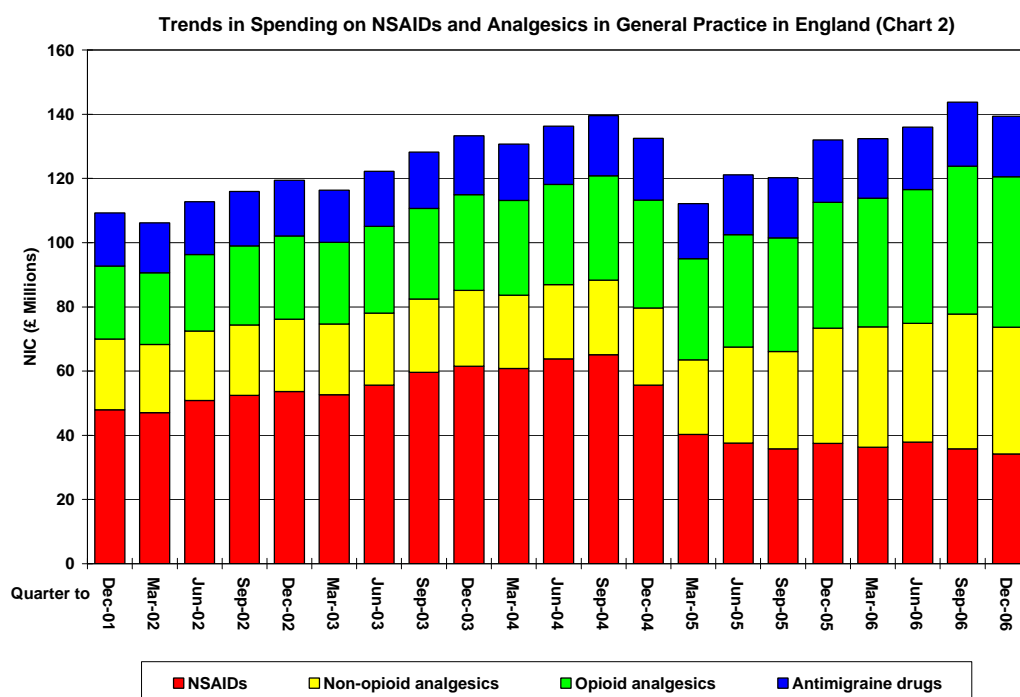
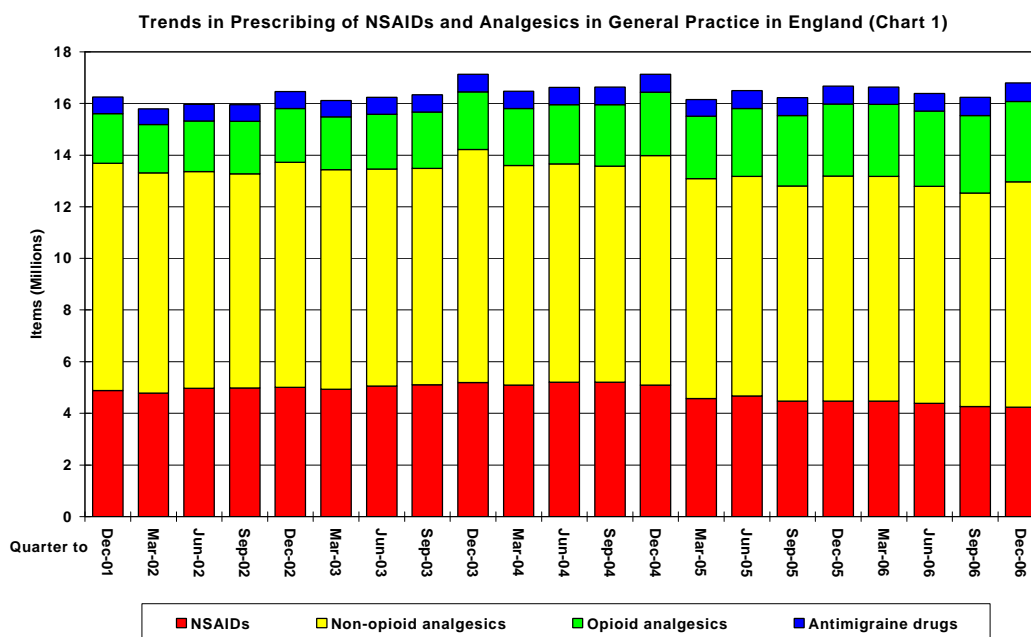


Analgesic Drugs

Pain is a universal human experience. It is the third most common reason why people visit their General Practitioner. Chronic pain severe enough to seriously affect quality of life is estimated to affect between 19% and 25% of adults. Chart 1 shows that, despite little change in overall analgesic volumes, prescribing of opioids has increased with a corresponding increase in cost (chart 2). The cost of prescribing non-opioids has also increased whilst expenditure on non-steroidal anti-inflammatory drugs (NSAIDs) has fallen. Management of pain can be challenging and evidence to support most clinical practice is limited. A pragmatic structured approach, with appropriate non-drug treatment addressing the psychological, cultural and social as well as biological factors, is required.



The World Health Organisation's three step analgesic ladder underpins most pain management guidance. It is estimated that up to 88% of patients obtain satisfactory pain relief with this approach. An elaborated version of the analgesic ladder, providing advice on treatment for acute and chronic mild to moderate pain, has been published by the Medicines and Healthcare Products Regulatory Agency/Committee on Safety of Medicines (MHRA/CSM) and endorsed by the British Pain Society¹. Substituting or adding drugs in a stepwise manner according to response and tolerability may be less helpful for persisting non-cancer pain than for acute pain and pain related to cancer. Treatment should start at the step of the ladder appropriate to the severity of the pain being experienced and doses should be titrated following regular reassessment of response.

MILD TO MODERATE PAIN

Step 1 – Paracetamol (1g up to four times a day). Paracetamol remains the first choice analgesic for mild-to-moderate persistent pain. It is well tolerated, effective and inexpensive. People who seek advice on pain control often report that they have already tried paracetamol with little success; they may have used inadequate doses².

Step 2 – Substitute low-dose ibuprofen (e.g. 400mg three times a day). Reliable long-term comparative trials have not been conducted and any short-term efficacy advantages of NSAIDs over paracetamol are likely to be small³. Oral NSAIDs reduce pain in the short term for osteoarthritis (OA) of the knee; however the advantage over placebo is small. There are no important differences in efficacy between NSAIDs⁴ and choice is based on safety, patient factors and cost. Low dose ibuprofen has the lowest risk of serious upper GI complications.

Step 3 – Add paracetamol 1g four times a day to low-dose ibuprofen. Combining an NSAID with paracetamol may allow lower NSAID doses to be used.

Step 4 – Continue paracetamol and replace ibuprofen with alternative NSAID. The lowest effective dose of NSAID should be prescribed and the need for long-term use should be reviewed periodically. Based on GI safety and cost, diclofenac 25–50mg three times a day would be suitable. Naproxen is associated with a lower risk of thrombotic events and may be preferred where cardiovascular risk is of concern. A weak opioid may be an alternative to an NSAID for people at high risk of NSAID-induced adverse effects.

Step 5 – Full therapeutic dose of a weak opioid (e.g. codeine 30–60mg up to four times a day) in addition to full dose paracetamol and/or NSAID. Weak opioids may be considered earlier (e.g in OA). Adding high doses (60 mg) of codeine to paracetamol provides additional analgesia, but also increases drowsiness and should be reserved for patients with more severe pain when the response to paracetamol and/or an NSAID has been inadequate⁵.

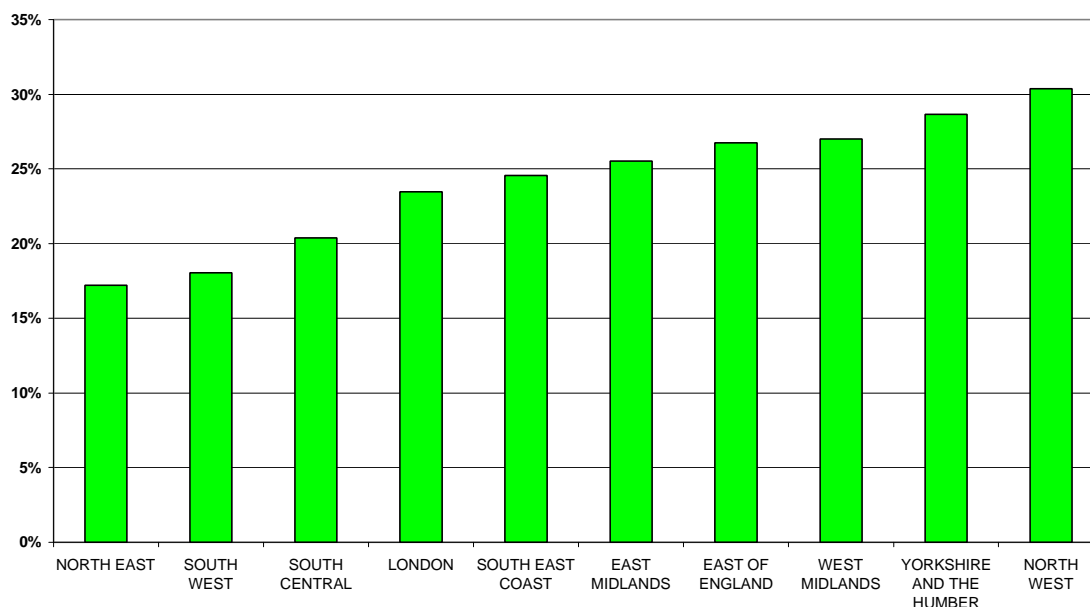
Fixed combination analgesics have a limited role, but may be convenient. If used, full therapeutic doses should be prescribed. Effervescent combination formulations are expensive, contain very high concentrations of sodium and offer no advantages for patients who are able to swallow tablets. Co-proxamol is implicated in almost one fifth of UK drug related suicides. A MHRA/CSM review of safety and effectiveness concluded that there is no identifiable group in whom the risk:benefit balance may be positive. A gradual withdrawal was announced in January 2005 to allow long-term users an opportunity to move to suitable alternatives. All licenses for co-proxamol will be cancelled at the end of 2007. Prescribers contemplating continuing treating patients with co-proxamol after licenses are cancelled are advised to consult GMC guidance.

A Cochrane review concluded that the potential for adverse effects greatly disadvantages tramadol compared to other treatments for OA⁶. There is no evidence that modified release (m/r) tramadol preparations provide any advantages. They are considerably more expensive than alternatives. Chart 3 shows the variation in prescribing of m/r tramadol between Strategic Health Authorities. Tramacel[®], a tramadol/paracetamol combination, provides a sub-therapeutic dose of paracetamol and offers patients little advantage in terms of efficacy, adverse effects or convenience compared with current standard analgesics.

Step 6 – Consider a therapeutic trial of a tricyclic antidepressant or an antiepileptic. For the small minority of patients who do not respond at Step 5, a therapeutic trial of a tricyclic antidepressant (e.g. amitriptyline) for neuropathic pain or pain which disturbs sleep, or an antiepileptic (e.g. carbamazepine/gabapentin) for neuropathic pain may be considered. There is no RCT evidence that newer agents such as gabapentin, pregabalin or duloxetine are any more effective or better tolerated than established

alternatives. Although evidence for short-term effects on acute neuropathic pain is contradictory, there is evidence that opioids are effective in both cancer-related and non-malignant neuropathic pain when used for longer (weeks to months). A Cochrane review suggested that low to moderate doses of opioids may be as effective as maximum doses of gabapentin⁷.

Strategic Health Authority Distribution of Prescription Items for Modified Release
Tramadol as a % of all Tramadol Items for Quarter to December 2006 (Chart 3)



SEVERE PAIN

Morphine is the opioid of first choice for moderate to severe pain for reasons of familiarity, availability and cost. Hydromorphone and oxycodone may be considered as alternatives for the small proportion of patients who develop intolerable adverse effects with oral morphine. Switching between opioids can complicate pain management and is not recommended for non-specialists without expert advice. There is little good evidence to support the practice of switching opioids to reduce adverse effects⁸. Alternatives include: reducing the dose of opioid (and possibly adding non-opioid or adjuvant analgesics); managing adverse effects symptomatically; and switching the route of administration.

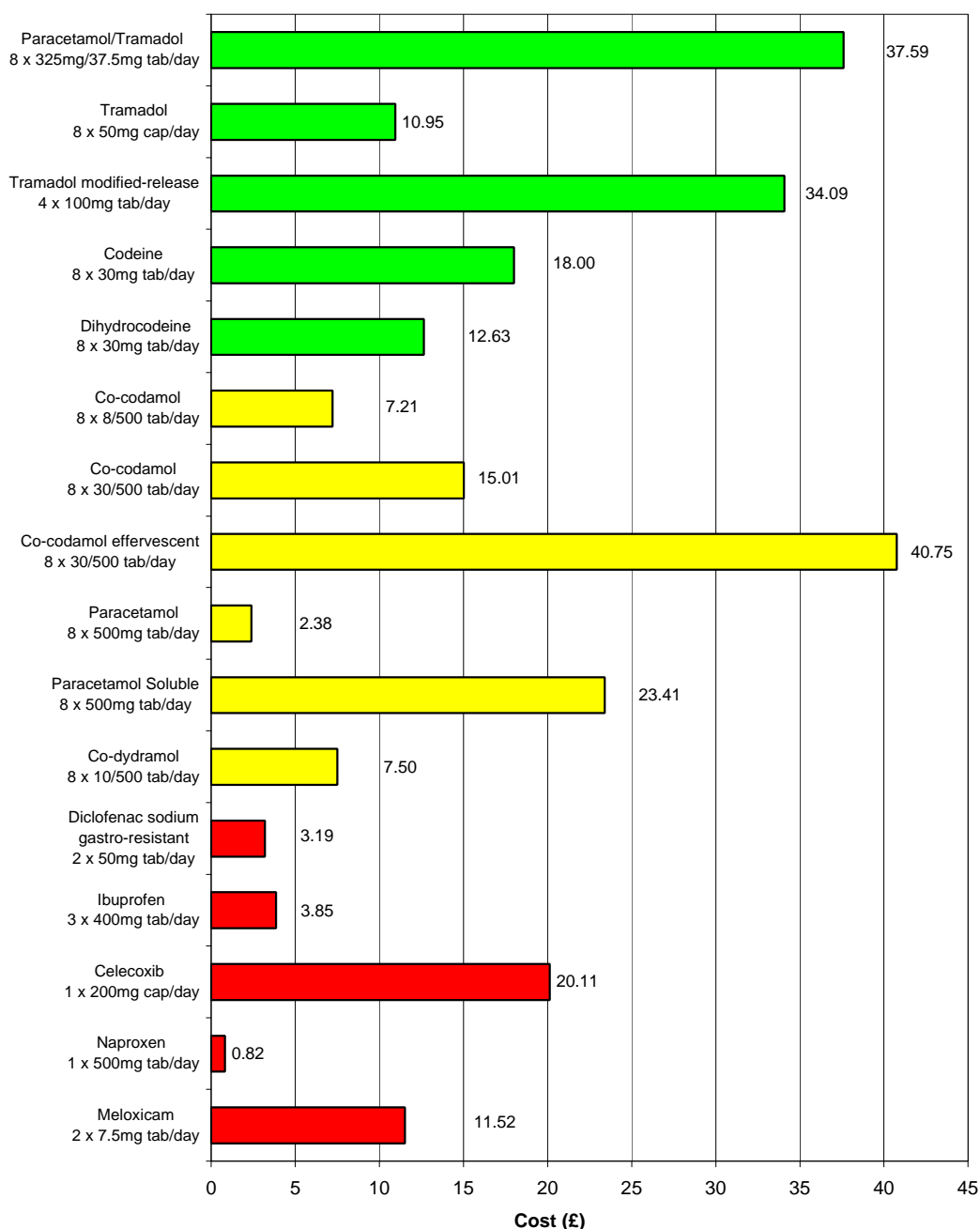
Fentanyl patches may be an alternative to sub-cutaneous infusion for patients with stable opioid requirements who are unable to tolerate oral medications⁹. They lack flexibility for managing patients with fluctuating pain or for titrating in uncontrolled pain; analgesic effects are not obtained for 12-24 hours. A role for transdermal buprenorphine in the management of chronic pain has not yet been established.

MIGRAINE

The evidence base for many acute anti-migraine drugs is poor. Many patients with migraine respond to simple analgesics. Aspirin, paracetamol or ibuprofen are effective first-line treatments for acute migraine, especially when given early in an attack¹⁰. Addition of an anti-emetic may reduce nausea and vomiting and increase analgesic absorption; evidence for combining aspirin and metoclopramide is better. Opioid containing analgesics should be avoided. Oral triptans may be suitable when migraine attacks are unresponsive to adequate doses of analgesic and anti-emetic. Current evidence suggests that there are no major differences in efficacy between the available oral triptans¹¹. Intranasal or subcutaneous preparations are expensive and inconvenient and should be reserved for patients who have not responded to oral therapy or where vomiting is a problem.

Prophylaxis with a beta-blocker (first line) or an alternative (e.g. amitriptyline) should be considered when either: acute treatments are contraindicated or ineffective; acute treatment is required more than twice a week; disability lasting 3 days or more occurs more than twice a month, or; attacks are severe or prolonged¹².

Cost for 28 Days



Prices based on Drug Tariff April 2007. Dose based on WHO DDDs where possible, otherwise BNF stated dose. The WHO DDD is a unit of measurement based on the assumed average maintenance dose in adults. It may not necessarily reflect the actual dose used.

PRESCRIBING DATA

(Reporting quarter = October-December 2006, Index quarter = October-December 2001)

Non-opioid analgesic (98% paracetamol and paracetamol combinations) are prescribed more often than other drugs for pain. Prescription volumes have shown little change over the last 5 years (8.7 million prescription items, 69% of all analgesics), whereas costs have increased by 80% to £39.4 million (37% of all spending on analgesics). Paracetamol and paracetamol with codeine account for 82% of non-opioid items and 85% of costs. Prescriptions and expenditure have both risen, to 3.9 million (up 33%) costing £12.4 million and 3.2 million (up 42%) costing £21 million, respectively. Due to the impending

withdrawal of co-proxamol, there has been an 88% decrease to 270,000 items, costing just under £1 million. There has been little change in the volume of prescribing of paracetamol with dihydrocodeine, but expenditure has increased by 73%.

Overall, NSAID items have declined by 13% to 4.2 million, costing £34.2 million. Diclofenac prescriptions are most common, 1.9 million items (45%) at £15 million (44%), with ibuprofen next, 1.1 million items (25%) at £3.4 million (10%). Prescribing of ibuprofen has decreased by 20% over the last 5 years, with diclofenac prescribing increasing by 7%. 15% of all NSAID prescriptions (625,000 items, a 30% decrease) were for Cox-II selective inhibitors (meloxicam, celecoxib, etoricoxib, etodolac, lumiracoxib, rofecoxib and valdecoxib). Spend on Cox II selective inhibitors has fallen by 43% to £11 million.

There has been a 62% increase in opioid analgesic items with a two-fold increase in expenditure (3.1 million items, £46.8 million). Opioids account for 25% of all analgesic prescribing and 45% of costs for the reporting quarter. The most commonly prescribed opioid analgesic is Tramadol (38% items, 26% cost) with 1.2 million items at a cost of £12 million. Oxycodone, buprenorphine and fentanyl prescribing have increased markedly; 98% of fentanyl prescribing and 93% of spending being attributed to the patches. Diamorphine prescribing declined 29%, probably due to recent shortages. There was a 57% increase in morphine items to 381,000 (12% of all opioids).

Over the last 5 years gabapentin prescriptions have increased three-fold to 331,000 items per quarter. Costs have increased much less (2.5% to £6.7 million), due to availability of generic gabapentin. Pregabalin became available from July 2004 and prescribing reached 139,000 items, £11.2 million for the reporting quarter. Prescriptions for triptans have increased by 22% to 400,000, whilst costs have grown by 12% to £16 million.

SUMMARY

- Managing pain requires a pragmatic structured approach, which includes appropriate non-drug treatment and which addresses psychological, cultural and social as well as biological factors.
- Newer drugs have not been shown to have any consistent advantages over established alternatives (e.g. paracetamol, ibuprofen, amitriptyline and morphine).
- Transdermal analgesics offer few advantages and should only be used in patients who have specific problems with oral therapy.
- Prophylaxis and non-drug management are important for migraine

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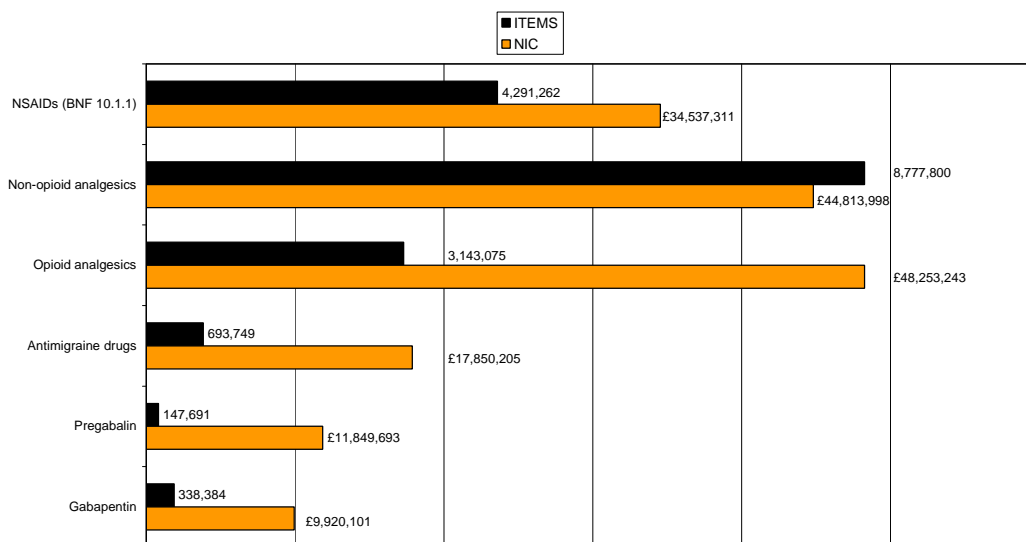
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Prescribing and Spending on NSAIDs and Analgesics in England for Quarter to March 2007



	Quarter to March 07	
	National	
	ITEMS/1000 PUs	NIC/1000 PUs
Fentanyl	2.09	£170.67
Oxycodone	1.56	£82.00
Morphine	5.46	£60.42
Tramadol	16.85	£177.14
Buprenorphine (BNF 4.7.2)	1.58	£61.23