Reduction of anxiety symptoms after 1 week

A new study published in *International Clinical Psychopharmacology* shows that Lyrica (pregabalin) is an effective, fast-acting and well-tolerated treatment for generalized anxiety disorder.

Generalized anxiety disorder is the most common single anxiety disorder in the UK, affecting around 4% of the adult population, which manifests in both physical and psychological symptoms. Anxiety disorders such as generalized anxiety disorder, as well as incurring high health-care costs, have a well-documented impact on patients and on society.

More than 58% of people who take a period of time off work as a result of their anxiety have taken more than 28 days off at some point, with the average costs of lost employment estimated to be £6850 per patient per year.

To date, pregabalin has been used to treat generalized anxiety disorder in secondary care, where it is regarded as a valuable treatment option often following the use of selective serotonin-reuptake inhibitors and serotonin noradrenaline reuptake inhibitors. However, most patients are diagnosed in primary care, making the availability of effective, well-tolerated treatments in this setting crucial. Moreover, early treatment of generalized anxiety disorder may prevent the onset of co-morbidities such as depression.

The *International Clinical Psychopharmacology* publication details results from the PEACE (Pregabalin Efficacy in Anxiety: Clinical Evaluation) study, an 8-week randomized, placebo controlled study, conducted to evaluate the efficacy of pregabalin and venlafaxine-XR in the treatment of generalized anxiety disorder. Treatment with pregabalin resulted in a significant improvement in generalized anxiety disorder symptoms, relative to placebo, after just 4 days.

Sleep disturbance, a common co-morbidity of generalized anxiety disorder was significantly improved with pregabalin *vs* placebo. Venlafaxine XR demonstrated a significant improvement *vs* placebo by the end of week 2 in this study, but did not demonstrate any benefits to co-morbid sleep disturbance.

The study also investigated the tolerability and safety of the treatments, with results showing that pregabalin was generally well tolerated. Dropout rates as a result of adverse events for the pregabalin, venlafaxine XR and placebo arms were 12.4%, 17.6% and 5.5% respectively.

Kasper S, Herman B, Nivoli G et al (2009) Efficacy of pregabalin and venlafaxine-XR in generalized anxiety disorder: results of a double-blind, placebo-controlled 8-week trial. *Int Clin PsychoPharm* **24**(2): 87–96

Cystatin C level and renal function in haematopoietic stem cell transplantation

A study presented at the 35th Annual Meeting of the European Group for Blood and Marrow Transplantation evaluated cystatin C as a possible new marker for renal dysfunction in patients who have received a haematopoietic stem cell transplant.

The medical records of 95 haematopoietic stem cell transplantation (75 allogeneic and 20 autologous) recipients who had at least one chance to monitor serum cystatin C level during the last 2 years in one institution were retrospectively reviewed, and evaluated cystatin C as a possible new marker which can predict subsequent renal dysfunction.

Of 95 transplant recipients, 35 patients developed acute kidney injury a median of 48 days (range 0–664 days) after haematopoietic stem cell transplantation, while worsening chronic kidney disease stage was observed in 24 patients during observational periods. Cystatin C level was not influenced by autologous transplant (P=0.311), but significantly elevated after allogeneic transplantation (P<0.001).

Pretransplant advanced disease status also had an influence on cystatin C level before transplantation (P=0.004) Multivariate analysis disclosed that the use of calcineurin inhibitor was a major cause of cystatin C elevation (odds ratio 7.09, P=0.017). There was also a strong inverse correlation between cystatin C and estimated glomerular flow rate (r=-0.749, P<0.001).

The authors concluded that cystatin C measurement could be a useful clinical tool to identify haematopoietic stem cell transplantation recipient at increased risk for chronic kidney disease.

Muto H, Ohashi K, Ando M et al (2009) Cystatin C level as a marker of renal function in haematopoietic stem cell transplantation. 35th Annual Meeting of the European Group for Blood and Marrow Transplantation, Göteborg, Sweden (R 1245)

Coronary patient treatment does not meet standards

Large proportions of European coronary patients are failing to achieve lifestyle, risk factor and therapeutic targets for the prevention of further disease, according to results of the third EUROASPIRE survey (Kotseva et al, 2009). The survey, conducted on behalf of the European Society of Cardiology, analysed medical records and interviewed almost 9000 patients with coronary heart disease in 22 countries of Europe.

'It is a matter of the greatest professional concern that so many coronary patients are not being managed to the standards set in European prevention guidelines and as a result are at increased risk of atherosclerotic disease and a shorter life expectancy,' said Professor David Wood from the National Heart & Lung Institute in London, the principal investigator of EUROASPIRE III.

Lifestyle, risk factor and therapeutic targets for the prevention of cardiovascular disease are clearly set out in the Joint European Societies guidelines, and give the highest priority to those with coronary disease.

Kotseva K, Wood D, De Backer G et al (2009) EUROASPIRE III: A survey on the lifestyle, risk factors and use of cardioprotective drug therapies in coronary patients from twenty-two European countries. *Eur J Cardiovasc Prev Rehabil* (epub ahead of print) doi: 10.1097/HJR.0b013e3283294b1d

New approach to dyslipidaemia treatment

Treating patients who have primary hypercholesterolaemia or mixed dyslipidaemia with a combination of nicotinic acid and laropiprant, and simvastatin led to decreased low-density lipoprotein cholesterol and triglyceride and increased high-density lipoprotein cholesterol levels.

Results from a phase III clinical study published in the *British Journal of Cardiology* show that treating these patients with Tredaptive 2 g (nicotinic acid and laropiprant), co-administered with simvastatin (pooled across 20 mg or 40 mg doses) (*n*=609), reduced low-density lipoprotein cholesterol by nearly 48%, increased high-density lipoprotein cholesterol by nearly 28%, and reduced triglyceride levels by about 33% after 12 weeks of treatment (Gleim et al, 2009).

The primary endpoint was change in low-density lipoprotein cholesterol levels in patients treated with Tredaptive 2 g co-administered with simvastatin compared to those treated with Tredaptive 2 g alone.

Secondary endpoints included change in all lipid levels in patients treated with 2 g of the drug and simvastatin (pooled) compared to those treated with simvastatin alone.

In the other treatment arms, Tredaptive 2 g alone (*n*=192) reduced low-density lipoprotein cholesterol by 17%, increased high-density lipoprotein cholesterol by approximately 23%, and reduced triglycerides by nearly 22%; and simvastatin alone (pooled) (*n*=585) reduced low-density lipoprotein cholesterol by 37%, increased high-density lipoprotein cholesterol by 6%, and reduced triglycerides by nearly 15%.

Dr Christie M Ballantyne, Associate Chief and Professor of Medicine, Baylor College of Medicine

'The results in this study suggest that nicotinic acid and laropiprant, used with a statin, could offer another approach to treat patients with dyslipidaemia,' said Christie M Ballantyne, associate chief and professor of medicine, Baylor College of Medicine, and co-author of the study.

Gleim G, Ballantyne C, Liu N et al (2009) Efficacy and safety profile of co-administered ER niacin/laropiprant and simvastatin in dyslipidaemia. *Br J Cardiol* **16**: 90–7

Imatinib recommended as first post-surgery treatment for gastrointestinal stromal tumours

Novartis has received a positive opinion from the European Medicines Agency's Committee for Medicinal Products for Human Use supporting European Union approval of imatinib (Glivec) as a post-surgery treatment for patients at significant risk of relapse following removal of c-KIT positive gastrointestinal stromal tumours. Patients who have a low or very low risk of recurrence should not receive adjuvant treatment.

Approximately 900 people in the UK are diagnosed with gastrointestinal stromal tumours each year and approximately 86% of those diagnosed will undergo surgery to remove the tumour or tumours. However, if left untreated after surgery, about 50% of patients may suffer a relapse within 2 years and recurrent tumours are often more aggressive and more difficult to treat than the initial tumour or tumours.

The Committee for Medicinal Products for Human Use recommendation is based on positive findings from a phase III study, published in the *Lancet* (DeMatteo et al, 2009).

The phase III, double-blind, randomized, multicentre study, led by the American College of Surgeons Oncology Group, examined adjuvant treatment of more than 700 gastrointestinal stromal tumour patients. The results showed that after 12 months of treatment, 98% of those receiving imatinib 400 mg daily after surgery remained recurrence-free, compared with 83% of those receiving placebo after surgery (hazard ratio 0.35; 95% confidence intervals 0.22–0.53; one-sided $P<0.0001$).

The investigators reported that imatinib therapy was well tolerated by most patients, with side effects similar to those observed in previous clinical trials with imatinib. These include gastrointestinal effects (diarrhoea, nausea), rash, and swelling (oedema).

DeMatteo R, Ballman KV, Antonescu CR et al (2009) Adjuvant imatinib mesylate after resection of localised, primary gastrointestinal stromal tumour: a randomised, double-blind, placebo-controlled trial. *Lancet* **373**: 1097–104

Insulin glargine injection halves nocturnal hypoglycaemia

Meta-analysis shows that once daily Lantus (insulin glargine injection) significantly reduces nocturnal hypoglycaemia in people with type 2 diabetes compared to NPH (neutral protamine Hagedorn) insulin.

Once daily Lantus showed a significantly lower risk of severe and symptomatic (<2.00 mmol/litre and <3.9 mmol/litre) nocturnal hypoglycaemia compared to NPH.

Rituximab approved for first-line use in chronic lymphocytic leukaemia

Rituximab (Mabthera) has been approved for first-line use in combination with chemotherapy in patients with previously untreated chronic lymphocytic leukaemia.

New GnRH-blocker for advanced prostate cancer

Degarelix (Firmagon), a new gonadotrophin-releasing hormone receptor blocker for the treatment of patients with advanced hormone-dependent prostate cancer, has been launched at the 24th Annual European Association of Urology Congress in Stockholm.

ASCO GENITOURINARY CANCERS SYMPOSIUM
ORLANDO, FLORIDA, 26–28 FEBRUARY

New prognostic markers needed to assess prostate cancer risk

Prognostic markers are used routinely in the diagnosis and management of genitourinary cancers – yet there is still little evidence to support their use. And as Dr Andrew Vickers (Memorial Sloan-Kettering Cancer Centre, New York) made clear, although the use of prostate-specific antigen (PSA) testing has transformed detection, monitoring and treatment strategies in men with prostate cancer, only about 25% of those with elevated PSA levels actually have the disease.

'What do we need to know before we use a molecular marker in clinical practice?' he asked. 'First and foremost, that the use of the marker will improve clinical outcomes.'

Dr Vickers reported 'the near total absence' of any clinical papers in the literature that have examined the clinical implications of using such markers. A case in point, he said, was pre-treatment PSA velocity. According to his research, this had been the subject of 87 papers – none of which had evaluated the use of this particular marker in terms of clinical outcomes.

He went on to cite data from a systematic review of tumour markers in which only 14 of 129 (11%) reported a measure of predictive accuracy. Only one paper compared accuracy of the marker involved to a standard clinical model. Despite this, about 40% of the papers made clinical recommendations.

Many attempts had been made, said Dr Vickers, to track and define the development of molecular markers in terms of phases – much the same as in phase I, II and III clinical trial of pharmaceutical drugs – but this had not caught on.

He posed five questions for clinicians to answer before they invested any credibility in molecular markers as the basis for management strategies in prostate cancer:

1. Can the marker be measured accurately and reproducibly?
2. Does the marker distinguish between convenience samples of different groups?
3. Is the marker associated with clinical outcome in the sort of patients to which the marker would be applied in clinical practice?
4. Does the marker provide additional information already available to a clinician?
5. Does the use of the marker improve clinical outcome?

Dr Vickers emphasized that missing cancer is much worse than performing an unnecessary biopsy.

He concluded that despite the lack of evidence, molecular markers such as early prostate cancer antigen were still being promoted aggressively. 'While most markers may be necessary,' commented Dr Vickers, 'they are not sufficiently accurate to provide support for clinical interpretation or predictive value for clinical outcomes.'

Stephen Pinn

Long-term safety with sorafenib in advanced renal cell cancer

The long-term safety of sorafenib, an oral multi-kinase inhibitor for advanced renal cell cancer, has been demonstrated in new data from the large phase III TARGET study.

Outlining the background to these findings, Dr Thomas Hutson, Baylor Sammons Cancer Centre, Dallas, Texas, said that sorafenib was the first new agent for more than a decade to be approved in this setting – based largely on the significant increase in progression-free survival in TARGET (Treatment Approaches in Renal Cancer Global Evaluation Trial) compared to placebo (5.5 *vs* 2.8 months, hazard ratio=0.44, $P<0.000001$).

TARGET also showed a 39% increase in survival for sorafenib over placebo (hazard ratio=0.71, $P=0.015$) before crossover of placebo patients to sorafenib (400 mg twice daily).

In this presentation, Dr Hutson and colleagues provided a descriptive analysis of safety and efficacy in TARGET patients treated with sorafenib for >1 year. Of 903 patients, 169 patients were randomized to sorafenib and treated for >1 year, 27 of whom were treated for >2 years. Owing to crossover from placebo-treated patients to sorafenib, only six patients actually received placebo for >1 year.

At baseline, metastatic disease was most evident in the lung (74%), but also in the liver (23%) and the bone (18%), and 83% of patients had received prior cytokine therapy. Baseline medical history included 13% with coronary artery or ischemic heart disease, while 43% of patients had hypertension – 10.7% also had diabetes and 5.9% were anaemic.

Patients treated with sorafenib for >1 year had a median progression-free survival of 10.9 months and a response rate of 22.5%; a further 75% remained stable. Dr Hutson emphasized that because only 45 of the 169 patients died by the data cut-off, median overall survival could not be estimated.

Drug-related adverse events were mainly grades 1 and 2, and occurred early during therapy. A total of 31% and 22% of patients respectively required dose interruption and reduction.

In summary, said Dr Hutson, patients on sorafenib for long duration did not experience new toxicity or an increase in the overall incidence of treatment-related adverse events. Toxicity was not cumulative and no increase in grade 3/4 adverse events was observed.

He commented: 'Despite the fact that more than 50% of these patients had underlying cardiovascular morbidity, long-term treatment with sorafenib was not associated with an increased incidence of cardiac toxicity.'

Dr Hutson concluded: 'Long-term treatment of advanced renal cell cancer patients with sorafenib is medically manageable with a predictable side-effect profile.'

Stephen Pinn

ASCO GENITOURINARY CANCERS SYMPOSIUM
ORLANDO, FLORIDA, 26–28 FEBRUARY

Tyrosine kinase inhibition to treat prostate cancer

Hormone- and castration-resistant prostate cancer pose a significant clinical challenge. Although there is no standard therapy for prostate cancer patients who have progressed following docetaxel therapy, vascular endothelial growth factor has been implicated in tumour blood vessel formation and in disease progression.

Dr Joyson Karakunnel (National Institutes of Health, Bethesda, Maryland) reported early phase II data on cediranib, an oral, small molecule inhibitor of receptor tyrosine kinases which influence vascular endothelial growth factor.

A total of 35 patients have been enrolled in this study, the main objective of which is a 30% 6-month probability of progression-free survival as determined by clinical and radiographic criteria – not a rise in prostate-specific antigen alone.

At baseline, median prostate-specific antigen values were 153 ng/ml (range 13.4–1587 ng/ml), while most patients (27/35) were ECOG status 1 (seven ECOG 2, one ECOG 0). There was documented evidence of bone disease in 33 (94%) patients, and measurable disease in 23 (66%).

The starting dose of cediranib was 20 mg daily, with dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) carried out every 2 months. DCE-MRI has been used in previous studies to as a response indicator for anti-angiogenic therapies.

To date, he reported, there have been 13 of 23 evaluable patients with tumour shrinkage, four meeting the criteria for partial response. Decreases in lymph node metastases, lung, liver and bone lesions have been recorded.

DCE-MRI has found 14 bone and 17 soft lesions. However, prostate-specific antigen levels have not corresponded well with imaging findings, and in many cases have risen, not fallen, with therapy.

He said that adverse events were similar to other drugs in this class, and included four grade 4 toxicities – one each of pain, disseminated intravascular coagulopathy, haemorrhage/CNS and uric acid.

Dr Karakunnel concluded that the safety and early activity profile of cediranib makes it a promising candidate for the post-docetaxel management of patients with castrate-resistant prostate cancer.

'Preliminary data suggest that cediranib does have a direct effect on the microcirculation and vasculature,' he said. 'However, additional accrual is required to better characterize the response rate, the discrepancy between prostate-specific antigen and standard imaging changes, and to establish evidence of a clinical correlation for DCE-MRI.'

Dr Karakunnel is hoping to be able to report survival data in approximately 4 months.

Stephen Pinn

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FDG-PET in management of bladder cancer

A study from the Memorial Sloan-Kettering Cancer Center, New York, sought to investigate the value of 8F-2-deoxyglucose positron emission tomography (FDG PET) in initial staging, treatment response and suspected recurrence of bladder cancer; and to assess the impact of PET results on clinical management.

The study of 57 bladder cancer patients (aged 54–91 years) included both a patient-based analysis and a separate organ-specific, lesion-based analysis. Pre- and post-PET surveys showed that clinicians changed original planned management after PET results in 63% of cases and that clinicians felt that PET scan avoided more tests in 70% of cases.

Risk factors for thromboembolic events in patients with testicular cancer

Men receiving cisplatin-based chemotherapy for metastatic germ cell tumours are at particularly high risk of thromboembolic events, but prophylactic anticoagulation is not routinely used.

All men treated with cisplatin-based chemotherapy for metastatic germ cell cancer at the London Regional Cancer Program, Ontario, Canada, from January 1978 to December 2007 were identified. Data including type and timing of thromboembolic events were extracted by retrospective chart review. Multivariable analyses were used to identify predictors of thromboembolic events.

A total of 196 eligible patients were identified with median age 31 years (range 15–75 years). None had received prophylactic anticoagulation. Thirty-two thromboembolic events were identified in 29 patients (overall incidence 14.8%; 95% confidence interval 9.8–19.8%). Most were deep venous thromboses, and five patients died as a result of a thromboembolic event or its complications.

Age greater than 30 years (P=0.033) and elevated lactate dehydrogenase levels (P=0.029) were independently associated with an increased risk of thromboembolic events. If both adverse risk factors were present, the risk of thromboembolic events on treatment was 21.7%. If neither were present, the negative predictive value was 97%.

The overall thromboembolic events incidence rate of 14.8% is consistent with prior reports. The risk of thromboembolic events appears greatest during chemotherapy and shortly thereafter.

These data support the use of prophylactic anticoagulation for selected patients starting chemotherapy for metastatic germ cell cancer. However, confirmation of these findings is needed to optimize this treatment.