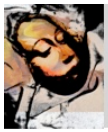

The European Delirium Association

Annals of Delirium

July 2010

Editorial

Welcome to this second edition of Annals of Delirium, an eclectic publication designed to educate, inform and provoke. The field of delirium study is moving at an increasing pace; it is difficult to keep up with all the information now available in the medical literature and hold down a full-time job (as most of us do). Hopefully this will help keep you up to date until we can all submerge ourselves on the feast of information that will be available at the European Delirium Association annual Congress in November.

In this edition our President Jouko Laurila reflects on a delirium conference he attended in the States and looks forward to the EDA Congress in Amsterdam. Dr Barbara Kamholz outlines the progress being made in the USA regarding delirium. Dr Colm Cunningham from Trinity College Dublin has provided a summary of his published paper recently published in Neurobiology of Aging on animal models in delirium. It is a fundamental step to start pinning down the pathophysiology of delirium. Andrew Teodorczuk left those of us who attended the education workshop in the Leeds meeting last October with food for thought. He has now written a paper for the Annals, which I am sure you will find interesting. Again we have the editor's choice – recent publications you might have missed and our news section including the results of our website poll.

If there's any delirium related matter you would like to share with your colleagues at home and abroad then send it in to the Annals and we will publish it! (Editor's approval permitting).

Personal experiences of delirium for the EDA website: request for help

Personal experiences of delirium are an extremely effective way of gaining the attention of healthcare workers either in the lecture theatre or on the wards. These stories are also an important way of enhancing clinical expertise in delirium practitioners.

Because of this we would like to start a new initiative of collecting these experiences and stories for the EDA website, with some also published in the EDA newsletter. The extent of delirium throughout the community means that clinicians often have their own stories; for instance one of my surgical colleagues clearly remembers during a bout of childhood pneumonia getting particularly upset at the large pile of coal that was sharing his bed. Clinicians will frequently also have had contact with patients or colleagues who have had delirium and who are willing to share their experiences with others.

We would like to invite you to share delirium experiences and stories with the wider community so they can be used to inform and persuade people to take greater care of delirium. Any length or format (ie. including pictures) is acceptable. All languages are very welcome; if an English translation could be provided this would be helpful but this is not required. All experiences and stories will be fully anonymised. Please email or write to me the Editor (all communications will be strictly confidential and handled by the Editor only until anonymised).

met vriendelijke groet!

Valerie Page
Editor,
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Dear Readers,
As most of you have already noticed, the scientific programme of the 5th Scientific Congress on Delirium is now published online (www.europeandeliriumassociation.com).
And what a programme! Sophia de Rooij and colleagues have done brilliantly.
The congress covers many topics familiar to delirium audiences but also features some thrilling new openings, such as *Delirium in Palliative Care* and *Delirium Tremens* – both of which are highlighted also by workshops.
Once again the keynote speakers are among the brightest stars in the delirium sky. There's no doubt also that the younger scientists will send their abstracts to Amsterdam, the most important delirium event in the world in 2010. Please subscribe as soon as possible, send your abstracts and spread the word about this congress to all your colleagues wherever you go!
A month ago, on June 8-9, I was privileged to take part to an American delirium conference, *Advanced Delirium Science* in Baltimore, Maryland. The conference was organised by the Department of Veteran Affairs Employee Education System and Office of Geriatrics and Extended Care. It was an educational event with some new data presented, as well. There were over 100 participants. Speakers included Joseph Francis, James Rudolph and Barbara Kamholz. In addition to them, I especially enjoyed the delirium demonstration in which Joseph Flaherty (geriatrician) acted as a delirious World War II veteran and Sharon Gordon (psychiatrist) her "Nurse Betty".
While everything went wrong in the imaginary play happening in the middle of the night, the audience had to through the reasons why and suggest alternative ways for Nurse Betty to handle her difficult night shift.
Attached to this conference was also a follow-up meeting of the ongoing establishment of the American Delirium Society.
I had a chance to present the whole audience with the history and aims of EDA, as well as EDA's influence as a source of information, research network, and as an important arena for general multidisciplinary discussion. I also mentioned our Annals of Delirium and, naturally, advertised our forthcoming Amsterdam congress. I was very pleased to notice that many of the participants already new about the congress and were even planning to attend (must be Barbara Kamholz's influence).

Let's all meet in Amsterdam!
Jouko Laurila

An animal model of delirium during dementia.

Last month saw the publication, on-line, of studies describing the first animal model purposefully designed to mimic delirium during dementia. The paper, entitled

"Systemic inflammation induces acute working memory deficits in the primed brain: relevance for delirium" has been published in the journal *Neurobiology of Aging* and comes from the laboratory of Dr. Colm Cunningham in Trinity College Dublin (Murray et al., 2010). The findings reported represent the strongest empirical evidence yet that systemic inflammation and ongoing chronic neurodegeneration interact to produce acute and transient impairments in cognitive function in the brain region in which prior pathology has occurred, and suggest that this model has the potential to reveal insights into inflammatory routes to delirium.

This research has its genesis in the original description of microglial priming. In those original experiments (Cunningham et al., 2005) we showed that the major brain macrophage population, the microglia, was partially activated, or "primed", in response to their sensing of degenerative changes in the diseased brain. These cells then respond more robustly to subsequent inflammatory challenges, whether these challenges are made directly to the CNS or in the periphery. We had already proposed the existence of these primed microglia and hypothesized that these exaggerated CNS responses could be a key risk factor for delirium in the aged and demented population in a Nature Reviews Neuroscience article in 2003 but its demonstration required rather involved experiments.

In the current study we started with an animal model of progressive amyloidosis, synaptic loss, neurodegeneration and microglial activation (the ME7 model of prion disease), which also produces progressive impairments in reference and working memory. In the early, asymptomatic, stages of disease we then superimposed a systemic challenge with bacterial endotoxin (lipopolysaccharide, LPS 100μg/kg) to mimic a mild to moderate gram-negative bacterial infection, since such infections frequently trigger episodes of delirium in the aged and demented population. We hypothesized that hippocampal synaptic loss and accompanying microglial activation during chronic neurodegeneration in the ME7 model would predispose these animals to acute dysfunction in the hippocampus upon systemic inflammatory activation. LPS induced acute and transient working memory deficits in ME7 animals on a novel T-maze working memory task, but did not do so in normal animals. LPS-treated ME7 animals showed heightened and

prolonged transcription of inflammatory mediators in the CNS, compared to LPS-treated normal animals, despite having equivalent levels of circulating cytokines. These data provide a rationale for the finding that, while elevated systemic cytokines such as IL-6 and IL-8 are associated with delirium in hip fracture patients, pre-existing cognitive impairment remains the stronger predictor of delirium.

Similarly the finding that even higher doses of LPS did not induce acute deficits in normal animals suggests that even the exaggerated inflammatory mediator production facilitated by primed microglia may not be sufficient, alone, to induce the acute dysfunction. The vulnerability of hippocampal function may be caused by a loss of 'cognitive reserve'. That is to say that there may be a threshold below which hippocampal synaptic activity must drop before dysfunction is observed on this working memory task. The current data are consistent with the hypothesis that disease lowers synaptic activity towards this hypothetical threshold and that LPS precipitates a drop below this threshold and the occurrence of working memory deficits.

Can we really model delirium in mice?

Delirium is obviously a complex syndrome comprising impairments in attention, orientation, memory, level of arousal, perception and affect, and psychotic disturbances. It is not reasonable to expect that we can replicate all of these features in a non-verbal animal such as a mouse. However, we have chosen to focus on a number of key features that are potentially analogous to some core cognitive and temporal features of delirium.

1) Episodes are of acute onset and transient and can be distinguished from chronic cognitive impairments.

2) The interaction of systemic inflammation and existing or incipient dementia is one very common multi-factorial etiological route to clinical delirium and is mimicked in a biologically relevant way in the current study.

3) There are similarities in the nature of the cognitive deficits observed in the T-maze and allocentric Y-maze and some of those in human delirium: WHO ICD-10 diagnostic criteria include "impairment of recent memory…..disorientation for time as well as, in more severe cases, for place": Our previous studies showed that ME7+LPS animals made significantly more errors in learning the location of a fixed exit in a reference memory task, but could remember this location if the environment was completely familiar before experiencing LPS-induced sickness (Cunningham et al., 2009). Adding the temporal components required for performance in the working memory T-maze reveals acute and transient dysfunction even in a familiar environment. Thus LPS-induced impairments become apparent when the processing and retention of novel, trial-specific information, for just 30 seconds is required to

accurately perform the task. Using Hart's cognitive test for delirium, patients with delirium perform particularly badly relative to patients with dementia on tasks requiring retention and processing of novel, trial-specific information over similar periods of time.

Thus, we propose that systemic inflammation can target particular brain regions on the basis of existing pathology in those regions and that the current model allows us to study these interactions. More global pathology, as observed in Alzheimer's disease for example, would predict more global cognitive dysfunction upon systemic inflammatory insult. Therefore the current hippocampal-centred model, with good reason, predicts only a subset of delirium symptoms. It is also worth mentioning that the working memory alternation task used here is also acetylcholine-dependent and therefore the current data are not inconsistent with a hypocholinergic explanation of delirium. Our current studies in the laboratory are directly assessing the role of acetylcholine in these acute impairments.

The pathophysiology of delirium is poorly understood and the lack of biologically relevant animal models has severely limited basic research. It is now our priority, equipped with this new model system to examine which inflammatory pathways must be activated in order to produce the acute and transient working memory deficits reported here.

Full reference:

Carol Murray, David Sanderson, Chris Barkus, R.M.J. Deacon, J.N.P. Rawlins, David Bannerman and Colm Cunningham. (2010) Systemic inflammation induces acute working memory deficits in the primed brain; relevance for delirium during dementia. *Neurobiology of Aging (In press,* doi:10.1016/j.neurobiolaging.2010.04.002)

This paper is **OPEN ACCESS.**

Work leading up to these findings:

Cunningham, C., Campion, S., Lunnon, K., Deacon, R.M.J, Rawlins, J.N.P. and Perry, V.H. (2009) Systemic inflammation superimposed on chronic neurodegeneration induces acute behavioural and cognitive changes and accelerates neurological decline. *Biological Psychiatry* 65(4):304-12.

Cunningham, C., Wilcockson D.C., Campion, S., Lunnon K. and Perry, V.H. (2005) Central and systemic endotoxin challenges exacerbate the local inflammatory response and increase neuronal death during chronic neurodegeneration. *Journal of Neuroscience* 25(40) 9275-9284.

Perry V.H., Newman, T.A. Cunningham, C. (2003). The impact of systemic infection on
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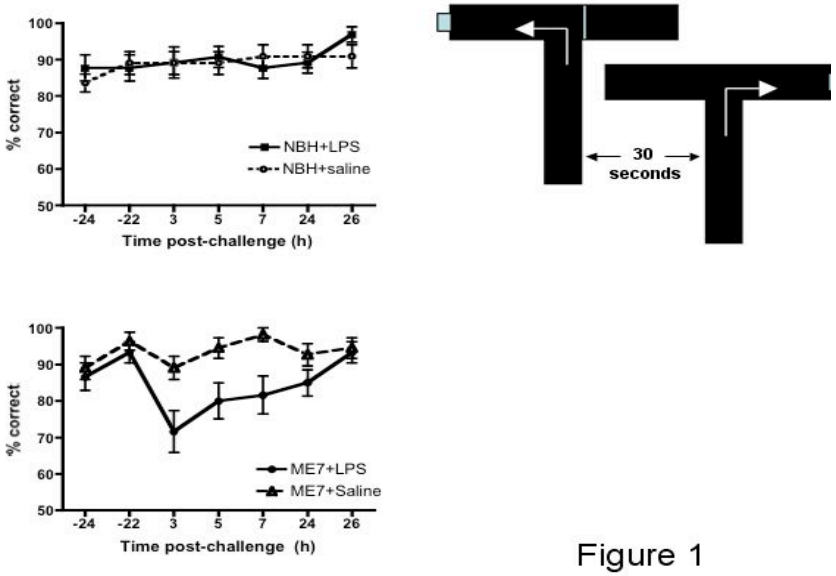

Figure 1

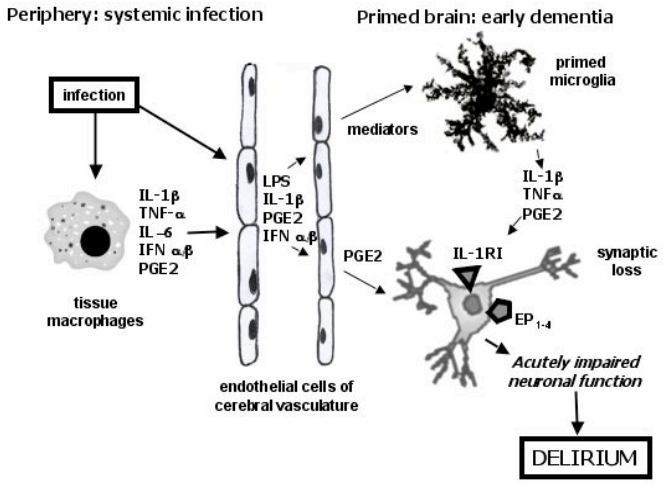

Figure 1

In the working memory T-maze alternation task, in which the mouse must remember, for just 30 seconds, which arm they first visited in order to inform the direction they must turn to escape the maze on being replaced there, normal animals (NBH) perform well and are not affected by LPS. ME7 animals can also maintain good performance in this maze but show acute and reversible working memory deficits upon systemic challenge with LPS to mimic bacterial infection.

Figure 2

A hypothetical scheme to explain the effects of systemic LPS on cognitive function in the 'primed' brain. In this scheme 'priming' refers to both the increase in microglial priming, thereby exaggerating local inflammatory mediator production, but also to synaptic loss, making specific neuroanatomical regions more vulnerable to disruption of function. LPS may activate local tissue macrophages but also may act directly at the cerebral vasculature. PGE2 can diffuse across the blood brain barrier whereas the other molecules depicted are more likely to signal across the blood brain barrier by interacting with specific receptors on the endothelial layer. Abbreviations: IL-1b: interluekin 1 beta, TNF-a: tumour necrosis factor alpha, IL-6: interleukin 6, IFNa/b: interferon alpha/beta, PGE2: prostaglandin E2, IL-1RI: IL-1 receptor I, EP1-4: prostaglandin E receptors 1-4, LPS: lipopolysaccharide

Delirium education: paradoxes and contradictions

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Within the field of delirium education an important paradox exists. Despite growing research evidence for the effectiveness of training interventions, rather puzzlingly, educators working in the hospital struggle to change staff behaviour through teaching.

Historically, education has been a mainstay in delirium management. Rockwood and colleagues originally demonstrated that raising awareness of delirium plays a key role towards improving recognition (Rockwood et al., 1994). More recent studies show educational interventions not only prevent incident delirium, but also reduce medication use, length of stay and severity (Inouye et al., 1999, Milisen et al., 2001, Lundstrom et al., 2005, Pierre, 2005).

Yet, delirium educators report problems with translating these strong research findings to the local setting. A pragmatic multi-site study showed, even with additional teaching, hospital staff have considerable difficulty adopting theoretically sound guidelines to influence care outcomes in a positive manner (Young and George, 2003).

In part, the paradox can be attributed to the fact that education is a social process; what works in one setting may not be suitable for another with different teacher, learner and environmental factors.

However, a further controversy is that many interventions are deficient in educational theory. Despite the old adage that, “nothing is more practical than a good theory”, little attention has been paid to its role in delirium education (Teodorczuk et al., 2009).

This paper aims to introduce readers to relevant educational theories which can improve teaching and be applied in a local setting. The first part will examine traditional theories and the second will consider a more contemporary theory.

Traditional educational theories include behaviourism, cognitivism, humanism (including adult learning theory), social constructivism and social learning (Merriam *et al.*, 2007). Though all hold different stances in terms of the mechanisms which lead to learning, they are similar in that they consider learning which occurs at an individual level (Table 1). General guidance for educators is to adopt a blended approach in order to shape the teaching to meet the needs of the learner and goals of the educational encounter. Hence, if the purpose of education is to improve assessment of cognitive state, a teacher may adopt a behaviourist approach combined with an element of modelling to shape learning towards optimal practice of the skill.

Theory	View of learning	Focus of teaching encounter	Example of applying theory into practice
Behaviourist	A change in an individual's behaviour	Adapting the environment to shape the learner's actions	Rewarding good delirium practice through praise
Cognitivist	An information building process and prior knowledge play a central role in organising learning	Trying to structure the content of a teaching encounter to enable a learner to "assimilate" the material	Activating prior knowledge of delirium and addressing any misunderstandings
Social constructivism	A social process in which the context and conditions of learning are crucial	Creation of a "reflective dialogue" to enable critical thinking to occur	Encouraging the learner to reflect on own practice of delirium management and think critically about how it could be improved
Humanism	Self-growth is the key component of learning	Creating the conditions to help the learners achieve their own development	Encouraging the learner to take responsibility for learning and identifying own cases to learn around
Vicarious learning	Learning occurs as a result of observing and modelling	Teacher models best practice	Shadowing a liaison nurse who is an expert in delirium management

Table 1 Traditional learning theories – theory and practice

Despite an understanding of these educational theories being necessary for delirium education, traditional theories alone may be insufficient to bring about an improvement in delirium care in the complex ward environment. Arguably, such “individual level” learning theories may be less applicable in the workplace because the key difficulty that staff encounter resides with implementation, not assimilation, of knowledge. For example, a doctor may “know” that prescribing a drug in a particular clinical encounter is potentially dangerous, but this may not stop such behaviour if the ward expectation is to prescribe.

A contemporary theory with a high degree of applicability to delirium education is Engestrom’s Social Activity Theory (Engestrom, 2009). Activity theory, originated from Vygotsky’s work, and seeks to tackle the problem of changing behaviour across boundaries and agencies. In contrast to more traditional theories, it views knowledge as residing outside of individuals and within organisations. Accordingly knowledge is shared across socio-cultural boundaries, rather than being vertically transmitted in a traditional fashion.

A central tenet of the theory is that organisational challenges are not resolvable by the sum total of separate individuals. Furthermore, learning should occur by an “expansive" process. This cycle of expansion involves questioning; contradiction analysis; modelling; examining the model; implementing the model; examining and finally consolidating new practice.

In practice, social activity theory has been used in the Helsinki Boundary Crossing Lab project to improve previously dysfunctional care in paediatric hospitals. A major contradiction or “knot” was identified between the person centred care pathway in the community and the disease centred protocols in hospital. As a result of a developmental dialogue between agencies, a learning agreement was set out which resulted in improved coordination and communication with clearer loci of responsibility, reduced duplication of visits and greater sharing of knowledge amongst providers. Ultimately, Engestrom argues, this higher level learning, though potentially more dangerous because it involves challenging systems, brought about greater change than a traditional educational approach.

Social Activity Theory is suited to complex care scenarios with multiple agency involvement. As such, it is particularly applicable to delirium care. Moreover, from our preliminary exploration of staff’s learning needs, it is evident that the greatest barriers to learning are at an organisational and system level. Social Activity Theory has the potential to address these barriers and generate innovative transformational methods of change. Clearly the contradictions which have to be resolved will vary between hospitals and no blue print will exist; however adoption of a broader view of education and identification of the contradictions which compromise care will facilitate organisational learning.

In summary, this brief paper has given an account of the controversies within delirium education and limitations of traditional approaches. Furthermore, the need for conceptualisating education beyond an individual level and integrating more contemporary educational theory are outlined. Returning to the paradox of why delirium educators struggle to change behaviour through teaching, arguably the answer rests with the difficulty that staff encounter implementing new knowledge within the organisations where they work. To bring about real change, system learning should proceed in tandem with traditional education approaches.

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Acknowledgements.
This paper is based on a workshop facilitated at the European Delirium Association Scientific Meeting, Leeds 2009. I would like to thank Dr Sally Corbett, workshop co-facilitator for her help.

Establishment of the American Delirium Society

The American Delirium Society ("ADS") held its first official meeting on June 9, immediately following the second national United States Veterans Affairs ("VA") Administration conference on delirium which had been held June 8-9 of this year. These conferences were planned by the National Veterans Affairs Working Group on Delirium, which has been meeting monthly by phone conference for 5 years, and which has largely formed the composition of the free-standing ADS. The ADS is being established as a non-profit organization and has already received its first grant to assist with this effort. The goals of the ADS are to be an educational, clinical, and research resource for work in the field within the United States, with the intention to collaborate with other delirium societies such as the European Delirium Association (EDA). Funding and logistical support for the American Delirium Society's first annual conference have already been offered and next year's meeting will be held in June in Indianapolis, Indiana, at the Regenstrief Institute, which has been the source of widely regarded achievements in the field of geriatrics. As the ADS is further organized, terms of membership will be clarified and the website will be further enhanced to assist with meeting the society's goals. We will eagerly welcome members s soon as we are able to do so!

The Second Annual Veterans Administration Conference on Delirium

The first and second national VA meetings on delirium were held in June of 2009 and June 8-9 of 2010 in Baltimore, Maryland, US, to advance awareness of the critical nature and massive health impact of delirium within the VA as well as to educate about identification and management. These largely clinical conferences were primarily attended by VA personnel with some participation by non-VA clinicians. It is notable that as a large and comprehensive healthcare system with a severely medically and psychiatrically impaired populations, the VA has welcomed work on delirium. We were very pleased to have the President of the EDA, Jouko Laurila, attend the meeting this year and to provide some comments about his work and that of the EDA. Specific topics addressed by this year's meeting included work undertaken by members of the national working group to establish mental status evaluation as a 6th vital sign as well as to identify the frequency and reliability of current diagnoses of delirium within VA nationally. Some popular clinical sessions included a live demonstration of ways to manage acutely agitated, delirious patients as well as sessions that provided concrete management advice from social work, nursing, and medical areas of service. Further sessions were held on identifying and managing delirium in the ICU. One of the National Working Group's goals is to rapidly advance clinical awareness of, and skill in managing, delirium within the VA.

Editors Choice: Did you see?

Randomized Trial of a Delirium Abatement Programme for Postacute Skilled Nursing Facilities. Marcantonio E, Bergmann MA, Kiely DK et al. Journal of American Geriatrics Society 2010; 59: 1019-1026.

Editorial – Paper Geriatrics. Levenson S. JAGS 2010; 59: 1184-1185

The objectives were to determine whether a delirium abatement program (DAP) would shorten the duration of admissions into postacute care units. This was a cluster randomised trial of 8 study sites within the greater Boston area, Massachusetts. Did it work? Without wanting to spoil the surprise the accompanying editorial by Steven Levenson makes the wise suggestion:

"Before developing more protocols and tools to treat specific conditions such as pain, weight loss and delirium, it may be time to pay much more attention to critical generic competencies that underlie the management of complex patients and their diverse syndromes (e.g. the ability to collect and organize information and examine evidence, present a chronological story of events in an orderly fashion, reason inductively and deductively, seek and identify causation, define and solve problems, and provide a valid rationale for conclusions)."

Using psychostimulants in end-of-life patients with hypoactive delirium and cognitive disorders: A literature review. Elie D, Gagnon P, Gagnon B, Giguere A. Canadian Journal of Psychiatry 2010; 55: 386-93

This review is published in French so in keeping with our multinational organisation. This review of "de delirium hypoactive and de troubles cognitifs" in patients with advanced cancer concludes that the (limited) evidence to date supports the use of methylphenidate.

Cerebrospinal fluid in long-lasting delirium compared with Alzheimer's dementia. Caplan G, Kvelde T, Lai C et al. Journal of Gerontology 2010; June 7 epub ahead of print.

The hypothesis that delirium is caused by acute episodes of neuronal cell death was investigated by using CSF markers of cell death – lactate, neuron-specific enolase and S100B. This cohort study, which compared 20 patients with over 5 days of delirium and 20 patients with Alzheimer's Disease, asks lots of questions.

Study of rivastigmine for delirium in intensive care stopped after deaths

This multi-centre study had been co-ordinated by the University Medical Centre, Utrecht in the Netherlands. According to the BMJ news report they had recruited 104 of a planned 440 patients in this double blind, placebo trial by the time of an interim analysis. There had been 12 deaths in the 54 patients who had received the drug and 4 deaths of 50 patients in the placebo group. While the difference had not reached statistical significance they decided to stop the trial on the basis that they were not sure the agent was safe in intensive care patients and the trial data had not shown a decrease in the duration of delirium at the time of analysis. The Utrecht hospital stressed that the decision had no consequences for patients with Alzheimer's disease for whom rivastigmine has been licensed in Europe since 1997.

Antipsychotics good or bad?

66 visitors to the members area of the European Delirium Association website were asked if they agreed or disagreed with the statement: "Antipsychotics should only be used as a last resort in delirium" The results were : ·

Yes 43 65%
No 23 35%

The next poll will again appear on the Health Professionals page on the site at

www.europeandeliriumassociation.com/delirium-information/

The European Delirium Association
5th Scientific Congress on Delirium

Thursday 11 and Friday 12 November 2010, Amsterdam, The Netherlands. Keynote speakers include Professor Sharon Inouye, Professor Wes Ely and Professor Alastair Macdonald. More details available from www.europeandeliriumassociation.com. The closing date for abstract submission is August 31st.

American Delirium Society Annual Conference 2011

The American Delirium Society's first annual conference will be held from June 7-8 2011, in Indianapolis, Indiana, at the Regenstrief Institute, which has been the source of widely regarded achievements in the field of geriatrics. The conference has also received academic and financial support from Malaz Boustani, MD, MPH, whose work on frailty and delirium is centred at the Institute.