NHS Lincolnshire

Prescribing and Clinical Effectiveness Bulletin

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What's new this month:

- **Altretinoin capsules (Toctino) are approved for use by dermatologists in the treatment of severe, chronic hand eczema; there is no primary care role (see page 3).**
- **Aripiprazole injection (Abilify) is approved for use within Lincolnshire Partnership Foundation Trust for the rapid control of agitation and disturbed behaviours; there is no primary care role (see page 3).**
- **Fentanyl buccal tablets (Effentora) and fentanyl sublingual tablets (Abstral) are both approved for use in adult patients with cancer experiencing breakthrough pain where oral morphine is inappropriate or inadequate and adequate background analgesia is already established (see page 4).**
- **The Veterans Affairs Diabetes Trial is reviewed (see page 5).**
- **NICE have approved sunitinib (Sutent) for use as a first line treatment for advanced and/or metastatic renal cell carcinoma (see page 9).**
- **NICE have issued separate Clinical Guidelines on Antisocial Personality Disorder, Borderline Personality Disorder and Rheumatoid Arthritis (see pages 9 to 12)**
- **The Medicines and Healthcare products Regulatory Agency (MHRA) have raised safety concerns relating to antiepileptics and decreased bone mineral density and the use of over the counter cough and cold remedies in children, They have also provided advice to prescribers on the use of off-label or unlicensed medicines (see page 12).**

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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. Steps will be taken to ensure the widest possible distribution across NHS Lincolnshire and within United Lincolnshire Hospitals Trust (ULHT) and Lincolnshire Partnership Foundation Trust (LPFT)
. Both paper and electronic copies will be circulated initially with a view to evolving into complete electronic distribution as soon as we are confident that all key stakeholders can access E-mail. There are also plans to make all bulletins, guidelines, formularies, new product assessments, care pathways and other PACEF publications available through the NHS Lincolnshire website.

SUMMARY OF PACEF DECISIONS: APRIL 2009 UPDATE

Drug	Indication(s)	Traffic Light Status
Alitretinoin capsules (Toctino)	Licensed for the treatment of severe, chronic hand eczema unresponsive to treatment with potent topical corticosteroids.	RED; for dermatologist use only.
Anakinra inj (Kineret)	Licensed for rheumatoid arthritis	RED-RED
Aripiprazole IM injection (Abilify)	Licensed for the rapid control of agitation and disturbed behaviours in patients with schizophrenia or in patients with manic episodes in Bipolar I Disorder, when oral therapy is not appropriate.	RED; approved for use within LPFT only.
Fentanyl buccal tablets (Effentora)	Licensed for the management of breakthrough pain (BTP) in adult patients with cancer already receiving opioid treatment for chronic cancer pain.	GREEN For second line use only in adult patients with cancer experiencing BTP where oral morphine is judged to be unsuitable or inadequate and where adequate background analgesia is already established.
Fentanyl sublingual tablets (Abstral)	Licensed for the management of breakthrough pain (BTP) in adult patients with cancer already receiving opioid treatment for chronic cancer pain.	GREEN For second line use only in adult patients with cancer experiencing BTP where oral morphine is judged to be unsuitable or inadequate and where adequate background analgesia is already established.
Sunitinib capsules (Sutent)	First line treatment for advanced and/or metastatic renal cell carcinoma.	RED For specialist use only

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 or tertiary care **only** and has **no role 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; in the coming months PACEF will be 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.

NEW DRUG ASSESSMENT: ALITRETINOIN CAPSULES (TOCTINO)

Alitretinoin (Toctino) is a retinoic acid derivative available as 10mg and 30mg capsules and licensed for the treatment of severe, chronic hand eczema unresponsive to treatment with potent topical corticosteroids.

Two randomised controlled trials have demonstrated the efficacy of alitretinoin for this indication. The BACH (Benefit of Alitretinoin in Chronic Hand Dermatitis) study compared alitretinoin 10mg and 30mg with placebo in 1032 patients treated for 24 weeks. Both dose regimens of alitretinoin were significantly more effective than placebo, but the 30mg dose resulted in better and faster responses. A second study evaluated the safety and efficacy of a second 12-24 week course of alitretinoin 10mg or 30mg in 117 patients with severe chronic hand eczema who had previously responded to treatment in the BACH study but whose symptoms had returned. Re-treatment was effective and well-tolerated with the highest response rates again being seen in the 30mg dose group.

The main adverse events identified in these studies included headache, dry mouth and erythema; increases in cholesterol and triglyceride levels occurred as well as asymptomatic changes in thyroid stimulating hormone levels. Adverse events were generally dose-dependent and reversible. Alitretinoin is teratogenic and contraindicated in woman of childbearing potential unless all of the conditions of a defined Pregnancy Prevention Programme are met.

The current treatment options for patients with severe, chronic hand eczema unresponsive to topical steroids are all unlicensed (i.e. topical or oral immunosuppressants or psoralen plus exposure to ultraviolet A radiation (PUVA)). While no comparative trial data exists between alitretinoin and any of these alternatives, alitretinoin offers the advantage of being both licensed and evidence-based. Its use may delay or potentially remove the need to use PUVA or immunosuppression in these patients. An average treatment course of alitretinoin costs approximately £1500.

PACEF Recommendation:
Alitretinoin is the first licensed oral treatment for patients with severe chronic hand eczema which is unresponsive to topical corticosteroids. It has not been compared in clinical trials with current treatment options, but is licensed and of proven efficacy. Alternatives such as oral immunosuppressants carry risks and require extensive monitoring; PUVA is inconvenient for patients and carries a long-term risk of skin cancer. As a result of this alitretinoin is designated RED; it is approved for use within secondary care by dermatologists only. This guidance will be reviewed when NICE publish their Technology Appraisal of alitretinoin later in the year.

NEW DRUG ASSESSMENT: ARIPIPRAZOLE IM INJECTION (ABILIFY)

Aripiprazole is an atypical antipsychotic. The solution for injection (Abilify) is licensed for the rapid control of agitation and disturbed behaviours in patients with schizophrenia or in patients with manic episodes in Bipolar I Disorder, when oral therapy is not appropriate.

Aripiprazole appears to have broadly similar efficacy to haloperidol in reducing acute agitation, with less over-sedation, lower risk of Extra-Pyramidal Side Effects (EPSEs) and overall better tolerability under trial conditions. The efficacy of aripiprazole IM 9.75mg may be lower than that of olanzapine IM 10mg; aripiprazole and olanzapine

IM are broadly comparable in terms of cost. There are no head-to-head RCTs comparing aripiprazole with any other IM atypical antipsychotics.

PACEF Recommendation:
Aripiprazole IM injection is designated RED for use within LPFT only. The use of aripiprazole IM should be limited to the treatment of agitation in inpatients for whom the drug is indicated and who are not receiving regular antipsychotic medication (other than oral aripiprazole). If follow-on treatment with regular antipsychotic medication is required following a successful response to aripiprazole IM, then oral aripiprazole should be the drug of choice.

RAPID ASSESSMENTS: FENTANYL BUCCAL TABLETS (EFFENTORA) AND FENTANYL SUBLINGUAL TABLETS (ABSTRAL)

Guidance from the *Palliative Care Formulary* on the management of breakthrough pain (BTP) emphasises the importance of ensuring adequate background analgesia. There are two types of BTP: **predictable (incident)** related to movement or activity (e.g. swallowing, coughing) and **unpredictable (spontaneous)** unrelated to movement or activity. Predictable BTP can often be managed by the timing of a procedure or movement to coincide with the peak plasma concentration of analgesic medication or by giving an extra dose of regular analgesia.

Assuming adequate background analgesia, if further opioid based analgesia is required for BTP, the first line option is to give an additional as required dose of standard release morphine often administered orally as liquid or tablets. The disadvantage of oral morphine in this context is that episodes of BTP are often of rapid onset and short duration (20-30 minutes), whereas oral morphine has a relatively slow onset (30 minutes) and a long duration (3-6 hours); this results in the patient receiving additional analgesia that is inadequate in the early stages of the BTP episode and excessive in the later stages. Second line options include fentanyl lozenges (Atiq) (licensed for BTP) and various unlicensed alternatives (e.g. fentanyl injection administered sublingually, SC or intravenously, alfentanil injection and IV ketamine).

As a result of this, PACEF approached the assessment of these two new fentanyl oral formulations aware that a second line role for fentanyl for BTP is already established, but also aware that the majority of available options are unlicensed.

Both fentanyl buccal tablets (Effentora) and fentanyl sublingual tablets (Abstral) are licensed for the management of BTP in adult patients with cancer already receiving opioid treatment for chronic cancer pain. The clinical evidence supporting the use of fentanyl buccal tablets (Effentora) comes from two randomised placebo controlled trials. Both trials included an initial open label dose titration period of 7 days during which it was established whether the patient was responsive to fentanyl buccal tablets and at what dose. Responsive patients were entered into the second randomised double blind phase of the trial which lasted for 21 days. In the second phase all patients were supplied with 10 tablets, seven of which contained the dose of fentanyl buccal they responded to in the first phase plus 3 placebo tablets; these tablets were taken in a predefined random order and allowed comparison of active treatment and placebo in each patient. A trial of similar construction was also reviewed for fentanyl sublingual tablets (Abstral). All of the trials reviewed confirmed that adequate pain relief was achieved with both products at a pre-established effective dose within ten minutes of administration. From the dose titration stages of the two Effentora trials, only two thirds of patients (62-67%) treated with Effentora

obtained symptomatic relief; this suggests that not all types of BTP benefit from buccal fentanyl therapy. The lack of comparative data against alternative opioids also means that we have no way of determining whether either of these treatments is superior or inferior to other alternatives.

Adverse effects reported the Effentora trials included application site pain, ulcer or burning; the most common reported adverse effects were nausea and dizziness (10%). The most commonly reported side effects for Abstral were nausea, vomiting, constipation, headache, somnolence, fatigue and dizziness.

A cost comparison of these agents compared to alternatives reveals the following:

Drug	**Strength**	**Cost (£) per dose**
Fentanyl buccal tablets (Effentora)	**All strengths**	**£20.56 (4) £5.14 per dose**
Fentanyl sublingual (Abstral)	**All strengths**	**£49.99 (10) £4.99 per dose**
Fentanyl lozenge (Atiq)	All strengths	£18.58 (3) £6.19 per dose
Morphine tablets (Sevredol)	10mg	£5.61 (56) £0.10 per dose
Morphine tablet (Sevredol)	20mg	£11.21 (56) £0.20 per dose
Morphine solution	10mg/5ml	£1.78(100ml) £0.09 per 5ml (10mg) dose
Morphine solution	20mg/ml	£4.98 (30ml) £0.17 per 20mg dose.
Oxycodone (OxyNorm) capsules	5mg	£11.59 (56) £0.21 per dose
Oxycodone (OxyNorm) capsules	10mg	£23.19 (56) £0.41 per dose
Oxycodone (OxyNorm) capsules	20mg	£46.38 (56) £0.83 per dose

PACEF Recommendation:
PACEF acknowledge the second line role of fentanyl preparations in the management of BTP where adequate background analgesia is already established. The trial evidence in support of both fentanyl buccal tablets (Effentora) and fentanyl sublingual tablets (Abstral) is limited, but establishes that both products are effective at delivering symptomatic relief of BTP within ten minutes of administration. Both products are also significantly lower in price than the only alternative licensed oral fentanyl preparation, Atiq lozenges. As a result of this, both fentanyl buccal tablets (Effentora) and fentanyl sublingual tablets (Abstral) are designated: GREEN. Both products are second line and should only be used in adult patients with cancer experiencing BTP where oral morphine is judged to be unsuitable or inadequate and where adequate background analgesia is already established.

NEW TRIAL ASSESSMENT: THE VETERANS AFFAIRS DIABETES TRIAL (VADT)

Randomised controlled trials set up to investigate the relative benefits/disbenefits of intensive blood glucose control compared to standard control in the management of type 2 diabetes mellitus (DM) have proved disappointing in their failure to show significant reductions in adverse cardiovascular (CV) outcomes related to intensive therapy. In fact, intensive blood glucose control, if done too aggressively, may even

increase the risk of adverse outcomes. Recently, the ACCORD and ADVANCE studies were set up to assess whether more intensive glucose control strategies offered any significant advantage over standard therapies with regard to major CV events. In both of these studies, greater reductions in HbA1c levels were not associated with significant improvements in important patient-oriented outcomes (with the exception of reduced nephropathy in ADVANCE). Indeed, in ACCORD, intensive therapy was associated with an increased risk of death, although the target HbA1c of 6% was lower than that generally advised by NICE and downward shifts in HbA1c were achieved rapidly. The Veterans Affairs Diabetes Trial (VADT) was set up to compare the effects of intensive and standard glucose control on cardiovascular events in long-standing type 2 diabetic patients in an attempt to reduce uncertainty in this area.

VADT randomly assigned 1791 military veterans (mean age, 60.4 years; 97% male) with a suboptimal response to therapy for type 2 DM to receive either intensive or standard glucose control. The mean number of years since the diagnosis of diabetes was 11.5 and 40% of the study participants had already had a CV event.
The goal in the intensive therapy group was an absolute reduction of 1.5 percentage points in the glycated haemoglobin level, as compared with the standard therapy group. In both groups, patients with a body mass index (BMI) of 27 or more were started on two oral agents, metformin plus rosiglitazone; those with a BMI of less than 27 were started on glimepiride plus rosiglitazone. Patients in the intensive-therapy group were started on maximal doses, and those in the standard therapy group were started on half the maximal doses. The primary outcome was the time to the first occurrence of any one of a composite of CV events including myocardial infarction (MI), stroke, death from CV causes, new or worsening congestive heart failure, surgical intervention for cardiac, cerebrovascular, or peripheral vascular disease, inoperable coronary artery disease and amputation for ischemic gangrene. Secondary cardiovascular outcomes included new or worsening angina, new transient ischemic attacks, new intermittent claudication, new critical limb ischemia, and death from any cause. Secondary outcomes also included microvascular complications (retinopathy, nephropathy, and neuropathy). Adverse events, including hypoglycaemia, were also monitored.

Both groups started with an average HbA1c of 9.4%. At the end of the study (after a median follow-up 5.6 years), the standard therapy group achieved an average HbA1c of 8.4% and the intensive therapy group 6.9%. The effect of this on the primary end-point was that 264 events (33.5%) occurred in the standard therapy group and 235 events (29.5%) in the intensive therapy group (a relative reduction of 11.9%; absolute reduction 4%). While there were fewer events in the intensive therapy arm, this did not achieve statistical significance. There was also no statistically significant difference between the groups in any of the secondary outcomes, although there was a non-significant trend towards decreased incidence and severity of diabetic retinopathy in the intensive therapy group. In terms of safety, the most common adverse effect was hypoglycaemia with significantly more episodes in the intensive therapy group.

A number of issues arose from the PACEF assessment of this trial:
(1) There are considerable differences between the methodology of this study and standard UK practice in the management of type 2 DM. This makes the application of these findings to a UK population problematic.
(2) Changes to medication following the initial choice and dose of oral agents (either metformin or glimepiride along with rosiglitazone) and subsequent addition of insulin (where necessary) were determined by a protocol which allowed for the use of any

approved drug at the discretion of the investigator. Details of doses and drugs used in this latter stage of the trial are not detailed in the paper. This makes it difficult to draw clear conclusions from these results.
(3) Changes in therapeutic agents have occurred since this trial was designed and the availability of these new agents was limited during the trial.
(4) The results of VADT cannot be extrapolated to women as they only made up 2.9% of the study population.
(5) It is possible that the study was under-powered to adequately discriminate between the intensive and standard therapy arms. The authors of the study acknowledge this and attribute it to a lower event rate than anticipated.
(6) The average duration of follow up may have been insufficient to show the later CV benefits of lower HbA1c. VADT does not address the question of the effects of early intensive therapy as the recruited population were all long-standing sufferers of diabetes.
(7) Rosiglitazone was used in initial therapy which may have had some confounding effect due to its recognised cardiovascular problems.

PACEF Observations:
Large observational studies show a strong link between hyperglycaemia (as measured by HbA1c) and both macrovascular and microvascular complications; such complications are observed to show a marked reduction with tighter blood glucose control. Traditionally, observational data has been used to support the hypothesis that the lower the HbA1c the better. On the other hand, RCTs largely report no significant reductions in CV adverse outcomes associated with more intensive hypoglycaemic therapy compared to standard therapy. The VADT appears to corroborate the results of previous RCTs in showing no significant cardiovascular benefits of intensive hypoglycaemic therapy. However, the trial also corroborates previous observational findings in that it identifies a trend towards lower adverse CV outcomes with intensive therapy (although this doesn't achieve statistical significance); important microvascular complications such as retinopathy and nephropathy were also shown to be reduced by more intensive treatment to lower HbA1c targets. The increased risk of hypoglycaemia with intensive therapy is also identified. Ultimately, VADT makes a solid contribution to ongoing debate, but does not lend itself to definitive conclusions. PACEF will continue to monitor this area of study and issue further guidance in the future.

Reference: Duckworth W et al., 'Glucose Control and Vascular Complications in Veterans with Type 2 Diabetes', *New England Journal of Medicine* 2009; **360:** 129-39.

NEW TRIALS IN BRIEF: APRIL 2009

Efficacy and Safety of Insulin Analogues: *CMAJ* 2009; 180(4): 385 – 397.

This is a systematic review of the efficacy and safety of rapid and long acting insulin analogues in type 1 and type 2 DM. Minimal differences were found in HbA1c between newer insulin analogues and conventional insulins and benefits in terms of reduced hypoglycaemia were inconsistent. There were insufficient data to determine whether insulin analogues are better than conventional insulins in reducing complications or death related to diabetes.

Reference: Singh SR et al. 'A systematic review of the efficacy and safety of rapid and long acting insulin analogues in type 1 and type 2 diabetes mellitus'. CMAJ 2009; 180(4): 385 – 397.

Atrial Fibrillation and Atrial Flutter with Bisphosphonates: *Public Library of Science* 2009; 4:e4720

This is a retrospective safety analysis which uses the United Kingdom General Practice Research Database to assess the risk of atrial fibrillation (AF) and atrial flutter in women exposed to the oral bisphosphonates, alendronic acid and risedronate sodium. This is the largest study providing data around AF as a possible side effect of bisphosphonate use. It did not find any evidence of an overall increased risk of AF or atrial flutter with either drug, but did detect a small increased risk during the first few months of alendronic acid therapy.

PACEF Recommendation: Prescribers are reminded of previous coverage of this topic in *PACE Bulletin* Volume 2, No 13. Our advice remains that the risk of atrial fibrillation associated with oral bisphosphonates is minimal if it exists at all and is unlikely to offset the confirmed benefits of these drugs in the prevention of fractures. Current evidence does not challenge standard NICE advice to utilize weekly generic alendronic acid as the first line bisphosphonate of choice. MHRA advice is that the balance of risks and benefits of bisphosphonates remains favourable. PACEF will continue to keep this issue under review.

Reference: Grosso A et al. 'Oral bisphosphonates and the risk of atrial fibrillation and flutter in women: a self-controlled case-series safety analysis'. Public Library of Science 2009; 4: e4720.

Self Monitoring of Blood Glucose (SMBG) in Type 2 Diabetes Mellitus: *Health Technology Assessment* 2009; 13(15): 1-72

An RCT of 453 non-insulin treated type 2 diabetic patients in UK general practice who were randomised to one of 3 groups: (1) usual care and 3 monthly HbA1c; (2) usual care and SMBG with patient training and clinician interpretation of results; and (3) usual care and SMBG with additional training of patients in interpretation and application of results. There was no statistically significant difference between the 3 groups in the primary outcome of HbA1c at 12 months. An economic analysis suggests that SMBG is unlikely to be cost-effective if used routinely. The authors comment that the trial cannot exclude the possibility that SMBG may be helpful in non-insulin treated type 2 diabetics with: either symptoms of hypoglycaemia or motivation to make alterations to behaviour that leads to consistent changes in blood glucose or where there is strong patient preference for self-monitoring.

PACEF Recommendation:
Standard PACEF advice is that SMBG is recommended in type 1 DM, but is not recommended as standard for all type 2 diabetics. In type 2 DM, it should be used if the patient is on insulin or is experiencing hypoglycaemia, hyperglycaemia or other symptoms of poor diabetic control; it can also be a useful addition to education on diet and lifestyle and for patients with intercurrent illness. It is unlikely to be necessary in patients controlled on diet and exercise alone. A typical frequency of testing for a type 2 diabetic not on insulin is once or twice a week. Patients drawing regular prescriptions for large quantities of blood glucose testing strips need to be identified and reviewed.

Reference: Farmer AJ et al. 'Blood glucose self monitoring in type 2 diabetes: a randomised controlled trial'. *Health Technol Assess* 2009; 13(15): 1-72.

NICE TECHNOLOGY APPRAISAL 169: *SUNITINIB FOR THE FIRST-LINE TREATMENT OF ADVANCED/OR METASTATIC RENAL CELL CARCINOMA* (MARCH 2009)

The key recommendations are as follows:

- **Sunitinib is recommended as a first-line option for people with advanced and/or metastatic renal cell carcinoma** who are suitable for immunotherapy and have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.

PACEF Recommendation:
Sunitinib (Sutent) is designated RED and approved for specialist use as a first line treatment for advanced and/or metastatic renal cell carcinoma.

NICE CLINICAL GUIDELINE 77: *ANTISOCIAL PERSONALITY DISORDER* (JANUARY 2009)

The key recommendations are as follows:

- Staff working with patients with antisocial personality disorder should recognise that a positive and rewarding approach is more likely to be successful than a punitive approach. Staff should explore treatment options in an atmosphere of hope and optimism explaining that recovery is possible; they should also build a trusting relationship, work in an open, engaging and non-judgemental manner, and be consistent and reliable.
- Cognitive problem-solving skills training should be considered for children aged 8 years and older with conduct problems if: (1) the child's family is unwilling or unable to engage with a parent training programme; (2) additional factors, such as callous and unemotional traits in the child, may reduce the likelihood of the child benefiting from parent-training programmes alone.
- Healthcare professionals in forensic or specialist personality disorder services should consider, as part of a structured clinical assessment, routinely using: a standardised measure of the severity of antisocial personality disorder such as Psychopathy Checklist –Revised (PCL-R) or Psychopathy Checklist – Screening Version (PCL-SV). A formal assessment tool such as Historical, Clinical, Risk Management – 20 (HCR-20) to develop a risk management strategy should also be used routinely.
- For people with antisocial personality disorder with a history of offending behaviour who are in community and institutional care, consider offering group-based cognitive and behavioural interventions (e.g. programmes such as 'reasoning and rehabilitation') focused on reducing offending and other antisocial behaviour.
- Services should ensure that there are clear pathways for people with antisocial personality disorder so that the most effective multi-agency care is provided.
- Services should consider establishing antisocial personality disorder networks, where possible linked to other personality disorder networks.
- Pharmacological interventions should not be routinely used for the treatment of antisocial personality disorder or associated behaviours of aggression, anger and impulsivity.
- The effective treatment of co-morbid disorders such as attention deficit hyperactivity disorder, misuse or dependence on drugs or alcohol may necessitate pharmacotherapy.

NICE CLINICAL GUIDELINE 78: *BORDERLINE PERSONALITY DISORDER* (JANUARY 2009)

The key recommendations are as follows:

- Staff working with patients with borderline personality disorder should explore treatment options in an atmosphere of hope and optimism explaining that recovery is possible. They should also build a trusting relationship, work in an open, engaging and non-judgemental manner, and be consistent and reliable. Bear in mind that many people will have experienced rejection, abuse and trauma and encountered stigma often associated with self-harm and borderline personality disorder.
- Anticipate that withdrawal and ending of treatments or services, and transition from one service to another, may evoke strong emotions and reactions in people with borderline personality disorder.
- Community mental health services should be responsible for the routine assessment, treatment and management of people with borderline personality disorder.
- Teams working with people with borderline personality disorder should develop comprehensive multidisciplinary care plans in collaboration with the service user (and there family or carers where agreed with that person).
- Twice weekly psychotherapy sessions may be considered.
- Do not use brief psychological interventions (of less that 3 months' duration) outside of the service specified above.
- Mental health trusts should develop multidisciplinary specialist teams and/or services for people with personality disorders staffed by people with specific expertise in the diagnosis and management of borderline personality disorder.
- Drug treatment should not be used specifically for the treatment of borderline personality disorder or for the individual symptoms of behaviour associated with the disorder (e.g. self-harm, emotional instability, risk taking behaviour and transient psychotic symptoms).
- Do not use antipsychotic drugs for the medium and long-term treatment of borderline personality disorder.
- Consider drug treatment for the overall treatment of co-morbid conditions.
- Consider cautious short-term use (no longer than a week) of sedative medication as part of the overall treatment plan for people with borderline personality disorder in crisis.
- Aim to reduce or stop unnecessary drug treatment.
- Provide people with borderline personality disorder who have sleep problems with general advice about sleep hygiene (e.g. bedtime routine, avoiding caffeine, reducing activities likely to defer sleep and employing activities likely to encourage sleep). Short-term use of drugs for insomnia may be considered; consider alternative drugs such as sedative antihistamines.

NICE CLINICAL GUIDELINE 79: *RHEUMATOID ARTHRITIS* (FEBRUARY 2009)

The key recommendations are as follows:

Referral for specialist treatment

- Refer for specialist opinion any person with suspected synovitis of undetermined cause.
- Urgent referral is required if: the small joints of the hands or feet are affected; or more than one joint is affected; or there has been a delay of 3 months or longer between onset of symptoms and seeking medical advice.

Disease-modifying and biological drugs

- In people with newly diagnosed active rheumatoid arthritis (RA), offer a combination of disease-modifying anti-rheumatic drugs (DMARDs) (including methotrexate (MTX) and at least one other DMARD, plus short-term glucocorticoids) as first-line treatment as soon as possible, ideally within 3 months of the onset of persistent symptoms.
- In people with newly diagnosed RA for whom combination DMARD therapy is not appropriate (i.e. because of co-morbidities or pregnancy, during which certain drugs would be contraindicated), start DMARD monotherapy, placing greater emphasis on fast escalation to a clinically effective dose rather than choice of DMARD.
- In people with recent-onset RA receiving combination DMARD therapy and in whom sustained and satisfactory disease control has been achieved, cautiously try to reduce drug doses to levels that still maintain disease control.
- When disease is stable, cautiously reduce DMARD dosages. Return promptly to disease-controlling dosages at the first sign of a flare.
- When introducing new drugs to improve disease control, consider decreasing or stopping pre-existing rheumatological drugs once disease is controlled.

Monitoring disease

- In people with recent-onset active RA, measure C-reactive protein (CRP) and key components of disease activity (using a composite score such as DAS28) monthly until treatment has controlled the disease to a level previously agreed with the person with RA.
- Measure CRP and key components of disease activity regularly to inform decision making about increasing or decreasing treatment.
- Offer annual review to: (1) assess disease activity and damage and measure functional ability; (2) check for co-morbidities (e.g. hypertension, ischaemic heart disease, osteoporosis and depression); (3) check for complications (e.g. vasculitis, disease of the cervical spine, lung or eyes; (4) organise cross-referral within the multidisciplinary team (MDT); (5) assess the effect of RA on the person's life.
- Make sure people with RA have ongoing drug monitoring.

The multidisciplinary team (MDT)

- People with RA should have access to a named member of the multidisciplinary team (MDT) (e.g. a specialist nurse) who is responsible for coordinating their care.

Surgery

- Do not let concerns about the long-term durability of prosthetic joints influence decisions to offer joint replacements to younger people.
- The main expected benefits of surgery are: pain relief; improvement or prevention of further deterioration of joint function; and prevention of deformity.

Diet and complementary therapies

- There is no strong evidence of benefit related to any special diets; the Mediterranean-style diet should be encouraged.
- There is little evidence for the long-term efficacy of complementary therapies, although some may provide short-term symptomatic benefit.

Anakinra (Kineret)

- Anakinra is not recommended for RA, except in a controlled, long-term clinical study. Patients already receiving anakinra can continue until they or their consultant consider it appropriate to stop. Anakinra should not be offered with tumour necrosis factor alfa therapy.

Glucocorticoids

- Glucocorticoids should be offered short-term for flares.

- Consider short-term treatment with gluococoticoids (oral, IM or IA) to rapidly improve symptoms in people with newly diagnosed RA if they are not already taking glucocorticoids as part of DMARD combination therapy.
- Consider long-term glucocorticoids only when complications have been fully discussed and all other treatments have been offered.

Symptom control

- If pain control is not adequate, offer analgesics (e.g. paracetamol, codeine or compound analgesics) to potentially reduce the need for long-term treatment with NSAIDs or COX-2 inhibitors.
- Prescribe NSAIDs/COX -2 inhibitors at the lowest dose for the shortest time possible. Co-prescribe with a proton pump inhibitor (choose the least expensive).
- Because of potential gastrointestinal, liver and cardio-renal toxicity of NSAIDs/COX-2 inhibitors: (1) assess risk factors (including age) when choosing a drug and dose; (2) assess and monitor patient risk factors over time; (3) consider other analgesics if the patient is already taking low-dose aspirin for another condition.
- If NSAID/COX-2 inhibitors do not control symptoms satisfactorily, review the DMARD/biological regimen.

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

Antiepileptics

- Long-term use of carbamazepine, phenytoin, primidone and sodium valproate is associated with decreased bone mineral density that may lead to osteopenia, osteoporosis and increased fractures in at-risk patients. Vitamin D supplementation should be considered for at-risk patients who are taking these medicines long-term.
- At risk patients are defined as those who are immobilised for long periods, those who have inadequate sun exposure and those with inadequate dietary calcium intake.

Off-label use or unlicensed medicines: prescribers' responsibilities

- There are clinical situations when the use of unlicensed medicines or use of medicines outside the terms of the license (i.e. 'off-label') may be judged by the prescriber to be in the best interest of the patient on the basis of best evidence. Such practice is particularly common in paediatrics; many medicines used for children are off-label or unlicensed.
- The responsibility that falls on a healthcare professional when prescribing an unlicensed or 'off-label' medicine may be greater that when prescribing a licensed medicine within the terms of its license.
- The risks of prescribing unlicensed or 'off-label' medicines include: lack of information about or unexpected adverse reactions, uncertain product quality and discrepant product information or labelling (e.g. absence of information, information in a foreign language, Patient Information Leaflet inconsistent with off-label use etc)

Advice for prescribers

- Before prescribing an unlicensed medicine, be satisfied that an alternative licensed medicine would not meet the patient's needs.

- Before prescribing a medicine 'off-label', be satisfied that such use would better serve the patient's needs than an appropriately licensed alternative.
- Before prescribing an unlicensed medicine or using a medicine 'off-label':
    - Be satisfied that there is sufficient evidence base and/or experience of using the medicine to show its safety and efficacy.
    - Take responsibility for prescribing the medicine and for overseeing the patient's care, including monitoring and follow-up
    - Record the medicine prescribed, the reasons for prescribing and that you have discussed the issue with the patient.

- Give patients sufficient information about the proposed treatment, including known serious or common adverse reactions, to enable them to make an informed decision.
- Explain the reasons for prescribing an unlicensed medicine or using a medicine 'off-label'.
- Report all suspected adverse reactions.

PACEF Recommendation: Prescribers are referred to the NHS Lincolnshire Policy relating to the Use of Unlicensed Medicines. This policy will be reviewed and updated with reference to the MHRA recommendations.

Over-the-counter cough and cold medicines for children

- Cough and cold remedies containing antitussives (dextromethorphan and pholcodine), expectorants (guaifenesin and ipecacuanha), nasal decongestants (ephedrine, oxymetazoline, phenylephrine, pseudoephedrine and xylometazoline) and antihistamines (brompheniramine, chlorphenamine, diphenhydramine, doxylamine, promethazine and triprolidine) should no longer be used in children under 6 years as the balance of benefits and risk has not been shown to be favourable.
- There is no robust evidence that cough and cold remedies containing these ingredients work; following some reports of harm, it has now been determined that the risk outweighs these negligible benefits.
- Products for children between 6 and 12 will continue to be available in pharmacies where advice can be given.
- Some combinations (such as cough suppressants and expectorants) are being phased out.
- All liquid products containing these ingredients will in future be in a child resistant container
- Newly packaged products reflecting this advice will start to be introduced into pharmacies later in 2009 in time for the 2009/10 winter cough and cold season.

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