

### Product stability analysis

Unlike first generation neurotoxin complexes which require an effective cold-chain for storage and distribution, Xeomin® does not need to be refrigerated. An unopened vial can be safely transported and stored at room temperature conditions, of up to 25°C, for up to 3 years.<sup>1</sup> To validate these storage conditions Grein et al<sup>12</sup> performed a series of tests as defined in the ICH Q1A(R2) guideline on stability testing of drug products. Samples were stored at a range of temperatures including 5°C and 25°C and underwent a series of temperatures stress tests. Samples were tested in real time and under accelerated conditions using qualified incubators with narrow temperature tolerances.

The authors confirmed that there were no detrimental effects on the quality of Xeomin® across a range of temperature stress tests and that storage of Xeomin® at ambient conditions (25°C) for up to three years will not negatively affect its activity. The authors concluded that, in the case of Xeomin®, complexing proteins are not required to achieve product stability.<sup>12</sup>

#### KEY POINTS SUMMARY

Studies presented at Dystonia Europe 2008 (17–19 October 2008, Hamburg, Germany) have confirmed that:<sup>2,3,4,5,12</sup>

- Xeomin® is an effective treatment for the symptoms of spasmodic torticollis and blepharospasm
- Patients switched from their existing Botulinum toxin therapy to Xeomin® experienced comparable efficacy and tolerability
- Post-marketing surveillance of an estimated 62,000 patients worldwide has not identified any new safety concerns for Xeomin®
- Prior to reconstitution Xeomin® can be stored without refrigeration (≤25°) for up to three years

#### References

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4. Benecke R, Grafe S, Sassini I, Comes G. *Clinical safety of NT 201 (Xeomin®): a meta-analysis*. Poster presentation at Dystonia Europe 2008, Hamburg, Germany, 17–19 October 2008. (P33)
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12. Grein S, Mander GJ, Taylor HV. *NT 201 is stable without refrigeration: Complexing proteins are not required for stability of botulinum neurotoxin type A preparations*. Poster presentation at Dystonia Europe 2008, Hamburg, Germany, 17–19 October 2008. (P32)

Xeomin® prescribing information can be found on page 39.

#### EDITOR'S CHOICE

### Side-effects of anticonvulsants

In this study the authors take a fairly rigorous view of the studies they are assessing and in the tradition of meta-analyses many less rigorous studies are excluded. They identified adverse effects which occurred more frequently (+) or significantly more frequently (++) in the treatment arm than in the placebo arm. I have added weight change and my impression of some older drugs in purple. The study supports the view that most drugs have a similar range of toxic effects but that lamotrigine is cleaner than the others with regard to cognitive effects. Sodium channel blocking drugs all seem to cause ataxia and diplopia – as is commonly recognised in clinical practice. Topiramate only caused a trend towards depression; it is more of a problem in my clinical experience. This is representative of the problem with this study, which is that the less common but severe side effects such as major depression and psychosis are not common enough to reach clinical significance in the studies used, so that the differences between drugs are under-emphasised. It is nevertheless interesting to see that the similarities are greater than the differences; perhaps we should just toss a coin. – *MRAM*

*Zaccara G, Gangemi PF and Cincotta M.*

**Central nervous system adverse effects of new anti-epileptic drugs. A meta-analysis of placebo- controlled studies.**

**SEIZURE**

**2008;17:405-21.**

	CBZ	GBP	LAM	LEV	OXC	PGB	SVA	TOP	ZON
Somnolence	++	++	+	++	++	++	++	++	++
Fatigue	++	+	+	++	++	++	++	++	+
Dizziness	++	++	++	+	++	++	+	++	++
Ataxia/diplopia	++	+	++	+	++				
Tremor		+	+	++			++		
Cognitive	+					+	+	++	
Anxiety								+	
Depression				+				+++	+
Psychosis				+					
Psychological behavioural				+				+	+
Headache		+	++	+	+	+	+	+	+
Weight change	++					++	++	+	

†/++ Mx subjective view

### DEPRESSION: prevention of perinatal depression

If you identify depression in the last trimester of pregnancy, is there anything you can do to promote remission.. and avoid all the harmful consequences of poor bonding with the child? Well, intervention X reduces the prevalence of depression at 6 months after birth from 53% to 23%, and this effect is sustained for 12 months. Not bad. But what is remarkable is that agent X is not a drug, but cognitive behavioral therapy; more surprising still it is administered not to the affluent eloquent but to unselected mothers in rural Pakistan. People charmingly referred to as “Lady Health Workers” had a brief training and then administered one session of CBT every week for 4 weeks in the last month of pregnancy, three sessions in the first postnatal month, and nine 1-monthly sessions thereafter. The cost of this is not laid out. Sadly for the investigators, none of the infant-related outcomes differed significantly. Good on the Wellcome for funding work on an unglamorous condition, with negative pharmaceutical value, amongst overlooked peoples. – *AJC Rahman A, Malik A, Sikander S, Roberts C, Creed F.*

**Cognitive behaviour therapy-based intervention by community health workers for mothers with depression and their infants in rural Pakistan: a cluster-randomised controlled trial.**

**LANCET**

**2008;372(9642):868-9.**

### HEADACHE: transformed migraine and analgesia

#### ★★★ RECOMMENDED

Two point five percent of those with episodic migraine converted to chronic (transformed) migraine over a one year period. This report, which won the Harold G Wolff Lecture award for 2008, comes from the massive 120,000 population study (the American Migraine Prevalence and Prevention Study),

which followed 8219 (6.8%) migraineurs over five years. Of those migraineurs identified in 2005, 209 (2.5%) developed chronic migraine by 2006. This figure seems low, but the follow up was only one year, and this is likely to be at least one explanation. Unsurprisingly, higher baseline headache frequency was a risk factor for transforming to chronic migraine. Use of barbiturates and opiates were associated with increased risk of chronic migraine, even after adjusting for co-variables including baseline headache frequency and severity. Triptans were not associated with increased risk of transition from episodic to chronic migraine. Non-steroidal anti-inflammatory drugs (NSAIDs) had a variable effect, with a protective effect at low to moderate headache frequency, but an increased risk of transition to chronic migraine at high levels of monthly headaches. It is important that chronic migraine is now a recognised entity, as some previous classifications excluded those with daily headache from migraine; leaving them in a diagnostic and treatment limbo. What are the implications for us in the United Kingdom? Codeine use in headache patients is common, although barbiturate use is not. Other workers, particularly Diener, recognise opiate users as a refractory group of chronic migraineurs. It is often difficult to persuade these patients that the uncomfortable period of opiate withdrawal is worth it. Preventing this situation is important. The association between opiate use and chronic migraine is a strong argument for adequate and early prophylaxis to reduce the transformation from episodic to daily headache. There is still much work to be done on this, starting in primary care and emergency departments. – *HAL*

*Bigal ME, Serrano D, Buse D, Scher A, Stewart WF, Lipton RB.*

**Acute Migraine Medications and Evolution From Episodic to Chronic Migraine: A Longitudinal Population-Based Study.**

**HEADACHE**

2008;48:1157-68.

### **PARKINSON'S DISEASE: deciphering the dyskinesias**

The development of levodopa induced dyskinesias (LIDs) is inevitable in patients with Parkinson's disease as they advance with their condition. The basis of these drug induced movement disorders has been debated for many years and has become a topic of even further interest since the description of graft induced dyskinesias in patients transplanted with fetal ventral mesencephalic tissue. One of the most popular hypotheses relates LIDs to a failure of dopamine storage in the remaining nigral dopaminergic terminals such that levodopa cannot be buffered and dopamine is released synchronously with each levodopa dose. Of late a second major theory has been evolving that relates LID to the mishandling of levodopa in 5HT nerve terminals in the striatum which then releases dopamine as a false transmitter again in an unregulated way. Finally others relate LIDs to the conversion of levodopa to dopamine in non neuronal cells which lack the capacity to regulate the release of the dopamine so formed. Indeed in the striatum the major determinant of dopaminergic levels at the synaptic level (outside of its release and thus synthesis) is its inactivation via dopamine transporters. Thus an abnormality in dopamine transporters, as would be the case for 5HT and non neuronal cellular release of dopamine, would cause dopamine to be released in an unregulated fashion. In other words the released dopamine cannot be taken up and thus there will be a pulsatile delivery of dopamine in time with the oral administration of the drug. This in turn will act via the postsynaptic dopamine receptors to effect downstream changes with the induction of long term LIDs. Lee et al have now added another part to the story using 6 hydroxydopamine lesioned rats. They show that once there is a greater than 60% denervation of the striatum, LIDs can be induced and this can be attributed to terminal sprouting from the intact nigrostriatal dopaminergic neurons. These sprouted terminals are capable of releasing dopamine but lack the necessary apparatus to transport and store it and thus contribute to LIDs. Thus once a threshold is passed when terminal sprouting with dopamine release is the dominant mode of synaptic dopamine delivery to the striatum, LIDs ensue. This paper contains an interesting series of experiments designed to confirm this observation and whilst not proven as the mode by which these dyskinesias occur in patients, does nevertheless help explain why LID's may occur. However the reality is, as the authors themselves acknowledge, that this is probably only one of several different mechanisms, all of which contribute to LID's and which in theory are all amenable to treatment with the expectation that LIDs can be better avoided and treated. – *RAB*

*Lee J, Zhu WM, Stanic D, Finkelstein DI, Horne MH, Henderson J, Lawrence AJ, O'Connor L, Tomas D, Drago J, Horne MK.*

**Sprouting of dopamine terminals and altered dopamine release and uptake in Parkinsonian dyskinesia.**

**BRAIN**

2008;131(Pt 6):1574-87. Epub 2008 May 16.

### **STROKE: Functional Electrical Stimulation can reduce unilateral spatial neglect after stroke**

Spatial inattention or 'neglect' to the contralesional side is common in acute stroke. This deficit resolves in many cases but there are a small proportion of patients in whom the problem persists. Since severe and persistent spatial neglect prevents this sub-group of patients from regaining independence after stroke there is much interest in finding rehabilitation strategies to treat it. Unilateral spatial inattention is considered to be a syndrome because a variety of symptoms have been identified. This makes development of effective treatments that can be applied to very severely affected patients a challenging task and to date long-lasting treatments have been lacking. A proof of principle study reported recently in *Neuropsychological Rehabilitation* may be the start of a new lead in resolving this important clinical problem. Functional electrical stimulation (FES), a treatment that is normally applied to people with hemiparesis to activate muscles and bring about movement, was applied in this case to see if proprioceptive information on the contralesional side would improve patients' spatial awareness. The treatment was tested on four severely affected right hemisphere stroke patients and in three of them the treatment effects were remarkable. An A-B-A treatment-withdrawal design was used. Each patient was assessed weekly on a number of clinical tests over the baseline period of 4 weeks. A treatment phase immediately followed by a phase in which the stimulation was applied to the wrist/finger flexors and extensors of the forearm on the ipsilesional side (4 weeks). After that a second treatment phase stimulating the contralesional forearm (4 weeks) was delivered followed by a withdrawal phase (4 weeks) and a final follow up assessment 16 weeks after that. Thus the design allowed the effects of stimulation on spatial neglect to be separated from its effect on arousal by applying the electrical stimulation first to the arm on the ipsilesional side, before it was applied to the arm contralateral to the lesioned hemisphere. In three of the four patients the time series plots of performance remained consistently poor until the stimulation was applied to the contralesional side, then performance was greatly improved and was maintained through to the follow up assessment. The fourth patient did not change in performance throughout. The authors suggest that FES activates a proprioceptive map within the right parietal lobe whose level of activation is otherwise diminished by the lesion and that this both increases awareness of the contralesional side and stimulates functional interactions with the environment. This is a very simple treatment to apply in clinical practice and deserves further investigation to see if clinically meaningful results can be found in a larger study. – *AJT*

*Harding P, Riddoch MJ.*

**Functional Electrical Stimulation (FES) of the upper limb alleviates unilateral neglect: A case series analysis.**

**NEUROPSYCHOLOGICAL REHABILITATION**

2008, DOI: 10.1080/09602010701852610

### **HEADACHE: olfactory hypersensitivity and migraine**

This report gives another fascinating example of changes in the brain of patients with migraine. Visual hypersensitivity in migraine, and related physiological and blood flow changes, are well documented. Although less common, olfactory hypersensitivity both during and between migraine is established, and odours may trigger migraine. This study examined regional cerebral blood flow, in headache-free periods, in migraineurs with documented olfactory hypersensitivity. Regional cerebral blood flow in the left piriform cortex and antero-superior temporal gyrus was increased in 12 subjects in periods without odour stimulation, compared to 11 controls. During odour stimulation, migraineurs showed increased activation of frontal (left inferior and right middle frontal gyri), temporo-parietal regions, posterior cingulate gyrus and right locus coeruleus. These studies show a change in cerebral blood flow in these odour-sensitive migraineurs "at rest" and during activation. The authors point out that the study doesn't tell us the physiological mechanism of the changes. We don't know whether this represents a chronic change in cerebral flow consequent on migraine, or a primary change in the regulation of olfactory responses. It also doesn't tell us the mechanism of olfactory hallucinations as a migrainous aura, which must be distinguished from ictal olfactory aura by the clinical setting, in particular their long duration. It does add to the evidence that there is something different both about how people with migraine process sensory input, and how their brain is between headaches. – *HAL*

*Demarquay G, Royet JP, Mick G, Rylvlin P.*

**Olfactory hypersensitivity in migraineurs: a H2150-PET study.**

**CEPHALALGIA**

2008;28:1069-80.

## PARKINSON'S DISEASE: dopamine and the sleeping brain

Proper sleep is important for the well being of us all and problems with inappropriate sleepiness during the day can be a feature of many neurological conditions, perhaps best described in Parkinson's disease (PD). In a recent issue of the Journal of Neuroscience two papers touch on the role of dopamine in this whole process. In the first of these papers Volkow et al study the effect of sleep deprivation on the dopaminergic systems in the striatum and thalamus using PET. These workers took healthy subjects and studied them after a night of normal restful sleep and again after a night of sleep deprivation. They looked at the dopaminergic system with two PET ligands- 11C-Cocaine which labels dopamine transporters and 11C raclopride (RAC) which labels mainly D2 receptors. They found that RAC (but not 11C-Cocaine) binding in the striatum and thalamus was decreased after sleep deprivation and that this reduction correlated with the level of tiredness, fatigue and cognitive dysfunction. The decrease in RAC signal implies that sleep deprivation increases dopamine release as this PET ligand competes with endogenously released dopamine [or alternatively that sleep deprivation alters dopamine receptors directly]. This suggests that in an attempt to maintain arousal, in the face of lost sleep the dopaminergic system at these sites upregulates anyway, although proving that this is truly the case will require further work. However, Qu et al show that, in mice, modafinil induced wakefulness is dependent on dopamine receptors- D1 and D2 in particular. This is demonstrated using standard pharmacological studies as well as the D2 receptor deficient mice. These studies therefore tell us that dopaminergic stimulation underlies wakefulness, or at least contributes to it in the face of either sleep deprivation or the administration of modafinil. However, how this exactly plays out with other systems involved with sleep and wakefulness is not clear, nor why some diseases with dopaminergic loss, such as PD, cause problems with somnolence. Nevertheless it does show that this most basic of processes is complex and that dopamine is integral to its regulation. – **RAB Volkow ND, Wang GJ, Telang F, Fowler JS, Logan J, Wong C, Ma J, Pradhan K, Tomasi D, Thanos PK, Ferré S, Jayne M.**

**Sleep deprivation decreases binding of [11C] raclopride to dopamine D2/D3 receptors in the human brain.**

JOURNAL OF NEUROSCIENCE  
2008;28:8454-61.

**Qu WM, Huang ZL, Xu XH, Matsumoto N, Urade Y.**  
Dopaminergic D1 and D2 receptors are essential for the arousal effect of modafinil.

JOURNAL OF NEUROSCIENCE  
2008;28:8462-9.

## STROKE: thrombolysis after 3 hours....?

\*\*\* RECOMMENDED

Just when we had just got our heads around thrombolysis for those lucky 4% of patients who get to an appropriate place within three hours of their stroke, the goalposts may be moving. There have been several previous suggestions that intravenous tPa might be effective beyond the 3 hour window established by the NINDS study. But this is the most convincing evidence to date. The Safe Implementation of Treatments in Stroke (SITS) study is not a trial though. It is a systematic collection of real-world thrombolysis from approximately 700 centres in 300 countries. There is no control group. Instead, the SITS investigators have trawled through their database for the 664 patients who received their tPa between 3 and 4.5 hours after their stroke and compared their outcome with those 11,865 souls who got the juice within the conventional window. The bottom line is that there was no difference in the rate of symptomatic intracerebral haemorrhage (2.2% versus 1.6%); mortality at 3 months (12.7% versus 12.2%); or independence at 3 months (58.0% versus 56.3%). The trouble is that nearly 60% of the 3-4.5 hour group actually received their thrombolysis in the 20 minutes after the magic 3 hour cut-off, so the 4 hour tail-end charlies may not have benefited as much as first seems. One thing is for sure though.... If you have decided to thrombolys within the 3 hours but the porters, radiographers and pharmacy conspire against you and the Cinderella hour has just past.... No worries. Give the IV push. It'll be alright.... – **AJC**

**Wahlgren N, Ahmed N, Dávalos A, Hacke W, Millán M, Muir K, Roine RO, Toni D, Lees KR; for the SITS investigators.**

Thrombolysis with alteplase 3-4.5 h after acute ischaemic stroke (SITS-ISTR): an observational study.

THE LANCET  
2008;372:1303-9.

## EPILEPSY: predictive value of functional imaging

The trouble with studies looking into the selection of patients for epilepsy surgery, is that they are generally retrospective. They take a group of patients who have successfully undergone surgery and ask the question what criteria were the most reliable in selecting them. Of course, the problem with this approach is that it does not tell you how these factors relate to the patients who did not do well or to those who were rejected during the assessment. Perhaps that is not surprising, since one is never going to operate on patients whose investigations are not concordant, so the predictive value of non-concordance will never be known. Nevertheless, this pair of studies with the words "predictive value" in the title grabbed my attention. Do they truly address this question prospectively? What they did was to look at quite a large number of patients with refractory epilepsy, either with no clear structural abnormality on MRI or with such diffuse changes that further studies were needed to localise the onset of the epilepsy. These included intracranial EEG, magnetic source imaging (MSI), ictal SPECT and PET scans. Since MSI is a new technique, it was not considered in the process of deciding where to place intracranial electrodes. None of these tests is a gold standard, although 84% of patients with localised intracranial EEG did well with surgery. In predicting intracranial EEG, MSI had a positive predictive value of 90% (PET was 71%) and a negative predictive value of 42.3% (PET was 23.5%). SPECT was less sensitive or specific than PET. That MSI was most concordant with SEEG, no doubt reflecting the similarity of what the techniques measure. Combining PET and MSI or SPECT and MSI, improved predictive value, compared to MSI alone. So whilst the question of the true positive predictive value is perhaps not answerable, it is interesting that the most predictive test for intracranial EEG results in imaging negative patients in this study was MSI, an investigation, which is not widely available. However, when it came to predicting the outcome of epilepsy surgery in the second of the two papers, all three investigations performed similarly and again they supplemented each other. Reassuringly, when all the investigations were localising, the odds ratio for seizure freedom was 9.6 but the combination of MSI and PET seemed to be more predictive than MSI and ictal SPECT. So we come back to the view that the more tests which are concordant, the greater the predictive value and MSI is a useful new tool in the box whose role is increasingly defined and no doubt more centres will be looking to establish the technology. – **MRAM**

**Knowlton RC, Elgavish RA, Bartolucci A, Ojha B, Limdi N, Blount J, Burneo JG, Ver Hoef L, Paige L, Faught E, Kankirawatana P, Riley K, Kuzniecky R.**  
Functional imaging: II. Prediction of epilepsy surgery outcome.

ANN NEUROL  
2008;64(1):35-41.

**Knowlton RC, Elgavish RA, Limdi N, Bartolucci A, Ojha B, Blount J, Burneo JG, Ver Hoef L, Paige L, Faught E, Kankirawatana P, Riley K, Kuzniecky R.**  
Functional imaging: I. Relative predictive value of intracranial electroencephalography.

ANN NEUROL  
2008;64(1):25-34.

### Journal reviewers

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