95% CI -17.44 to 8.49; p= 0.49) and hand-OA ΔVAS 2.94 mm (95% CI -10.03 mm to 15.92 mm; p = 0.65).
Number of patients experiencing a pain reduction of ≥ 30% or ≥ 50% were not significantly different between the CBD group and placebo; 27 (40%) vs. 24 (40%) p > 0.99 and 17 (25%) vs. 16 (27%) p = 0.99 respectively.
There was no significant difference in the number of patients who had adequate analgesic effect at the phone visit and used 20 mg until the end of the study: 17 (25%) in the CBD group vs. 17 (27.9%) in the placebo group; p = 0.87.

No significant differences were found for the exploratory outcomes when comparing the change from baseline between the CBD group and placebo group: HAQ-DI 0.03 (95% CI-0.11 to 0.18), PSQI -0.71 (95% CI -1.99 to 0.55), HADS depression -0.04 (95% CI -0.79 to 0.70), HADS anxiety -0.69 (95% CI -0.41 to 2.75) and PCS 1.07 (95% CI -1.73 to 3.88).

Two patients in the CBD group experienced serious adverse events not deemed related to the study drug (One episode of fainting and a case of ductal carcinoma). Two patients in the placebo group experienced serious adverse events (One shoulder fracture and one episode of serious hypertension). One patient in the placebo group experienced an allergic reaction. One-hundred-and-nineteen adverse events were reported, and

patients treated with CBD experienced more ear-nose-throat related AE's (8 vs 0) and more skin related AE's (3 vs 0), but none of these were categorized as allergic reactions.

Methodological considerations

Study 3 is the largest study examining the analgesic effects of CBD monotherapy. Strengths of the trial are the duration of the interventional period (12 weeks), the large sample size, randomization of patients and blinding of participants, treating physician and data assessor.
The aim of the present study was to examine the analgesic effects of CBD as addon therapy in patients with hand-OA or PsA with at least moderate chronic pain. Synthetic CBD was chosen because this allowed for CBD to be tested without the interference of other plant constituents including THC, terpenes, and flavonoids. At present avoidance of THC is preferable because of its restrictions for the patients including driving and operation of heavy machinery. Furthermore, evidence of a beneficial effect of adding THC is currently lacking in humans. Evidence for an increased effect of adding terpenes and flavonoids is also lacking, and we urge caution with the generalisability of these results in regard to other CBD formulations.
The dose of CBD used in the present trial might be too low to produce a sufficient plasma concentration optimal for receptor binding[52] and studies in patients with epilepsy use doses often surpassing 1000 mg daily[181] . However, the dose used in this trial is in par with what surveys show that patients use[28], what is used in similar RCT's[122] and other clinical trials and endorsed in consensus recommendations[24].
Neither CBD nor placebo treatment led to a significant change in HADS anxiety or depression scores. The anxiolytic effects of CBD have been explored during simulated public speaking[216] but results have been conflicting[157,291] and although there is preclinical evidence for antidepressant properties, human trials have failed to demonstrate these[134]. It should be noted that participants in this trial had mean low HADS anxiety and depression scores at baseline and results could be different in patients with concomitant psychiatric morbidity.
Patients with PsA who participated in the study did not have active peripheral arthritis at baseline (swollen joints evaluated by a trained professional) and patients with hand-OA did not have a diagnosis of erosive hand-OA. This needs to be taken into consideration and future studies could explore CBD in patients with a greater degree of inflammatory disease.

Conclusion

We found neither clinically nor statistically significant differences in pain intensity between patients receiving 20 to 30 mg CBD daily for 12 weeks or a placebo. Additionally, there were no difference in sleep quality, scores for anxiety, depression, or pain catastrophizing between groups.

Study 4

Study objectives

The objectives of this study were to assess whether treatment with CBD could modify QST parameters. Furthermore, to identify potential predictors of effect of CBD treatment in patients included in the NordCAN study.

Study design, population, and methods

This study was designed as an exploratory secondary analysis of the NordCAN study (study 3)[262]. Patients with complete QST data at baseline were included in the analysis. Patient population and outcome measures (PROMs and QST) for this study are described in the methods section of study 2 and study 3.

Effect of CBD treatment on QST parameters was determined by examining change from baseline to end of treatment in the CBD group and comparing with the placebo group.
To explore potential predictors of treatment effect patients were stratified based on response to treatment. Responders were defined as patients experiencing a reduction of ≥ 30 % pain intensity[74][210] after 12 weeks of treatment. Baseline values were then compared between responders and non-responders in the CBD group and placebo group and significant differences between responders and non-responder were compared between groups (CBD responders vs. placebo responders).
Lastly two models were created using multiple linier regression with the purpose of explaining the variance in treatment response. The dependant variable for the models was the relative change in pain intensity from baseline to end of treatment. The independent variables for model 1 where CRP, HADS depression, HADS anxiety, PCS, PSQI, positive treatment expectancy (positive domain of the SETS), TSP and CPM. Independent variables for model 2 were chosen via backwards selection based on the Akaike information criterion and so separate versions of model 2 were created for the entire group, patients receiving CBD only and patients

receiving placebo only. Regression coefficients are reported as standardized coefficients.
For a more detailed description of methods and statistical analysis, see Appendix D (Manuscript 4).

Results

One hundred and twenty-eight patients with hand-OA (58%) or PsA (42%) were included in the analysis. When assessing the effect of CBD treatment on QST parameters, the only significant change from baseline in the CBD group was a decrease in PTT at the most painful finger joint (42.56 kPa, 95% CI 2.39 kPa to 86.51 kPa p = 0.03). This change was not significantly different from the change seen in the placebo group (between group difference 23.95 kPa; 95% CI -32.50 kPa to 80.87 kPa; p = 0.40).
Fifty-one patients experienced ≥ 30% pain reduction (53% in the CBD group 47% placebo: p > 0.99).
While CBD responders had a higher HAQ at baseline when compared with CBD non-responders (0.86 vs 0.58: p = 0.04) the baseline HAQ of CBD responders was not significantly different from the placebo responders (mean difference 0.24; 95% CI -0.036 to 0.55; p = 0.11). There were no other significant differences in PROMs or QST measures between responders and non-responders in the groups.

The predictive value for Model 1 (adjusted R^2) was 9% for all patients, 8% for the CBD group, and 3% for the placebo group. Independent predictor variables for the entire group were TSP (b = -0.22 p = 0.04), CPM (b = -0.24 p = 0.02), and baseline pain intensity (b = 0.24 p = 0.02). Baseline pain intensity was the only independent predictor in model 1 for the CBD (b = 0.28 p = 0.05) and no predictors were identified in the placebo group.
The predictive value for Model 2 was 11% for all patients 13% for the CBD group and 8 % for the placebo group. Independent predictor variables for the entire group were TSP (b = -0.21 p = 0.03), CPM (b = -0.24 p = 0.01), and baseline pain intensity (0.23 p = 0.01). Baseline pain intensity was the only

independent predictor for the CBD (0.26 p = 0.04) and placebo group (0.16 p = 0.03) in model 2.

Methodological considerations

Study 4 is an exploratory analysis of study 3 and some analyses were planned post hoc. Thus, any positive results from the prediction model can primarily be used for hypothesis generation and design of future trials experiments.
No power calculation was done prior to analysis and the study could be underpowered with regards to detecting minor differences between groups, especially when subgrouping.
The same limitations mentioned in study 2 and 3 apply to study 4 regarding dose of study drug, study population and use of PROMs.

Conclusion

Twelve weeks of CBD treatment with 20 to 30 mg had no effect on QST parameters (Local and widespread PPT, TSP and CPM) when compared to a placebo. No baseline parameters where significantly different between patients who responded to CBD with a decrease in pain intensity of ≥ 30 % when compared to patients with a similar response receiving placebo. Lastly, linier regression models showed poor adjusted R^2 values (11 % for the entire group, 13 % for CBD only and 8 % for placebo only) when explaining the variance in pain intensity difference from baseline to end of treatment. Pain intensity at baseline was the only consistent significant independent variable with standardized regression coefficient ranging from 0.16 to 0.26.

Chapter 4. Discussion

The overall aim of the thesis was to explore the relationship between pain intensity and excess mortality in patients with PsA (Prognosis), to assess the presence of pathological pain mechanisms in patients with PsA and Hand-OA (Mechanisms), to examine the analgesic effects of CBD treatment in patients with PsA and Hand-OA (Treatment) and finally to explore whether different biopsychosocial factors could predict treatment effect with CBD.

Patients with RA experience excess mortality when compared with the background population[70] but whether this is true for patients with PsA remains unsettled due to conflicting results[3,4,40,71,88,154,185,195,239,273]. Chronic pain is prevalent among patients with PsA even though disease modifying drugs exist[119,141,172]. Patients with PsA are also at elevated risk of developing comorbidities associated with excess mortality[196].
Study one showed that although pain intensity was associated with increased odds of excess mortality in a crude model, this association disappeared in models adjusting for other variables including comorbidities and recent redeemed glucocorticoid prescription[261]. This result is similar to those of trials conducted in patients with RA[2,45,69,242,276,283] and indicates that factors other than pain intensity contribute to the excess mortality seen in patients with inflammatory arthritis.

Other risk factors of excess mortality were identified in study one. The major risk factor was concomitant cancer with an OR of 7.17 (95% CI 4.70 to 10.93) followed by redeeming a prescription for glucocorticoids during the last year with an OR of 5.60 (95% CI 3.71 to 8.45) and cardiovascular disease with an OR of 3.04 (95% CI 2.06 to 4.49). Few studies have examined risk factors associated with excess mortality in PsA. Gladman and colleagues conducted a study with a small sample of patients with PsA. where they primarily analysed PsA specific variables at baseline in relation to excess mortality (i.e., joints with active disease, radiological damage, nail involvement) [104]. They found an increased risk of excess mortality among patients with elevated erythrocyte sedimentation rate (RR = 3.60), radiological signs of joint damage (RR = 3.37) and decreased excess mortality among female patients (RR = 0.42). The same group conducted a

larger study and identified cardiovascular disease (HR = 1.67: 95% CI 1.12 to 2.49) cancer (HR = 1.79 95% CI 1.22 to 2.61) and high acute phase reactant (HR = 1.56 95% CI 1.14 to 2.13) as potential risk factors, but did not describe if acute phase reactant was a cumulative measure or a baseline value[83].
A large proportion of patient cases (49% of the cases and 13% of the controls) had been prescribed oral glucocorticoids during the preceding year and a three-fold likelihood of excess mortality was observed among those prescribed glucocorticoids. Oral glucocorticoids are not usually recommended for patients with PsA due to risk of flareup of psoriasis but are part of the treatment regimen in a range of diseases including cancer, COPD, inflammatory bowel disease, myopathies and vasculitis all with risk of excess mortality in and off themselves. Glucocorticoids are also prescribed to patients with PsA where contraindication to other anti-inflammatory drugs exist. Glucocorticoid use is related to excess mortality in models adjusted for concomitant disease in patients with RA[188] and while this could also be the case in the present study odds for excess mortality among patients redeeming a prescription for glucocorticoids could be inflated due to perimortal bias.

In study 2 patients with hand-OA or PsA and chronic pain of at least moderate intensity showed signs of central sensitization measured with pressure algometry, when compared with healthy pain-free controls. This indicates that the pain experienced in the respective diseases involve factors besides inflammation and cartilage degradation.
Fibromyalgia is considered a disease of central sensitization by some[31] and 59 patients in the cohort fulfilled the criteria for fibromyalgia (39% of patients with hand-OA and 52% with PsA).This corresponds with previous observations in PsA cohorts (17% to 64 %)[34,84,142,258,259]. No similar trials have examined the prevalence of patients with hand-OA and concomitant fibromyalgia, but due to the large prevalence of female patients with hand-OA, it is expected that a greater percentage will have concomitant fibromyalgia compared with patients with knee-OA where the prevalence is previously shown to be 10% to 35%[75,115,165].
Patients with fibromyalgia reported higher HAQ and catastrophizing scores than patients without fibromyalgia, a finding which is supported by similar trials in patients with PsA[34]. Studies have also shown that concomitant fibromyalgia is associated with decreased QoL among patients with PsA[258,259] and knee-OA[165]. Study 2 adds credence to the hypothesis that patients with concomitant fibromyalgia are further along a severity

continuum and that disability in concomitant fibromyalgia represents an unmet need.
Patients with concomitant fibromyalgia had a significantly greater TSP score than patients without fibromyalgia who in turn had a greater TSP score than healthy controls. Previous studies have shown that PDQ score could be associated with a greater degree of altered pain processing [6,125] and patients in the present study with concomitant fibromyalgia had greater PDQ scores compared to those without. These results indicate that fibromyalgia could represent patients with a greater degree of pathological central pain processing.

CBD is currently used by many patients with joint pain[60,153], yet no RCT has been conducted to prove its efficacy as an analgesic or anti-inflammatory agent in humans with joint disease[96]. We conducted the first RCT examining whether 20 mg to 30 mg CBD could alleviate pain in patients with PsA or Hand-OA and found no difference in treatment effect when the results from the CBD group was compared with those of the placebo group.

Study 3 was the first longitudinal RCT conducted with CBD monotherapy (without additional THC). Three other RCT's have been conducted using single dose regimens and short term follow-up finding no effect when comparing CBD treatment with a placebo[22,72,231].
The mean analgesic effect of CBD, that is difference from baseline was 11.68 mm (95% CI 5.33 mm to 18.0 mm) which would not be considered clinically significant [199]. Thus, even if an inflated placebo response was present, the effect of CBD was minimal.
As was mentioned in the methodological considerations for the study, the low dose could explain the negative findings. Hobbs and colleagues examined the bioavailability of two different oral CBD solutions (water soluble and lipid soluble) with a dose equalling 30 mg of CBD and found maximal plasma concentrations in the low ng/ml range (2.82 for water soluble and 0.65 for lipid soluble)[124] while most of CBD's targets require concentration in the micromolar range[52]. Higher concentrations can be achieved either by changing mode of ingestion (smoking or iv. Infusion[197]) or by increasing the dose[35].
CBD is often touted as a sleep aid but the present study found no significant change from baseline in neither the CBD nor placebo group. An open label case study of 47 patients with anxiety disorder and 25 patients with sleep disorder followed in an outpatient psychiatric clinic found only minor if any

improvements in PSQI scores and no statistical analysis was done to verify significance[233].
The occurrence of SAEs in the trial were low and not considered due to the intervention. CBD was generally well tolerated. Patients in the CBD group experienced more adverse events related to the skin and the upper respiratory tract but none of these were related to allergic reactions and the events were heterogenous in nature. Diarrhea is the most common side-effect observed in CBD trials, when excluding trials where patients are using CBD together with anti-epileptics[53]. No patients in the CBD group experienced diarrhea in study 3.

Factors influencing the pain experience varies in severity even among patients with the same underlying diagnosis[82] as was shown in study two. Large variance in analgesic effect is seen in pharmacological trials even when examining previously proven therapies[95], and many drugs showing promise in preclinical trials fail to translate from animal to human as was seen with study three. This has led to researchers proposing a more mechanistic approach to treatment and subgrouping of patients based on different domains of the pain experience[79].

Besides a decrease in PPT at the most painful joint, which was not significantly different from placebo, treatment with CBD did not modulate any QST parameters. These results are similar to those of Van de Donk and colleagues[72] who observed no significant difference in PTT when comparing a CBD rich plant substance with a placebo.
An analysis was done to compare baseline values between responders and non-responders in both the CBD and placebo group, but no significant differences were found between CBD responders and placebo responders. Lastly two linier regression models with psychological and QST parameters previously shown to influence pain were created and while baseline pain was a consistent independent predictor the models had overall poor predictive capabilities.
These results could indicate that the dose of CBD was insufficient to produce an analgesic effect. As mentioned in the methodological considerations for study 3 larger doses are used in epilepsy trials[181] and plasma concentrations of CBD could be too low[52]. Three RCT's have tested a single dose of CBD (18.4mg, 400mg and 800mg) against placebo and found no significant difference in pain outcomes[22,72,231] and no significant difference in pain intensity reduction between groups was

observed in study 3. Thus, a possibility is that CBD monotherapy has no analgesic effect. Studies in different patient population, especially neuropathic pain where preclinical models have shown promise, need to be performed and larger doses need to be examined.

Chapter 5. Conclusion and perspectives for future research

Pain was associated with excess mortality in a large-scale national psoriatic arthritis cohort, but the association disappeared once additional confounders were included in the analysis. These results in combination with similar trials in patients with RA indicate that factors such as comorbidities (COPD, DM, cancer, and CVD) and glucocorticoid use are greater drivers of excess mortality.

But, pain is still a problem in patients with PsA and Hand-OA and patients with at least moderate pain intensity display signs of abnormal pain processing including widespread hyperalgesia, facilitated TSP, and inhibited when compared with healthy controls. Furthermore, these patients report decreased sleep quality, greater catastrophizing and increased disability and these factors are even more comprehensive in the subgroup of patients with concomitant fibromyalgia.

At present no effective treatment exists for chronic pain and an increasing number of patients with joint pain and patients with fibromyalgia are using CBD as an analgesic, but the first RCT (NordCAN) with CBD 20 mg to 30 mg as an add-on treatment for chronic joint pain found no significant difference in reduction in pain intensity neither clinically nor statistically when comparing with a placebo. This was the case for the primary outcome (pain intensity) and exploratory outcomes (sleep quality, disability, catastrophizing, anxiety, and depression). CBD was well tolerated, and no serious adverse drug reactions were observed.

Previous analgesic drugs have failed when tested in a clinical placebo-controlled setting despite promising preclinical trials. Due to great heterogeneity among patients with chronic pain, researchers have proposed subgrouping patients based on underlying pain mechanisms and psychosocial parameters to ensure that drug failure is not due to said heterogeneity. An exploratory analysis of the NordCAN trial found that CBD could did not change QST parameters when compared with a placebo and the results were the same when limiting the analysis to patients who experienced a benefit of CBD (responders with a reduction in pain intensity of ≥ 30 %). No baseline parameter was different between responders and non-responders when comparing with a placebo group. Different regression models found that the only consistent variable explaining variance in

treatment effect (relative reduction in pain intensity) was pain intensity at baseline.

Perspective for future research

Redeeming a prescription for oral glucocorticoids was associated with excess mortality in patients with PsA but little is known about this population. Future studies should investigate this subgroup and examine specific cause of death, reason for glucocorticoid prescription and comorbidities associated with oral glucocorticoid use.

Patients with hand-OA and PsA have different degrees of altered pain processing and psychological factors which can influence the pain experience. But if and how this influences treatment and prognosis has yet to be examined. Future studies could stratify patients at the time of diagnosis and follow the cohort to see if these factors impact treatment or prognosis.

Optimal CBD dose for analgesic effect is not known. Trials with a different (higher) dose and in different patient populations (neuropathic pain, greater degree of inflammation) should be performed.

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