CEDR
CERCLE
D'ETUDE DE LA DOULEUR
EN RHUMATOLOGIE
2010

Limoges 2010 recommendations on the use of opioids in chronic noncancer pain

An educational program for French rheumatologists

What is the CEDR? Where is Limoges?

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Background (1)

Opioids in France: a long way for physicians

- Restricted laws: specific prescription forms until 1997
- Limited duration length for opioids: 28 days
- Indications restricted to cancer pain except for morphine, until 2009= fentanyl, 2010= oxycodone
- Under-utilisation of opioids for many years: France was at the 17th rank in 1999 in Europe for morphine consumption per inhabitant
- Pain is the first symptom in rheumatology but opioids are rarely prescribed (less than 1% of analgesic drugs prescribed)
- Limoges 1999: the first French recommendations in osteo-articular conditions.

Recommendations for the optimal use of morphine in chronic rheumatic noncancer pain.

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Background (2)

Opioids in France: a long way for the patients

- Fear of tolerance
- Fear of masking the symptoms: is pain a helpful symptom?
- Opioid use is associated to cancer pain

Perrot S, Bannwarth B, Bertin P, Javier RM, Glowinski J, Le Bars M, Treves R. Use of morphine in nonmalignant joint pain: the Limoges recommendations. TheFrench Society for Rheumatology. Rev Rhum Engl Ed. 1999;66(11):571-6.

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GPs prescriptions in France in 2002

- Analgesics = 18% of GPs prescriptions
- Level 1 and NSAIDs = 68% of analgesics.
- Level 3 analgesics (opioids) = 3% of analgesics.
- Anti-convulsants, antidepressants and level 3: less than 0,5 % of patients

THALES : étude n° 8112/MSS/25-04-2003 réalisée pour le COEGD à le demande de SANESCO

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Rheumatologists' prescriptions in 2002

- NSAIDs and level 2 analgesics: 73% of total prescriptions
- An average of 1.5 million of patients treated for pain by rheumatologists per year in France:
  - 87% are prescribed NSAIDs
  - 50% precribed analgesics step 2
  - 27% muscle relaxants
  - less than 1% are prescribed step 3 analgesics

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WHO ladder and musculoskelettal pain: still relevant?

WHO ladder is not dedicated to noncancer pain,

It is used by extrapolation.

It was useful when provided to improve cancer pain management

- Numerous musculoskelettal pain conditions, different mechanisms and clinical symptoms:
  - One drug is not enough
  - WHO ladder may lead to misusage and mistakes (ex opioids in fibromyalgia)
  - NSAIDs are more powerful in many rheumatic conditions than opioids

- Other conditions :
  - Neuropathic pain

WHO ladder should be modified and new classifications developed to improve pain management

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New classifications… (1)
D. Lussier et P. Beaulieu
IASP Press, Pharmacology of Pain, 2010

Anti-nociceptive analgesics

- Non opioids :
  - Paracetamol
  - NSAIDs
- Opioids
- Cannabinoids

Anti-hyperalgesics :

- NMDA Antagonists
- Anticonvulsants : Gabapentine, prégabaline, Lamotrigine
- Nefopam
- Coxibs

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New classifications…(2)
D. Lussier et P. Beaulieu
IASP Press, Pharmacology of Pain, 2010

Modulators of inhibiting and excitating descending controls

Tricyclic Antidepressants

SNRIs

Modulateurs of transmission and peripheral sensitization :

Local anesthetics

Carbamazepin, Oxcarbazepin, Topiramate

Capsaïcin

Mixed* : antinociceptive *analgesics and descending inhibitor or excitatory inhibiting controls modulators

Tramadol

Tapentadol

***Others* :**

Calcitonin

Bisphosphonates

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A first project for rheumatologists and musculoskeletal pain: Limoges 1999 Recommendations

- In 1999: very few papers on opioids and rheumatic pain
- WHO ladder not relevant
- CEDR was established in 1997: french rheumatic society and french pain society
- Recommendations on opioids in chronic noncancer pain:
  - 10 experts
    - Rheumatologists
    - Pain specialists
    - Pharmacologists
    - Methodologists
- Expert analyses and recommendations: 16 recommendations 1999

Since pain is a ubuquitous symptom, one should develop links between pain societies and specific societies

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Since 1999

- Limoges' recommendations have been widely diffused and well accepted by French rheumatologists, in hospital and private practice
- It is used as a reference in rheumatological practice
  - Because it is adapted to french system: patients, physicians, rheumatology…
  - Adapted to indications,

National recommendations may help the diffusion of better clinical practice since it is more appropriate to the local specifities than international guidelines.

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Changes since 1999

- Many papers on opioids and rheumatic pain
  - Better level of evidence in opioid use in noncancer pain
- Several new opioid substances marketed and approved in Europe and in France: fentanyl, oxycodone, sophidone…
- Limitation in the use of Coxibs and NSAIDs

Need for update and new recommendations

Les Recommandations du CEDR

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2010

Limoges 2010 recommendations on the use of opioids in chronic noncancer pain

An educational programme for french rheumatologists

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Limoges recommendations 2010: 5 steps

1. Opinion survey of French rheumatologists on opioids
2. Define specific issues to address in new recommendations
3. Develop recommendations as for the first version:
    1. Expert panel
    2. Literature analysis and scoring
    3. First set of recommendations
    4. Delphi method
    5. Last round and final recommendations
4. Diffusion of recommendations
5. Impact of recommendations

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Limoges 2010 - Préalable

1.	Il existe maintenant diffˇrents opio•des forts disponibles en rhumatologie, ayant fait lÕobjet dÕˇtudes cliniques de bonne qualitˇ. Dans ce contexte, de nouvelles recommandations basˇes sur les preuves et sur lÕavis dÕexperts ontˇtˇ dˇvelopp ˇes pour aider les cliniciens ˆ utiliser les opio•des forts dans les douleurs ostˇo-articulaires.	Grade A
2.	Les objectifs dÕun traitement par opio•de fort pour les douleurs rhumatologiques sont de diminuer la douleur et de rˇactiver la fonction de patients non amˇliorˇs par les autres traitements mˇdicamenteux et non mˇdicamenteux bien menˇs.	Grade D
3.	LÕintroduction dÕun opio•de fort nˇcessite une dˇmarche diagnostique complˌte, en cas de doute, il sera lˇgitime de solliciter un avis auprˌs dÕune structure spˇcialisˇe de prise en charge de la douleur.	Grade D.
4.	Il nÕy a pas de recommandation pour utiliser un morphinique plut™t quÕun autre. Nˇanmoins la forme per os est privilˇgiˇe en premiˌre intention, ainsi que les formes ˆ libˇration prolongˇe.	Grade C.

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An example of the recommendations concerning OA: literature analysis

- 9 valid studies, good methodological score (Jadad ≥ 4)
- Drug tested :
  - Transdermal Fentanyl
  - Oxycodone
  - Oxymorphone
  - Morphine Sulfate
  - Tapentadol
- Conditions tested:
  - Lower limb OA
  - OA without more precision
  - Patients on surgery waiting list

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OA (1)

Auteur Année	Indication	Traitement	Schéma étude	Nombre de patients	Posologie	Durée	Critère douleur	Effet antalgique	Score de Jadad
Caldwell 2002	Arthrose genou ou hanche	1. Sulphate de morphine LP (une prise par jour) 2. Placebo	ECR DA Double masquage	295 patients	30 mg/j le matin ou le soir ou 15 mg (2 fois par j) ou placebo	4 semaines	VAS (douleur Womac)	Effet taille estimé à 0,35 |0,02-0,67] sur composante douleur du Womac entre sulphate de morphine 30 mg le matin et placebo	5
Cadwell 1999	Arthrose	1.Oxycodone LP (2 fois par jour) 2.Oxycodone + acétaminophène 4 fois par jour 3.Placebo	ECR DA Essai de sevrage	Phase de titration : 167 Phase double aveugle 107 pts	20 à 60 mg/j	Ttitration : 30 jours (oxycodone 5 mg 4 fois par jour) Double aveugle : 30 jours	Intensité de douleur (0 à 3)	La douleur a augmenté dans les 3 groupes après la phase de titration, mais dans moins dans les 2 groupes oxycodone par rapport au placebo (p < 0,0001)	5
Hartrick 2009	Patients en attente de prothèse articulaire	1.Tapentadol libération immédiate (TIL) 2.Oxycodone (OXYC) 3. Placebo	ECR DA	666 patients 659 patients analysés	TIL50mg TIL75mg OXYC (IL) 10mg PLa	10 jours	Douleur sur échelle numérique ne 11 points (matin et soir durant toute l'étude)	Différence SPID 5 jours TIL 50mg 101,2 p < 0,001 TIL 75 mg 97,5 p < 0,001 OXY 10 mg 111,9 p < 0,001	4

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OA (2)

Markenson **2005**	Arthrose	1.Oxycodone (OXYC) 2.Placebo (PLA)	ECR DA	109 patients randomisés 107 patients analysés	OXYC : 12 mg tous les 12 heures PLA : toutes les 12 heures. Adaptation des doses toutes les 24 heures.	3 mois	Composante douleur du BPI (Brief Pain Inventory)	ES 0,41 |0,03-0,79]	5
Roth 2000	Arthrose (pas critère ACR)	Oxycodone 10 mg (OXYC 10 mg) Oxycodone 20 mg (OXYC 20) Placebo (PLA)	ECR DA	133 patients 45 PLA	OXYC 10 mg) 2 fois/j OXYC 20 mg 2 fois/j PLA 2 fois/j	2 semaines	Intensité douleur sur échelle numérique en 4 points.	Diminution statistiquement significative entre les groupes oxymorphone et le placebo sur la douleur.	4
Zautra 2005	Arthrose	Oxycodone (OXYC 10) Placebo (PLA)	ECR DA	107 patients randomisés 104 patients analysés	OXYC 20 mg/j	2 semaines	Intensité douloureuse sur EN en 11 points. Nombre de patients s'améliorant de plus de 2 points.	Répondeurs : OXYC 10 : 40 % (22/55) PLA : 10 % (5/49) p < 0,001)	4

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OA (3)

Kivitz 2006	Arthrose de hanche et de genou Patient recevant déjà des opioïdes ou une traitement suboptimal avec AINS et paracétamol.	1.Oxymorphone libération prolongée (OXYM) 3 doses 2. Placebo (PLA)	ECR DA	370 patients randomisés 198 patients ont fini l'étude.	1. OXYM (ER) 10 mg x 2 j semaine 1 et 2 2. OXYM (ER) 20 mg x 2 j semaine 1 et 40 mg x 2 j semaine 2 3. OXYM (ER) 20 mg x 2 j semaine 1 et 50 mg x 2 j semaine 2	2 semaines	Intensité douloureuse sur VAS Womac	La diminution de l'intensité de douleur entre inclusion et le fin était de OXYM 10mg : - 21mm (Diff avec PLA NS) OXYM 40 mg : -28 mg (diff avec PLA 0,012) OXYM /50 mg -29 mg (diff avec PLA 0,006) PLA – 17 mm	4
Matsumoto 2005	Arthrose genou ou hanche	1.Oxymorphone libération prolongée LP 2 doses (OXYM) 2. Placebo (PLA)	ECR DA	370 patients randomisés	OXYM : 40 mg/j ou 20 mg/j ou placebo	4 semaines	Changement douleur sur EVA de 0 à 100 la semaine 3	Différence avec placebo du changement des intensités douloureuses entre inclusion et Semaine 3 OXYM 9 p < 0,0015	4
Langford 2006	Arthrose de hanche et de genou	1.Fentanyl transdermique (FEN) 2.Placebo (PLA)	ECR DA	399 patients randomisés	Patch cutané libérant 25µg/h de fentanyl ou placebo identique tous les 3 jours	6 semaines	Aire sous la courbe douleur WOMAC	Aire sous la courbe FEN – 20 (ESM 1,4) PLA -14,6 (ESM 1.4) Effet taille estimé 0.30 [0,11-0,50]	5

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Recommendations on OA - In rheumatological literature: EULAR (2003): no opioids?

- Jordan KM, Arden NK, Doherty M, et al; EULAR Recommendations 2003: an evidence based approach to the management of kneeosteoarthritis: Report of a Task Force of the Standing Committee forInternational Clinical Studies Including Therapeutic Trials (ESCISIT). Ann Rheum Dis. **2003;**62:1145-55. .

Table 4 Summary of the effect size versus placebo, quality scores, and number of studies identified

Intervention	Number of studies	Positive to placebo	Quality score (range)	Quality score (median)	Effect size versus placebo
Acetaminophen/paracetamol	5	1/1	17–26	20	
Opioid analgesic/other	6	2/3	11–24	19	
NSAID					
Conventional NSAID	130	27/31	5–27	17	0.47, 0.50, 0.76, 0.96,
Coxibs	5	4/4	18–25	23	0.50
Antidepressant	1	1/0	16	–	
Topical NSAID	9	5/7	18–26	22	−0.05, 0.16, 0.31, 0.91, 1.03
Topical capsaicin	2	2/2	21, 26		0.41, 0.56
Sex hormones	2	0/1	15, 20		
SYSADOA					
Glucosamine	8	4/6	14–27	24	0.43, 0.53, 1.02
Chondroitin	5	5/5	20–27	24	1.23, 1.37, 1.44, 1.50
Diacerein	1	1/1	22	22	
ASU	3	3/3	21–24	23	0.32, 1.72
Nutrients	2	2/2	4,25	–	0.65

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Recommendations on OA - In rheumatological literature: OARSI (2008): opioids only in specific circumstances

« The use of weak opioids and narcotic analgesics can be considered for the treatment of refractory pain in patients with hip or knee OA, where other pharmacological agents have been ineffective, or are contraindicated. Stronger opioids should only be used for the management of severe pain in exceptional circumstances. Non-pharmacological therapies should be continued in such patients and surgical treatments should be considered. »

Zhang W, Moskowitz RW, Nuki G, et al. OARSI recommendations for the management of hip and knee osteoarthritis, Part II: OARSI evidence-based,expert consensus guidelines. *Osteoarthritis Cartilage*. 2008;16(2):137-162.

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In pain literature:

Clinicians may consider a trial of chronic opioid therapy (COT) as an option if chronic noncancer pain is moderate or severe, pain is having an adverse impact on function or quality of life, and potential therapeutic benefits outweigh or are likely to outweigh potential harms (strong recommendation, low-quality evidence).

Clinicians and patients should regard initial treatment with opioids as a therapeutic trial to determine whether COT is appropriate (strong recommendation, low-quality evidence).

DIRE

D.I.R.E. Score: Patient Selection for Chronic Opioid Analgesia
For each factor, rate the patient's score from 1-3 based on the explanations in the right hand column

Score	Factor	Explanation
	Diagnosis	1 = Benign chronic condition with minimal objective findings or no definite medical diagnosis. Examples: fibromyalgia, migraine headaches, non-specific back pain. 2 = Slowly progressive condition concordant with moderate pain, or fixed condition with moderate objective findings. Examples: failed back surgery syndrome, back pain with moderate degenerative changes, neuropathic pain. 3 = Advanced condition concordant with severe pain with objective findings. Examples: severe ischemic vascular disease, advanced neuropathy, severe spinal stenosis.
	Intractability	1 = Few therapies have been tried and the patient takes a passive role in his/her pain management process. 2 = Most customary treatments have been tried but the patient is not fully engaged in the pain management process, or barriers prevent (insurance, transportation, medical illness). 3 = Patient fully engaged in a spectrum of appropriate treatments but with inadequate response.
	Risk	(R= Total of P+C+R+S below)
	Psychological:	1 = Serious personality dysfunction or mental illness interfering with care. Example: personality disorder, severe affective disorder, significant personality issues. 2 = Personality or mental health interferes moderately. Example: depression or anxiety disorder. 3 = Good communication with clinic. No significant personality dysfunction or mental illness.
	Chemical Health:	1 = Active or very recent use of illicit drugs, excessive alcohol, or prescription drug abuse. 2 = Chemical coper (uses medications to cope with stress) or history of CD in remission. 3 = No CD history. Not drug-focused or chemically reliant.
	Reliability:	1 = History of numerous problems: medication misuse, missed appointments, rarely follows through. 2 = Occasional difficulties with compliance, but generally reliable. 3 = Highly reliable patient with meds, appointments & treatment.
	Social Support:	1 = Life in chaos. Little family support and few close relationships. Loss of most normal life roles. 2 = Reduction in some relationships and life roles. 3 = Supportive family/close relationships. Involved in work or school and no social isolation.
	Efficacy score	1 = Poor function or minimal pain relief despite moderate to high doses. 2 = Moderate benefit with function improved in a number of ways (or insufficient info- hasn't tried opioid yet or very low doses or too short of a trial). 3 = Good improvement in pain and function and quality of life with stable doses over time.

_____Total score = D + I + R + E

Score 7-13: Not a suitable candidate for long-term opioid analgesia
Score 14-21: Good candidate for long-term opioid analgesia
Reproduced with permission from Miles Belgrade[4]

Chou R, Fanciullo G, Fine PG, et al; American Pain Society–American Academy of Pain Medicine Opioids Guidelines Panel. Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. J Pain. 2009; 10(2):113-129.

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LIMOGES 2010 recommendations in OA

-Strong opioids can be prescribed –after failure or lack of efficacy of usually recommended analgesic treatments –or if there is a contra-indication for surgery, –or when waiting for surgery	Grade A
-In lower limb OA, it is preferable to use long term opioids allowing pain and function improvement.	Expert consensus

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Limoges recommendations 2010: for different conditions, different populations

1. Conditions:
    1. Fibromyalgia
    2. Inflammatory joint disorders: rheumatoid arthritis, spondylarthropathies
    3. Low back pain
    4. CRPS1
    5. Osteoporosis
    6. Gout, chondrocalcinosis
2. Populations:
    1. Elderly patients
    2. Pregnancy
    3. Paediatry
    4. Renal and hepatic failure
3. Specific use in rheumatology: go low, go slow
4. Strategies and analgesic combinations

Consider improvement of both pain and function in musculoskeletal pain

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Limoges recommendations 2010: 5 steps

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Two more steps to develop

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Conclusions

Recommendations and guidelines at a national level may help to

-Improve knowledge in drug benefit

-Reduce reluctance for new therapeutic options

-reduce the gap between pain management and management of underlying conditions

-improve the popularity of an unknown european city