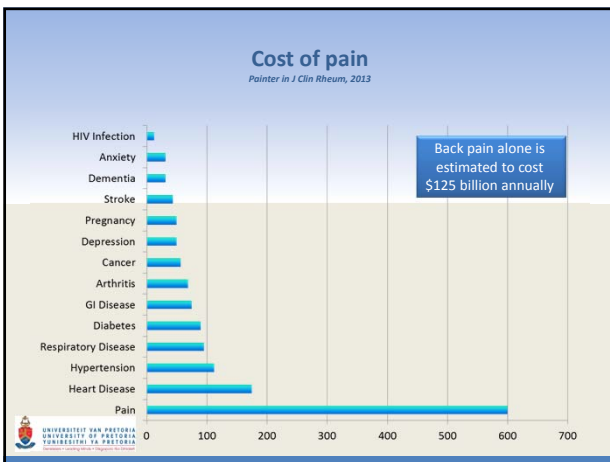


Pain Management Current perspectives



Helgard Meyer, FCFP(SA)
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Wilgers MR Medical Centre

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Topical Review

PAIN

Updating the definition of pain

Williams et al in Pain, 2016




“Pain is a distressing experience associated with actual or potential tissue damage with sensory, emotional, cognitive, and social components.”


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Acute pain

Holdcroft in Core topics in Pain, 2005

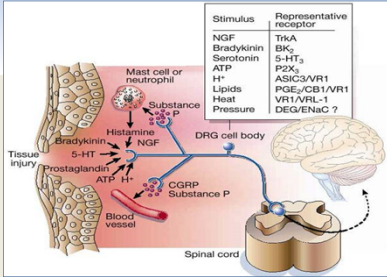


- Normal biological response
- Protects / promotes healing
- Unrelieved acute pain:
 - ↑ catecholamines
 - ↑ heart rate
 - Shallow breathing
 - Shock
 - Delayed healing
- Nervous system effects
- May evolve into chronic pain
- Must be treated and its cause be removed




Peripheral sensitization

Woolf in Pain, 1986

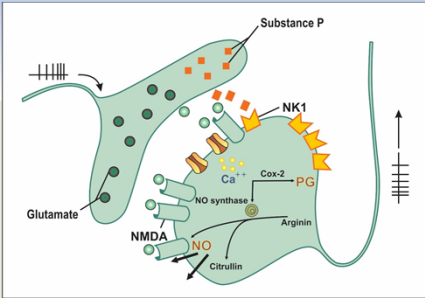



Stimulus	Representative I receptor
NGF	TrkA
Bradykinin	BK ₂
Serotonin	5-HT ₃
ATP	P2X ₃
H ⁺	ASIC3/VR1
Lipids	PCSK ₂ /CB1/VR1
Heat	VR1/VR1-1
Pressure	DEG/ENaC ?




Central sensitization

Woolf in Rheum Dis Clin, 2002





Chronic pain

Holdcroft in Core topics in Pain, 2005




- Persists longer than the expected time for healing (>3 months)
- No "warning" function
- Underlying disease may be absent
- Pain becomes the "disease"
- Emotional / psychosocial factors important
- Complex to treat
 - Interdisciplinary approach
- Management vs eradication



Warning

Focussing only on pain intensity in the assessment of chronic pain patients

Sullivan in Pain, 2016



Commentary
PAIN
The fifth vital sign revisited
James N. Campbell

➤ Results in the strongest analgesics for the wrong patients.



"Higher pain intensity in chronic musculo-skeletal pain mostly indicates more emotional and psychosocial factors."



Assessment of patients in chronic pain

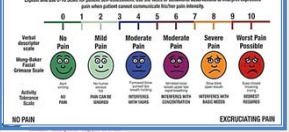
Mackichan in Rheum Dis Clin North Am, 2008
Meyer in SA Fam Pract, 2011

- Unique and personal experience
- Personal report
- Subjective (PQRST)
- DN4
- Measure

Universal Pain Assessment Tool

This pain assessment tool is intended to help patients rate their pain according to individual patient needs. Explain and use the icons for general pain assessment and the icons or individual descriptors to report specific pain when patient cannot communicate further pain intensity.



Brief Pain Inventory

Circle the best number that describes how, during the last week, you have felt about each item.

General Activity	1	2	3	4	5	6	7	8	9	10
Movement										
Working ability										
Normal work (not heavy work outside the home and community)										
Social relations										
Change in sleep										
Experiences of life										

Treatment goals for chronic pain patients

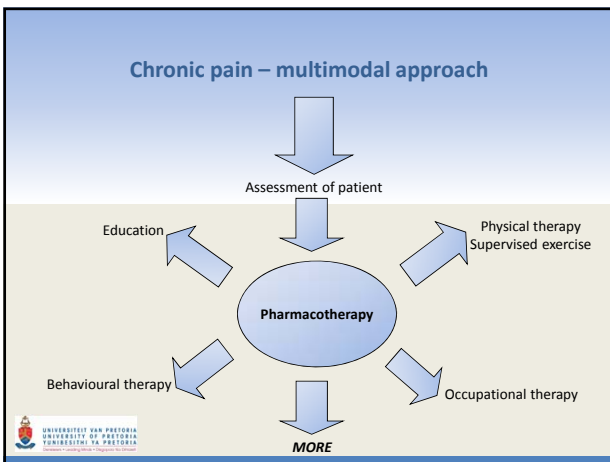
*Ashburn in Lancet, 1999
Meyer in SA Fam Pract, 2007*



- Reduction of pain (30% is clinically significant)
- Improvement in co-morbidities (e.g. mood and sleep)
- Improve patient's functioning


Return to work

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Department of Family Practice - Registraarsentrum



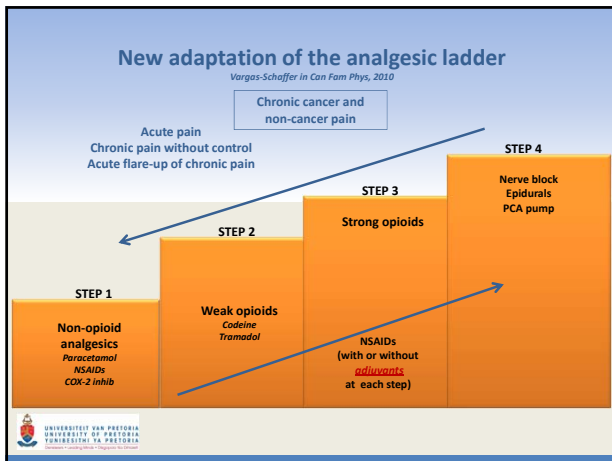
Pharmacotherapy

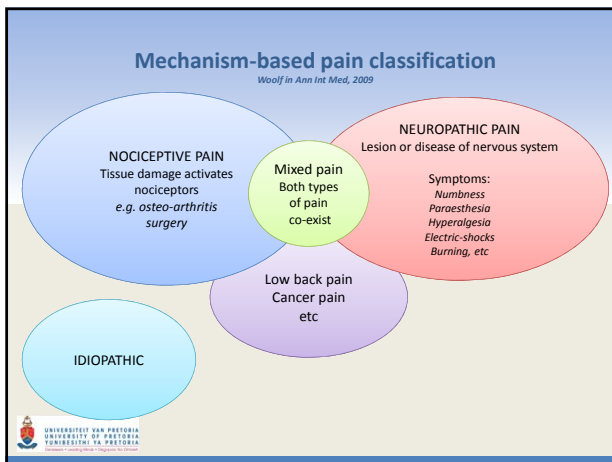
Granow in Anaes and Int Care, 2010

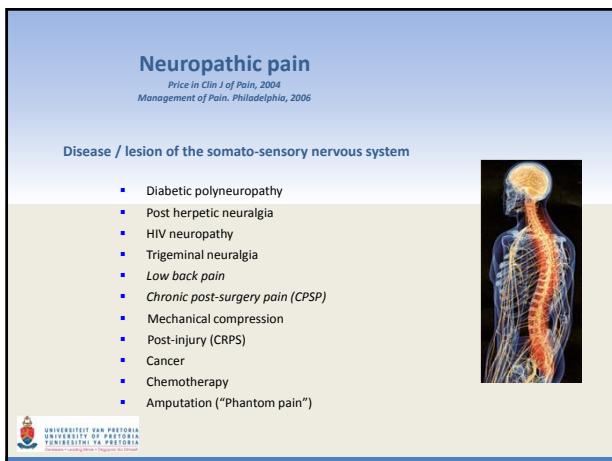



<p>Primary analgesics</p> <ul style="list-style-type: none"> ▪ Paracetamol ▪ NSAID's / COX-2 inhibitors <i>Ibuprofen Diclofenac Naproxen Celecoxib Etoricoxib, etc</i> ▪ Opioids <ul style="list-style-type: none"> ▪ Mild <i>Codeine Tramadol</i> ▪ Strong: <i>Morphine Hydromorphone Buprenorphine Oxycodone Fentanyl Tapentadol</i> 	<p>Adjuvant analgesics</p> <ul style="list-style-type: none"> ▪ Tricyclics <i>Amitriptyline, Cyclobenzaprine</i> ▪ SNRI's <i>Duloxetine, etc.</i> ▪ Anticonvulsants: <i>Carbamazepine Gabapentin Pregabalin</i> <p>Local anaesthetics</p> <p>Diverse analgesics <i>Ketamine Cannabinoids Muscle relaxants</i></p> <p>Topical analgesics <i>Lidocaine patch Capsaicin patch</i></p>
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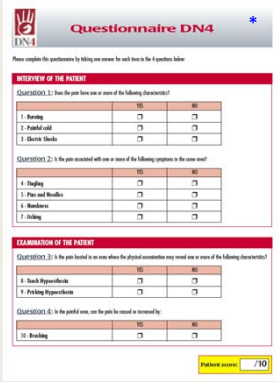




Douleur Neuropathique 4
Bouhassira et al in Pain, 2005.

Score $\geq 4/10$

Specificity: 90%
Sensitivity: 83%



Questionnaire DN4

Please complete the questionnaire by ticking one answer for each item in the 4 questions below.

INTERVIEW OF THE PATIENT

QUESTIONNAIRE 1: Does the pain have one or more of the following characteristics?

	Yes	No
1. Boring	<input type="checkbox"/>	<input type="checkbox"/>
2. Burning/ cold	<input type="checkbox"/>	<input type="checkbox"/>
3. Electric shocks	<input type="checkbox"/>	<input type="checkbox"/>

QUESTIONNAIRE 2: In the year associated with one or more of the following symptoms, to the same extent?

	Yes	No
4. Tingling	<input type="checkbox"/>	<input type="checkbox"/>
5. Pain and Swelling	<input type="checkbox"/>	<input type="checkbox"/>
6. Numbness	<input type="checkbox"/>	<input type="checkbox"/>
7. Itching	<input type="checkbox"/>	<input type="checkbox"/>

EXAMINATION OF THE PATIENT

QUESTIONNAIRE 3: In the year limited to one when the physical examination may reveal one or more of the following characteristics?

	Yes	No
8. Back Hypersensitivity	<input type="checkbox"/>	<input type="checkbox"/>
9. Pinching Hypersensitivity	<input type="checkbox"/>	<input type="checkbox"/>

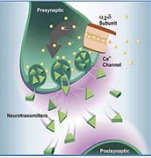
QUESTIONNAIRE 4: In the painful area, over the year has there been a remission?

	Yes	No
10. Remission	<input type="checkbox"/>	<input type="checkbox"/>

Patients points: **7/10**

Pharmacotherapy in chronic neuropathic pain

Dworkin et al in Pain, 2007



First line

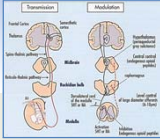
- **Antidepressants**
 - Tricyclics (*amitriptyline*)
 - SNRI's (*duloxetine*)
- **α - δ ligands**
 - Pregabalin
 - Gabapentin

Second line

- **Tramadol**
 - Severe pain
 - Acute flare-up

Third line

- **Strong opioids**
 - Very careful patient selection
- **Cannabinoids**





Algorithm for osteoarthritis of knee

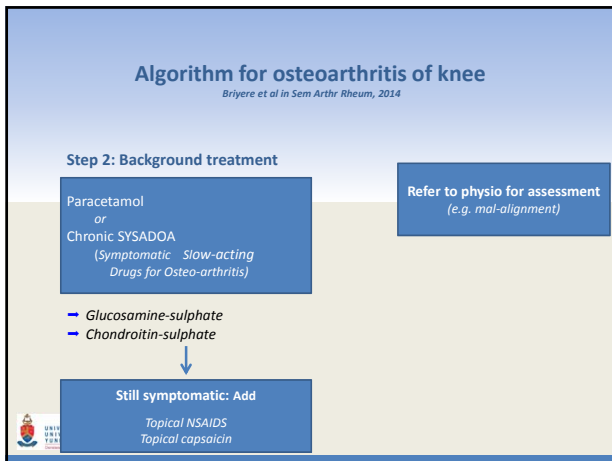
Briyere et al in Sem Arthr Rheum, 2014

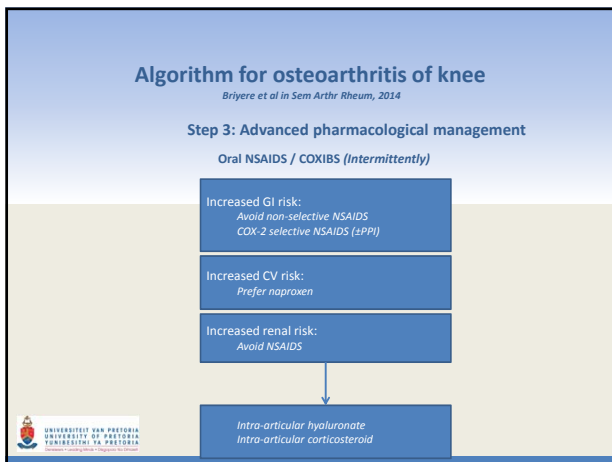
Step 1: Core set

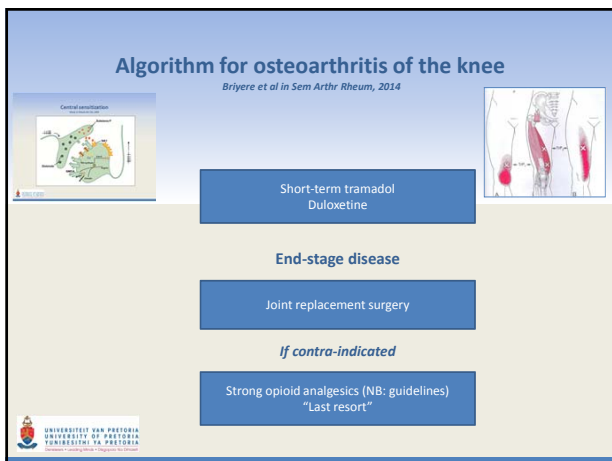
- Information / education
- Weightloss
- Exercise (aerobic, strengthening)
- Combinations of treatment












Paracetamol

*Nikles in Am J Ther, 2005
Schug in Clin Rheum, 2006
Nikles in Am J Ther, 2005
Schug in Clin Rheum, 2006*



Central effect?

- COX-2 inhibition (central prostaglandins)
- Serotonergic anti-nociceptive
- NMDA receptor (via NO)
- Cannabinoid receptors

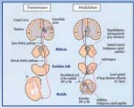
Proven synergy

- NSAIDs
- Tramadol
- Opioids

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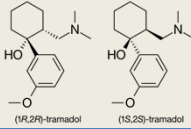
Tramadol

*Cicero et al in Drug Alcohol Dep, 1999
Schug in Anaesth Int Care, 2000
Epstein et al in Biol Psych, 2006
Rafa in J Clin Pharm, 2008
Barkin in Am J Therap, 2008
Park et al in Clin Rheum, 2012
Smith et al in Drug Eval, 2013*



- Central acting atypical opioid
- Both mono-aminergic and opioid effects
- Also NMDA antagonist activity
- Much less opioid receptor affinity than morphine

Very low abuse potential (< 1/100 000)

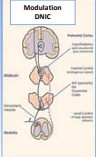


(1R,2R)-tramadol (1S,2S)-tramadol

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Tramadol

*Schug in Anaesth Int Care, 2000
Epstein et al in Biol Psych, 2006
Rafa in J Clin Pharm, 2008
Barkin in Am J Therap, 2008
Park et al in Clin Rheum, 2012
Smith et al in Drug Eval, 2013*




- Pro-drug (CYP2-D-6)
- Adverse effects (serotonergic)
 - Nausea, vomiting
 - Dizziness, headache, sweating
 - Lowers convulsion threshold
 - Serotonin syndrome (very rare)

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Analgesic combinations

Schug in Clin Rheum, 2006




Rational combinations:

- Different receptors / mechanisms
- Improved efficacy (NNT)
- Reduced individual dosages
- Less side effects
- NB in mixed pain states

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www.up.ac.za

Serotonin syndrome

*Boyer et al in New Eng J Med, 2005
Bockley et al in BMJ, 2014
www.drugs.com (±1000 drugs)*




Clinical diagnosis

- Neuromuscular:
 - Tremor, shivering
 - Hyper-reflexia, ankle clonus, ocular clonus
- Autonomic:
 - Tachycardia, mydriasis
 - Sweating, hyperthermia
- Mental:
 - Anxious, agitation
 - Confusion, delirium

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High potency opioids in chronic pain

*Evans in Best Practice, 2000
Russell in Pain Medicine, 2002
Niesch et al in Cochrane Rev, 2009
Noble et al in Cochrane Rev, 2010*




Short term use for acute pain
End-of-life pain
Chronic non-cancer pain – controversial

- Morphine sulphate
- Fentanyl
- Oxycodone, etc



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SA Guidelines for long term high potency opioid therapy in chronic non-cancer pain
Raff et al in SAMJ, 2014 (Suppl)




“... appropriate and very careful patient selection and follow-up is paramount ...”

- Opioid risk assessment
- Psycho-social assessment

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Adverse effects of opioid therapy
Raff et al in SAMJ, 2014



- Respiratory depression
- Nausea, vomiting
- Constipation
- Bladder dysfunction
- Pruritus
- Tolerance / dependence / addiction
- Endocrinological e.g. ↓ testosterone and libido
- Opioid induced hyperalgesia

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Chronic widespread pain
*Gran In Res Clin Rheum, 2003
Yunus In Best Pract Rheum, 2007*




- ±10-12% of general population
- Mostly musculo-skeletal
- Mostly a spectrum of disorders
 - Psychiatric disorders
 - Rheumatic disorders
 - Pain disorders
 - Sleep disorders
- Fibromyalgia in 30-40% of patients with CWP

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Other causes of chronic widespread pain


*Daoud et al in Curr Pain and Headache Rep, 2002
Gerwin in J of Musc Skel Pain, 2004*



Psychiatric disorders <ul style="list-style-type: none"> Mood disorders Somatoform pain disorders Unresolved emotional issues (<i>chronic anger</i>) 	Drugs <ul style="list-style-type: none"> Opioid induced hyperalgesia (including OTC's) Statins ARV's Antipsychotics
Spondyloarthritis <ul style="list-style-type: none"> Ankylosing spondylitis Reactive arthritis Psoriatic arthritis, etc. 	Neoplastic conditions <ul style="list-style-type: none"> Myeloma Metastatic breast cancer etc.
Sleep disorders <ul style="list-style-type: none"> Primary insomnia Obstructive sleep apnoea Restless legs syndrome 	Hormonal / Metabolic <ul style="list-style-type: none"> Hypothyroidism Hyperparathyroidism Type 2 diabetes mellitus Iron deficiency Vit D deficiency
Chronic fatigue syndrome	Infections <ul style="list-style-type: none"> HIV Tuberculosis "Brucellosis"

Statin-induced myalgia

*Thompson et al in JAMA, 2003
Joy et al in Ann Int Med, 2009*




- Up to 10% of patients on statins (rhabdomyolysis rare)
- Often long lag period
- Often generalized myalgia
(More severe in hip- and shoulder girdles)
- Intensity varies
- Risk factors
 - Family history
 - Physically very active
 - Females
 - Alcohol
 - Low BMI
 - Grapefruit

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Sesheko, Lesame, Gonye, Dreyer, de Vries

1990 ACR classification criteria for FMS

Woolfe et al in Arthr Rheum, 1990



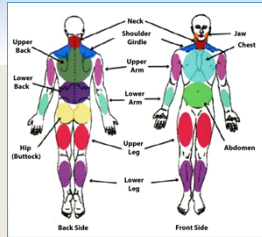
- Widespread musculoskeletal pain > 3 months in all 4 quadrants
- ≥ 11/18 painful tender points with digital pressure of 4kg/cm²

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Sesheko, Lesame, Gonye, Dreyer, de Vries

2010 ACR diagnostic criteria for FMS

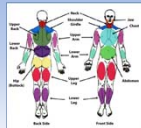
Wolfe et al in Arth Care Res, 2010

- Widespread Pain Index (WPI)
 - 19 body areas
- Symptom Severity Scale (SS)
 - Fatigue: 0-3
 - Sleep: 0-3
 - Cognitive: 0-3
 - Somatic symptoms: 0-3
- Diagnostic
 - WPI ≥ 7 SS ≥ 5
 - WPI 3-6 SS ≥ 9
 - At least 3 months



Canadian guidelines for diagnosis and management of FMS

Canadian Guidelines for FMS in Rheum Arthr, 2013
Fitzcharles et al in Pain Res Manag, 2013



Recognized as a valid pain syndrome based on recent neurophysiological evidence

- Paradigm shift in diagnosis:
 - Diagnose and manage most "concentrated" in primary care
 - Do not "over-investigate"
- Not "all-or-nothing" phenomenon ("**fibromyalgia-ness**")

Emphasis on non-pharmacological strategies



Diagnosis of FMS

Clauw in Am J of Med, 2009
Canadian Guidelines for FMS in Rheum Arthr, 2013
Clauw in JAMA, 2014



- Physical examination ("**mandatory**")
 - Exclude other causes of widespread MSK pain
 - Detect peripheral pain generators
 - NB: Soft tissue pressure tenderness**

- Blood tests:

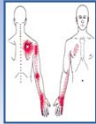
"Excessive testing contributes to uncertainty and fear and worsens prognoses"

 - FBC/ESR
 - CRP
 - TSH/T4
 - Creatinekinase (CK)
 - 25-OH-D
 - Calcium



Peripheral pain generators in FMS

*Borg-Stein J in Rheum Dis Clin N Am, 2002
 Meyer in Curr Pain Headache Rep, 2002
 Bennett in Rheum Dis Clin North Am, 2002
 Ablin et al in Joint Bone Spine, 2008
 Clauw in J Clin Psych, 2008
 Giamberardino in IASP Clin Updates, 2008
 Gerwin in Phys Med Rehab Clin N Am, 2014*




- Myofascial trigger points
- Osteo-arthritis
- Endometriosis
- Disc herniation
- Headaches
- Tendonitis
- Surgery

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Treatment of FMS Non-Medication

*Goldenberg in JAMA, 2004
 Pooks in Curr Opin Rheum, 2007
 Clauw in J of Clin Rheum, 2007*




<h4>Non-pharmacological</h4> <p>Strong evidence</p> <ul style="list-style-type: none"> ▪ Cardiovascular exercise ▪ Patient education ▪ Cognitive behavioral therapy ▪ Multimodal approach 	<h4>Pharmacological</h4> <p>Modest evidence</p> <ul style="list-style-type: none"> ▪ Pregabalin ▪ Duloxetine } FDA approved ▪ Amitriptyline ▪ Cyclobenzaprine ▪ Tramadol ± paracetamol
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Cannabinoids for treatment of chronic non-cancer pain; a systematic review of randomized trials

Lynch et al in British J of Clin Pharm, 2012



Themed Issue
Endocannabinoids
Edited by Cherry Wainwright

20 recent good quality randomized trials:

- Cannabisoids are modestly effective and a safe treatment option for chronic non-cancer (predominantly neuropathic) pain.
- Smoked cannabis effective in HIV-neuropathy
- Some evidence in FM and RA
- Evidence base is growing
- Need more long-term studies

Read today!

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