

All Wales Medicines Strategy Group

Grŵp Strategaeth Meddyginiaethau Cymru Gyfan



Tramadol

Educational

Resource Materials

Educational Slide Set

November 2013

These educational resource materials have been prepared by a multiprofessional collaborative group, with support from the All Wales Prescribing Advisory Group (AWPAG) and the All Wales Therapeutics and Toxicology Centre (AWTTC), and has subsequently been endorsed by the All Wales Medicines Strategy Group (AWMSG).

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Tramadol Educational Resource Materials

Towards appropriate tramadol
prescribing

Aims

- To raise awareness of the potential harms associated with the misuse and diversion of tramadol
- To provide information and training to support the appropriate prescribing and dispensing of tramadol
- To tackle inappropriate prescribing and dispensing of tramadol and reduce the risks associated with misuse and diversion of supplies

Background

Concern regarding the use of tramadol has been raised by Welsh Government, prompted by an Advisory Council on the Misuse of Drugs (ACMD) expert group review. Tramadol accounts for an increasing number of deaths and reports to the National Poisons Information Service. It is subject to abuse and dependence and there are concerns with regard to interactions. Deaths related to the misuse of tramadol increased from 83 in 2008 to 175 in 2012. The ACMD recommended that the UK Government reclassify tramadol as a controlled class C substance, and place it within Schedule III of the Misuse of Drugs Regulations. A consultation was launched by Crime Prevention Minister Jeremy Browne, which closed on the 11 October 2013.

Top line analysis of tramadol prescribing has been undertaken by the Welsh Analytical Prescribing Support Unit (WAPSU) and the difference in prescribing rates between health boards has been identified. Tramadol prescribing rates in Wales are higher than in England but lower than in NE England, an area of similar demographics. Review of current tramadol prescribing in primary and secondary care is essential to ensure appropriate use of tramadol within NHS Wales.

All Wales Toxicology and Therapeutics Centre (AWTTC) organisations with the support of the All Wales Prescribing Advisory Group (AWPAG) have developed resource materials with the aim of supporting healthcare professionals in Wales to review the prescribing of tramadol within the context of pain management.

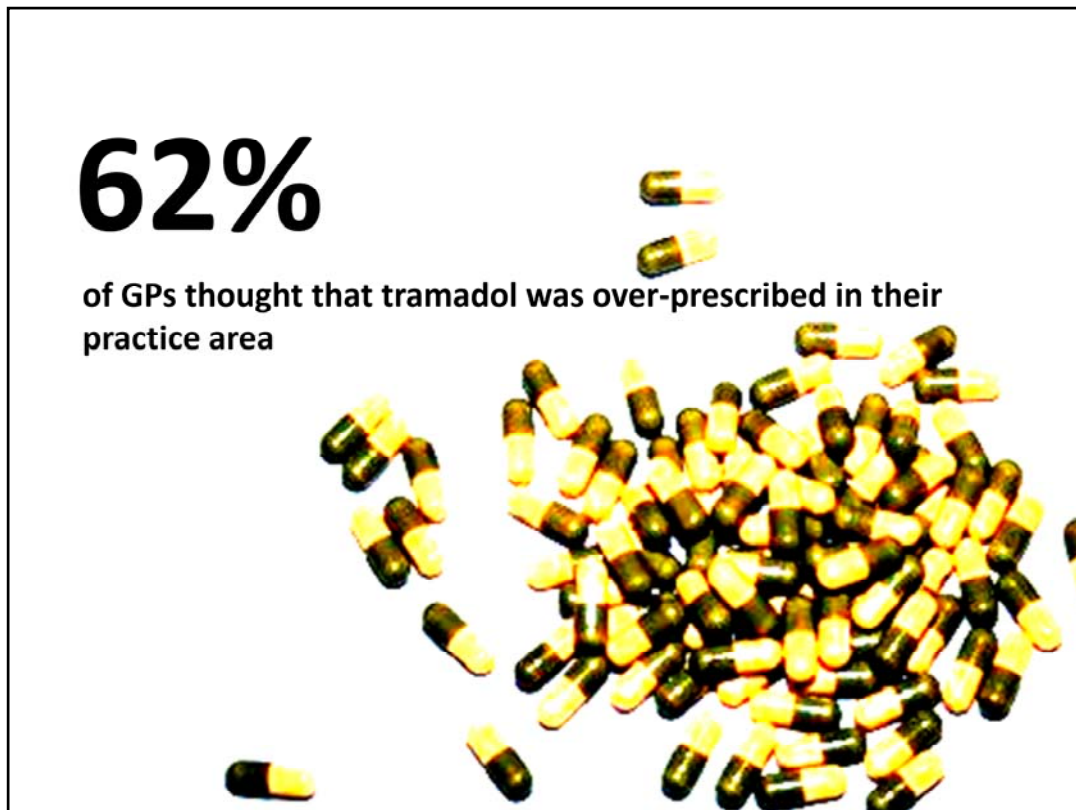
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Survey results

Primary care

The primary care survey was sent to all GP practices in Wales asking practice managers to forward to GPs. There are 483 GP practices in Wales (with around 2,022 GPs in Wales) and from these, 262 GPs responded. The results are detailed in the following slides.



62% of the GPs that responded thought that tramadol was over-prescribed in their practice locality.

53%

of GPs perceived there to be a problem with dependence on tramadol
in their practice area

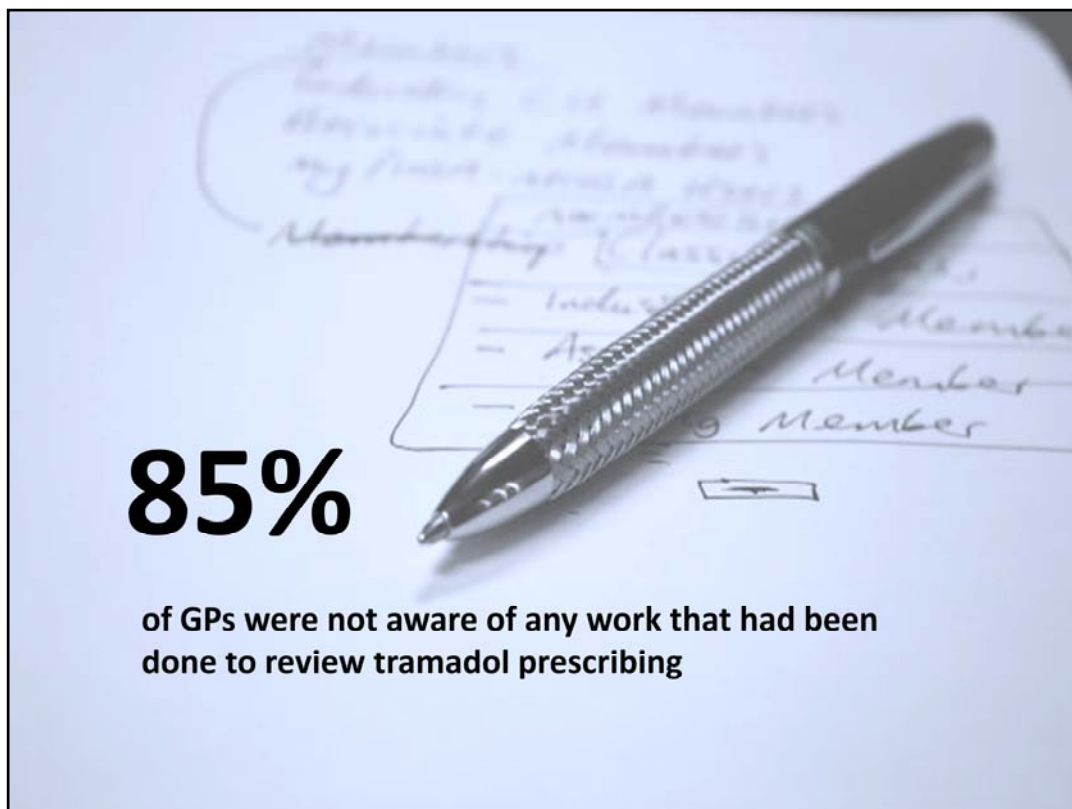


53% of the GPs that responded perceived there to be a problem with dependence on tramadol in their practice area.

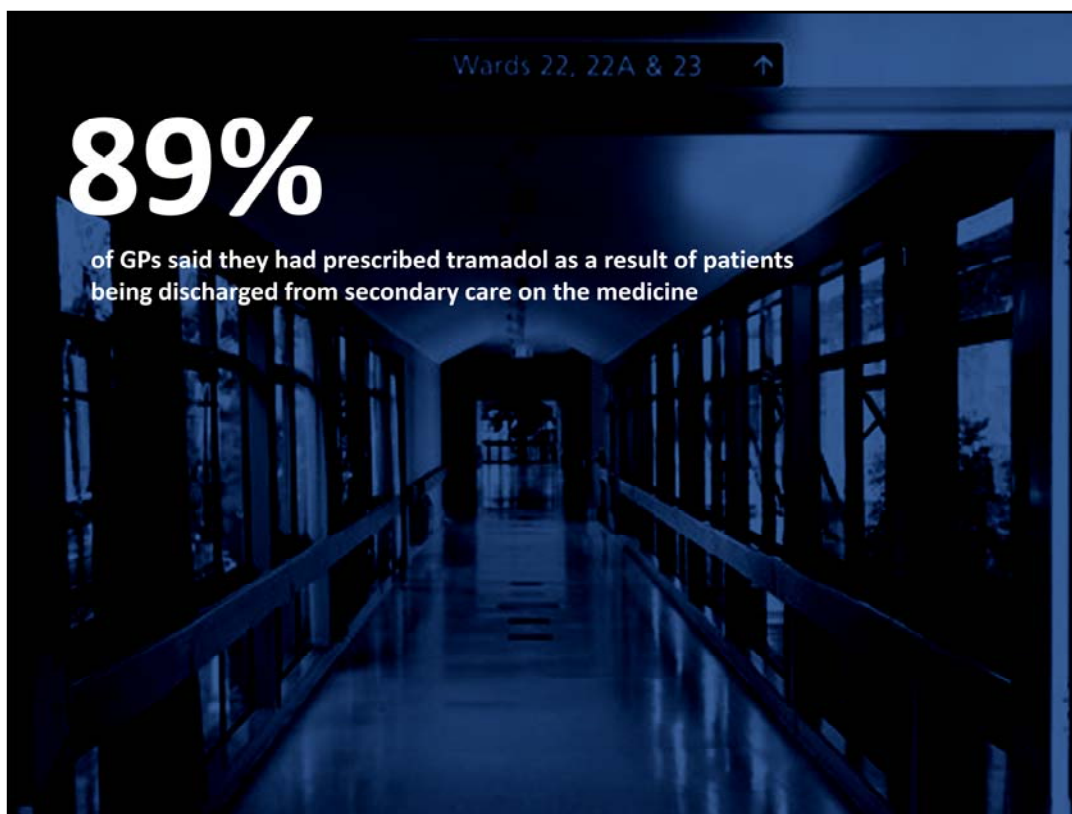
50%

of GPs were aware of patients obtaining tramadol from sources other than prescription

50% of the GPs that responded were aware of patients obtaining tramadol from sources other than prescription. These sources included family and friends, the street and the internet.



85% of the GPs that responded were not aware of any work that had been done to review tramadol prescribing in their practice locality.



89% of the GPs that responded said they had prescribed tramadol as a result of patients being discharged from secondary care on the medicine. When asked which departments, the most frequently mentioned departments were orthopaedics, surgical wards and emergency departments.

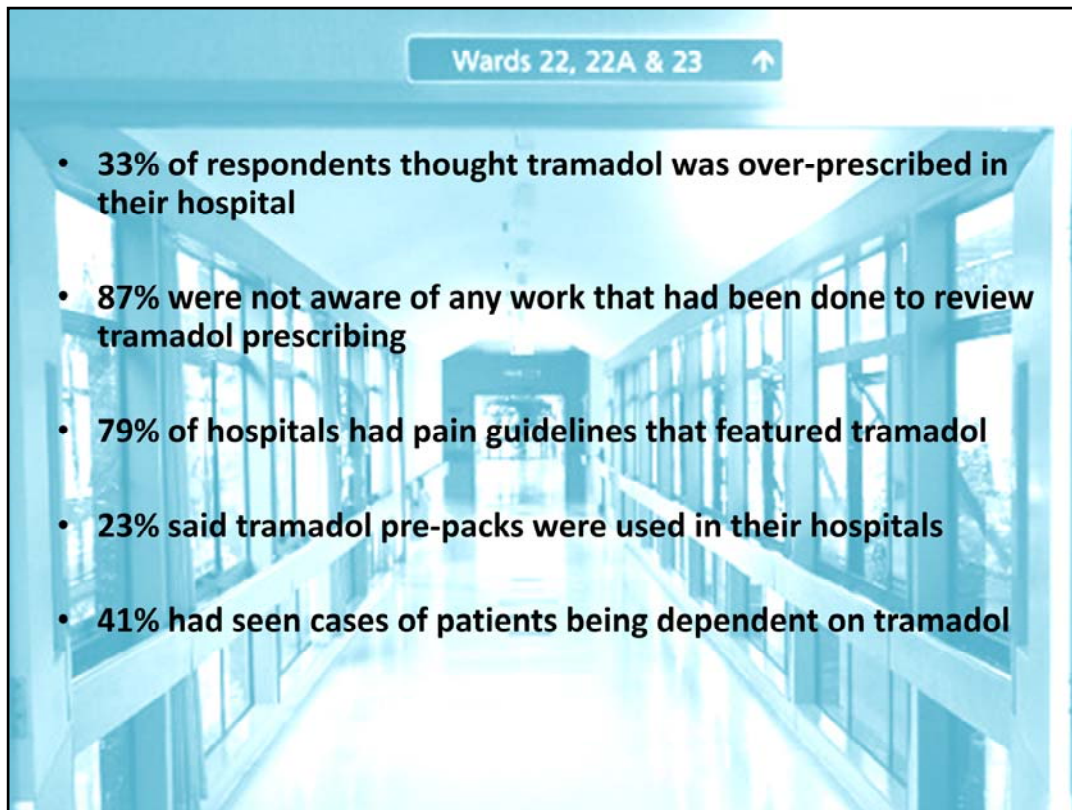
Some busy departments stock tramadol as 'pre-packs', which can be given to the patient directly from the ward and do not require the patient to go via pharmacy for supplies.

Other results from the primary care survey included:

- 61% of the GPs that responded were concerned about some of their patients taking more than the prescribed dose of tramadol.
- 81% of the GPs that responded had had patients who had experienced an adverse reaction to tramadol.
- 86% of the GPs that responded found tramadol a useful analgesic and felt that it has a place in therapy.
- Encouragingly, only 3% of GPs would use tramadol first line for severe pain.

Secondary care

A second survey was sent out to prescribers in secondary care with an interest in substance misuse and pain management. There were 51 responses.



When asked what resources prescribers felt would be useful to support the appropriate prescribing of tramadol in their hospitals, the most frequently mentioned resources were:

- National and local audit
- Educational slides
- Patient information leaflets
- Newsletters and bulletins
- Development of pain guidelines

Feedback from the surveys has helped to inform the development of the educational resource materials.

What are the issues?

Tramadol

- Accounts for an increasing number of deaths and reports to the National Poisons Information Service
- The 'dual mechanism' increases the potential for adverse effects, particularly in overdose
- Subject to abuse and dependence
- Interacts with other drugs including SSRIs, MAOIs, tricyclics, epilepsy medication and warfarin

Office for National Statistics (ONS) data show deaths in England and Wales more than doubled from 83 in 2008 to 175 in 2012. Figures relate to the number of deaths involving tramadol from ONS data published 28 August 2013: http://www.ons.gov.uk/ons/dcp171778_320841.pdf.

Other deaths relating to drug poisoning in England and Wales 2012

- The number of deaths involving heroin and morphine fell slightly in 2012 to 579, from 897 in 2008; however, they remain the substances most commonly involved in drug poisoning deaths.
- Deaths involving paracetamol fell from 260 in 2008 to 182 in 2012.
- Deaths involving 'other opioids' (including codeine and dihydrocodeine) decreased from 381 in 2008 to 348 in 2012.

National Poisons Information Service (NPIS) data show a steady increase in the number of telephone enquiries in the UK. Enquiries increased from not appearing at all in the top ten pharmaceutical agents involved in telephone enquiries in 2008-2009 to seventh on the list with 691 enquiries in 2012-2013. TOXBASE accesses for tramadol increased from 12,136 in 2008-2009 to 19,712 in 2012-2013 (NPIS Annual Report 2008-2009 and 2012-2013).

The dual mechanism: Tramadol has a unique dual-action pharmacological profile that increases the risk of adverse effects in overdose. Opioids such as tramadol exhibit weak agonist activity at opiate receptors in the brain and may contribute towards euphoria and respiratory depression. In addition, tramadol enhances serotonergic and noradrenergic systems in the brain by inhibiting their reuptake mechanisms.

- Selective serotonin re-uptake inhibitors (SSRIs) including fluoxetine, sertraline, citalopram and paroxetine
- Monoamine oxidase inhibitors (MAOIs) including phenelzine, isocarboxazid and tranylcypromine
- Tricyclic anti-depressants (TCA) including amitriptyline, dosulepin, lofepramine
- Alcohol – Enhanced hypotensive and sedative effects when alcohol given with opioid analgesics
- Please note: not an exhaustive list – refer to BNF or Stockley's Drug Interactions for more information on interactions and clinical importance and management.

Tramadol

- Risk of the potentially fatal **serotonin syndrome** is increased by interactions that increase serotonin activity

Symptoms of serotonin syndrome occur within minutes to hours and may include:

- Agitation or restlessness
- Diarrhoea
- Fast heart beat and high blood pressure
- Hallucinations
- Increased body temperature
- Loss of coordination
- Nausea
- Overactive reflexes
- Rapid changes in blood pressure
- Vomiting

Reference – Serotonin Syndrome – A.D.A.M. Medical Encyclopedia
<http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0004531/>

Tramadol and Wales

- Tramadol usage in Wales is higher than in England
- Tramadol prescribing in NHS Wales increased by 25% from year ending March 2009 to year ending March 2013
- Tackling the issues surrounding the misuse and diversion of supplies of tramadol in Wales is a priority for AWMSG
- A quality improvement and audit toolkit will be made available to health boards in December 2013

These data refer to defined daily doses (DDD) per 1,000 patients in 2008-2009 to 2012-2013. Tramadol usage in Wales is higher than in England. However, Wales has lower prescribing rates than the North East of England, an area with comparable demographic and socioeconomic characteristics (data from CASPA and ePACT).

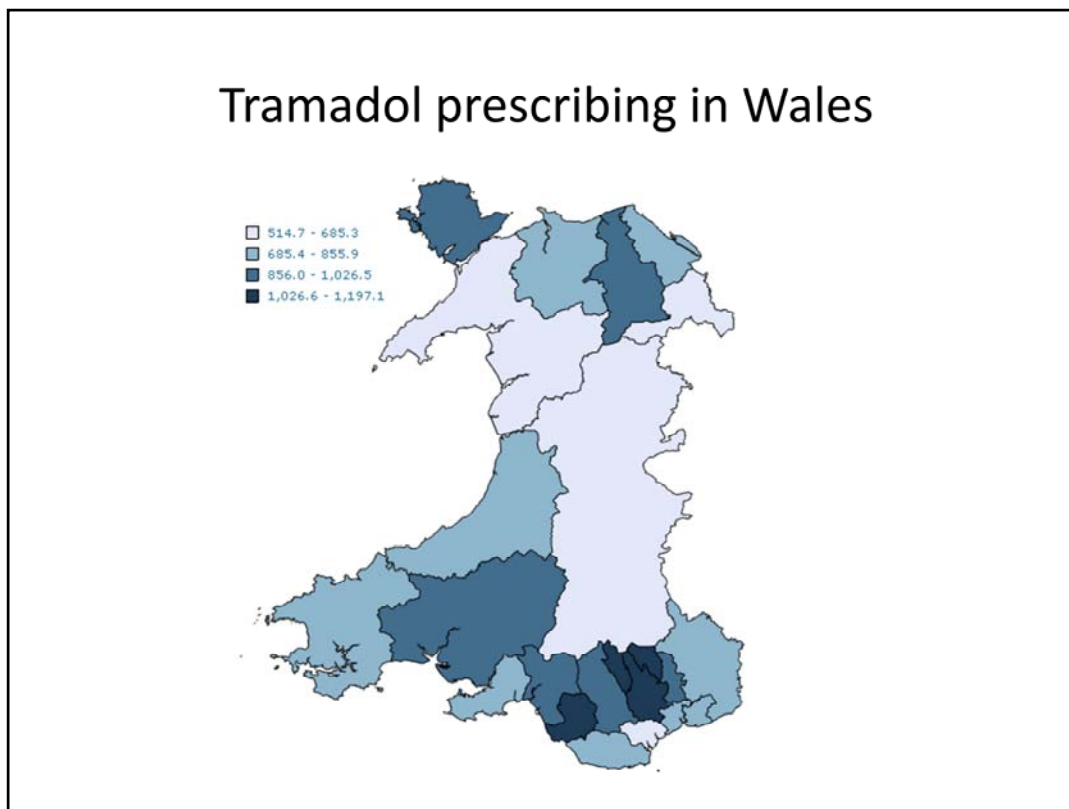
The DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults. It is a statistical measure of drug consumption, defined by the World Health Organisation (WHO). It is used to standardise the comparison of drug usage between different drugs or between different healthcare environments. The DDD is not to be confused with the therapeutic dose or with the dose actually prescribed by a physician for an individual patient.

Other reference sources:

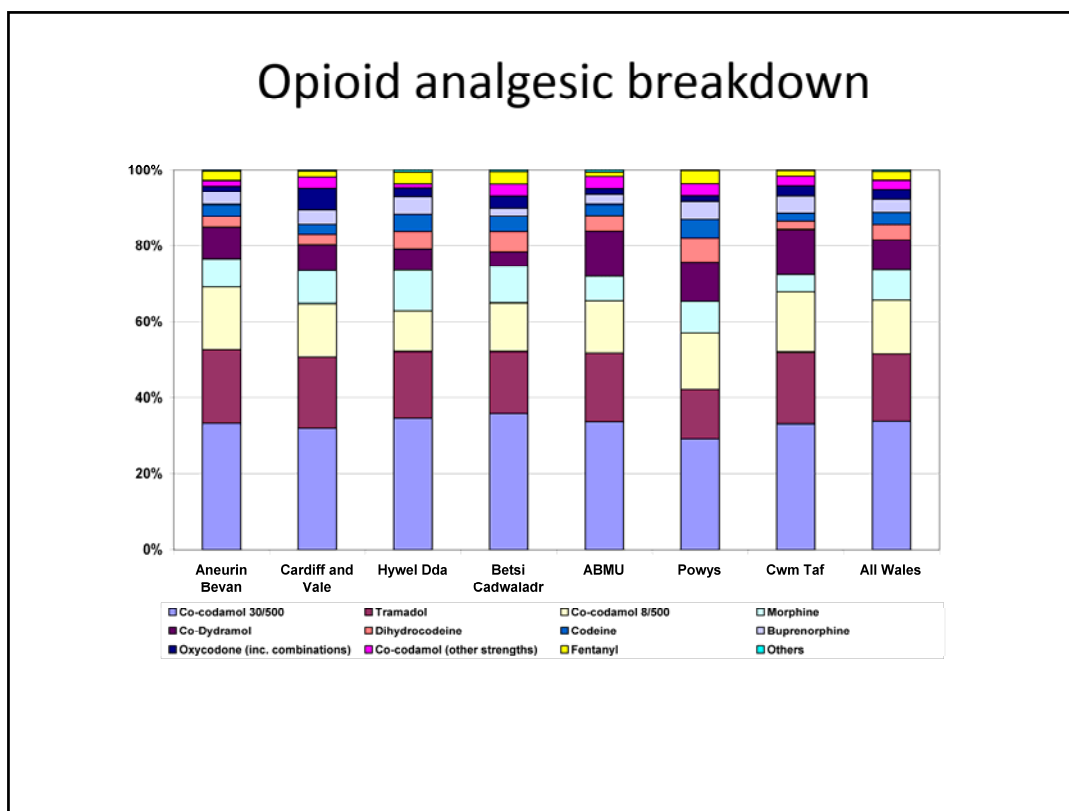
See top line prescribing analysis available on AWMSG website:

<http://www.awmsg.org/awmsgonline/docs/awmsg/medman/Primary%20Care%20Prescribing%20Analysis%20Tramadol.pdf>

Tramadol prescribing in Wales



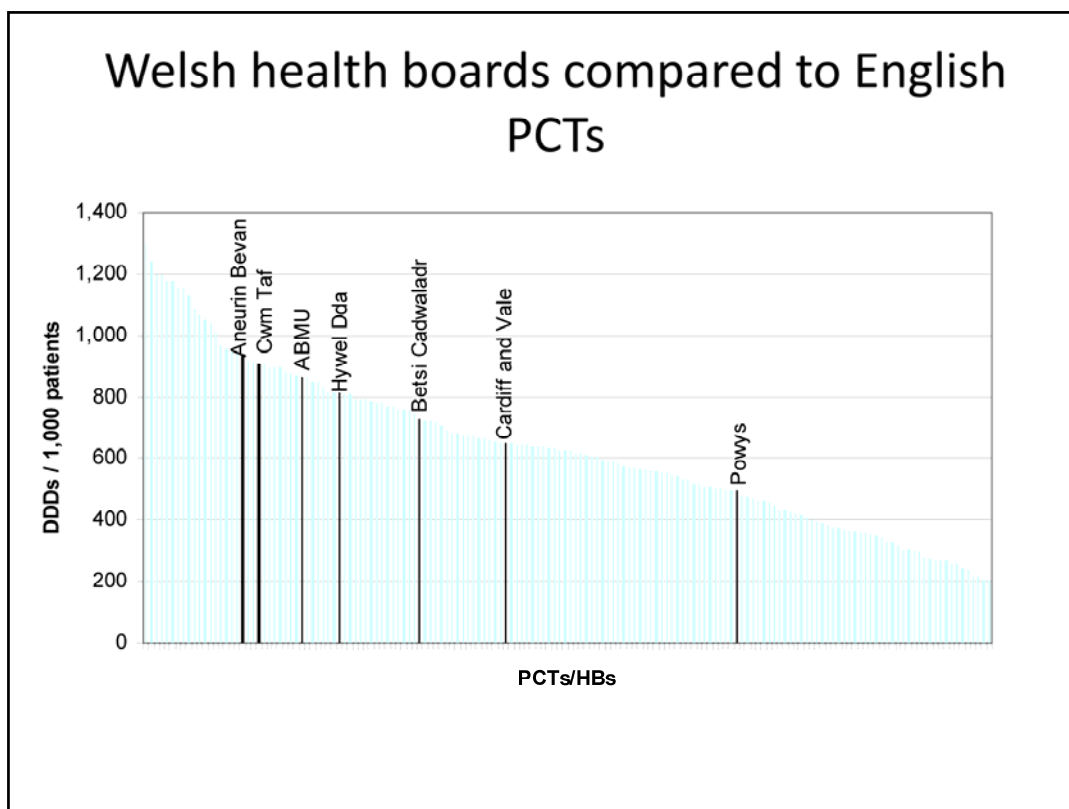
A map of Wales comparing the prescribing of tramadol as DDDs per 1,000 patients across the different localities for the quarter ending June 2013. The data show the variation between the geographical regions of Wales, with higher prescribing rates in areas of Aneurin Bevan Health Board, Cwm Taf Health Board and Abertawe Bro Morgannwg University Health Board and the lowest prescribing rates seen in Powys Teaching Health Board and areas of Betsi Cadwaladr University Health Board.



Tramadol prescribing as a percentage of total opioids including co-codamol and co-dydramol

Prescribing of tramadol accounts for 42% of the total opioids prescribed (quarter ending June 2013). The 42% refers to tramadol within the drug basket of opioids in CASPA and does not include combination products such as co-codamol and co-dydramol; however, this graph shows tramadol compared to other commonly prescribed opioid analgesics including co-codamol and co-dydramol to give a more complete picture within the context of prescribing in pain.

The data shows that tramadol accounts for a large proportion of opioid prescribing in all health boards and also shows that there is some variation between health boards, particularly for tramadol.



Tramadol prescribing in Welsh health boards compared to English primary care trusts (PCTs) for the quarter ending March 2013 (DDD per 1,000 patients)

The data show that most health boards in Wales sit within the higher end of this chart and indicate that Welsh health boards prescribe more tramadol (DDD per 1,000 patients) than most PCTs in England. Please note that PCTs were replaced by CCGs in March 2013. The borders and areas of the CCGs differ from those of the PCTs and therefore data for comparison of old PCTs with new CCGs is not readily available beyond March 2013.

Key prescribing points

- **To minimise the risk of dependence**

- Treatment is short and intermittent
- Only use for moderate to severe pain where first-line medication, such as codeine or co-codamol, is not appropriate
- Prescribe regular paracetamol concurrently to encourage tramadol use on a 'when required' basis
- Use with great caution in patients with a history of addiction or dependence
- Use with caution in patients with depression
- Patients receiving repeat prescriptions for tramadol are reviewed on a regular basis

- **To minimise the risk of adverse effects**

- Patients with a history of epilepsy or those susceptible to seizures should only be treated with tramadol if the reasons to do so are compelling
- Tramadol should be used with caution in patients taking medication that interacts, such as warfarin, SSRIs, TCAs and MAOIs
- Tramadol should be used with caution in patients with renal impairment and the dose adjusted according to the GFR
- Medicines reconciliation and medicines use reviews (MURs) are useful tools to help minimise the risk of interactions
- Any serious adverse events should be reported using the yellow card scheme

Interactions

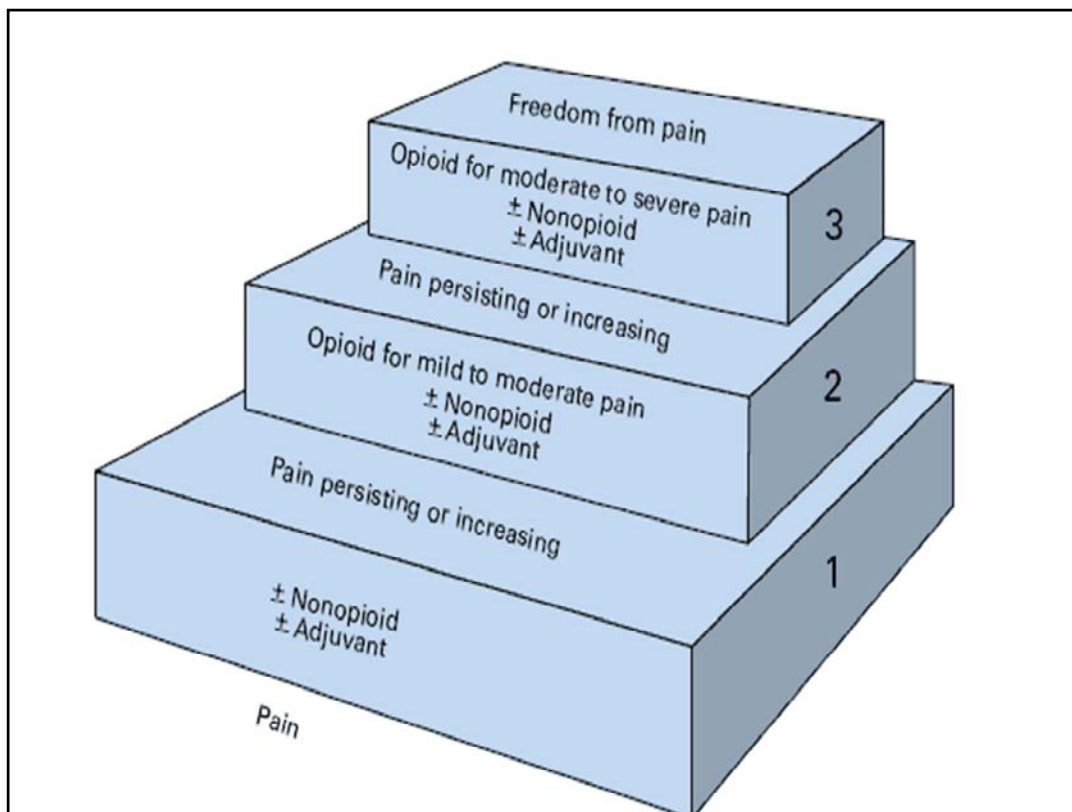
- SSRIs – Selective serotonin re-uptake inhibitors - including fluoxetine, sertraline, citalopram and paroxetine
- TCAs – Tricyclic anti-depressants – including amitriptyline, dosulepin, lofepramine
- MAOIs – Monoamine oxidase inhibitors – including phenelzine, isocarboxazid and tranylcypromine
- Alcohol – Increased hypotensive and sedative effects

Please note: this is not an exhaustive list – refer to BNF or Stockley's Drug Interactions for more comprehensive information on interactions and clinical importance and management.

- Medicines reconciliation, MURs and discharge medicines reviews (DMRs) play an important role in minimising the risks associated with inappropriate tramadol use. Discussions and counselling with patients can help to inform them of maximum doses, interacting medicines, interaction with alcohol and duration of use, as well as more broad conversations about pain in general. For example, use of over the counter medicines (co-codamol 8/500 preparations) may not be mentioned by the patient without prompting.

- Yellow Card Centre Wales (YCC Wales) offers education and training sessions about suspected adverse drug reactions to all healthcare professionals and patient groups. More information is available at: <http://www.yellowcardwales.org/>.

WHO analgesic ladder



WHO analgesic ladder developed for cancer pain

There are many local adaptations of the WHO analgesic ladder that are relevant to specific specialisations and are more detailed. See local pain guidelines where appropriate.

Simple analgesics i.e. paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs)

Weak opioids i.e. codeine

Strong opioids i.e. morphine, fentanyl, oxycodone, pethidine, tramadol

Adjuvants - adjuvant analgesics are drugs which were not originally for pain but rather for other conditions but have been found to be effective in difficult to manage pain, particularly neuropathic pain. They are a diverse group of drugs that includes antidepressants, anticonvulsants (antiseizure drugs), and others, for example, topically applied pain relief.

Tramadol in the WHO analgesic ladder

- Codeine is advised as first line within step 2 of the analgesic ladder
- Tramadol is a strong opioid and has a place in therapy when alternatives are not tolerated or effective
- Tramadol use should be short and intermittent for acute pain to reduce the risk of dependence
- If pain is non-nociceptive, e.g. neuropathic pain, a neuropathic agent may be more appropriate
- If the patient is suffering from a chronic pain condition, a review of their pain management would be appropriate

Acute Pain versus Chronic Pain

- There are distinct differences between the two types of pain
- After around three months, pain stops being acute and becomes chronic
- Physiological and pathological changes occur
- Chronic pain requires regular review and a pain management plan

Acute pain versus chronic pain management

- It is important to understand the patient's needs and to be aware of the differences between acute and chronic pain.
- After around three months, pain stops being acute and physiological and pathological changes occur.
- Pain becomes persistent or chronic and needs to be managed like any other long-term condition.
- A holistic approach to pain management is needed, of which medication is a part.
- It is important to ensure the appropriate prescribing of opioids in chronic pain conditions.
- It is important to understand the difficulties of persistent pain and how it can be managed.

When a patient is initiated on tramadol on an acute prescription, the patient should be reviewed at three months. After this time, there is evidence to suggest that the pain has become chronic and the prescriber may need to review the patient with respect to chronic pain management.

There are many resources available to read more about chronic pain management if this is identified as a learning need, as well as your local pain teams.

- WeMeReC – Pharmacovigilance distance-learning modules
- Pain Community Centre – Cardiff University
- BMJ learning modules
 - Chronic low back pain
 - Pain management programmes for chronic pain

Tramadol dosing

- **Immediate-release 50 mg tramadol capsules**
 - Take ONE or TWO capsules up to a maximum of FOUR times a day when required
 - Maximum dose is 400 mg DAILY
- **Modified-release tramadol preparations**
 - 100 mg/150 mg/200 mg
 - TWICE daily dosing
 - Maximum dose is 400 mg DAILY

Tramadol dosing should be tailored to the individual needs of the patient, rather than using a standard '50-100mg 4-6 hourly MAX 400mg in 24 hours' dose, as this would encourage short and intermittent dosing and a step-up approach to pain relief from tramadol.

Renal dosing

- Tramadol and its metabolites are almost completely excreted by the kidneys
- Renal Handbook – third edition
 - **GFR (ml/min)**
 - 20–50 ml/min – Dose as in normal renal function
 - 10–20 ml/min – 50–100 mg every 8 hours initially then titrate dose as tolerated
 - <10 ml/min – 50 mg every 8 hours initially and titrate dose as tolerated
- Caution in elderly
 - Reduced elimination
 - Half-life extended
 - Start at low doses and titrate if tolerated

Remember – differences between absolute glomerular filtration rate (GFR), estimated GFR (eGFR) and creatinine clearance (CrCl).

eGFR may not be appropriate to determine renal function in patients with acute illness, the very elderly, patients with extremes of BMI, amputees and pregnant patients.

Please see BNF and Renal Drug Handbook for more information on clinical importance and management.

Please note that the information in the Renal Drug Handbook is compiled from a wide range of sources and from the clinical experience of the editorial board of the UK Renal Pharmacy Group, all of whom are involved in the pharmaceutical care of renally impaired patients. As such, some of the information in the Renal Drug Handbook may not be in accordance with the licensed indications or use of the drug.

Stepping down or stopping tramadol safely

- Avoid abrupt withdrawal after long-term treatment
- For patients taking regular tramadol, or those who may be dependent on tramadol, a careful approach is required
- If it is appropriate for a patient's tramadol to be stepped down or stopped, it is important to note that the dose must be reduced slowly to ensure the patient's safety and to minimise the risk of withdrawal symptoms and/or adverse reactions
- If there are issues with chronic pain or dependence on tramadol, referral to a specialist service may be appropriate

Advice for stepping down or stopping tramadol

Avoid abrupt withdrawal after long-term treatment. Where physical dependence to tramadol develops, the withdrawal syndrome can be severe, with symptoms typical of opiate withdrawal sometimes accompanied by atypical symptoms including seizures, hallucinations and anxiety. For patients taking regular tramadol, or those who may be dependent on tramadol, a careful approach is required. If it is appropriate for a patient's tramadol to be stepped down or stopped, it is important to note that the dose must be reduced slowly to ensure the patient's safety and to minimise the risk of withdrawal symptoms and/or adverse reactions.

To encourage patient engagement and concordance, a suggested approach would be to reduce the dose at each reduction step, e.g. by one 50 mg dose, and to titrate by how the patient manages, rather than by setting time limits for the next reduction. Every patient and their circumstances will be different, and a prudent and individually tailored approach is required.

If there are issues with chronic pain or dependence on tramadol, referral to a specialist service may be appropriate.

Interactions

- **Warfarin** – Tramadol enhances the anticoagulant effect of coumarins. May increase the INR and ecchymoses
- **Antidepressants** – Increased risk of convulsions and CNS toxicity, including serotonin syndrome, with SSRIs, MAOIs, TCAs
- **Alcohol** – Increased hypotensive and sedative effects
- **Anti-epileptics** – Increased risk of seizures with epileptic patients; however, effects of tramadol reduced by carbamazepine

See Stockley's Drug Interactions for comprehensive list of interactions and advice on clinical importance and management.

Also be aware of interactions with OTC medicines, for example co-codamol.

INR – International Normalised Ratio

Side effects

Common

- Dizziness
- Drowsiness
- Constipation

Less common

- Hallucinations
- Confusion
- Convulsions

Rare

- Addiction
- Withdrawal effects (e.g. anxiety, sweating and stomach pains)

Tramadol and convulsive threshold

- Seizures have occurred at therapeutic doses
- Risk increases if dose > 400 mg daily
- Consider additive risk if patient on other drugs that can lower convulsive threshold e.g. ciprofloxacin
- Need very compelling reasons to treat an epileptic with tramadol

Hepatic impairment

- Usual cautions about sedatives and risk of hepatic encephalopathy apply
- Avoid use or reduce dose

See BNF.

Case study

(From WeMeReC pharmacovigilance distance-learning module, May 2013)

During a routine nursing home visit, you are asked to see a resident urgently. The staff are concerned that Mrs Griffiths, who is 82 years old, appears drowsy and less communicative than normal.

O/E: drowsy, constricted pupils, BP 132/68 mmHg,
pulse 60 beats/min, respiratory rate 10 breaths/min.

Medication: ramipril 5 mg OD for hypertension
tramadol SR 100 mg BD for back pain
diclofenac 50 mg TDS (Rx 1 wk ago for knee pain).

1. What do you think is the cause of Mrs Griffiths' current symptoms?
2. What would you do next?

Data from WeMeReC pharmacovigilance distance-learning module, May 2013, based on the first 200 of 472 responses received to the case study. More than one answer may have been given to a question, so the percentages may not total 100.

Comments from Dr Alison Thomas, Medical Director, Yellow Card Centre Wales, and Consultant Physician, Cardiff and Vale University Health Board are included in *italics*.

- Most GPs (89%) suspected that tramadol toxicity was the cause of the symptoms.
- Over half of GPs (54%) thought that diclofenac could have contributed to these symptoms, either alone (some suggested a possible bleed), or with ramipril, possibly by causing impaired renal function.
- Many GPs (50%) mentioned renal failure or kidney injury as a possible contributory factor, either causing the symptoms or increasing the risk of tramadol toxicity.
- 19% would administer naloxone if it was available, and 10% would dial 999, or otherwise arrange an emergency admission.

"Tramadol toxicity is the most likely explanation for Mrs Griffiths' drowsiness, in the context of small pupils and reduced respiratory rate. The combination of NSAID and ACE inhibitor is the likely cause of her renal failure, with poor fluid intake in a drowsy patient a potential contributing factor. The elderly are more sensitive to the effects of opioids, and patients with renal failure are at increased risk of toxicity from tramadol.

"Tramadol acts centrally with weak agonist activity at the opioid receptors, and blocks the reuptake of serotonin and norepinephrine. Naloxone does not fully reverse the effects of tramadol in overdose. There have been reports of seizures associated with administration of naloxone, although tramadol overdose itself is also associated with seizures."

Case study (continued)

(From WeMeReC pharmacovigilance distance-learning module, May 2013)

You arrange for Mrs Griffiths to be admitted to hospital.

On admission, her serum urea is found to be 28.4 mmol/L and serum creatinine 320 micromol/L.

Following appropriate treatment, her renal function improves, she makes a good recovery, and is discharged ten days later.

You discuss the case at a practice meeting and one of your colleagues suggests that you submit a Yellow Card.

3. On the Yellow Card form, how would you describe the suspected reaction?

- 10% of GPs would describe the reaction as serious, severe, or requiring hospital admission.
- 17% would mention opioid toxicity and 13% would mention that an interaction may have occurred.
- 13% included all three drugs (tramadol, diclofenac and ramipril) when describing the suspected reaction.

“You only need to suspect an ADR to submit a Yellow Card report; causality does not have to be proven. The suspected drug(s) should be included in the ‘suspected drugs’ section. All other medication taken, including OTC and herbal remedies, should be noted in the ‘other drugs’ section. You should provide as much clinical information as possible regarding the suspected ADR including time course, any treatment required and the outcome for the patient.

“In this case, I would include the renal function as it provides additional information on the severity of the reaction. If naloxone was administered you may also want to comment on this, and how the patient responded.”