IL TRATTAMENTO DEL DOLORE NEUROPATICO:
GLI OPIPIOIDI

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Servizio di Terapia del dolore, Tossicologia d’urgenza e Anestesia
Seconda Università di Napoli
Are opioids effective in relieving neuropathic pain?

Dellemijn P.

Source
Department of Neurology and Clinical Neurophysiology, Saint Joseph Hospital, Veldhoven, The Netherlands.

Abstract
The purpose of this review is to identify important issues and to review the data that underlie the controversial effectiveness of opioids in relieving neuropathic pain. This controversy seems related to the use of multiple definitions of neuropathic pain together with its distinct mechanisms in both experimental animal models and human neuropathic pain syndromes, methodological shortcomings in available randomized controlled clinical trials, different methods of pain assessment, the inappropriate use of terms like efficacy and responsiveness, differential responses in spontaneous versus evoked pains, interindividual differences to specific opioids and opioid doses, and duration of follow-up. New randomized controlled clinical trials with opioids in neuropathic pain are still needed. These studies should include larger patient samples with rigorously defined homogeneous neuropathic pain syndromes. Active placebo's mimicking side-effects should be included in the double-blind design, and control of unmasking should be performed. Individual titration of the opioid dose and active management of side-effects in long-term follow-up studies need to measure both pain relief and quality of life.

Lack of analgesic effect of opioids on neuropathic and idiopathic forms of pain.

Arnér S, Meyerson BA.

Source
Department of Anaesthesia, Karolinska Hospital, Stockholm, Sweden.

Abstract
The aim of the present study has been to assess the responsiveness of various types of chronic pain to opioids given i.v. and tested against placebo in a double-blind, randomized fashion. Pain classified as primary nociceptive was effectively alleviated (P greater than 0.001) while neuropathic deafferentation pain was not significantly influenced by morphine or equivalent doses of other opioids. Also 'idiopathic' pain, defined as chronic pain with no or little demonstrable pathology, failed to respond. The results were not related to whether the patients were regular users of narcotic analgesics or not. The outcome of our double-blind opioid test has proved useful to justify a continued, or discontinued, use of narcotic medication in individual patients. It may also support the indication and choice of invasive stimulation procedures (spinal cord or brain). The results of the study illustrate the misconception of chronic pain as an entity and highlight the importance of recognizing different neurobiological mechanisms and differences in responsiveness to analgesic drugs as well as to non-pharmacological modes of treatment. The opioid test has thus become a valuable tool in pain analysis and helpful as a guide for further treatment.
La gestione del dolore neuropatico è in continuo cambiamento a causa dell’estrema variabilità di risposta interindividuale alle diverse molecole rispetto ai multipli tentavi di trovare un approccio terapeutico razionale e ripetibile.

Nel 2010 sono state elaborate le linee guida dalla NeuPSIG (Neuropathic Pain Special Interest Group of the International Association for the Study of Pain) sul managment farmacologico del dolore neuropatico.
Le linee guida NeuPSIG raccomandano l’utilizzo degli oppioidi nei pazienti che non hanno risposto ai farmaci di prima linea (antiepilettici, antidepressivi) (Livello A).
Vengono inoltre raccomandati come farmaci di prima linea:
- nei pazienti con dolore acuto neuropatico;
- nei pazienti con componente neuropatica del dolore oncologico;
- nelle esacerbazioni di dolore neuropatico severo;
- come accompagnamento nella tritazione di un farmaco di prima linea, qualora sia necessario un rapido sollievo.

**TABLE 1. Stepwise Pharmacological Management of Neuropathic Pain**

| Step 1 | Assess pain and establish the diagnosis of NP; if uncertain about the diagnosis, refer to a pain specialist or neurologist  
Establish and treat the cause of NP; if uncertain about availability of treatments for cause of NP, refer to appropriate specialist  
Identify relevant comorbidities (eg, cardiac, renal, or hepatic disease, depression, gait instability) that might be relieved or exacerbated by NP treatment or that might require dosage adjustment or additional monitoring of therapy  
Explain the diagnosis and treatment plan to the patient and establish realistic expectations |
|---|---|
| Step 2 | Initiate therapy for the disease causing NP, if applicable  
Initiate symptomatic treatment with one or more of the following:  
A secondary-amine TCA (nortriptyline, desipramine) or an SSNRI (duloxetine, venlafaxine)  
A calcium channel \(\alpha_{2-3}\) ligand, either gabapentin or pregabalin  
For patients with localized peripheral NP, topical lidocaine used alone or in combination with one of the other first-line therapies  
For patients with acute NP, neuropathic cancer pain, or episodic exacerbations of severe pain and when prompt pain relief during titration of a first-line medication to an efficacious dosage is required, opioid analgesics or tramadol may be used alone or in combination with 1 of the first-line therapies  
Evaluate patient for nonpharmacological treatments and initiate if appropriate |
| Step 3 | Reassess pain and health-related quality of life frequently  
If substantial pain relief (eg, average pain reduced to \(\leq 3/10\)) and tolerable adverse effects, continue treatment  
If partial pain relief (eg, average pain remains \(\geq 4/10\)) after an adequate trial, add one of the other 4 first-line medications  
If no or inadequate pain relief (eg, \(<30\%\) reduction) at target dosage after an adequate trial, switch to an alternative first-line medication |
| Step 4 | If trials of first-line medications alone and in combination fail, consider second- and third-line medications or referral to a pain specialist or multidisciplinary pain center |

NP = neuropathic pain; SSNRI = selective serotonin norepinephrine reuptake inhibitor; TCA = tricyclic antidepressant.
From Pain,\textsuperscript{12} with permission of the International Association for the Study of Pain® (IASP®). This table cannot be reproduced for any other purpose without permission.
L’obiettivo della terapia oppioide nel dolore neuropatico è di fornire una adeguata analgesia, mantenere o migliorare la qualità della vita con accettabili eventi avversi. Diversi sono i farmaci oppioidi esistenti in commercio ed ognuno di essi ha peculiarità tale da giustificarne l’utilizzo in alcune forme di dolore neuropatico.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Equianalgesic Potency*</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Oral</td>
<td>Parenteral</td>
</tr>
<tr>
<td>Morphine</td>
<td>30 mg</td>
<td>10 mg</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>7.5 mg</td>
<td>1.5 mg</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>20 mg</td>
<td>–</td>
</tr>
<tr>
<td>Methadone</td>
<td>5 mg</td>
<td>**</td>
</tr>
<tr>
<td>Levorphanol</td>
<td>4 mg</td>
<td>2 mg</td>
</tr>
<tr>
<td>Meperidine</td>
<td>300 mg</td>
<td>75 mg</td>
</tr>
<tr>
<td>Fentanyl***</td>
<td>–</td>
<td>100 mcg</td>
</tr>
<tr>
<td>Codeine</td>
<td>200 mg</td>
<td>130 mg</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>30 mg</td>
<td>–</td>
</tr>
<tr>
<td>Oxymorphone</td>
<td>10 mg</td>
<td>1 mg</td>
</tr>
<tr>
<td>Nalbuphine</td>
<td>–</td>
<td>10 mg</td>
</tr>
<tr>
<td>Butorphanol</td>
<td>–</td>
<td>2 mg</td>
</tr>
<tr>
<td>Pentazocine</td>
<td>50 mg</td>
<td>30 mg</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>–</td>
<td>0.4 mg</td>
</tr>
<tr>
<td>Propoxyphene</td>
<td>180-240 mg</td>
<td>–</td>
</tr>
</tbody>
</table>

(Derby, 1998 [R]; American Pain Society, 2003 [Low Quality Evidence]; Krantz, 2009 [Low Quality Evidence])
Dal momento che il dosaggio ottimale di un oppioide varia da paziente a paziente, ogni soggetto dovrebbe essere sottoposto a tritazione, usando dosaggio di provata efficacia nei diversi trail di dolore neuropatico e prediligendo le formulazione a rilascio prolungato.
• Azione agonista sui recettori degli oppioidi con selettività specifica sui μ

• Potenziamento dei meccanismi fisiologici dell’analgesia mediante la ricaptazione della noradrenalina e l’incremento delle concentrazioni della serotonina a livello centrale
TRAMADOLO A LENTO RILASCIO

Innovazione tecnologica
- Sollievo rapido e prolungato per 24 h\textsuperscript{[2]}

\begin{itemize}
  \item \textbf{Rivestimento esterno a rilascio rapido}
    \begin{itemize}
      \item concentrazioni plasmatiche efficaci entro 2 h dalla somministrazione\textsuperscript{[3,5,6]}
    \end{itemize}
  \item \textbf{Rivestimento interno a rilascio controllato}
    \begin{itemize}
      \item efficacia per 24 h\textsuperscript{[2]}
    \end{itemize}
\end{itemize}

- Curva farmacocinetica ottimale per un prodotto in monosomministrazione

[Graph showing comparison of tramadol plasma concentrations]

Confronto delle concentrazioni plasmatiche medie di tramadololo dopo somministrazione singola di formulazioni di tramadololo a rilascio prolungato.

(Confronto diretto e confronto con dati di letteratura)\textsuperscript{[3,6]}

\textsuperscript{[2]} Studio clinico con placca dermo-retinale.
\textsuperscript{[3,5,6]} Studio clinico con placca dermo-retinale.
**Analysis 1.1. Comparison I Tramadol versus placebo, Outcome I Achievement of 50% pain relief.**

Review: Tramadol for neuropathic pain

Comparison: I Tramadol versus placebo

Outcome: I Achievement of 50% pain relief

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Tramadol n/N</th>
<th>Placebo n/N</th>
<th>Risk Ratio M-H/Fixed 95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H/Fixed 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bourau 2003</td>
<td>41/63</td>
<td>31/65</td>
<td>1.37 [1.04, 1.81]</td>
<td>54.1 %</td>
<td>1.37 [1.04, 1.81]</td>
</tr>
<tr>
<td>Hartill 1998</td>
<td>43/63</td>
<td>23/64</td>
<td>1.90 [1.31, 2.74]</td>
<td>40.5 %</td>
<td>1.90 [1.31, 2.74]</td>
</tr>
<tr>
<td>Sindrup 1999b</td>
<td>11/34</td>
<td>3/33</td>
<td>1.35 [1.09, 1.62]</td>
<td>5.4 %</td>
<td>1.35 [1.09, 1.62]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>150</strong></td>
<td><strong>152</strong></td>
<td><strong>1.70 [1.36, 2.14]</strong></td>
<td>100.0 %</td>
<td>1.70 [1.36, 2.14]</td>
</tr>
</tbody>
</table>

Total events: 95 (Tramadol), 57 (Placebo)

Heterogeneity: CHi² = 4.21, df = 2 (P = 0.12); I² = 53%

Test for overall effect: Z = 4.62 (P < 0.00001)

Despite these concerns, this review has shown a definite beneficial effect of tramadol over placebo in the treatment of neuropathic pain.
La buprenorfina è un oppioide semisintetico derivato dalla tebaina, agonista del recettore mu e antagonista del recettore K, legandosi ad entrambi i recettori con elevata affinità.

Sono stati ampiamente superati i dati iniziali sul possibile effetto tetto analgesico della buprenorfina, sebbene essa mostri ancora un effetto tetto sulla depressione respiratoria, che viene di contro sfruttato come caratteristica positiva.

Tali caratteristiche permettono una prolungata durata d’azione e un pronunciato effetto antiiperalgesico (addotto teoricamente alle proprietà K antagonista).

Di particolare importanza nella gestione del dolore neuropatico cronico è stata l’introduzione in commercio della formulazione transdermica.
Combination therapy with transdermal buprenorphine and pregabalin for chronic low back pain

Vincenzo Pota, Manlio Barbarisi, Pasquale Sansone, Marco Moraci, Maria Caterina Pace, Maria Beatrice Passavanti & Caterina Aurilio

Appendix 3
DNA Neuropathic Pain Diagnostic Questionnaire
Please complete this questionnaire by ticking one answer for each item in the list of questions below.

Screening visit (V0): n = 45
Recruitment visit (V1): n = 44
Patients received transdermal buprenorphine 35 µg/h

Week 1
V2 visit: n = 44
Week 2
V3 visit: n = 44
Week 3
V4 visit: n = 44
Patients randomized

Transdermal buprenorphine 35 µg/h + pregabalin 300 mg/day (group A; n = 22)

Week 4
V5 visit: n = 22
Week 5
V6 visit: n = 22
Week 6

Transdermal buprenorphine 35 µg/h + placebo (group B; n = 22)

Week 4
V5 visit: n = 22
Week 5
V6 visit: n = 22
Week 6
Il trattamento iniziale con buprenorfina transdermica dei 44 paziente in studio ha dimostrato un buono controllo del dolore con una riduzione della VAS del 50% ed ha determinato anche una riduzione statisticamente significativo della quantità di paracetamolo usato come rescue medication durante la prima fase dello studio da V1 to V4 (V1: 1840.9 ± 805.3 mg vs V2: 431.8 ± 340.9 mg vs V3: 568.1 ± 545.4 mg vs V4: 454.5 ± 547.1 mg; p < 0.05).
CLINICAL REPORT

Transdermal Buprenorphine for Central Neuropathic Pain: Clinical Reports

Cristiana Guetti, MD; Chiara Angeletti, MD; Franco Marinangeli, MD; Alessandra Ciccozzi, MD; Giada Baldascino, MD; Antonella Paladinini, MD; Giustino Varrassi, MD

Department of Anesthesiology and Pain Medicine, University of L’Aquila, L’Aquila, Italy
Sia l’attività agonista sui recettori µ (MOR) sia l’inibizione del reuptake della noradrenalina (NRI) contribuiscono all’analgesia.

Analgesia a “largo spettro” sul dolore nocicettivo e neuropatico*

È necessaria una minore attività sui recettori µ per uno stesso effetto analgesico (µ-sparing effect)

Migliorata tollerabilità (meno effetti collaterali rispetto agli altri oppioidi)
L’attività complementare e sinergica MOR-NRI

Riduzione della trasmissione ascendente + Potenziamento dell’inibizione discendente

References: Tzschentke TM. et al. Drugs of Today 2009, 45 (7): 483-49
Entrambi i meccanismi d’azione del tapentadolo si basano su una singola molecola che è metabolizzata tramite una 0-glucuronidazione in un metabolita inattivo.

Il tramadolo, anche esso dotato di meccanismo d’azione duplice, invece, è una mistura racemica di due enantiomeri e produce un metabolita attivo.

Mentre sia l’enantiomero(-) che l’enantiomero (+) producono analgesia tramite l’inibizione del reuptake della noradreanalina e serotonina, di contro l’effetto mu-agonista si basa principalmente sull’enantiomero(+) di O-desmetil-tramadolo, un metabolita attivo. Quindi, il contributo relativo dei due differenti meccanismi d’azione cambia nel tempo; man mano che viene metabolizzata la molecola si riduce l’effetto noradrenergico e serotoninergico e aumenta l’effetto oppioide.

Infine, il tramadolo è metabolizzato dal CYTP450, enzima polimorfico negli uomini, quindi metabolizzatori lenti non presentano una soddisfacente analgesia.
Differential contribution of opioid and noradrenergic mechanisms of tapentadol in rat models of nociceptive and neuropathic pain

Wolfgang Schröder *, Jean De Vry, Thomas M. Tzschentke, Ulrich Jahnel, Thomas Christoph
Ritardato sviluppo di tolleranza di tapentadolo rispetto a morfina in un modello di dolore neuropatico

Tapentadolo inibisce la motilità gastrointestinale in misura nettamente inferiore rispetto a morfina.
Tapentadolo PR efficace e ben tollerato in pazienti con LBP cronico precedentemente non trattati o non responsivi agli analgesici del I e II step WHO
Casistica

176 pazienti con LBP (175 valutati per l’efficacia)
- 49 senza componente neuropatica
- 126 con componente neuropatica “dubbia/certa” al PainDetect

Età media: 59.7 anni

Sesso: 111 donne e 65 maschi

BMI medio: 29.9

Intensità media basale del dolore: 7.4 NRS

Terapia analgesica pregressa:
- 87 naive da oppioidi
- 88 pre-trattati con oppioidi II step WHO
• Endpoint
  • Riduzione dell’intensità del dolore (NRS)
  • Riduzione dell’intensità dei sintomi tipici del dolore neuropatico (PainDETECT)
  • Soddisfazione del paziente (scala verbale a 5 punti)
  • Tollerabilità

• Disegno dello studio:
Significativa riduzione del dolore dopo 12 settimane di trattamento (p <0.0001):
- 3.7 nei pazienti senza componente neuropatica
- 4.0 nei pazienti con componente “dubbia/certa”
Dosi medie di tapentadolo: nei pazienti con componente neuropatica dubbia o certa (dolore misto) i dosaggi risultano tendenzialmente inferiori rispetto ai quelli dei soggetti con dolore nocicettivo puro.
Tapentadolo PR riduce sia l’intensità di tutti i sintomi tipici del dolore neuropatico (NPSI scale) che frequenza e durata delle esacerbazioni di dolore nelle 24 ore.
Miglioramento sia dell’ansia che della depressione (scala HADS)

A. Anxiety

B. Depression

Muller M. EFIC 2011
Depression, anxiety, health-related quality of life and pain in patients with chronic fibromyalgia and neuropathic pain

Lise Gormsen a,*, Raben Rosenberg b, Flemming W. Bach c, Troels S. Jensen a

a Department of Neurology, Danish Pain Research Centre, Aarhus University Hospital, Denmark
b Center for Basic Psychiatric Research, University Psychiatric Hospital in Aarhus, Risklov, Denmark
c Department of Neurology, Aalborg University Hospital, Aalborg, Denmark
Chronic pain treatment in patients with depressive disorders
• E’ un agonista oppiaceo senza proprietà antagoniste e ha un’affinità per i tre recettori oppiacei del cervello e del midollo spinale.

• Ha un’elevata biodisponibilità assoluta che arriva all’87% dopo una somministrazione orale.

• Ha una emivita di eliminazione di circa 3 ore ed è metabolizzato principalmente in norossicodone e ossimorfone.
Efficacy of oxycodone in neuropathic pain
A randomized trial in postherpetic neuralgia

C. Peter N. Watson, MD, FRCP(C); and Najib Babul, PharmD
Figure 1. Mean daily visual analog scale (VAS) and categorical scale (CAT) scores for overall pain during the final week of treatment after controlled release (CR) oxycodone and placebo.
Efficacy of Controlled-Release Oxycodone in Postherpetic Neuralgia

- Steady pain: Placebo 55, CR oxycodone 34, P=0.0001
- Brief pain: Placebo 42, CR oxycodone 22, P=0.0001
- Allodynia: Placebo 50, CR oxycodone 32, P=0.0004

N=50

Prolonged-release oxycodone enhances the effects of existing gabapentin therapy in painful diabetic neuropathy patients

Magdi Hanna, Cathy O’Brien, Margaret C. Wilson

* Pain Centre Research Unit, King’s College Hospital, Denmark Hill Campus, Bessemer Road, London SE5 9PJ, UK
* Pain Research Statistics, Barnham House, High Street, Peckham, King’s Lynn, Norfolk PE22 9EL, UK
* Mundipharma Research Limited, Cambridge Science Park, Milton Road, Cambridge CB4 0GW, UK

Received 2 February 2007; received in revised form 10 December 2007; accepted 16 December 2007

Available online 8 February 2008

Diagram:

- Patients enrolled n = 406
- Screen failures n = 68
- Patients randomized n = 338

Placebo n = 169
- Completed Study n = 128 (78%)
- Withdrawn n = 37 (22%)
- Not analyzed n = 4 (2%)
  - Adverse events n = 9 (24%)
  - Subject’s choice n = 6 (16%)
  - Administrative n = 2 (5%)
  - Lack of therapeutic effect n = 20 (54%)

OxyContin® n = 169
- Completed study n = 121 (74%)
- Withdrawn n = 42 (26%)
  - Not analyzed n = 6 (4%)
  - Adverse events n = 27 (64%)
  - Subject’s choice n = 9 (21%)
  - Administrative n = 0 (0%)
  - Lack of therapeutic effect n = 6 (14%)

* 4 placebo and 6 study drug patients were excluded from the full analysis because they lacked any diary data following randomisation.
OSSICODONE/NALOXONE A RILASCIO CONTROLLATO

• combinano l’analgesia dell’ossicodone con l’antagonismo periferico del naloxone

Efficacia provata negli anni sul dolore cronico

L’assunzione per os previene il legame periferico e pre-epatico

L’assunzione per os non antagonizza l’azione centrale dell’ossicodone

A randomised controlled trial with prolonged-release oral oxycodone and naloxone to prevent and reverse opioid-induced constipation

Winfried Meissner a, Petra Leyendecker b, Stefan Mueller-Lissner d, Joachim Nadstawek c, Michael Hopp b, Christian Ruckes b, Stefan Wirz e, Wolfgang Fleischer b, Karen Reimer b,c

Mean pain intensity (NAS score)

- Placebo (n = 50)
- Naloxone 10 mg (n = 51)
- Naloxone 20 mg (n = 51)
- Naloxone 40 mg (n = 50)

Bowel function (NAS score)

- Placebo (n = 50)
- Naloxone 10 mg (n = 51)
- Naloxone 20 mg (n = 51)
- Naloxone 40 mg (n = 50)
Il metadone è un vecchio analgesico oppioide strutturalmente simile agli alcaloidi derivati dall’oppio.
E’ un mistura racemica di S- e R- metadone che sono stati usati per anni che è stato usato per anni come potente analgesico e come terapia di mantenimento della dipendenza da oppioidi.

l’S-metadone prevene il re-uptake delle monoamine in maniera simile agli antidepressivi triciclici e ha inoltre un attività NMDA antagonista, proprietà che suggeriscono la sua specificità nella gestione del dolore neuropatico.
Methadone in the Management of Intractable Neuropathic Noncancer Pain

D. E. Moulin, D. Palma, C. Watling, V. Schulz


Table 1: Patient Characteristics

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Failed back syndrome with nerve root fibrosis</td>
<td>12</td>
</tr>
<tr>
<td>Complex regional pain syndrome (type 1)</td>
<td>9</td>
</tr>
<tr>
<td>Central pain syndrome</td>
<td>7</td>
</tr>
<tr>
<td>Peripheral neuropathies</td>
<td>6</td>
</tr>
<tr>
<td>Post-surgical pain syndrome</td>
<td>5</td>
</tr>
<tr>
<td>Post-herpetic neuralgia</td>
<td>3</td>
</tr>
<tr>
<td>Cauda equina syndrome</td>
<td>3</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>5</td>
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</tbody>
</table>

Table 3: Clinical Characteristics of Methadone Treatment (N=50)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean ± SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial target dose (mg/day)</td>
<td>50 ± 4.0</td>
</tr>
<tr>
<td>Maintenance (maximal) dose (mg/day)</td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>121.4 ± 24.1</td>
</tr>
<tr>
<td>Responders (N = 26)</td>
<td>159.8 ± 28.9</td>
</tr>
<tr>
<td>Non-responders (N = 24)</td>
<td>78.0 ± 15.4</td>
</tr>
<tr>
<td>Time to maximal dose (months)</td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>6.2 ± 1.5</td>
</tr>
<tr>
<td>Responders (N = 26)</td>
<td>8.3 ± 1.6</td>
</tr>
<tr>
<td>Non-responders (N = 24)</td>
<td>3.7 ± 1.2</td>
</tr>
<tr>
<td>Duration of treatment (months)</td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>13.9 ± 2.6</td>
</tr>
<tr>
<td>Responders (N = 26)</td>
<td>21.3 ± 2.9</td>
</tr>
<tr>
<td>Non-responders (N = 24)</td>
<td>5.5 ± 1.7</td>
</tr>
<tr>
<td>Pain relief (Responders N = 26)</td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>4</td>
</tr>
<tr>
<td>Moderate</td>
<td>15</td>
</tr>
<tr>
<td>Marked</td>
<td>6</td>
</tr>
<tr>
<td>Complete</td>
<td>1</td>
</tr>
</tbody>
</table>
QTc Interval Screening in Methadone Treatment

Mori J. Krantz, MD; Judith Martin, MD; Barry Stimmel, MD; Davendra Mehta, MD; and Mark C.P. Haigney, MD

**Description:** An independent panel developed cardiac safety recommendations for physicians prescribing methadone.

**Methods:** Expert panel members reviewed and discussed the following sources regarding methadone: pertinent English-language literature identified from MEDLINE and EMBASE searches (1966 to June 2008), national substance abuse guidelines from the United States and other countries, information from regulatory authorities, and physician awareness of adverse cardiac effects.

**Recommendation 1 (Disclosure):** Clinicians should inform patients of arrhythmia risk when they prescribe methadone.

**Recommendation 2 (Clinical History):** Clinicians should ask patients about any history of structural heart disease, arrhythmia, and syncope.

**Recommendation 3 (Screening):** Obtain a pretreatment electrocardiogram for all patients to measure the QTc interval and a follow-up electrocardiogram within 30 days and annually. Additional electrocardiography is recommended if the methadone dosage exceeds 100 mg/d or if patients have unexplained syncope or seizures.

**Recommendation 4 (Risk Stratification):** If the QTc interval is greater than 450 ms but less than 500 ms, discuss the potential risks and benefits with patients and monitor them more frequently. If the QTc interval exceeds 500 ms, consider discontinuing or reducing the methadone dose; eliminating contributing factors, such as drugs that promote hypokalemia; or using an alternative therapy.

**Recommendation 5 (Drug Interactions):** Clinicians should be aware of interactions between methadone and other drugs that possess QT interval–prolonging properties or slow the elimination of methadone.

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Opioids in chronic non-cancer pain, indications and controversies

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