OPIOIDS FOR CHRONIC NON-CANCER PAIN

PostScRxipt
from the
NHSGGC Area Drug & Therapeutics Committee
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The updated NHSGGC Primary Care Guidelines for the management of chronic pain include a new section on the use of potent opioids for non-cancer pain. This was felt to be both an important issue and an area of concern. Important, because although it has been proven that opioids can be effective in chronic non-cancer pain, they are often under-used. It is an area of concern, because inappropriate opioid prescribing can worsen an already grave and disabling situation. Dr Mick Serpell, Consultant and Senior Lecturer in Anaesthesia & Pain Management based at Stobhill ACH, discusses some of the issues.

National guidelines tend to be generic, and sell the philosophy of utilising opioids, supported by provision of the evidence behind such practice. Our local guidelines go further. They actually recommend specific drugs, doses, duration and provide tools to identify those high risk patients who should not be exposed to opioids unless their care is co-ordinated by expert pain and addiction specialists.

The opioid section of the chronic pain guideline is available at **http://www.staffnet.ggc.scot.nhs.uk/Clinical%20Info/Pages/default.aspx** in two forms, a more practical three-page document and an online, unabridged six-page version, which includes more details and references.

Patient factors
The most important aspect for effective and safe prescribing of opioids is patient selection. Prescribing opioids for non-cancer pain is entirely different from cancer pain. In the latter, opioids are appropriate in almost all patients with severe pain and in whatever dose is required and tolerated. For non-cancer pain, patient selection is pivotal.

All patients can potentially become addicted to opioids, but screening tools can aid patient stratification and so identify and exclude those patients at higher risk. Under these circumstances, the incidence of addiction or abuse, or aberrant drug behaviour, is less than 1%. Factors which place patients at higher risk of abusing opioids include:

- **active or previous history of alcohol or other drug abuse,**
- **borderline personality disorders,**
- **depression or psychotic disorders ,**
- **current or previous suicide attempts,**
- **household members with drug abuse/psychiatric issues,**
- **poor response to opioids previously,**
- **absence from work for more than six months.**

Opioid prescribing should be initiated only by specialists in any patient who is at higher risk of addiction.

Pain type
Certain types of pain are more opioid responsive. These include clearly defined nociceptive and neuropathic pains, especially if they have improved with previous exposure to an opioid. Diffuse pain, such as some types of low back pain, fibromyalgia, visceral or somatiform pain is poorly responsive.

Pain may improve with opioid	Pain unlikely to improve with opioid
• Improvement with acute opioids in the past • Failed with conventional non-opioid drugs • Failed with non-drug therapy • Diagnosis - nociceptive - neuropathic - combined	• No improvement with acute opioids in the past • Diagnosis - Possible somatoform disorder

Prescribing
A trial of opioid should only be undertaken after screening and stratification. Both clinician and patient should have a clear agreement of what outcomes must be achieved in order to consider the trial a success. A reduction in pain severity (~30%) is the usual requirement but, more importantly, there should be clear improvement in some other area of their physical function, activities of daily living or quality of life. The guidelines have information on how these parameters can be assessed. In some circumstances, a lower degree of analgesia may be acceptable if there are clear cut improvements in other important domains.

Just as in cancer pain, opioid administration should follow the principles of using regular long-acting preparations by the oral route, and active or preventive management of side effects such as nausea, constipation and itch. The differences with non-cancer pain are:

- **use of short acting opioids for breakthrough analgesia is actively discouraged,**
- **opioids should rarely, if ever, be given by the parenteral route,**
- **the ceiling dose should be limited to the equivalent of 200mg of morphine a day. In practice, most patients who respond well do so at a dose equivalent to less than 100mg of morphine daily.**

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Website
http://www.ggcformulary.scot.nhs.uk

Latest ADTC decisions

MAJOR changes to the *Formulary*

Ⓢ **Dronedarone (Multaq®)** In adult clinically stable patients with a history of, or current, non-permanent atrial fibrillation (AF) to prevent recurrence of AF or to lower ventricular rate. Total *Formulary*. Restricted to use in patients in whom beta-blockers, class 1c drugs and amiodarone are contraindicated, ineffective or not tolerated and who do not have a diagnosis of heart failure.

Ⓢ **Prilocaine hydrochloride (Prilotekal®)** Spinal anaesthesia. Total *Formulary*. Restricted to use in spinal anaesthesia in ambulatory surgery settings such as day surgery units.

Added with MINOR changes to the *Formulary*

Ⓢ **Valganciclovir (Valcyte®)** Prevention of cytomegalovirus (CMV) disease in CMV negative patients who have received a solid organ transplant from a CMV positive donor. The marketing authorisation has been amended to allow the duration of CMV prophylaxis in kidney transplant patients to be increased from 100 days to 200 days post-transplantation. Total *Formulary*. Acknowledge new indication.

Ⓢ **Filgrastim (Nivestim®)** Reduction in duration and incidence of neutropenia and febrile neutropenia, mobilisation of peripheral blood progenitor cells. Total *Formulary*. Acknowledge new biosimilar.

Ⓢ **Cefixime (Suprax®)** Uncomplicated gonorrhoea in adults (unlicensed indication, ADTC appeal). Total *Formulary*. Restricted to use in accordance with Sandyford treatment protocol.

NON-*Formulary*

- **Botulinum toxin type A (Azzalure®, Vistabel®)** Temporary improvement in the appearance of moderate to severe glabellar (frown) lines.
- **Colesevelam (Cholestagel®)** Hypercholesterolaemia.
- **Erlotinib (Tarceva®)** Monotherapy for maintenance treatment in patients with locally advanced or metastatic non-small cell lung cancer.
- **Fenticonazole (Gynoxin®)** Vulvovaginal candidiasis.
- **Ferric carboxymaltose (Ferinject®)** Iron deficiency when oral iron preparations are ineffective or cannot be used.
- **Golimumab (Simponi®)** Alone or in combination with methotrexate, for the treatment of active and progressive psoriatic arthritis in adults.
- **Histamine dihydrochloride (Ceplene®)** Maintenance therapy for adult patients with acute myeloid leukaemia in first remission concomitantly treated with interleukin-2.
- **Ivabradine (Procoralan®)** Chronic stable angina pectoris in combination with beta-blockers.
- **Miconazole muco-adhesive buccal tablet (Loramyc®)** Oropharyngeal candidiasis in immunocompromised patients.
- **Sorafenib (Nexavar®)** Hepatocellular carcinoma.
- **Trastuzumab (Herceptin®)** HER2 positive metastatic adenocarcinoma of the stomach or gastro-oesophageal junction.
- **Velaglucerase (Vpriv®)** Long-term enzyme replacement therapy in patients with type 1 Gaucher disease.

Ⓢ specialist use only Ⓢ specialist initiation only

1 Dronedarone (Multaq®) added to the NHSGGC *Formulary* for restricted use

Dronedarone was accepted for restricted use by SMC for adult clinically stable patients with a history of, or current, non-permanent atrial fibrillation (AF) to prevent recurrence of AF or to lower ventricular rate. It is restricted to use in patients in whom beta-blockers, class 1c drugs and amiodarone are contra-indicated, ineffective or not tolerated and for patients who do not have a diagnosis of heart failure. Treatment should be initiated by specialists only.

Dronedarone appears less effective than amiodarone in reducing AF recurrence but has the potential for improved tolerability. As with any new drug, its real-life safety is still being discovered. The MHRA has recently advised **(http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON108677)** that dronedarone may be associated with an elevated risk of worsening, or new-onset, heart failure and with liver toxicity. Patients should be vigilant for the symptoms of heart failure or liver toxicity and should undergo regular liver-function testing.

AF is the most frequently encountered sustained arrhythmia. It is associated with an increased risk of cardiovascular events including stroke, greater all-cause mortality and has a detrimental impact on quality of life. Dronedarone is an anti-arrhythmic agent in the same class as amiodarone.

Placebo controlled studies have shown a median time to a documented recurrence of AF of 116 days in the dronedarone group and 53 days in the placebo group. By 12 months, the rate of recurrence was 64% in the dronedarone group and 75% in the placebo group (hazard ratio [HR] 0.75; 95% confidence interval [CI]: 0.65 to 0.87).

A comparative study looked at patients with documented AF for more than 72 hours, for whom cardioversion and anti-arrhythmic treatment were indicated and who were receiving oral anticoagulants. Patients with paroxysmal AF, atrial flutter or severe congestive heart failure were excluded. Patients were randomised to dronedarone or amiodarone for at least six months.

The primary efficacy endpoint was recurrence of AF or premature study drug discontinuation for intolerance or lack of efficacy. The incidence at 12 months was 75% in the dronedarone group and 59% in the amiodarone group (HR 1.59; 95% CI: 1.28 to 1.98). This was mainly driven by AF recurrence which was more frequent in the dronedarone group (64%) than the amiodarone group (42%). Driven mainly by intolerance, the premature drug discontinuation component was less frequent in the dronedarone group (10% versus 13%).

The occurrence of thyroid, hepatic, pulmonary, neurological, skin, eye, or gastrointestinal (GI) events, or premature study drug discontinuation following an adverse event was 39% and 44% in the dronedarone and amiodarone groups, respectively, at 12 months. Dronedarone had a significantly lower incidence of clinically severe adverse events.

Discontinuation due to lack of efficacy was greater with dronedarone (21% versus 5.5%) and discontinuation due to adverse events was greater with amiodarone (13% versus

18%). SMC clinical experts have indicated that the side-effect profile of amiodarone is problematic and that there is an unmet need for a better tolerated alternative, particularly in younger patients.

Dronedarone costs £819 a year (400mg twice daily) compared to £37 for amiodarone (200mg daily).

For full details of all ADTC decisions and links to SMC recommendations go to:

www.ggcformulary.scot.nhs.uk/Latest%20news/formulary%20update%20bulletin.pdf

2 Dabigatran:

New indication for use under development

The manufacturer of dabigatran has submitted an application for marketing authorisation for a new indication of prevention of stroke and systemic embolism in adults with atrial fibrillation. This medicine is currently licensed for thromboprophylaxis following elective hip/knee replacement but is non-*Formulary* in NHSGGC as rivaroxaban was the preferred option.

If a licence is granted, SMC will assess the product and make recommendations for use in Scotland. This advice will be considered by ADTC and, given the projected budget impact, it will also be considered by PMG. Should there be a decision to use this product, a local implementation plan will be required before NHSGGC *Formulary* status is formalised.

Until the sequence of events from licence to *Formulary* status is complete, all NHSGGC prescribers should refrain from using this medicine. Negligible prescribing is expected while dabigatran remains unlicensed for this indication. Once licensed, initiation by hospital specialists should only be in exceptional circumstances (through the non-*Formulary* process) until local *Formulary* status, prescribing protocols and implementation arrangements are in place.

The projected budget impact for this proposed development poses an unprecedented challenge to the NHS and, subject to SMC advice, a managed introduction is essential. Your support to ensure this is effectively managed is appreciated.

How does SMC link with NHSGGC *Formulary* processes?

Since 2002 the Scottish Medicines Consortium (SMC) has advised NHS Boards in Scotland on the clinical and cost-effectiveness of all new medicines and new indications for existing medicines. NHSGGC Area Drug & Therapeutics Committee, through the *Formulary* and New Drugs Subcommittee, considers each SMC advice document and consults with appropriate local specialists to determine whether the medicine/indication should be added to the *Formulary*.

All medicines that have still to be assessed by SMC are automatically non-*Formulary* and prescribing is discouraged. This non-*Formulary* status remains until the medicine has completed the local process, which could include protocol or service development, an implementation plan or financial impact consideration by the Prescribing Management Group.

Medicines/indications not recommended by SMC will not be added to the *Formulary*. Medicines accepted by SMC may be added to *Formulary* but not always. SMC may accept a medicine with a restriction; as a minimum that same restriction will be applied in NHSGGC, but an additional local restriction could be imposed to narrow the niche further.

Prescribers are expected to use the NHSGGC *Formulary* as their guide to medicines status **(http://www.ggcformulary.scot.nhs.uk/)** The rationale for some recent differences between SMC and the *Formulary* are highlighted;

- SMC accepted (with restriction) metformin SR for diabetes on October 2009 but it was not added to the *Formulary*. This was because there was only marginal, if any, clinical benefit but the potential financial impact was significant if use of this formulation became routine.
- Epoetin theta and bivalirudin were accepted by SMC but not added to the *Formulary* because it was considered that there were sufficient alternatives.
- Ulipristal was accepted by SMC for emergency hormonal contraception up to 120 hours post unprotected intercourse (as per licence). The local view was that an appropriate, lower cost medicine (levonorgestrel) can be used up to 72 hours, so ulipristal should be reserved for cases presenting between 72 and 120 hours.

3 *Formulary* status of hepatitis B antivirals

In December 2009, the ADTC changed the restriction on certain drugs used in the treatment of hepatitis B. Adefovir, entecavir, lamivudine and tenofovir should now be initiated by, or on the advice of, a specialist, but prescribing may be continued by a GP. Patients who are suitable for treatment will be initiated at a department of Infectious Diseases or Gastroenterology. Where clinically indicated, the specialist will write to the patient's GP, requesting that they continue to provide antivirals. The specialist centre will provide ongoing monitoring of any toxicities and response to treatment.

The next online issue of the *Formulary* will reflect this change. In the meantime, we would be grateful if colleagues in primary care could note the change of status of these drugs.

Erectile dysfunction:

Prescribing for patients with severe distress

PCA(M)(2011) 4 *Treatment of Erectile Dysfunction: Patients with Severe Distress* **(http://www.sehd.scot.nhs.uk/pca/PCA2011(M)04.pdf)** confirms some relaxation of current restrictions on prescribing of these treatments. Currently, all prescribing must be carried out by the specialist service. In future, all eligible patients will be able to receive treatment on NHS prescription from their GP following assessment or advice by the relevant consultant.

Before changes are made to the way in which these patients are treated, the Clinical Services Subgroup of the Sexual Health Planning Group is identifying the relevant consultants who will provide that assessment and advice and the Primary Care Prescribing Management Group is confirming that clinical capacity and funding are in place.

Until the new services are finalised, all clinicians involved in the treatment of these patients are requested to maintain the status quo. More details will follow as soon as the new arrangements are in place.

Opioids for chronic non-cancer pain *contd from page 1*

General rules for administering opioids in chronic non-malignant pain suggest using a single long-acting oral preparation. Patients who are currently being treated with step 2 opioid drugs like dihydrocodeine should have these replaced entirely with the step 3 drug.

There is no evidence that any one opioid is more effective than another. However, short-acting drugs like pethidine can produce more euphoria, possibly resulting in a higher risk of addiction. Partial agonists or mixed agonist/antagonists like buprenorphine should be avoided.

Starting opioid therapy

Drug	Dose
First line: Morphine Sulphate MR (MST®)	10mg BD up to a maximum of 90mg BD
Second line: Oxycodone MR (Oxycontin®)	5mg BD up to a maximum of 60mg BD

A prescribing indicator is being introduced in primary care which will look at opioid choice. Morphine is the most cost-effective choice. Transdermal fentanyl patches are suitable for use when the oral route is not possible. These should be prescribed by brand as they are not interchangeable.

The trial should be concluded in a timely manner (usually no more than 8 to 12 weeks) and start at a low dose. The dose should be titrated upwards according to pain relief and side-effects to a level which delivers the required outcomes, but is below the pre-set ceiling level. It is important to have regular monitoring of efficacy and side effects and a single clinician responsible for the prescribing. Side effects should be treated early or prophylactically.

If the trial is unsuccessful, an alternative opioid from the guideline can be considered or the patient should be referred to the local chronic pain service. If the trial is successful, the opioid prescription can be continued in the longer term with regular reviews to ensure continuing efficacy, minimal side effects and absence of signs of misuse or addiction as shown below.

Signs of drug misuse or addiction

Yellow flags	Red flags
• complaining for more opioids • requesting 'specific' opioids • drug hoarding in good spells • openly acquiring other opioids • unsanctioned increase in dose • resisting change in therapy despite 'tolerable' adverse effects	• prescription forgery or loss • stealing or selling drugs • injecting drug • concurrent abuse of alcohol or other drugs • multiple dose escalations • frequent drug seeking from other sources • deterioration of function • resistance to change in therapy despite clear adverse effects

NB: These signs can appear similar to pseudoaddiction (the patient's attempt to obtain better pain relief). When pain is relieved, these behaviours cease.

New Chair for the ADTC

Dr Jonathan Fox has stepped down from his role as Chair of the ADTC, a position he has held since June 2007. He has been a member of the Scottish Medicines Consortium for a number of years and has recently been appointed as Chair of SMC's New Drugs Committee. We wish him success in his new role. Our new Chair introduces herself below.

My name is Jane Gravil and I am the new Chair of NHSGGC Area Drug & Therapeutics Committee. I graduated from Glasgow University, trained in the West of Scotland and was appointed consultant chest physician at the Royal Alexandra Hospital in 1996. I joined the RAH DTC early on, which sparked my interest in medicines management, and within a short time I became Chair. I served on the Argyll & Clyde ADTC, the New Drugs Committee of SMC and, since the creation of the new NHSGGC, I have co-chaired the New Drugs & Formulary Subcommittee.

As a physician I have always had a keen interest in good quality prescribing, with the mantra 'do no harm' and pursuing a conservative approach of start low and change one thing at a time etc. I was delighted when Clyde secured clinical pharmacists in every ward.

If I could change one thing it would be to curb the prescribing of medicines with limited value or the inappropriate use of medicines. How many times do I see an inpatient with a touch of indigestion or a minor coffee ground vomit prescribed 40mg omeprazole, or a mild COPD patient on long term carbocysteine? And there are many more examples. There is always pressure to do something when, in fact, it is okay to say "let's wait and see". It is often thought in modern medicine that we can fix everything, and if it can be done it should be; including poly-pharmacy for frail elderly patients with terminal illnesses or increasing doses in patients who don't comply with what they have already.

On the other hand medicines, such as monoclonal antibodies in Crohn's disease or rheumatoid arthritis, can be life-changing but we sometimes beat ourselves up worrying about the cost. So at a time when the financial situation is difficult, I would like to encourage doctors and non-medical prescribers to carefully consider the impact and real benefit to each patient of every medicine prescribed to free up the resources to make the big differences.

NHS Greater Glasgow and Clyde

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