NHS Lincolnshire

Prescribing and Clinical Effectiveness Bulletin

Volume 3; Number 8 **August 2009**

What's new this month:

- **Oxycodone/naloxone prolonged release tablets (Targinact) have not been approved for use (see page 3).**
- **The Nicorette Invisipatch has been approved for use; the 25mg strength should be reserved for heavy smokers and those who have tried and failed to quit on lower strength NRT formulations (see page 4).**
- **NICE have issued clinical guidelines on the diagnosis and treatment of schizophrenia (see page 6)**
- **New shared care guidelines are available on the use of mycophenolate, sirolimus and tacrolimus for maintenance of immunosuppression after kidney transplantation in adults (see page 8)**
- **Practices are encouraged to register for the Resources for Effective Sleep Treatment Education (REST-Ed) collaborative (see page 9)**
- **Further advice is available from the MHRA on the interaction between clopidogrel and proton pump inhibitors (see page 9)**

CONTENTS

Page 3	**PACEF: Key Principles of Working**
Page 3	**Rapid Drug Assessment: Oxycodone/Naloxone prolonged release tablets (Targinact)**
Page 4	**Rapid Drug Assessment: Nicorette Invisipatch**
Page 5	**New Trials in Brief: Antibiotic prescribing for lower respiratory tract infections; Aspirin for primary prevention of cardiovascular events; Blood glucose and cardiovascular outcomes; Rosiglitazone and cardiovascular outcomes**
Page 6	**NICE Clinical Guideline 82: *Schizophrenia* (May 2009)**
Page 8	**Shared care guidelines: *Mycophenolate, Sirolimus and Tacrolimus for maintenance of immunosuppression after kidney transplantation in adults***
Page 8	**MHRA: *Drug Safety Update* (June 2009): Antipsychotics and risk of venous thromboembolic events; Chloral hydrate and Triclofos; Topical ketoprofen and photosensitivity reactions; Clopidogrel and proton pump inhibitors**

This bulletin has been created specifically to convey details of decisions taken at the Prescribing and Clinical Effectiveness Forum (PACEF) to all stakeholders across the Lincolnshire Healthcare Community in both primary and secondary care. Back issues of the *PACE Bulletin* and other PACEF publications are available through the NHS Lincolnshire website (www.lpct.nhs.uk).

SUMMARY OF PACEF DECISIONS: JUNE 2009 UPDATE

Drug	Indication(s)	Traffic Light Status
Mycophenolate mofetil capsules 250mg and tablets 500mg (CellCept)	Licensed for the prophylaxis of acute renal transplant rejection (in combination with ciclosporin and corticosteroids) under specialist supervision	AMBER NB Shared care guideline is available
Mycophenolic acid tablets 180mg and 360mg (Myfortic)	Licensed for the prophylaxis of acute renal transplant rejection (in combination with ciclosporin and corticosteroids) under specialist supervision	AMBER NB Shared care guideline is available
Nicorette Invisipatch 10mg, 15mg and 25mg transdermal patches	Nicotine replacement as an aid to smoking cessation	GREEN N.B. 25mg strength is only indicated in exceptionally heavy smokers (at least 15 cigarettes a day) and those who have tried to quit and failed on lower strength 16hour or 24 hour patches.
Oxycodone/naloxone prolonged release tablets 10mg/5mg and 20mg/10mg (Targinact)	Licensed for the treatment of severe pain.	RED-RED
Sirolimus tablets 1mg and 2mg and oral solution 1mg/ml(Rapamune)	Prophylaxis of organ rejection in kidney allograft recipients (initially in combination with ciclosporin and corticosteroid, then with corticosteroid only)	AMBER NB Shared care guideline is available
Tacrolimus capsules 500microgram, 1mg and 5mg (Prograf)	Prophylaxis of organ rejection in kidney allograft recipients and allograft rejection resistant to conventional immunosuppressive regimens	AMBER NB Shared care guideline is available

RED-RED: This signifies that a product is **not recommended** for prescribing in **either** primary or secondary care. All new products are classified as RED-RED pending assessment by PACEF.
RED: This signifies that a product has been approved for use within secondary care, tertiary care or a primary care hosted specialist service only and **should not be routinely prescribed in primary care**. RED drugs may be used within ULHT or LPFT subject to approval for use within each Trust. ULHT/LPFT reserve the right to determine whether or not RED drugs will be used within their Trusts. RED classification does not automatically signify that a drug will be available within secondary/tertiary care.
AMBER: This signifies that a drug has been approved for use in primary care **subject to specialist initiation; a shared care guideline (SCG) may also be required**. The main purpose of the SCG will be to clearly define both specialist and GP responsibilities. Not all AMBER drugs that require SCGs are currently covered by formal documents; PACEF are working to rectify this.
GREEN: This signifies a product that is **approved for initiation in either primary or secondary care**. Specialist initiation and shared care guidelines are not considered necessary.

REPORTING INCIDENTS TO THE NATIONAL PATIENT SAFETY AGENCY (NPSA)
The NPSA are keen to encourage the anonymous reporting of patient safety errors and systems failures both from healthcare professionals and patients. The National Reporting and Learning System (NRLS) has been set up to facilitate this process. Healthcare professionals can either report patient safety incidents through their local risk management scheme or directly into the NRLS using the eForm on the NPSA website. Please access www.npsa.nhs.uk for more information. **All healthcare professionals are encouraged to report incidents, errors and systems failures; the aim is to help the NHS to learn from things that go wrong.**

PACEF: Key Principles of Working

In an attempt to ensure a standardized approach to the introduction of new medicines and medicines evaluation across the NHS, a range of common principles have been agreed across the NHS Organisations within the East Midlands Strategic Health Authority. Many of these principles are crucial for future decision making at PACEF and our Local Exceptional Cases Committee. Key points are as follows:

Guidance produced by NICE

- **The PCT has a legal duty to make treatments approved within NICE Technology Appraisals available to patients within 3 months of the date of publication of the TA. These treatments will receive the highest priority.**
- All other NICE Guidance is advisory and will be carefully considered when developing strategies, planning services and prioritising resources. The PCT reserves the right to depart from NICE guidance, if the PCT has good reason to do so.

Use of cost-effectiveness, value for money and cost-effectiveness thresholds

- **PCT assessments about whether a treatment provides value for money will adopt a screening financial threshold of £30,000 per Quality Adjusted Life Year (QALY). Failure to demonstrate that a treatment is below £30,000 per QALY will result in a treatment not being routinely funded**.

NEW DRUG ASSESSMENTS

RAPID DRUG ASSESSMENT: OXYCODONE/ NALOXONE PROLONGED RELEASE TABLETS (TARGINACT)

Targinact is a new prolonged release (PR) tablet formulation of oxycodone in combination with naloxone; it is licensed for the treatment of severe pain. The theory behind this combination is that the opioid antagonist, naloxone, will counteract the opioid induced constipation associated with oxycodone.

Constipation affects between 40 and 70% of patients taking opioids. The *Palliative Care Formulary* recommends that, as a general rule, most patients receiving an opioid regularly should also receive concurrent laxative therapy; fluid and fruit intake should also be increased.

Two randomised clinical trials were reviewed that showed that the addition of naloxone to oxycodone at licensed doses did not appear to produce the symptoms of opioid withdrawal or to reduce the analgesic effect of the oxycodone. The oxycodone/naloxone combination also reduced the need for concurrent laxative treatment in some patients in comparison to prolonged release oxycodone alone.

No data exists comparing oxycodone/naloxone (Targinact) with other opioids or opioids prescribed concurrently with a separate laxative. To date, trials have focused on patients with moderate to severe non-cancer pain; there is currently no published evidence to support the use of Targinact in patients with cancer related pain. Existing trials are also short-term (limited to twelve weeks) whereas constipation related to opioid use tends to be a chronic long term condition; there is also a lack of long term safety data. A cost comparison reveals the following:

Drug	Daily dose range	Cost (28 days)
Oxycodone/naloxone PR 10mg/5mg tablets (Targinact)	**1 tablet twice daily**	**£35.11**
Oxycodone/naloxone PR 20mg/10mg tablets (Targinact)	**1 tablet twice daily**	**£70.22**
Oxycodone 10mg modified release (MR) tablets (Oxycontin)	1 tablet twice daily	£25.41
Oxycodone 20mg MR tablets (Oxycontin)	1 tablet twice daily	£50.82
Morphine sulphate MR capsules 30mg (Zomorph)	1 tablet twice daily	£9.12
Morphine sulphate MR tablets 30mg (MST Continus)	1 tablet twice daily	£11.81
Senna tablets 7.5mg	2 to 4 tablets usually at night.	£1.76-3.52
Docusate sodium	Up to 500mg daily	£8.96
Lactulose solution	15ml twice daily	£7.39
Bisacodyl tablets 5mg	10mg at night	£1.83
Ispaghula husk	1 sachet 1-3 times daily	£1.84 -£7.32
Macrogol (Movicol)	1-3 sachets daily	£6.23- £18.70

PACEF Recommendation:

In published trials, oxycodone/naloxone PR tablets (Targinact) have been shown to marginally reduce laxative use in some patients without any impairment of analgesic effect or symptoms of opioid withdrawal. However, no comparative studies have yet been published comparing Targinact with separate opioid/laxative combination therapy. In addition, the short-term nature of existing studies provides no assurance of long-term safety, nor is there published data on the use of the product in the treatment of cancer pain. The cost in comparison to other opioids and standard laxatives is excessive, particularly when it is considered that many of the patients prescribed Targinact will still require concurrent laxative treatment. Fixed dose combination analgesics can also create problems during incremental dose adjustment and titration as it is impossible to adjust the dose of one component without adjusting the dose of both. After consideration of all these factors oxycodone/naloxone PR tablets (Targinact) are designated: RED-RED.

RAPID DRUG ASSESSMENT: NICORETTE INVISIPATCH

The Nicorette Invisipatch is a new 16 hour transdermal nicotine patch launched as an addition to the already extensive Nicorette range; 10mg, 15mg and a high strength 25mg version are all available. It is licensed for use as an aid to smoking cessation. The trial evidence supporting the use of the 25mg strength comes from the CEASE Study that was originally published in 1999. This large multicentre randomised controlled trial involving 3,575 patients concluded that use of both a 10mg and 15mg patch simultaneously in heavy smokers (defined as smoking at least 15 cigarettes a day for at least 3 years) was a more effective aid to smoking cessation than the 15mg patch. In 1999, a 25mg patch was not available; subsequent technological improvements have enabled the formulation of a 25mg patch that is both semitransparent and smaller than the standard Nicorette patch. A cost comparison revealed that the Nicorette Invisipatch was only marginally more expensive than alternative transdermal nicotine formulations.

PACEF Recommendation:

PACEF were convinced by the evidence from the CEASE Study that a 25mg 16 hour nicotine patch could offer additional support to particularly heavy smokers committed to quit. As a result of this, all three strengths of the Nicorette Invisipatch were designated: GREEN. The 25mg patch should only be used in patients smoking at least 15 cigarettes a day or in those who have tried and failed to quit on a lower strength 16hour or 24 hour patch.

NEW TRIALS IN BRIEF: JUNE 2009

Antibiotic prescribing for lower respiratory tract infections: *BMJ* 2009; 338: b1374

Forty GPs from 20 practices were trained to provide finger prick near patient C reactive protein (CRP) tests and/or a communication skills intervention. CRP is an inflammatory marker that is usually raised when any (bacterial or viral) infection is present. The GPs in the CRP test group prescribed significantly fewer antibiotics than those in the no test group (31% vs. 53%). Similarly those who received training in enhanced communication skills prescribed significantly fewer antibiotics than those who received no training (27% vs. 54%). The authors conclude that the use of CRP testing may help to support the safe withholding of antibiotics from people with low CRP values who probably won't benefit from antibiotic treatment anyway. However, the cost-effectiveness of such an approach needs careful assessment and the undoubted benefits of enhanced communication further exploration.

Reference: Cals JWL et al. Effect of point of care testing for C reactive protein and training in communication skills on antibiotic use in lower respiratory tract infections: cluster randomised trial. *BMJ* 2009;338:b1374, doi 10.1136/bmj.b1374

Aspirin for primary prevention of cardiovascular events: *The Lancet* 2009; 373: 1849– 60.

This is a meta-analysis of participants in six primary prevention trials and sixteen secondary prevention trials of low dose aspirin. In terms of secondary prevention, aspirin emerges as of significant benefit. In terms of primary prevention, the results are more equivocal. On the benefits side, in the primary prevention trials aspirin reduced serious vascular events by 12% (0.51% vs. 0.57% (control) per year). This was mainly due to a reduction in non-fatal myocardial infarction (MI); there was no significant difference in the risk of strokes and vascular mortality. In terms of harms, aspirin was associated with increased gastrointestinal and extra-cranial bleeds (0.10% vs. 0.07% (control) per year). This meta-analysis contributes to the ongoing debate over the net value of aspirin in primary prevention as the reduction in occlusive events has to be weighed against the increased risk of major bleeds.

Reference: Antithrombotic Trialists' Collaboration. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. *The Lancet* 2009; 373: 1849 – 1860. doi:10.1016/S0140-6736(09)60503-1

Blood glucose and cardiovascular outcomes: *Lancet* 2009;373:1765-1772.

This is a meta-analysis of five RCTs (ACCORD, ADVANCE, VADT (Veterans), UKPDS and PROactive) involving over 33,000 participants and assessing the effect of intensive blood glucose lowering in diabetes on the rate of death or cardiovascular outcomes compared with a standard regimen. The mean HbA1c was 0.9% lower for participants given intensive treatment than for those given standard treatment. Intensive glycaemic control resulted in a 17% reduction in non-fatal MI and a 15% reduction in CHD events. Intensive glycaemic control had no significant effect on stroke or all cause mortality. The Number Needed to Treat (NNT) over 5 years to prevent one MI or one CHD event was estimated as 87 and 69 respectively. This suggests a small benefit associated with intensive blood glucose control in type 2 diabetes in reducing CHD but not stroke or death.

Reference: Ray KK et al. Effect of intensive control of glucose on cardiovascular outcomes and death in patients with diabetes mellitus: a meta-analysis of randomised controlled trials. *The Lancet* 2009;373:1765-1772.doi:10.1016/S0140-6736(09)60697-8

Rosiglitazone and cardiovascular outcomes

4447 type 2 diabetics on metformin or sulphonylurea monotherapy (mean HbA1c 7.9%) were randomly assigned to additional rosiglitazone or metformin/ sulphonylurea combination therapy. 321 people in the rosiglitazone group and 323 in the control group experienced the primary outcome of cardiovascular hospitalisation

or cardiovascular death, during a mean follow up of 5.5 years. Rosiglitazone increased the risk of heart failure causing admission to hospital (61 people in the rosiglitazone group and 29 in the active control group). Fracture rates were also increased (mainly in women).

Reference: Home PD et al. Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicentre, randomised, open-label trial. *The Lancet*, Early Online Publication, 5th June 2009. doi:10.1016/S0140-6736(09)60953-3

NICE CLINICAL GUIDELINE 82: *SCHIZOPHRENIA – CORE INTERVENTIONS IN THE TREATMENT AND MANAGEMENT OF SCHIZOPHRENIA IN ADULTS IN PRIMARY AND SECONDARY CARE* (MARCH 2009)

The key points of the guideline are as follows:

Primary care and physical health

- **GPs and other primary healthcare professionals should monitor the physical health of people with schizophrenia at least once a year. Focus should be on cardiovascular disease risk assessment; people with schizophrenia are at a higher risk of CVD than the general population.**

Psychological interventions

- Cognitive behavioural therapy (CBT) should be offered to all people with schizophrenia either during the acute phase or later, including inpatient settings.
- Family intervention should be offered to all families of people with schizophrenia who live with or are in close contact with a service user either during the acute phase or later, including inpatient settings.

Pharmacological interventions

- For people with newly diagnosed schizophrenia, offer **oral antipsychotic medication**. Provide information and discuss the **benefits and side-effect profile of each drug** with the service user. The choice of drug should be made by the service user and healthcare professional together considering: (1) the relative potential of individual antipsychotic drugs to cause **extrapyramidal side effects** (including akathisia), **metabolic side effects** (including weight gain) and **other side effects** (including unpleasant subjective experiences).
- **Do not initiate regular combined antipsychotic medication**, except for short periods (for example when changing medication).

Interventions for people with schizophrenia whose illness has not responded adequately to treatment

- For people with schizophrenia whose illness has not responded adequately to pharmacological or psychological treatment: (1) review the diagnosis; (2) establish that there has been adherence to antipsychotic medication, prescribed at an adequate dose and for the correct duration; (3) review engagement with and use of psychological treatments and ensure that these have been offered; (4) consider other causes of non-response (e.g. co-morbid substance misuse (including alcohol), the concurrent use of other prescribed medication or physical illness).
- **Offer clozapine to people with schizophrenia whose illness has not responded adequately to treatment despite the sequential use of adequate doses of at least two different antipsychotic drugs. At least one of the drugs should be a non-clozapine second generation antipsychotic.**

Initiating treatment (first episode)

- **Urgently refer all people first presenting with psychotic symptoms in primary care to a local community-based secondary mental health**

service (early intervention services, crisis resolution and home treatment team, or community mental health team).

- Carry out a full assessment in secondary care, including assessment by a psychiatrist. Write a care plan with the service user and send a copy to the referring primary healthcare professional and service user.
- Include a crisis plan in the care plan, based on a full risk assessment. Define the roles of primary and secondary care in the crisis plan and include key clinical contacts in case of emergency or impending crisis.

Early intervention services

- Offer early intervention services to all people with a first episode or first presentation of psychosis irrespective of age or duration of untreated psychosis. Refer from primary or secondary care.

Early treatment

- **If it is necessary for a GP to start antipsychotic medication they should have experience in treating and managing schizophrenia.**
- **Before starting antipsychotics offer an electrocardiogram (ECG) if: (1) specified in the SPC; or (2) physical examination shows specific CV risk (e.g. high blood pressure); or (3) there is a personal history of CV disease; or (4) the service user is being admitted as an inpatient.**
- Consider treatment with antipsychotic medication as an individual therapeutic trial: (1) Record the indications, expected benefits and risks, and expected time for a change in symptoms and for side effects to occur; (2) **Start with a dose at the lower end of the licensed range and titrate slowly upwards within the dose range in the *BNF***: (3) **Justify and record reasons for dosages outside the range specified in the BNF or SPC**; (4) **Monitor and record efficacy, including changes in symptoms and behaviour, side effects, adherence, physical health;** (5) **Record the rationale for continuing, changing or stopping medication and the effects of such changes;** (6) **Carry out a trial of the medication at optimum dosage for 4-6 weeks.**
- **Discuss with the service user any prescribed and non-prescribed medication (including complementary therapies) currently in use as well as use of alcohol, tobacco and illicit drugs. Discuss their possible interference with the effects of prescribed medication and psychological treatments.**
- **When prescribing as required antipsychotic medication, review clinical indications, frequency of administration, therapeutic benefits and side effects each week as appropriate.** Check whether the dose is above the maximum in the *BNF* or SPC**.**
- **Do not use a loading dose of antipsychotic medication ('rapid neuroleptisation')**
- **Warn of a potential photosensitive skin response with chlorpromazine and advise using sunscreen if necessary.**

Rapid tranquillisation

- Consider rapid tranquillisation for people who pose an immediate threat to themselves or others during an acute episode.

The early post-acute period

- Inform service users about the high risk of relapse if medication is stopped in 1 to 2 years.
- If withdrawing anti-psychotic medication, do this gradually. Regularly monitor for signs and symptoms of relapse for at least 2 years after withdrawal.

Promoting recovery

- Develop and use practice case registers to monitor the physical and mental health of service users.

- Consider re-referral to secondary care if there is: poor treatment response, non-adherence to medication, intolerable side effects, co-morbid substance abuse or risk to the person or others.

Medication for promoting recovery

- Do not use antipsychotic medication solely during periods of relapse or symptom exacerbation.
- Consider offering depot/long-acting injectable antipsychotics when service users would prefer this and where avoiding covert non-adherence to medication is a clinical priority. Initially use a small test dose according to the *BNF* or SPC.

SHARED CARE GUIDELINES

PACEF have approved shared care guidelines entitled:

- *Mycophenolate mofetel or mycophenolic acid for maintenance of immunosuppression after kidney transplantation in adults*
- *Sirolimus for maintenance of immunosuppression after kidney transplantation in adults*
- *Tacrolimus for maintenance of immunosuppression after kidney transplantation in adults*

Copies are available from Cathy Johnson, Interface Lead Pharmacist at cathy.johnson@lpct.nhs.uk

MEDICINES AND HEALTHCARE PRODUCTS REGULATORY AGENCY (MHRA): *DRUG SAFETY UPDATE* (JUNE 2009)

Antipsychotics: risk of venous thromboembolic events

- Antipsychotic use may be associated with an increased risk of venous thromboembolic events (VTE).
- Some of the known side effects of antipsychotics (e.g. sedation, weight gain) are known risk factors for VTE; a direct or indirect causal association between antipsychotic use and VTE cannot be excluded.
- At present there is insufficient data to determine any difference in risk between atypical and conventional antipsychotics or between individual drugs.
- All possible risk factors for VTE should be identified before and during antipsychotic treatment and preventative measures taken.

Chloral hydrate (Welldorm) and Triclofos: not first-line options for insomnia

- Product information for chloral hydrate (Welldorm) and Triclofos has recently been changed to ensure that they are not used as first-line options for insomnia.
- They are indicated only for short-term treatment of severe insomnia which is interfering with normal daily life and where other therapies have failed; they should be used as an adjunct to non-pharmacological therapies.
- The use of hypnotics is not recommended in children or adolescents; where hypnotics are used it should be under the supervision of a specialist.
- Welldorm elixir can be used in children aged 2 or older as an adjunct to behavioural therapy and sleep-hygiene management. Duration of treatment should not usually exceed 2 weeks.

PACEF Recommendation:
Practices are reminded that the Resources for Effective Sleep Treatment (REST) Project are in the process of recruiting a new collaborative group known as REST-Ed. This group is designed to share the learning from the project to date and to encourage the wider adoption of non-pharmacological approaches to sleep management. The REST team have worked closely with Lincolnshire GPs and have consulted with patients to devise and test the sleep management package that will form the basis of the collaborative work. Practices interested in taking part should contact either Stephen Gibson (steve.gibson@lpct.nhs.uk) or Susan Ferguson (susan.ferguson@lpct.nhs.uk).

Topical ketoprofen: risk of photosensitivity reactions

- Topical ketoprofen causes photosensitivity reactions; users should be advised to avoid direct sunlight, ultraviolet rays, sunbeds or sunlamps.
- If skin reactions develop, ketoprofen should be stopped and medical attention sought.

Clopidogrel and proton pump inhibitors: possible interaction

- Clopidogrel can cause gastrointestinal symptoms and is frequently co-prescribed with a proton pump inhibitor (PPI). Co-prescribing of clopidogrel and aspirin further compounds the problem.
- The EU Committee for Medicinal products for Human Use (CHMP) has reviewed the available evidence for a possible interaction between clopidogrel and PPIs. **The data support a clinically significant interaction that makes clopidogrel less effective when given with a PPI.**
- **Concomitant use of a PPI and clopidogrel is not recommended unless considered essential.**
- The need for PPI therapy in patients taking clopidogrel should be reviewed at the patient's next appointment.
- Patients taking clopidogrel should be advised not to buy over-the-counter omeprazole.
- Further advice is expected from the MHRA in July 2009.

PACEF Recommendations:
(1) Clopidogrel should only be initiated in accordance with NICE guidance. Existing patients taking clopidogrel should be subject to regular review;
(2) Prescribers should re-evaluate the need to start or continue concurrent treatment with a PPI in patients taking clopidogrel. If the patient's risk of gastrointestinal adverse events can be reduced in any other way (e.g. through the avoidance of concomitant NSAIDs) this should be considered. If dyspepsia occurs with clopidogrel, consider a histamine H_2 – receptor antagonist such as ranitidine;
(3) Prescribers should be aware of the potential drug interaction between clopidogrel and PPIs when initiating or reviewing patients on the drug; PPIs should only be used in conjunction with clopidogrel where there is a specific indication and not for routine prophylaxis.
Further guidance will be issued by PACEF following the publication of the FDA review and any further advice from the MHRA.

Acknowlegements

Many thanks to Cathy Johnson, Interface Lead Pharmacist, and Gill Kaylor, Prescribing Adviser, for their contributions to this edition of the *PACE Bulletin*.

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