

Pain in Rheumatic Diseases

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1. Introduction

Pain is defined as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such a damage” (Merskey et al., 1986). It is a pivotal and the most impairing symptom in rheumatic diseases (Edwards et al., 2009; Fitzcharles et al., 2005; Sokka, 2003). Most patients consulting a rheumatologist suffer pain (Fitzcharles et al., 2005). Chronic pain influences physical and psychological status and causes impairment of quality of life as well as work disability (Dhanani et al., 2002; Kroenke et al., 2009; Skevington, 1998). For rheumatologists the assessment and treatment of pain is an integral part of daily patient care. Although remission of rheumatic diseases can be achieved with therapy with disease-modifying anti-rheumatic drugs (DMARDs) or biological pain can be still a troubling symptom. Pain is influenced by multiple factors such as genetics, experience, cultural and social background and psychological conditions (Gerez-Simon et al., 1989; Martinez et al., 1995; Mogil, 1999). Comorbid depression is associated with inflammation and worsens experience of pain (Kojima et al., 2009). Pain perception enhances the elevation of pro-inflammatory cytokines and activates a cascade of neurohumoral processes which can be dysregulated in patients with rheumatic diseases (Bingham et al., 2009; Edwards et al., 2009; Fitzcharles et al., 2005).

2. Types of pain and pathophysiology of pain in rheumatic diseases

Pain perception and the development of chronic pain is a complex process of neural integration implying response of peripheral tissue damage and transduction of information in peripheral and central nervous system (Bingham et al., 2009). Adequate pain management requires subtle differentiation of rheumatic pain. Pain can be divided into various classifications depending on anatomical origin in the musculoskeletal system or special aspects in pathophysiology. Articular pain is distinguished from extra-articular pain which can be subdivided into muscular/musculotendinous or neurogenic pain. Muscular pain is caused by muscle stress due to protective posture, impaired joint-function or malposition, myositis or cortisone-induced myopathy. Neurogenic compression syndromes or entrapment syndromes induce neurogenic pain (Engel, 2008). Figure 1 demonstrates differentiation of rheumatic diseases depending on pain localization and systemic inflammatory response. Tissue damage and chronic inflammation is not solely responsible for pain perception in rheumatic diseases. Chronic rheumatic pain can also be categorized into nociceptive/inflammatory, peripheral neuropathic and central neuropathic/functional

pain (Goldenberg, 2010; Goldenberg et al., 2011; Winfield, 2008). Due to complex pathophysiology rheumatic pain is often of mixed type and the concept of central neuropathic pain is currently the focus of research, in particular in chronic pain syndromes like fibromyalgia and chronic low back pain. Classical nociceptive pain pathway/sensation starts with depolarization of A δ and C fibers acting as primary afferent neurons (Bingham et al., 2009). Tissue damage as occurring in systemic inflammatory or degenerative rheumatic diseases as well as localized tenosynovitis, bursitis or arthritis can induce firing of peripheral neurons (Winfield, 2008). Nociceptors activate ascending dorsal horn neurons (lateral and medial spinothalamic tract) which transfer the signal to brainstem and thalamus thereby projecting to the somatosensory cortex, hypothalamus and limbic system (Bingham et al., 2009; Goldenberg, 2010; Schaible et al., 2006). Afferent sensory neurons induce the release of neurotransmitters such as glutamate, substance P and γ -aminobutyric acid (GABA) in the dorsal horn influencing pain transmission (Bingham et al., 2009; Fitzcharles et al., 2005; Goldenberg, 2010). Interneurons and descending spinal pathways like periaqueductal gray, serotonergic as well as noradrenergic systems modulate the pain pathway. Cannabinoid receptors and opioid receptors have inhibitory effects (Bingham et al., 2009). Despite dense sensory and sympathetic innervation of joint capsules, ligaments, menisci, periosteum, synovial blood vessels and subchondral bone normal joints are not innervated (Fitzcharles et al., 2005). In inflammation primary afferent neurons are sensitized and silent nociceptors start firing (Bingham et al., 2009; Fitzcharles et al., 2005; Schaible et al., 2006). Their activation threshold decreases and they are activated even by gentle and nonpainful stimuli. This process is called peripheral sensitization (Bingham et al., 2009; Edwards et al., 2009; Fitzcharles et al., 2005). Inflammatory molecules such as prostanoids, TNF, chemokines, kinins and growth factors are produced in damaged tissue and stimulate primary afferent neurons (Bingham et al., 2009; Fitzcharles et al., 2005). Vice versa activated peripheral neurons release inflammatory mediators. This neurogenic inflammation maintains a "vicious circle" of persistent activation of nociceptive and immune system causing chronic rheumatic pain (Goldenberg et al., 2011). TNF has neurostimulatory properties by inducing upregulation of expression of substance P in the central nervous system (Grassi et al. 1994; Tonussi & Ferreira, 1999). Persistent activation of nociceptors and increasing production of neurotransmitters and prostanoids results in central sensitization especially in sensory neurons of the dorsal horn (Bingham et al., 2009; Fitzcharles et al., 2005; Goldenberg, 2010; Schaible et al., 2006). Sustained local inflammation induces peripheral and central sensitization as well as pathological nerve growth with innervation of cartilage contributing to development of chronic pain in rheumatic diseases (Kidd & Urban, 2001; Niissalo, 2002). Furthermore tissue damage or entrapment can affect nociceptors and peripheral neuropathic pain can develop (Bingham et al., 2009; Goldenberg, 2010; Schaible et al., 2006). Patients complain of electrical sensations, burning pain, coldness, numbness or itching. In rheumatoid arthritis chronic inflammation denervates the synovium and may cause neuropathic pain or sensations of joint swelling (Bingham et al., 2009). Central neuropathic pain former known as functional pain is characterized by chronic widespread pain in different regions of the body as observed in fibromyalgia. Usually no structural abnormalities can be identified. This type of pain is often accompanied by symptoms like fatigue, depression, sleep disturbance and memory difficulties. Dysfunction in central nervous system and imbalance of neurotransmitters like norepinephrine, γ -aminobutyric

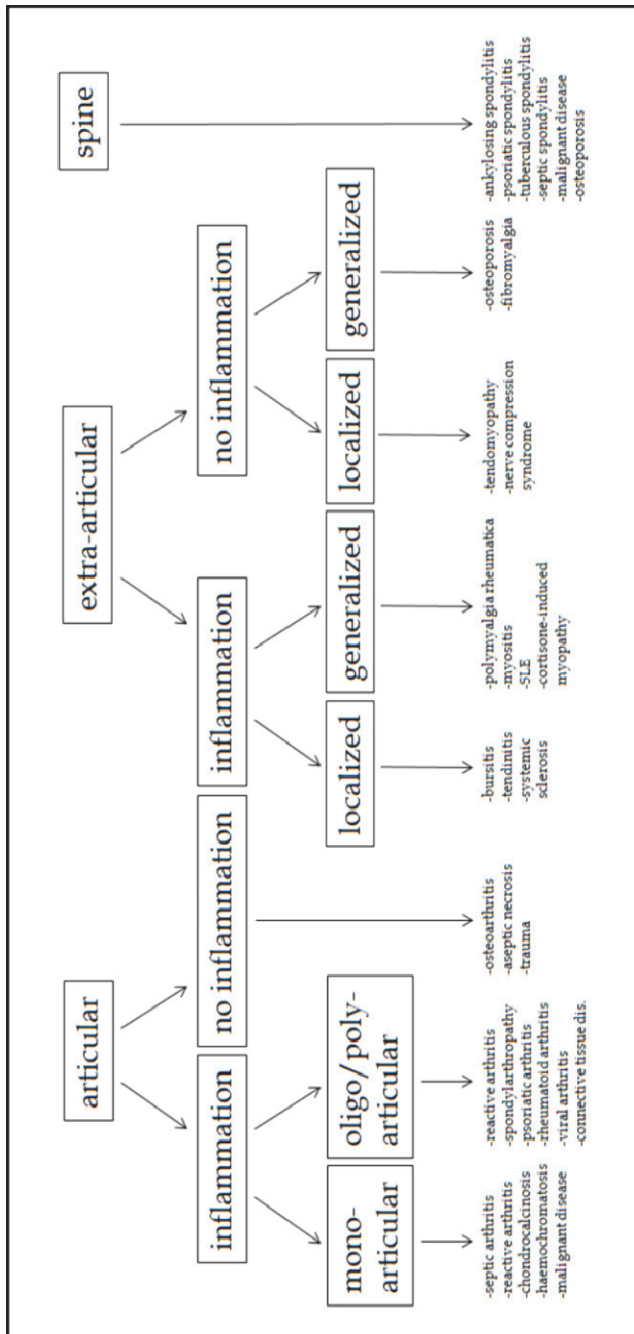


Fig. 1. Types of pain (Engel, 2008)

acid (GABA), serotonin, glutamate, and substance P can cause augmented central pain processing (Goldenberg et al., 2011). Functional neuroimaging studies could reveal that patients with central pain exhibit increased activity in brain regions involved in pain processing compared to healthy individuals (reviewed in Goldenberg et al., 2011). The stress-induced increase of cytokines like TNF could account for higher pain levels in patients with depression and anxiety (Dickens, 2002). Genetic and environmental factors like early life trauma, physical trauma, infections or emotional stress can contribute to the development of central neuropathic pain (Goldenberg et al., 2011). Central neuropathic pain is not only observed in patients with chronic pain syndromes like fibromyalgia but also seen in patients with osteoarthritis and rheumatoid arthritis (Hochman et al., 2010; Wendler et al., 2001). Patients with ankylosing spondylitis, psoriatic arthritis or osteoarthritis have a higher pain threshold compared with those of rheumatoid arthritis underlining the concept of sustained inflammation and pain perception in rheumatoid arthritis (Buskila et al., 1992; Gerecz-Simon et al., 1989). Allodynia or hyperalgesia are common sensations in patients with rheumatic diseases. Hypersensitivity to stimuli like gentle touching which are usually nonpainful is called allodynia. Hyperalgesia is defined as increased pain sensation due to lower pain threshold. The underlying pathophysiological factors are proposed to be changes in central pain processing and enhanced reactivity of immune mediators as seen in central and peripheral sensitization (Engel, 2008; Goldenberg et al., 2011; Winfield, 2008). Pain perception differs between rheumatic diseases and between individuals suffering from equal diseases making it difficult and challenging to distinguish the types of pain and to treat patients properly. The current concept of chronic rheumatic pain implies a complex, multifactorial pathophysiological model with nociceptive and neuropathic pain components called "mixed pain".

3. Pain assessment

Assessment of pain is required before the initiation of treatment to record efficacy of therapy (Fitzcharles et al., 2005; Sokka, 2003; Wendler, 2010). The patient's pain report is subjective and depends on emotion, cognition and behavior (Fitzcharles et al., 2005; Kojima et al., 2009; Sokka, 2003). Self-reporting questionnaires provide qualitative and quantitative assessment of pain and are validated for research purposes as well as for documentation of disease activity and effectiveness of therapy (Sokka, 2003). Pain assessment should be integrated in daily practice of rheumatologists during interview and examination and includes verbal and nonverbal communication such as movements and facial expression of the patients. Verbal rating scales, numeric rating scales, visual analogue scales or pictogram analogue scales have become widely used in clinical care (Sokka, 2003; Wendler, 2010). The pain visual analogue scale (VAS) is a reliable method for assessing the intensity of pain (Jensen et al., 1998; Sokka, 2003; Wendler, 2010). It is integrated in The Health Assessment Questionnaire (HAQ), a valid instrument for the measurement of functional disability, pain and global status (Fitzcharles et al., 2005; Sokka, 2003). The 10 cm scale is bordered on each side. The spectrum of pain ranges across a continuum from 0 (no pain) to 10 (very severe pain). In the numeric rating scale numbers describe the pain severity, therefore results are comparable for follow up. Figure 2 shows the visual analogue and the numeric rating scale.

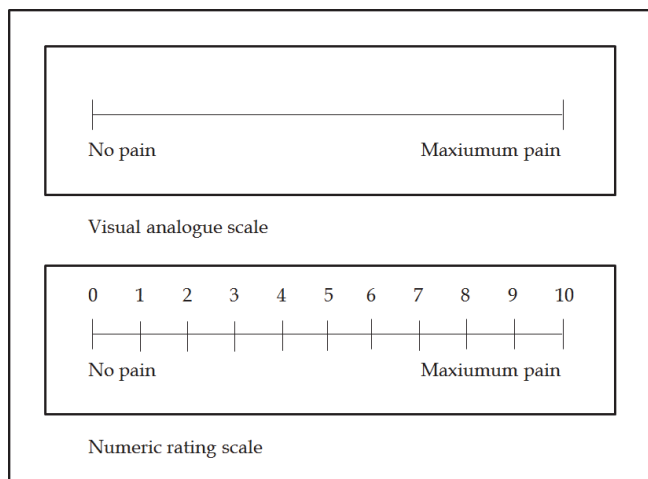


Fig. 2. Pain scales

When analyzing pain scores physicians should take into account various rheumatic diseases. In rheumatoid arthritis pain scores correlate with radiographic and laboratory results whereas fibromyalgia patients suffer severe pain in the absence of structural damage (Sokka, 2003). The first consultation of patients with pain should include a detailed interview and neurological and musculoskeletal examination of the patient (American Society of Anesthesiologists, 2010; Fitzcharles et al., 2005). A general medical history and history about the onset, quality, intensity, distribution and duration of pain, ameliorating and aggravating factors, symptoms, social and psychological impacts as well as previous therapies should be evaluated (American Society of Anesthesiologists, 2010). Body schemes, e.g. in the McGill pain questionnaire, facilitate the assessment of patients with chronic rheumatic diseases suffering from pain in various parts of the body (Wendler, 2010). Pain diaries can activate patients to document pain character and its influence in motion and function as well as to recognize effectiveness of treatment (Wendler, 2010).

4. Pain therapy in rheumatic diseases

Once the rheumatologist has assessed the patient's pain an adequate therapy has to be initiated. Optimal pain management should encompass multimodal interventions with pharmacological and non-pharmacological treatment strategies (American Society of Anesthesiologists, 2010; Fitzcharles et al., 2005). Non-pharmacological procedures include education, psychological care, physical and/or occupational therapy as well as joint protection and/or surgery.

4.1 Non-pharmacological pain treatment

Education has a tremendous effect on sufficient pain control in patients with rheumatic diseases. Information about the disease and therapeutic options can reduce the fear of long term consequences, such as loss of function, joint damage, chronic pain, and implications on social and family life. Self-management strategies provide patients with a wide range of

possibilities to influence their course of the disease. Exercise, joint protection techniques and appropriate use of pharmacological pain therapy encourage patients to cooperate with their attending physician (Goldenberg et al., 2011).

For sufficient pain control the psychological status of the patient has to be evaluated (Kojima et al., 2009). Depression can worsen the perceived pain. Therefore rheumatoid arthritis patients describing severe pain without active disease could benefit from psychological therapy (Kojima et al., 2009). Additional cognitive behavioral therapy, biofeedback, relaxation training and self-care education can improve the patient's well-being (American Society of Anesthesiologists, 2010; Kimura & Walco, 2007).

Patients with rheumatic diseases are often physically inactive. Physiotherapy and exercise programs support mental and physical health (Kimura & Walco, 2007; Roddy et al., 2005). Patients with rheumatic diseases should always be encouraged to get exercise. Due to chronic pain they often feel weak and fatigue causes impaired activity. On the one hand patients fear exacerbation of musculoskeletal pain when moving. Consequently avoidance of exercise deteriorates muscle strength and physical condition. On the other hand excessive exercise aggravates fatigue and flares can occur. Mild exercise like walking, water aerobics, and bicycling, being appropriate for age and condition, can support physical fitness and comfort (Winfield, 2008). Physical therapy with heat or cold can reinforce therapeutic effects. In particular in nociceptive pain application of moderate heat (e.g. paraffin, packs, hydrotherapy) can improve pain control. In generalized pain syndromes sauna, baths, showers or hot mud can be effective. Cold therapy (e.g. packs, sprays or immersion) is recommended in acute pain states as seen in flares of rheumatic diseases (Winfield, 2008). Transcutaneous electrical nerve stimulation (TENS) is an independent option of physical therapy at home.

Synovectomy and arthroplasty are therapeutic options in patients with continuous pain, joint deformity and functional loss (Kimura & Walco, 2007). The role of complementary therapies in pain management needs to be further examined (Fitzcharles et al., 2005). For optimal pain management a combination of different medications is often necessary. Rheumatologists have to prove efficacy of therapy and compliance of the patient. Discontinuation of treatment is required if side effects occur or if the therapy is ineffective.

4.2 Pharmacological pain treatment

Intra-articular injections, topical applications, selective and non-selective non-steroidal anti-rheumatic drugs (NSAIDs), opioids as well as adjuvant drugs are therapeutic options for pain control. DMARDs like methotrexate, sulfasalazine, leflunomide and biologicals are prescribed to reduce disease activity and to maintain remission. Reduced disease activity is associated with improved functional status and reduced pain (Kimura & Walco, 2007). However, pain remains to be a leading symptom in patients with rheumatic diseases. Due to serious side effects of long-term application high dose corticosteroids should only be prescribed in severe, life-threatening disease. Intra-articular injections can help to reduce localized joint inflammation and pain (Kimura & Walco, 2007). The number of injections is limited to three per year (Bernau & Heeg, 2003). Avoidance of systemic side effects is an advantage of topical analgesics such as capsaicin or topical NSAIDs like diclofenac, ibuprofen, ketoprofen, and piroxicam. Although plasma concentration is low after

absorption local application can reduce mild to moderate pain in arthritis (Kroenke et al., 2009; Mason et al., 2004).

4.2.1 Non-selective and selective cyclooxygenase inhibitors

Non-selective and selective cyclooxygenase inhibitors (coxibs) are potent analgesics with anti-phlogistic properties and are successfully used in the treatment of degenerative and inflammatory joint diseases (Schaible et al., 2006; Unger & Baerwald, 2010). Table 1 shows the most common selective and non-selective COX-inhibitors. Application of NSAID results in inhibition of prostaglandin synthesis which sensitizes nociceptors in inflamed joints and thereby causing pain in arthritis (Schaible et al., 2006; Unger & Baerwald, 2010). Furthermore central sensitization is followed by prostaglandin E2 (PGE2) release in the dorsal horns of the spinal cord (Bingham et al., 2009; Fitzcharles et al., 2005). However, gastrointestinal, renal, cardiovascular side effects and hepato-toxicity as well as platelet inhibition restrict their application (Kimura & Walco, 2007; Kroenke et al., 2009; Unger & Baerwald, 2010). Studies show that coxibs and traditional NSAIDs do not significantly differ in their cardiovascular side effects (reviewed in Luttosch & Baerwald, 2011; Unger & Baerwald, 2010). Therefore these agents should be administered in a low dose and for a short term only. Naproxen, paracetamol or opioids seem to be an option for pain control in patients with cardiovascular risk factors and should be preferred in these groups (Kroenke et al., 2009; Luttosch & Baerwald, 2011; Unger & Baerwald, 2010). Coxibs should be preferred in patients with risk of gastrointestinal complications due to their lower risk of developing a serious adverse event compared to non-selective cyclooxygenase-inhibitors (Unger & Baerwald, 2010). In persons 60 years or older, in those with gastrointestinal symptoms and in patients taking corticosteroids or antiplatelet agents a proton pump inhibitor should be coadministered with traditional NSAIDs, or a coxib should be prescribed (Kroenke et al., 2009).

Name	Half-time	Dose (mg)	Peculiarity	Contraindications
Etoricoxib	25 h	OA 30-60 1/day RA/SpA 90 1/day gout 120 1/day	high blood pressure is a contraindication	peptic ulcers or GI- bleeding cardio- /cerebrovascular diseases
Celecoxib	12 h	OA 200 1-2/day RA 100-200 2/day SpA 100-200 2/day or 200-400 1/day	allergy against sulfonamids is a contraindication	arterial occlusive disease heart failure impaired liver function crea-clear. <30 ml/min pregnancy breast-feeding Crohn`s disease
Diclofenac	1-2 h	50-150/day in 2-4 doses	high cardio-vascular risk	peptic ulcers, bleeding, perforation
Naproxen	14 h	500-1250/day in 1-3 doses	low cardio-vascular risc	renal and liver failure

Name	Half-time	Dose (mg)	Peculiarity	Contraindications
Piroxicam	14-160 h	10-20/day	severe skin reactions	heart failure bone marrow dysfunction ASS-induced asthma
Indometacin	2-3 h	50 1-3/day	short term administration allergic reactions	
Acemetacin	4 h	30 1-3/day		
Ketoprofen	1,5-2,5 h	50 1-4/day or 100 1-2/day	phototoxic and allergic reactions	
Phenylbutazon	70 h	200 1-2/day	SLE, pyrazol-allergy, thyroid gland dysfunction is a contraindication	
Meloxicam	20 h	OA 7,5-15/day RA/SpA 15/day	high COX-2-selectivity	
Ibuprofen	2-3 h	max. 800-1200/day	no combination with ASS	

ASS-acetylsalicyl acid, COX-cyclooxygenase, crea-clear.-creatinine-clearance, GI-gastrointestinal, OA-osteoarthritis, RA-rheumatoid arthritis, SLE-systemic lupus erythematoses, SpA-ankylosing spondylitis

Table 1. Characteristics of typical NSAIDs and coxibs (Unger & Baerwald, 2010)

4.2.2 Opioid therapy

If NSAIDs are insufficient or contraindications and interfering side effects, respectively, exist opioids can be considered for effective pain control (Pierer et al., 2010). However, side effects and potential addiction have previously restricted their use in pain therapy. Therefore opioid therapy should only be prescribed within a multimodal pain control concept in advanced inflammatory or degenerative disease if other analgesics are ineffective (Pierer et al., 2010; Siegel et al., 2008). Long term, controlled and randomized studies concerning opioid use in rheumatic diseases are lacking. In clinical practice a positive effect on sleep and musculoskeletal function especially in neuropathic pain, rheumatoid arthritis, osteoarthritis and low back pain can be observed (Pierer et al., 2010; Siegel et al., 2008). Opioids bind to opioid receptors found in the central and peripheral nervous system (Kimura & Walco, 2007, Lang et al., 2010; Siegel et al., 2008). Studies confirm that opioids show mild anti-inflammatory effects (reviewed in Kimura & Walco 2007). Endogenous opioid peptides are released in inflamed regions and bind to upregulated peripheral opioid receptors thereby controlling intrinsic pain pathways (Lang et al., 2010). Tramadol is a weak opioid beneficial especially in osteoarthritis, low back pain and fibromyalgia (Fitzcharles et al., 2005; Goldenberg et al., 2011; Kroenke et al., 2009). Nausea, vomiting, constipation, dizziness, somnolence, cognitive impairment, urinary retention and respiratory depression are major undesirable adverse effects (American Society of Anesthesiologists, 2010; Lang et al., 2010; Winfield, 2008). Therefore long term therapy is not recommended. In chronic nonmalignant pain only mild pain reduction is observed whereas functional outcome (unemployment, necessity of health care) is declining (Siegel et al., 2008). Pain intensity, vital parameters, musculoskeletal function, possible addiction and side effects have to be controlled regularly (Pierer et al.,

2010; Winfield, 2008). Upon initiation of opioids the dosage has to be titrated within the first two to three weeks (Winfield, 2008). After six weeks a significant pain reduction should be documented (Pierer et al., 2010). If optimal pain relief is not occurring opioid rotation should be considered (Kroenke et al., 2009). Exacerbation of pain should always be evaluated and the causes should be detected prior to increasing the dosage. If effective pain control does not occur after three months opioid therapy should be stopped. To avoid withdrawal symptoms a daily reduction of 10 % is strongly recommended (Pierer et al., 2010). Opioids should not be administered in patients with a history of or current substance use disorders (Kroenke et al., 2009). In older patients or patients with renal or liver function impairment the dose has to be reduced 25 % to 50 % (Kroenke et al., 2009; Winfield, 2008). Opioids should be administered with caution in older patients due to high risk of falls leading to fractures. There are insufficient data about the effect of long term therapy with opioids (Pierer et al., 2010). The WHO Three-Step Model for Pain Management provides an international accepted approach for effective pharmacological pain therapy and is demonstrated in Figure 3. The starting therapy step depends on the severity of pain. If the first treatment is insufficient the following step of the model should be initiated. Adjuvant drugs including antidepressants and anticonvulsants can be combined with the medications of the Three-Step Model.

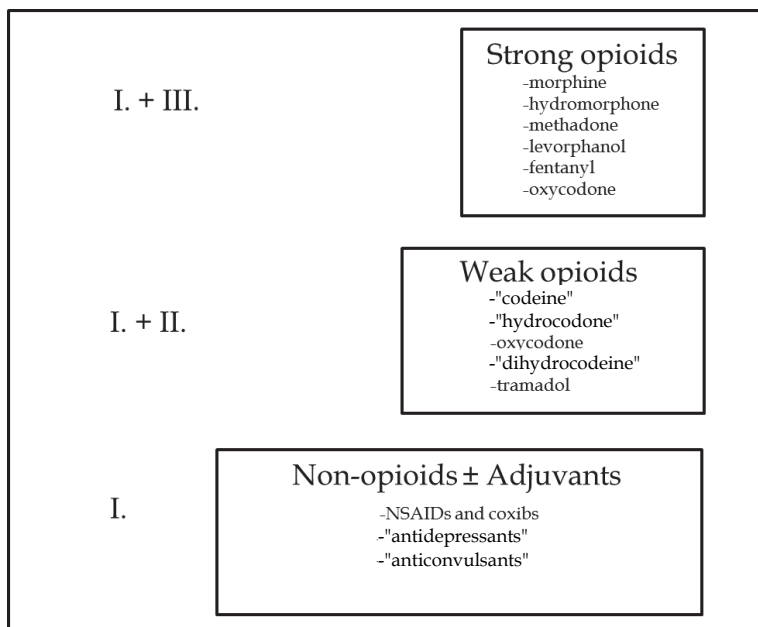


Fig. 3. WHO Three-Step Model of Pain management

4.2.3 Adjuvant drugs

Tricyclic antidepressants like amitriptyline are the most commonly used adjuvant medications to treat patients with rheumatoid arthritis or ankylosing spondylitis (Fitzcharles et al., 2005). Adjuvant drugs play a major role in management of fibromyalgia and seem to be the most effective medications in this condition (Godfrey, 1996). Sleep, mood and fatigue are positively influenced. The anticonvulsants gabapentin and pregabalin provide pain relief especially in neuropathic pain (American Society of Anesthesiologists, 2010; Kimura & Walco, 2007; Kroenke et al., 2009). They have neuromodulatory properties due to binding to calcium-channels in the central nervous system and inhibiting the release of neurotransmitters (American Society of Anesthesiologists, 2010; Kroenke et al., 2009). Cardiovascular side effects as well as somnolence or sedation can limit therapeutic application (American Society of Anesthesiologists, 2010; Kroenke et al., 2009). Antidepressants should be used with caution in older patients due to anticholinergic properties and the high risk of falls (Kroenke et al., 2009). Duloxetine and milnacipran interact with the serotonin and norepinephrine systems. Positive effects on pain and function could be demonstrated especially in fibromyalgia (Goldenberg et al., 2011). Figure 4 shows a stepwise summary of pharmacological and non-pharmacological pain control in rheumatic diseases.

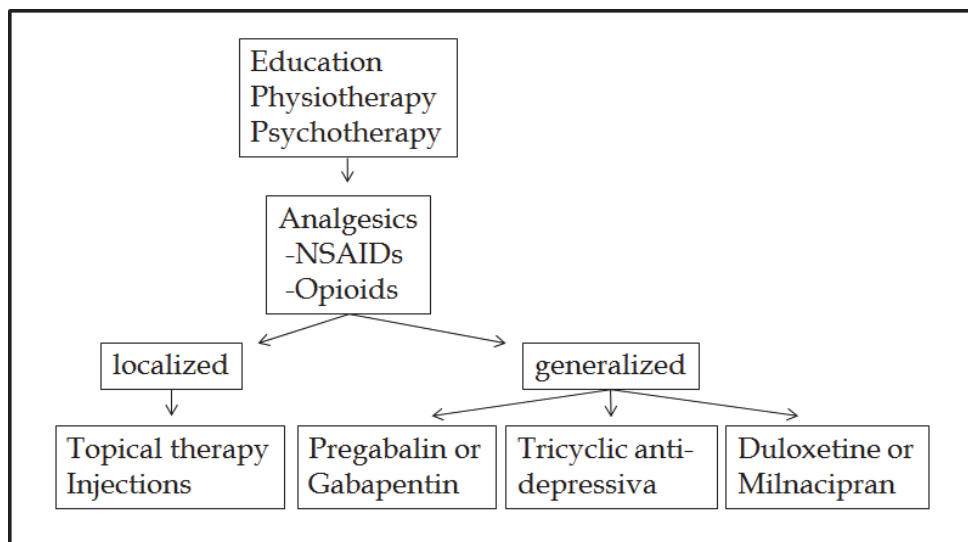


Fig. 4. Pain therapy in rheumatic diseases (Winfield, 2008)

4.2.4 Development of new medication

Pharmacological pain management is restricted due to significant side effects or contraindications of NSAIDs and opioids. Development of new medication is in the focus of current research. Tapentadol hydrochloride is a μ -opioid-receptor agonist and norepinephrine reuptake inhibitor for the treatment of moderate and severe pain exhibiting less gastrointestinal side effects compared to traditional opioids and is effective in

neuropathic and/or inflammatory pain (Wade & Spruill, 2009). Cardiovascular and gastrointestinal side effects limit pain control with NSAIDs. Naproxcinod is a new developed COX inhibiting nitric oxide donator (CINOD) which shows an improved safety profile due to release of nitric oxide (NO) (Wallace et al., 2009). NO acts in the vasculature inducing positive effects on blood pressure and mucosal integrity in the gastrointestinal tract (Wallace et al., 2009). Further studies are needed to evaluate the role of dopaminergic agents, N-methyl-D-aspartate (NMDA) receptor antagonists, γ -aminobutyric acid (GABA) agonists, and 5-hydroxytryptamine 3 receptor antagonist in complex pain syndromes with central pain components (Goldenberg et al., 2011).

5. Conclusion

Pain is a cardinal symptom in patients with rheumatic disease. It impacts functioning, quality of life and causes disability. The pain is frequently multifactorial in origin and has both central and peripheral components. Disease activity is only marginally related to the extent of pain severity, and pain-related presentation can differ widely between individuals. Cognitions and emotions contribute to different perception of pain. Although remission of rheumatic diseases can be achieved with use of oral DMARDs or biological therapies, treatment of pain can be a challenge in every day practice. Assessment of pain is pivotal for monitoring therapy response and must take into account various factors. Non-pharmacologic interventions, such as exercise and cognitive-behavioral therapy as well as the use of analgesics such as cyclooxygenase inhibitors or opioids should aim to achieve at better quality of life for patients with rheumatic diseases and should help to maintain function.

6. References

- American Society of Anesthesiologists Task Force on Chronic Pain Management and the American Society of Regional Anesthesia and Pain Medicine. (2010). Practice Guidelines for Chronic Pain Management. *Anesthesiology*, 112, pp. (810-835)
- Bernau, A. & Heeg, P. (2003). Intraarticular punctures and injections: indications-prevention of infection-technique- complications. *Orthopaede*, 32, 6, pp. (548-570)
- Bingham, B.; Ajit, S. K.; Blake, D. R. & Samad, T. A. (2009). The molecular basis of pain and its clinical implications in rheumatology. *Nature Clinical Practice Rheumatology*, 5, 1, pp. (28-37)
- Buskila, D.; Langevitz, P; Gladman, D. D.; Urowitz, S. & Smyhte, H. A. (1992). Patients with rheumatoid arthritis are more tender than those with psoriatic arthritis. *The Journal of Rheumatology*, 19, pp. (1115-1119)
- Dhanani, S.; Quenneville, J.; Perron, M.; Abdolell, M. & Feldmann, B. M. (2002). Minimal differences in pain associated with change in quality of life in children with rheumatic diseases. *Arthritis & Rheumatism*, 47, pp. (501-505)
- Dickens, C.; McGowan, L.; Clark-Carter, D. & Creed, F. H. (2002). Depression in rheumatoid arthritis: a systemic review of the literature and meta-analysis. *Psychosomatic Medicine*, 64, pp. (52-60)

- Edwards, R. R.; Wasan, A. D.; Bingham, C. O.; Bathon, J.; Haythornthwaite, J. A.; Smith, M. T. & Page, G. G. (2009). Enhanced reactivity to pain in patients with rheumatoid arthritis. *Arthritis Research & Therapy*, 11, R61, pp. (1-9)
- Engel, J. M. (2008). *Interdisziplinäre klinische Rheumatologie* (2nd edition), Zeidler, H.; Zacher, J.; Hiepe, F. A., ISBN 978-3- 540-34104-8, Berlin, Heidelberg
- Fitzcharles, M.-A.; Almahrezi, A. & Shir, Y. (2005). Pain-Understanding and challenges for the rheumatologist. *Arthritis & Rheumatism*, 52, 12, pp. (3685-3692)
- Gerecz-Simon, E. M.; Tunks, E. R.; Heale, J. A.; Kean, W. F. & Buchanan, W. W. (1989). Measurement of pain threshold in patients with rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, and healthy controls. *Clinical Rheumatology*, 8, pp. (467-474)
- Godfrey, R. G. (1996). A guide to the understanding and use of tricyclic antidepressants in the overall management of fibromyalgia and other chronic pain syndromes. *Archives of Internal Medicine*, 156, pp. (1047-1052)
- Goldenberg, D. L. (2010). The interface of pain and mood disturbances in rheumatic diseases. *Seminars in Arthritis and Rheumatism*, 40, pp. (15-31)
- Goldenberg, D. L.; Clauw, D. J. & Fitzcharles, M. A. (2011). New Concepts in Pain Research and Pain Management of Rheumatic Diseases. *Seminars in Arthritis and Rheumatism*, article in press
- Grassi, F.; Mileo, A. M.; Monaco, L.; Punturieri, A.; Santoni, A. & Eusebi, F. (1994). TNF α increases the frequency of spontaneous miniature synaptic currents in cultured rat hippocampal neurons. *Brain Research*, 659, pp. (226- 230)
- Hochman, J. R.; French, M. R.; Bermingham, S. L. & Hawker G. A. (2010). The nerve of osteoarthritis pain. *Arthritis Care & Research*, 62, pp. (1019-1023)
- Iwasaki, A.; Inoue, K. & Hukada, S. (1995). Distribution of neuropeptide-containing nerve fibers in the synovium and adjacent bone of the rat knee joint. *Clinical and Experimental Rheumatology*, 13, pp. (173-178)
- Jensen, M. P.; Miller, L. & Fisher, L. D. (1998). Assessment of pain during medical procedures: a comparison of three scales. *The Clinical Journal of Pain*, 14, pp. (343-349)
- Kidd, B. L. & Urban, L. A. (2001). Mechanisms of inflammatory pain. *British Journal of Anaesthesia*, 87, pp. (3-11)
- Kimura, Y. & Walco, G. A. (2007). Treatment of chronic pain in pediatric rheumatic disease. *Nature Clinical Practice Rheumatology*, 3, 4, pp. (210-218)
- Kojima, M.; Kojima, T.; Suzuki, S.; Oguchi, T.; Oba, M.; Tsuchiya, H.; Sugiura, F.; Kanayama, Y.; Furukawa, T. A.; Tokudome, S. & Ishiguro N. (2009). Depression, Inflammation, and pain in patients with rheumatoid arthritis. *Arthritis & Rheumatism*, 61, 8, pp. (1018-1024)
- Kroenke, K.; Krebs, E. E. & Bair, M. J. (2009). Pharmacotherapy of chronic pain: a synthesis of recommendations from systematic reviews. *General Hospital Psychiatry*, 31, pp. (206-219)
- Lang, L. J.; Pierer, M.; Stein, C. & Baerwald, C. (2010). Opioids in rheumatic diseases. *Annals of the New York Academy of Science*, 1193, pp. (11-116)

- Luttosch, F. & Baerwald, C. (2011). Treatment of pain in rheumatic diseases. *Deutsche Medizinische Wochenschrift*, 136, pp. (1598-1600)
- Martinez, J. E.; Ferraz, M. B.; Sato, E. I. & Atra, E. (1995). Fibromyalgia versus rheumatoid arthritis: a longitudinal comparison of the quality of life. *The Journal of Rheumatology*, 22, pp. 270-274
- Mason, L.; Moore, R. A.; Edwards, J. E., Derry, S. & McQuay, H. J. (2004). Topical NSAIDs for chronic musculoskeletal pain: systematic review and meta-analysis. *BMC Musculoskeletal Disorders*, 19, pp. (5-28)
- Merskey, H.; Lindblom, U. & Mumford, J.M. (1986). Pain terms: a current list with definitions and notes on usage. *Pain*, Suppl 3, pp. (215-221)
- Mogil, J. S. (1999). The genetic mediation of individual differences in sensitivity to pain and its inhibition. *Proceedings of the National Academy of Sciences USA*, 96, pp. (7744-7751)
- Nissalo, S.; Hukkanen, M.; Imai, S.; Tornwall, J. & Konttinen, Y. T. (2002). Neuropeptides in experimental and degenerative arthritis. *Annals of the New York Academy of Sciences*, 966, pp. (384-399)
- Pierer, M.; Malysheva, O.; Wagner, U. & Baerwald, C. (2010). Opioids for musculoskeletal pain. *Aktuelle Rheumatologie*, 35, pp. (184-188)
- Roddy, E.; Zhang, W.; Doherty, M.; Arden, N. K.; Barlow, J. & Birrell, F. (2005). Evidence-based recommendations for the role of exercise in the management of osteoarthritis of the hip or knee: the MOVE consensus. *Rheumatology (Oxford)*, 44, pp. (67-73)
- Schaible, H.-G.; Schmelz, M. & Tegeder, I. (2006). Pathophysiology and treatment of pain in joint disease. *Advanced Drug Delivery Reviews*, 58, pp. (323-342)
- Siegel, L.; Pierer, M.; Stein, C. & Baerwald, C. (2008). Opioids in musculoskeletal pain. *Zeitschrift für Rheumatologie*, 67, pp. (646-652)
- Skevington, S. M. (1998). Investigating the relationship between pain and discomfort and quality of life, using the WHOQOL. *Pain*, 76, pp. (395-406)
- Sokka, T. (2003). Assessment of pain in patients with rheumatic diseases. *Best Practice & Research Clinical Rheumatology*, 17, 3, pp. (427-449)
- Tonussi, C. R. & Ferreira, S. H. (1999). Tumor necrosis factor- α mediates carrageenin-induced knee-joint incapacitation and also triggers overt nociception in previously inflamed rat knee-joints. *Pain*, 82, pp. (81-87)
- Unger, S. I. & Baerwald, C. (2010). Pain Therapy with selective and non-selective cyclooxygenase inhibitors in rheumatology. *Aktuelle Rheumatologie*, 35, pp. (178-183)
- Wade, W. E. & Spruill, W. J. (2009). Tapentadol Hydrochloride: A Centrally Acting Oral Analgesic. *Clinical Therapeutics*, 31, 12, pp. (2804-2818)
- Wallace, J. L.; Viappiani, S. & Bolla, M. (2009). Cyclooxygenase-inhibiting nitric oxide donors for osteoarthritis. *Trends in Pharmacological Sciences*, 30, 3, pp. (112-117)
- Wendler, J. (2010). Assessment of pain in rheumatology. *Aktuelle Rheumatologie*, 35, pp. (172-177)
- Wendler, J.; Hummel, T.; Reissinger, M.; Manger, B; Pauli, E.; Kalden, J. R. & Kobal, G. (2001). Patients with rheumatoid arthritis adapt differently to repetitive painful

stimuli compared to healthy controls. *Journal of Clinical Neuroscience*, 8, pp. (272-277)

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