PostScRxipt
from the
NHSGGC Area Drug & Therapeutics Committee
Issue 35 September 2006

DOPAMINE AGONISTS FOR RESTLESS LEGS SYNDROME

Following a positive decision from SMC, pramipexole and ropinirole have been added to the Glasgow Formulary *for the symptomatic treatment of idiopathic restless legs syndrome (RLS). They are restricted to patients with severe RLS (symptoms resulting in significant disruption to sleep and impairment of daily living). Dr Jennifer Burns, Consultant Geriatrician at the Glasgow Royal Infirmary, reviews the evidence for these drugs and their place in therapy.*

RLS is characterised by a range of unpleasant motor and sensory symptoms which usually occur immediately on sitting or lying down, are worse in the evening and early in the night and are associated with an overwhelming desire to move (akathisia). RLS is temporarily relieved by activity and predominantly affects the lower limbs. It is estimated that 10-15% of adults have restless legs; it is commoner in woman and worse in pregnancy. RLS is idiopathic but can be associated with iron deficiency anaemia and renal disease and most patients have a family history. Additional features to support diagnosis include a history of periodic limb movements during sleep disturbance and a normal neurological examination with a chronic history.

Differential diagnoses include conditions associated with motor restlessness and sensory symptoms such as nocturnal leg cramps, peripheral neuropathy, vascular disease such as varicose veins or previous deep venous thrombosis, nocturnal dyskinesias in Parkinson's disease and sleep onset myoclonus/hypnic jerks.

Treating restless legs

For most people, RLS is a phenomenon rather than a disease. A full explanation with reassurance that it is not a feature of a serious, disabling or life threatening disorder is usually sufficient. Self-help measures include avoiding caffeine and alcohol before bedtime, avoiding standing or sitting for long periods, avoiding drugs that can aggravate or mimic the symptoms, eg CNS stimulants, diuretics, calcium channel blockers and tricyclic antidepressants. Patients with iron deficiency anaemia should have the cause investigated and be treated accordingly.

There will, however, be a few patients with severe symptoms that regularly disrupt sleep and affect daytime wakefulness. These patients may seek treatment. Various medications have been used as treatment but none have been licensed in the UK for RLS until this year. Two dopamine receptor agonists, ropinirole and pramipexole, are now licensed for the symptomatic treatment of moderate to severe idiopathic RLS.

Clinical trials for both drugs used an International Restless Legs Syndrome rating scale (IRLS) which can be found at **www.jr2.ox.ac.uk/bandolier/booth/booths/RLS.html** This 10 question patient-administered scale reflects the subjective assessment of the symptoms, associated sleep problems and impact on daily life. Scores range from 0-40 and patients were selected for the trial if their score was >15. Three double blind trials with pramiprexole had starting IRLS scores of 23-29, which were reduced by 9, 7 and 4 in the 40 point scale in comparison to placebo. Patients were also evaluated using the Clinical Global Impression of Improvement (CGI-I) scale. The percentage of responders was significantly greater in the pramipexole group compared to placebo (76% versus 43%, 63% versus 33% and 72% versus 51%). The data for ropinirole is similar; pooled analysis for patients with a baseline IRLS score of 24-40 shows a 4 point reduction in comparison with placebo and CGI-I scale of 60% versus 43% at week 12. It is interesting to note the significant placebo response.

In addition to the expected adverse effects, eg nausea, vomiting and somnolence, there is concern that augmentation of symptoms will develop in some patients. This worsening of symptom severity can extend to development of symptoms in other limbs or in the trunk. It has been reported with other dopaminergic therapy in 20-30% of patients on long term treatment. The short term clinical trial evidence and short term follow-up indicated that worsening of RLS was the most common adverse effect of severe intensity in the pramipexole trials (2.3% of pramipexole patients versus 1.8% placebo). In two 52 week follow up trials with ropinirole, 2.3% and 10% of patients experienced worsening of symptoms. Clinicians should warn patients of this possibility prior to initiating therapy. Longer term follow-up will be required to assess how problematic this will be.

Summary

- The diagnosis of RLS is clinical; if in diagnostic doubt, specialist referral is appropriate, eg to a neurologist with an interest in movement disorders.
- RLS symptoms vary in severity and duration from person to person.
- Mild RLS occurs episodically causing little distress.
- Moderate symptoms occur once or twice weekly causing a degree of disruption to sleep.
- Severe symptoms occur more than twice a week and result in significant disruption to sleep and impairment of daily living. A dopamine agonist may be considered after a full discussion with patients about the symptomatic nature of the treatment and potential adverse effects.
- Pramipexole and ropinirole are on the *Formulary* for treatment of patients with severe RLS.

In this issue . . .

ADTC decisions 2
- drugs considered to date
Interested in the work of the ADTC? 4

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

Alphabetical list of most recent ADTC decisions

For full details of SMC advice, visit **www.scottishmedicines.org** For previous ADTC decisions, visit **www.glasgowformulary.scot.nhs.uk**

Drug	Indication under consideration (There may be other licensed indications)	Glasgow decision	
Beclometasone (Clenil Modulite®)	Prophylactic management of mild, moderate or severe asthma in adults or children.	*Formulary*. Acknowledge new formulation.	√
Bortezomib (Velcade®)	Monotherapy for progressive multiple myeloma in patients who have received at least one prior therapy and who have already undergone or are unsuitable for bone marrow transplantation.	Non-*Formulary*.	x
Budesonide (Novolizer®)	Persistent asthma in adults and children >6 years.	*Formulary*. Acknowledge new formulation.	√
Carbetocin (Pabal®)	Prevention of uterine atony and excessive bleeding following delivery of the infant by Caesarean section under epidural or spinal anaesthesia.	Non-*Formulary*.	x
Cetuximab (Erbitux®)	In combination with radiation therapy for the treatment of patients with locally advanced squamous cell cancer of the head and neck.	*Formulary*, subject to review of place in therapy by Regional Cancer Advisory Network. Restricted to patients who are not appropriate for or unable to tolerate chemo-radiotherapy and who are of good performance status with no evidence of distant metastases. Restricted to use by specialists in the management of head and neck cancer.	√
Clobetasol propionate cutaneous foam (Clarelux®)	Short-course treatment of steroid responsive dermatoses of the scalp such as psoriasis, which do not respond satisfactorily to less potent steroids.	*Formulary*. Acknowledge new formulation.	√
Desmopressin oral lyophilisate (DesmoMelt®)	Primary nocturnal enuresis.	*Formulary*. Acknowledge new formulation.	√
Dinoprostone vaginal delivery system (Propess®)	Initiation of cervical ripening in patients at term (from 38th week of gestation).	Decision deferred for consultation with consultant obstetricians.	
Docetaxel (Taxotere®)	Hormone-refractory metastatic prostate cancer.	*Formulary*. Acknowledge new indication. Restricted to use by specialists for patients with a Karnofsky performance-status score is 60% or more, in line with NICE Technology Appraisal 101.	√
Duloxetine (Cymbalta®)	Diabetic peripheral neuropathic pain in adults.	*Formulary*. Acknowledge new indication. Restricted to initiation by prescribers experienced in the management of diabetic peripheral neuropathic pain, as second or third line therapy.	√
Efalizumab (Raptiva®)	Psoriasis.	*Formulary*. Restricted to initiation and supervision by specialist physicians in accordance with NICE Technology Appraisal 103.	√
Erlotinib (Tarceva®)	Locally advanced or metastatic non small cell lung cancer, after failure of at least one prior chemotherapy regimen.	Decision deferred to allow consultation with the Regional Cancer Advisory Group.	
Ertapenem (Invanz®)	Treatment of intra-abdominal infections in children and adolescents.	*Formulary*. Acknowledge new indication. Restricted to second line use under the advice of microbiologists or specialists in infectious diseases for community acquired infections resistant to conventional treatments.	√
Etanercept (Enbrel®)	• Moderate to severe active rheumatoid arthritis in adults. • Psoriasis	• *Formulary*. Acknowledge new formulation • *Formulary*. Acknowledge new indication	√ √
Fondaparinux (Arixtra®)	Prevention of venous thromboembolic events in patients undergoing abdominal surgery.	Non-*Formulary*.	x

Drug	Indication under consideration (There may be other licensed indications)	Glasgow decision	
Ibandronic acid (Bonviva®)	Osteoporosis in postmenopausal women to reduce the risk of vertebral fractures.	*Formulary*. Restricted to patients unsuitable for or unable to tolerate oral treatment options. Treatment initiation should be under specialist supervision.	√
Infliximab (Remicade®)	Psoriatic arthritis.	*Formulary*. Acknowledge new indication. Restricted to criteria in NICE Technology Appraisal 104.	√
Insulin glulisine (Apidra®)	Diabetes mellitus in adults where treatment with a short-acting insulin analogue is appropriate.	*Formulary*. Restricted to patients for whom regular human insulin is inappropriate.	√
Insulin, inhaled (Exubera®)	Adults with type 2 diabetes mellitus not adequately controlled with oral antidiabetic agents and requiring insulin, or adults with type 1 diabetes mellitus, in addition to long or intermediate acting subcutaneous insulin.	Non-*Formulary*.	x
Lansoprazole (Zoton FasTab®)	Use in patients for whom a proton pump inhibitor is appropriate and who cannot tolerate capsules because of feeding tubes and dysphagia.	*Formulary*. Restricted for specialist initiation in patients with narrow-bore feeding tubes.	√
Losartan / hydrochlorothiazide (Cozaar-Comp®)	Essential hypertension in patients whose blood pressure is not adequately controlled on hydrochlorothiazide or losartan monotherapy.	Non-*Formulary*.	x
Nebivolol (Nebilet®)	Stable mild and moderate chronic heart failure with standard therapies in patients ≥70 years.	Non-*Formulary*.	x
Paricalcitol (Zemplar®)	Prevention and treatment of secondary hyperparathyroidism in patients with chronic renal failure undergoing haemodialysis.	Non-*Formulary*.	x
Pegaptanib (Macugen®)	Neovascular (wet) age-related macular degeneration.	*Formulary*, subject to referral to the Prescribing Management Group for clarification of service delivery aspects. Restricted to patients with visual acuity between 6/12 to 6/60 (inclusive). It should be stopped if visual acuity falls below 6/60 during treatment or severe visual loss is experienced.	√
Pioglitazone / metformin (Competact®)	Type 2 diabetes mellitus in overweight patients unable to achieve sufficient glycaemic control at maximally tolerated doses of metformin.	*Formulary*. Acknowledge new formulation. Restricted to initiation by physicians experienced in the treatment of diabetes mellitus for patients who cannot be treated or controlled with a sulphonylurea in combination with metformin.	√
Pregabalin (Lyrica®)	Treatment of peripheral neuropathic pain in adults.	Non-*Formulary*.	x
Rivastigmine (Exelon®)	Mild to moderately severe dementia in patients with idiopathic Parkinson's disease.	Non-*Formulary*.	x
Ropinirole (Adartrel®)	Moderate to severe idiopathic restless legs syndrome (RLS).	*Formulary*. Acknowledge new indication. Restricted to use in patients with severe RLS (symptoms resulting in significant disruption to sleep and impairment of daily living).	√
Rosiglitazone/ metformin (Avandamet®)	In combination with a sulphonylurea, as triple oral therapy in patients (particularly overweight patients) unable to achieve sufficient glycaemic control despite dual oral therapy and unable or unwilling to take insulin.	*Formulary*. Acknowledge new indication. Restricted to initiation by physicians experienced in the treatment of diabetes mellitus for patients who cannot be treated or controlled with a sulphonylurea in combination with metformin.	√
Rotigotine (Neupro®)	Monotherapy for the signs and symptoms of early-stage idiopathic Parkinson's disease.	Non-*Formulary*.	x
Salmeterol (Serevent Evohaler®)	Regular symptomatic treatment of reversible airways obstruction in patients with asthma or COPD and prevention of exercise-induced asthma.	*Formulary*. Acknowledge new formulation.	√
Testosterone (Nebido®)	Adult male hypogonadism when testosterone deficiency has been confirmed by clinical features and biochemical tests.	Non-*Formulary*.	x

Drug	Indication under consideration (There may be other licensed indications)	Glasgow decision	
Testosterone gel (Testim®)	Adult male hypogonadism when testosterone deficiency has been confirmed by clinical features and biochemical tests.	*Formulary*. Acknowledge new formulation. Restricted to use as an alternative to gel patches for patients requiring transdermal delivery.	√
Tigecycline (Tygacil®)	• Complicated intra-abdominal infection.	• *Formulary*. Restricted to second line use under the advice of microbiologists or specialists in infectious disease.	√
	• Complicated skin and soft-tissue infections.	• *Formulary*. Restricted to second or third line use under the advice of microbiologists or specialists in infectious diseases.	√
Tipranavir (Aptivus®)	HIV-1 infection in combination with low dose ritonavir in highly pre-treated adult patients with virus resistant to multiple protease inhibitors.	*Formulary*. Restricted to use by HIV specialists for patients with tipranavir mutation score <4.	√
Topiramate (Topamax®)	Prophylaxis of migraine in adults.	*Formulary*. Acknowledge new indication. Restricted to initiation by specialists and treatment should be managed under specialist supervision or shared care arrangements in patients who have not responded to prophylactic treatment with at least one other agent.	√
Travoprost /timolol (DuoTrav®)	Open-angle glaucoma or ocular hypertension in patients insufficiently responsive to topical beta-blockers or prostaglandin analogues alone.	*Formulary*. Acknowledge new formulation.	√

Interested in the work of the ADTC?

The advent of single system working and the inclusion of Clyde practitioners has presented the opportunity to review the structure and functions of the ADTC. We are looking for volunteers from all relevant professions to help with this interesting agenda. Brief details of existing and emerging committees are given below.

The Area Drug and Therapeutics Committee leads the medicines agenda on behalf of the NHS Board. Its work covers strategic, operational, professional and financial aspects of medicines management. It aims to provide a strategic lead to promote good quality and cost-effective prescribing in balance with other healthcare interventions. It meets every two months.

The Formulary and New Drugs Sub-committee provides a link with the work of the Scottish Medicines Consortium. It advises on the introduction of new drugs, including new indications and new formulations, as well as co-ordinating the maintenance, updating and development of the *Formulary*. This group meets monthly.

The Drug Utilisation, Education and Practice Sub-committee manages the evaluation of medicines utilisation data and educational initiatives that help to ensure good quality prescribing. It meets every two months.

The Safer Use of Medicines Sub-committee is a new group for Glasgow, learning from experiences in Argyll & Clyde. This will be a strongly multidisciplinary group led by Clinical Governance and will meet monthly.

The Non-Medical Prescribing Sub-committee will develop policies and structures to support the extension of prescribing and will meet every two months. A sub-group will manage Patient Group Directions across the area.

The Antimicrobial Utilisation Sub-committee will have a wide remit looking at all aspects of antimicrobial use, including primary care. It will meet every two months.

The Communications Sub-committee takes responsibility for issuing publications (such as *PostScript*) and maintaining web-based information on all aspects of medicines use. The aim is to ensure timely communication of ADTC policy and decisions. The steering group meets quarterly, the editorial board meets monthly.

Anyone interested in becoming involved in any aspect of this wide range of work should contact:
Dr Kate McKean, Head of Pharmacy and Prescribing Support Unit (kate.mckean@sgh.scot.nhs.uk) or
Dr Keith Beard, Hospital Prescribing Adviser (keith.beard@gvic.scot.nhs.uk).

PostScRipt

NHSGGC
Area Drug & Therapeutics Committee
Chair: Professor M J Brodie

Publications Sub-group
Chair: Mrs A Thompson
Dr D Gaffney, Ms K Greschner, Dr A Power, Mr I Speirits, Mr C Tuhan, Ms J Watt

Published by the Publications Sub-group to reflect the views of the Area Drug & Therapeutics Committee but not necessarily those of NHS Greater Glasgow and Clyde.

PostScript
Editor: Mrs A Thompson
Medicines Management Adviser
NHS Greater Glasgow and Clyde,Gartnavel Royal Hospital, 1055 Great Western Road, Glasgow G12 0XH tel: 0141 211 0327 fax: 0141 211 3826

Web editor: Dr A Power

Design, layout and production control:
Strathcashel Publications Project Management (01505 850 344)
Printed by: Core Image, East Kilbride