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POLICY ON MANAGEMENT OF NON-*FORMULARY* PRESCRIBING

The August 2004 special edition of PostScript *highlighted some new approaches to prescribing management in Glasgow. The Prescribing Management Group has recently developed a policy on non-*Formulary *(NF) prescribing with input from, and approval by, the ADTC. This aims to promote use of the* Glasgow Formulary*, so improving the clinical and cost effectiveness of prescribing by concentrating on a smaller list of possible drug therapies for the majority of patients.*

The ADTC provides a robust system for NHS Greater Glasgow to secure good clinical advice and make evidence-based decisions about prescribing. Drugs included in the *Glasgow Formulary* are intended to cover the vast majority of patient requirements, providing clinicians with a range of cost-effective options. Where there is advice that a drug should be prescribed only on a limited basis, this will be marked in the *Formulary* "for restricted use".

NF drugs may still be prescribed where there is a clinical need. Since there should be few occasions where NF prescribing will be necessary, there is an expectation that such prescribing will not develop into a pattern of use. For the same reason, NHSGG guidelines will exclude NF drugs. Since new drugs cannot be considered for *Formulary* inclusion until after the SMC has published an opinion, the only new drugs prescribed routinely should be those with SMC approval.

There have been substantial efforts made to create a single system approach to *Formulary* management encompassing primary and secondary care. Each clinical sector has its own challenges in the application and monitoring of this policy.

In hospitals, work piloted in North Glasgow has been adopted in South Glasgow. A target list highlights NF drugs of high cost, high volume, or with a pending/recently negative SMC decision. For all drugs on this list a non-*Formulary* form needs to be signed by a consultant before distribution services will issue any drug to the requesting ward. For high cost NF drugs, the clinical director and general manager of the speciality also need to sign a high cost request form. Use of targeted drugs is monitored by completed forms and the Ascribe dispensing system tracks the amount issued.

Formulary representatives report trends in NF prescribing on a regular basis to the Prescribing Cost Control Team in the North and to the Drug & Therapeutics Committee (DTC) in the South. The appropriate forms and further information can be obtained on hospital intranets.

The unique circumstances of medicines in children, as discussed in *PostScript* 30, result in a high level of off-label use and therefore *Formulary* exclusion. Yorkhill DTC monitors NF requests at its quarterly meetings with final approval for supply resting with the Chief Pharmacist who also chairs the DTC.

In primary care, prescribing of drugs not approved by the SMC is reported quarterly to practices. Other NF prescribing is reported during routine practice visits. GPs often note that these products have been recommended by hospital practitioners. The policy states that GPs should be informed when an NF drug is recommended and reasons given why *Formulary* choices are not appropriate. Other methods of promoting the *Formulary* and Drugs of Choice scheme include prescribing indicators linked to incentive schemes or attainment of points under the new GP contract Quality and Outcomes Framework.

The NF policy aims to promote greater awareness and understanding of the *Formulary* and the SMC with prescribers. It should assist the managed introduction of new drugs and limit NF prescribing to patients who cannot be managed on *Formulary* options. The Drugs of Choice approach is complementary. Rather than assign NF status to less preferred drugs, with all the problems that would cause for supply, identifying a drug of choice encourages use of the preferred option.

Pregabalin

Pregabalin (Lyrica®) has not been added to the Glasgow Formulary *for treatment of neuropathic pain. It was launched in 2004 as an antiepileptic drug and for the treatment of neuropathic pain. It gained SMC approval and* Formulary *inclusion for use as adjunctive therapy in adults with partial seizures. In January 2005, the SMC issued notice it was not recommended for use for neuropathic pain as clinical and cost effectiveness had not been demonstrated. The company submitted additional data, but late in 2005 the SMC judged that the economic case for use in patients refractory to other treatment had not been made and so it was not recommended for use.*

The management of neuropathic pain is a notoriously difficult issue. SIGN 55 (Management of Diabetes) recommends tricyclic antidepressants first line in painful diabetic neuropathy with gabapentin as the next option. The Glasgow guidelines for managing neuropathic pain are to be updated shortly and will be circulated to all

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Incremental alphabetical list of published SMC advice on which Glasgow decisions have recently been taken.
For further information and a full list of SMC advice, visit **www.scottishmedicines.org**

Drug	Reason for consideration	Indication/Pharmacology	SMC decision in brief	Glasgow decision
Adalimumab (Humira®)	New indication	Treatment of active and progressive psoriatic arthritis in adults when the response to previous disease-modifying anti-rheumatic drug therapy has been inadequate.	Accepted for use within NHS Scotland.	*Formulary*. Acknowledge new indication.
Adefovir dipivoxil (Hepsera®)	Resubmission	For the treatment of chronic hepatitis B in adults who have either: • compensated liver disease with evidence of active viral replication, persistently elevated serum alanine aminotransferase levels and histological evidence of active liver inflammation and fibrosis; or • decompensated liver disease.	Accepted for restricted use within NHS Scotland. Restricted to patients who demonstrate lamivudine resistance.	*Formulary*. Approved for restricted use subject to local protocol by Hepatitis Treatment & Care Subgroup.
Alendronate / colecalciferol (Fosavance®)	Product update	Treatment of postmenopausal osteoporosis in patients at risk of vitamin D insufficiency.	Accepted for use within NHS Scotland.	Non-*Formulary*.
Calcipotriol / betamethasone diproprionate ointment (Dovobet®)	New medicine (Resubmission)	Initial topical treatment of stable plaque psoriasis vulgaris amenable to topical therapy.	Accepted for restricted use within NHS Scotland. Restricted to physicians experienced in treating inflammatory skin disease. The duration of treatment should not exceed four weeks.	*Formulary*. SMC restrictions apply.
Carmustine implant (Gliadel®)	New indication	Treatment of newly diagnosed high-grade malignant glioma as an adjunct to surgery and radiation.	Accepted for use within NHS Scotland.	*Formulary*. Approved for use subject to consultation with the Drugs in Oncology Group.
Ciclesonide inhaler (Alvesco®)	New medicine	Prophylactic treatment of persistent asthma in adults (18 years and older).	Accepted for use within NHS Scotland.	Non-*Formulary* following a review of inhaled corticosteroid section of *Formulary* by a multidisciplinary panel.
Cilostazol (Pletal®)	New medicine (Resubmission)	Improvement of the maximal and pain-free walking distances in patients with intermittent claudication, who do not have rest pain and who do not have evidence of peripheral tissue necrosis.	Not recommended for use within NHS Scotland.	Non-*Formulary*.
Diclofenac 1% gel patches (Voltarol Gel Patch®)	New formulation	Local symptomatic treatment of pain in epicondylitis and ankle sprain in adults.	Not recommended for use within NHS Scotland.	Non-*Formulary*.
Docetaxel (Taxotere®)	New indication	In combination with prednisolone for the treatment of hormone refractory metastatic prostate cancer.	Not recommended for use within NHS Scotland.	Non-*Formulary*.
Erlotinib (Tarceva®)	New medicine	Locally advanced or metastatic non-small cell lung cancer after failure of at least one prior chemotherapy regimen. No survival benefit or other clinically relevant effects of the treatment have been demonstrated in patients with epidermal growth-factor receptor negative tumours.	Not recommended for use within NHS Scotland.	Non-*Formulary*.
Etanercept (Enbrel®)	New indication	Treatment of adults with severe active ankylosing spondylitis who have had an inadequate response to conventional therapy.	Accepted for restricted use within NHS Scotland. Restricted to use in accordance with the British Society of Rheumatology guidelines of July 2004.	*Formulary*. Acknowledge new indication. SMC restrictions apply.
Exemestane (Aromasin®)	New indication	Adjuvant treatment of postmenopausal women with oestrogen receptor positive early invasive breast cancer, following 2-3 years of initial adjuvant tamoxifen therapy.	Accepted for restricted use within NHS Scotland. Restricted to initiation by breast cancer specialists.	*Formulary*. Acknowledge new indication. SMC restrictions apply.
Iloprost trometamol (Ventavis®)	New medicine	Treatment of patients with primary pulmonary hypertension, classified as New York Heart Association functional class III, to improve exercise capacity and symptoms as a second-line treatment where bosentan is ineffective or is not tolerated.	Accepted for restricted use within NHS Scotland. Restricted to use as an alternative in patients receiving other forms of prostacyclin treatment and to use by specialists in the Scottish Pulmonary Vascular Unit.	*Formulary*. SMC restrictions apply.
Oxaliplatin (Eloxatin®)	New indication	In combination with 5-fluorouracil and folinic acid, for the adjuvant treatment of stage III (Duke's C) colon cancer after complete resection of primary tumour.	Accepted for restricted use within NHS Scotland. Restricted to use under the supervision of an oncologist.	*Formulary*. Acknowledge new indication. SMC restrictions apply.
Palonosetron (Aloxi®)	New medicine	Prevention of nausea and vomiting associated with highly and moderately emetogenic cancer chemotherapy.	Accepted for use within NHS Scotland.	Non-*Formulary* following consultation with the Drugs in Oncology Group.
Solifenacin succinate (Vesicare®)	New medicine (Resubmission)	Symptomatic treatment of urge incontinence and/or increased urinary frequency and urgency as may occur in patients with overactive bladder syndrome.	Accepted for use within NHS Scotland.	Non-*Formulary*.
Zonisamide (Zonegran®)	New medicine	Adjunctive therapy in the treatment of adult patients with partial seizures with or without secondary generalisation.	Accepted for use within NHS Scotland. Restricted to initiation by physicians who have appropriate experience in the treatment of epilepsy.	*Formulary*. SMC restrictions apply.
Minocycline	ADTC appeal	Second-line alternative for patients with rheumatoid arthritis for whom the use of other DMARDs or anti-TNF therapy is inappropriate because of the risk of sepsis (unlicensed indication).	N/A	*Formulary*. Restricted to initiation by consultant rheumatologists for use in patients who could not be successfully treated with other DMARDs or anti-TNF therapy because of sepsis.

For all article references, check our website
http://www.glasgowformulary.scot.nhs.uk

Pregabalin *contd from page 1*

*prescribers. In line with ADTC policy on non-*Formulary *prescribing as detailed on page 1 of this edition, the guidelines will not contain any non-*Formulary *drugs, as use of these should be exceptional rather than routine.*

Dr Gavin Gordon, consultant in anaesthesia and pain management at the Victoria Infirmary, provides us with his thoughts on the use of pregabalin for neuropathic pain.

Asked to write for *PostScript*, fame at last! Such a pity that my CV now gets dusted rather than updated. Such musings led me to consider Pfizer's new drug, pregabalin, in the context of time and timing.

It is tempting to suggest that neuropathic pain (NP) did not exist when I was a student but that has more to do with terminology (think phantom pain) than my longevity. Indeed, such pain is far from uncommon, for instance painful diabetic neuropathy is estimated to affect 15% of Britain's 2 million diabetics[1].

A Medline search using neuropathic pain as keywords produces no entry before 1978, and yet in 2004 alone there were 479 articles. Interestingly, an international definition appeared only in 1994[2]. It defines NP, whatever its underlying cause, as "pain initiated or caused by a primary lesion or dysfunction of the nervous system", while peripheral NP carries the same definition but is restricted to the peripheral nervous system[3]. The definitions have brought some order to the research field, but by the mid-1990s many current treatments were already on the market, though unlicensed for this condition, eg amitriptyline.

Gabapentin is an antiepileptic drug (AED), licensed as adjunctive treatment for partial seizures, and was among the first drugs studied targeting NP. This indication was added to its licence in 1999. Pregabalin may be seen as having been developed to become its successor given the loss of gabapentin's patent[4]. The drugs are structurally alike and are believed to have a similar action on the calcium channel in the CNS. Pregabalin was granted a European marketing authorisation for treating peripheral NP (as well as similar antiepileptic indications to gabapentin) in 2004. It is more potent than gabapentin and therefore effective at lower doses, although there is no evidence that this has any clinical relevance[5]. While gabapentin benefited from an early entry into NP management, pregabalin's fate five years later has been to get caught in the mesh of the SMC's net. This comparatively new post-licensing filter has to be added to a drug's marketing authorisation and its licensed indications and dose as potential limitations to its use.

Clinical trials have shown that pregabalin is effective in reducing symptoms in painful peripheral neuropathies[6,7,8]. Pain scores are significantly reduced compared with placebo in both post herpetic neuralgia (PHN) and painful diabetic neuropathy (PDN).

The manufacturer's submission to SMC chose to compare these results with those of gabapentin, presumably on the grounds that it is the only other licensed oral medication for these conditions[9]. The results for both benefits and adverse events were comparable, but cost analysis indicated that pregabalin would be more expensive. When Pfizer resubmitted their application, the SMC did not feel that there was clear evidence of pregabalin being effective in patients in whom gabapentin had failed nor that the revised cost effectiveness data justified a change of heart.

Why is there contention about this lack of approval? The answer may be that there are currently only a small number of drugs in the *Glasgow Formulary* specifically licensed for treating NP. Phenytoin and carbamazepine have licenses for trigeminal neuralgia, gabapentin for NP and capsaicin cream for PHN or PDN (0.075% cream only under the supervision of a hospital consultant for PDN). Clearly there is not much room for manoeuvre for a condition that appears resistant to analgesics. Indeed no analgesic is licensed as such for NP, although several opiates are licensed for chronic pain.

There is an improving research and evidence base for managing NP which aids decision making. In addition to individual articles and the Cochrane database, mention should be made of the Bandolier website[10]. This group pioneered the standard of 50% pain relief as a goal of therapy and the use of numbers needed to treat (NNTs) against placebo as yardsticks and comparators.

The methodology is not perfect but it represented the pain equivalent of Mao's great leap forward. For instance, meta analysis from RCTs producing 50% pain relief in post herpetic neuralgia showed an NNT against placebo of 2.3 for AEDs and 3.0 for tricyclic antidepressants (TCAs). Although medication may not be suitable for everyone, such figures remain benchmarks for managing these painful conditions. In addition to AEDs and TCAs, there is evidence of benefit in NP for tramadol (non-*Formulary*), morphine and oxycodone[11]. Although opioids carry no specific licence for NP, they appear among first line treatments in American guidelines[11] along with lidocaine (lignocaine) patches which have a US (but not European) licence for PHN.

Where does pregabalin sit in the management of NP? As a non-*Formulary* product without SMC approval, it should be behind TCAs, gabapentin and other AEDs. The NHSGG guidelines for managing NP, which are soon to be revised, will no doubt address this thorny issue and provide structured guidance on managing this difficult condition.

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Pregabalin

References

(1) www.diabetes.org.uk
(2) Mersey and Bogduck IASP 1994 Classification of chronic pain 2nd edition.
(3)Neuropathic pain. Scadding J. Advances in clinical neuroscience and rehabilitation. 2003. 3 .2.
(4)Datamonitor January 2003 www.datamomitor.com
(5) www.drugdevelopment-technology.com/projects/pregabalin
(6)Pregabalin relieves symptoms of painful diabetic neuropathy. Dworkin et al. Neurogy 2003 60 1274
(7) Pregabalin reduces pain in post herpetic neuralgia. Sabatowski et al Pain 2004 109 26
(8)Pregabalin for treatment of painful diabetic neuropathy. Rosenstock J et al pain 2004 110 628
(9) www.scottishmedicines.org
(10) www.jr2.ox.ac.uk/bandolier
(11)Advances in neuropathic pain. Dworkin et al Arch. of neurology 2003 60 1524
(12)Combination therapy for neuropathic pain – which drugs, which combination, which patients? Raja SN et al NEJM 2005 352 1373.