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THERAPEUTICS INITIATIVE Evidence Based Drug Therapy



# Treatment of Pain in the Older Patient

Providing effective analgesia to a patient may seem routine, yet it is one of medicine's most satisfying achievements. Serious pain eventually afflicts virtually everyone, and is particularly prevalent in the elderly. Currently available analgesics control acute pain promptly and safely in the vast majority of patients. Unfortunately chronic pain typically presents a much more difficult challenge. **In a recent systematic review, the prevalence of pain in older people ranged from 62 to 83%, the most common type being musculoskeletal.**[1]

This Letter focuses on the evidence and principles for drug therapy of chronic non-malignant pain in the older person.

## What evidence is available about pain treatment in the elderly?

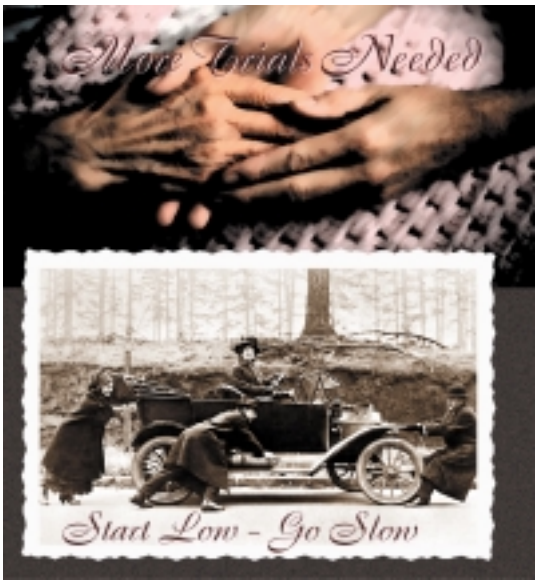
Surprisingly few clinical trials provide guidance on how best to treat pain in older people.[1] Recent *Clinical Practice Guidelines*[2,3] are substantially opinion-based. They reiterate the familiar adage, "start low and go slow", and also support use of opioids in the elderly for both malignant and non-malignant pain. These guidelines also suggest that a combination of drugs at low dose may be safer than increasing the dose of a single agent. However they offer no controlled trial data to support this approach, and it is possible that interactions between multiple drugs at low dose may be more dangerous than higher doses of a single drug.

Interpreting clinical trials of analgesics is especially difficult because side effects often compromise blinding. For example, a patient may interpret sedation as pain relief, without appreciating the risks of impairment as regards driving, falls, or mental function.

Older trials, while often of poor quality, tended to report more useful clinical endpoints, such as 'patient improved or did not'. More recent trials report average pain scores, which don't allow calculation of what proportion of patients have clinically significant pain relief.

## What if there is limited evidence from controlled trials?

Insufficient evidence about a drug is less critical in managing pain and other symptoms than when prescribing preventive therapy. The randomized controlled trial (RCT) evidence tells us that for most analgesics, only a minority of patients with chronic pain will respond. It is therefore up to the physician to establish that the therapy is in fact helping each individual patient. This can be achieved with a short therapeutic trial (usually 2 weeks). If the patient's pain or suffering are not substantially reduced, or if the side effects outweigh the benefit, then the therapy should be stopped. Even when the therapy is judged to be helpful, it is still necessary to reassess efficacy at regular intervals (say every 3 to 6 months) by stopping it altogether. **Ultimately improvement in function is the real goal of therapy.**




Most long-term therapies have some risks (such as falls with tricyclic and SSRI antidepressants, or GI hemorrhage with NSAIDs), and as a consequence, practitioners must continually balance the symptomatic and functional benefit against these risks.

The fact remains that long-term RCTs are needed in the elderly to measure serious adverse outcomes and provide physicians with better tools to calculate the benefit-harm ratio in individual patients.

## Do older persons respond differently to drugs?

Normal aging and associated organ dysfunction tend to increase sensitivity to both desirable and adverse effects of most drugs. Reduced renal function (even with "normal" serum creatinine), altered volume of distribution and a range of other factors all potentially increase elimination half-life and drug effect for many drugs. These features support the **"start low and go slow"** approach.

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## What is known about specific drugs for chronic pain?

We have reviewed the published literature on selected drugs, using standard search techniques to identify reports of double-blind RCTs. When choosing drugs for a therapeutic trial in chronic pain, it may be useful to classify patients as having either non-neuropathic or neuropathic pain.

### NON-NEUROPATHIC PAIN

#### A) "Muscle relaxants"

**Methocarbamol (Robaxin®)** including various formulations combined with acetaminophen, ASA, and codeine (e.g. Robaxacet-8®, Robaxisal-C®) have been available for decades. However we could find no well-controlled blinded studies that establish its efficacy. Methocarbamol has a short elimination half-life (2 hrs) and has significant side effects, including drowsiness, dizziness, and nausea in 4-5% of patients. The drug's popularity may be due to its sedative effect, or more likely to the effect of the other ingredients in combination tablets. Generic acetaminophen+/-codeine affords a less expensive and safer choice. **(see Table)**

**Cyclobenzaprine (Flexeril®)** like other tricyclics, has a complex route of metabolism. Elimination half-life is 1-3 days, and hence it can be given as a single bedtime dose. It has significant potential for many drug interactions, however, and side effects such as drowsiness, dry mouth and dizziness are common. Constipation, urinary retention, delirium or dysrhythmias may occur, particularly in older patients. **The manufacturer does not recommend use of cyclobenzaprine for periods longer than 2 to 3 weeks.** Only one RCT of reasonable size and duration has examined efficacy.[4] This was a Canadian study of 208 patients with fibromyalgia, which compared cyclobenzaprine (10-30 mg/d) with amitriptyline (10-50 mg/d) or placebo. At 1 month, 12% of cyclobenzaprine-treated patients and 21% of those taking amitriptyline showed improvement as compared with placebo. Most patients experienced side effects, and at 6 months neither drug provided any significant benefit.

**Benzodiazepines (diazepam, lorazepam, clonazepam, etc.)** are not analgesics and can potentiate the sedative side effects of other analgesics. Because of their potential to induce dependence, they are not indicated for chronic pain.

#### B) Antidepressants

**Tricyclics** such as amitriptyline, imipramine, and their metabolites nortriptyline and desipramine are widely used in chronic pain. They share anticholinergic side effects (constipation, dry mouth, urinary retention, delirium), sedation, weight gain and a propensity to fall. Average elimination half-live is long (1 day) and is greatly prolonged in genetically poor metabolizers (about 5% of people), in whom accumulation can occur well past one week at any dose.

For chronic back pain, a 1997 systematic review found no evidence that antidepressants are superior to placebo.[5] For other conditions, the evidence is mixed. In 41 patients with chronic non-malignant pain, amitriptyline at 25 mg/d was better than placebo within the first week.[6]

Overall, the published trials suggest that a minority of non-depressed patients with chronic pain attain a modest benefit.[7] This benefit must be weighed against the side effects listed above.[8] Evening dosing may improve the benefit-harm ratio for sedation. There is little evidence to support large doses. If pain is not clearly improved within a week at a low dose, titrate by doubling the dose. **A considered decision either to stop or to continue a tricyclic should be made within the first month of therapy.**

**SSRIs.** Clinical trials in headache, neuropathy, and fibromyalgia have produced conflicting results but on balance the trial data is not convincing that SSRI's are useful for analgesia.

#### C) Acetaminophen, NSAIDs and COX-2 inhibitors

**Acetaminophen remains the analgesic of first choice for mild to moderate non-neuropathic pain.** No conventional NSAID has proved better than any other in managing the pain of osteoarthritis (see Letter #4). Cox-2 inhibitors will be the subjects of a Letter later this year.

#### D) Glucosamine

At present there is no conclusive RCT evidence that glucosamine is effective in osteoarthritis.[9]

#### E) Methotrimeprazine (Nozinan®)

The only phenothiazine with analgesic properties, methotrimeprazine also has prominent sedative, anticholinergic, and hypotensive effects. These adverse effects may be tolerable in the short term, but likely outweigh its advantages in most long-term therapy. Like other phenothiazines it has a long half-life and a risk of extrapyramidal symptoms, including tardive dyskinesia.

#### F) Opioids

Sir William Osler presumably drew on clinical experience when he acclaimed morphine as "God's own medicine". Even so, there is surprisingly little evidence from controlled trials to guide the use of opioids for chronic non-malignant pain.[2] Standard recommendations favouring codeine/morphine over alternative opioids are not evidence-based. At higher cost, controlled-release formulations offer convenience of dosing and more consistent analgesia. Experience suggests that constipation can be addressed with diet,

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improved mobility, and laxatives, although controlled trials in this area are non-existent. Oral anileridine (Leritine®) and transcutaneous fentanyl (both analogs of meperidine) are occasionally useful in morphine-intolerant patients. Meperidine (Demerol®) has poor oral bio-availability and a short half-life. Normeperidine, a metabolite of both meperidine and anileridine, has a much longer elimination half-life than the parent drugs, and may also cause life-threatening convulsions, especially during chronic high dose therapy, or in patients with renal insufficiency associated with aging. Morphine and congeners are therefore preferable.

**Patient and prescriber misconceptions about the "addictive potential" may result in under-use of opioids for chronic pain in the elderly.** It is true that continuous chronic use is likely to induce pharmacologic tolerance and dependence, but is however unlikely to cause the destructive pattern of behaviour termed "addiction". As in the control of cancer pain, a decision to employ opioids should weigh the potential benefits of analgesia and improved function against the well-known side effects of constipation, nausea, sedation, and mental clouding. Concomitant use of anticholinergic and CNS-depressant drugs (including antispasmodics, antihistamines, tricyclics, benzodiazepines, and antipsychotics) should be minimized. **As with other drugs, opioid therapy should be continued only if symptoms and/or function clearly improve during a therapeutic trial.**

## NEUROPATHIC PAIN

### A) Antidepressants

**Amitriptyline and desipramine** were associated in a small trial with moderate or better pain relief in 74% and 61% of patients with painful diabetic neuropathy as compared with 41% of patients on placebo. Fluoxetine was similar to placebo.[10] The number needed to treat (NNT) for amitriptyline and desipramine is 3 and 5, respectively.

### B) Anticonvulsants

**Carbamazepine,** although widely used for chronic neuropathic pain, has limited RCT evidence for efficacy. Combining 3 placebo-controlled trials in trigeminal neuralgia yields a 2-week NNT of 2.6 for benefit, and a NNH of 3.4 for adverse effects (mainly drowsiness, dizziness and gait disturbance) over two weeks. Doses were mostly 400-1000 mg/day. A 30-person cross-over trial with carbamazepine in diabetic neuropathy suggests a modest benefit within 2 weeks at doses 600 mg/day or less.[11] Carbamazepine risks many interactions and toxicities of particular significance in the elderly (sedation, ataxia, hyponatremia, leukopenia). Its elimination half-life is about 12 hours. If improvement is not obvious within 2 weeks, the drug should be discontinued to avoid toxicity.

**Gabapentin (Neurontin®)** is an anticonvulsant of unknown mechanism, excreted unmetabolized by the kidney. The average 6-hour elimination half-life measured in young volunteers is prolonged in older people with diminished renal function. **Although gabapentin has been widely employed in various types of chronic pain, little evidence from high-quality controlled trials is available.** A recent 8-week double blind RCT (N=165) compared gabapentin with placebo in otherwise uncomplicated patients with **painful diabetic neuropathy.**[12] At 1,800 mg/d, a small benefit (1 point decrease on an 11 point pain score) was noted within 2 weeks. Benefit did not increase at higher doses, nor with longer therapy. The chance that a patient could discern a "moderate or marked" benefit attributable to gabapentin in an overall self-rating was 27% (NNT=4). The statistical validity of this number is questionable, and adverse effects such as dizziness (ARI=19%, NNH=5) and somnolence (ARI=16%, NNH=6) were frequent.

A similar 8-week RCT (N=229) in patients with **post-herpetic neuralgia** found a slightly larger average change in score (2/11 points) favouring gabapentin.[13] Again, the benefit was seen by 2 weeks at 1,800 mg/d. Somnolence (ARI=22%, NNH=5), dizziness (ARI=19%, NNH=5), and ataxia (ARI=7%, NNH=14) were common.

A small crossover RCT (N=19) compared gabapentin (900- 1,800 mg/d) with amitriptyline (25-75 mg/d) for diabetic neuropathy. Amitriptyline provided "moderate, a lot, or complete" pain relief in 67% of patients, vs. 52% of those on gabapentin ($P < 0.01$). Virtually all patients experienced adverse effects with each drug.[14] Gabapentin benefits at best a minority of patients with painful diabetic or post-herpetic neuropathy. Toxicity, but not analgesia, is dose-dependent. Stop the drug if pain relief does not clearly outweigh harm by 2 weeks.

### C) Local anaesthetics

**Mexilitine (Mexitil®)** is an anti-dysrhythmic drug structurally related to lidocaine, with similar CNS, GI, and cardiovascular adverse effects. It is metabolized by the liver, with an average elimination half-life of 10 hours in healthy volunteers. The potential for dangerous drug interactions is significant, and mexilitine increased mortality in early trials of dysrhythmia suppression after MI. Although it has been used in painful diabetic and other neuropathies since 1988, we could find no double blind RCT of adequate quality to demonstrate an unequivocal benefit. Many small trials have serious design flaws. Such studies generally exclude patients with CHF, renal failure, abnormal EKG, or concomitant beta-blocker use, so that reported adverse event rates are undoubtedly lower than might be expected in typical elderly patients.[15]

**TABLE: Common analgesics and doses for chronic pain in the elderly.**

| Drug | Starting dose | Usual Maximum dose | Daily cost* |
|---|---|---|---|
| Methocarbamol / ASA / $C_{1/2}$ | 1 tab bid | 2 tabs qid | $1.25 - 5.00 |
| Acetaminophen / $C_{1/2}$ | 1 tab bid | 2 tabs qid | $0.06 - 0.24 |
| Cyclobenzaprine | 10 mg hs | 30 mg hs | $0.38 - 1.15 |
| Amitriptyline | 10 mg hs | 75 mg hs | $0.01 - 0.03 |
| Desipramine | 10 mg hs | 75 mg hs | $0.19 - 0.78 |
| Imipramine | 10 mg hs | 75 mg hs | $0.01 - 0.04 |
| Nortriptyline | 10 mg hs | 75 mg hs | $0.14 - 0.81 |
| Methotrimeprazine | 2 mg hs | 25 mg hs | $0.06 - 0.12 |
| SR morphine | 10 mg bid | 60 mg bid | $0.70 - 2.56 |
| Carbamazepine | 100 mg bid | 400 mg bid | $0.24 - 0.96 |
| Gabapentin | 300 mg bid | 600 mg tid | $2.08 - 6.24 |
| Mexilitine | 100 mg bid | 200 mg tid | $0.76 - 1.50 |

* Prices are based on average cost to Pharmacare for 1999.

## Conclusions

- **Chronic pain, particularly of musculo-skeletal origin, is a common problem for the elderly.**
- **Long-term controlled trials in older people with chronic pain are lacking and are needed to guide rational therapy.**
- **Physiological changes that occur with aging make older individuals more sensitive to the effects of drugs.**
- **Most analgesic drugs provide modest benefit to only a minority of patients.**
- **Start with low doses and titrate; symptomatic and functional benefits are evident early (usually within 1-2 weeks).**
- **Benefit of each analgesic must be established by a therapeutic trial and reassessed regularly.**
- **Overall goal of analgesic therapy is improved function and quality of life.**

This Letter contains an assessment and synthesis of published (and whenever possible peer-reviewed) publications up to October 1999. We attempt to maintain the accuracy of the information in the Therapeutics Letter by extensive literature searches and verification by both the authors and the editorial board. In addition this Therapeutics Letter was submitted for review to 75 experts and primary care physicians in order to correct any identified shortcomings or inaccuracies and to ensure that the information is concise and relevant to clinicians.

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