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Satellite Symposia

SS01 – Pfizer, Inc. Satellite Symposium

A 20-year video case history: Behavior problems and caregiving

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Join Dr. Daniel Christensen as he chronicles two families' very different experiences with dementia. Both captured on videotape—and one for over 20 years—these stories will give attendees new insights into the devastating effects of dementia from the perspectives of the patient and caregiver, while still managing to bring to the forefront the triumph of the human spirit in times of intense challenge. Physicians at this Pfizer-sponsored symposium will learn how easy it often is to benefit patients and caregivers who are affected by dementia with relatively simple interventions. Other topics that will be explored in this session include the importance of early diagnosis of Alzheimer's disease (AD); behavioral issues associated with AD; managing patient and caregiver expectations throughout the course of the disease; and communicating the value of persistent treatment, even in a progressive disease like Alzheimer's.

SS02.1 – H. Lundbeck A/S Satellite Symposium

Chairman's introduction

Serge Gauthier

McGill Centre for Studies in Aging, Verdun, QC, Canada

Welcome to this satellite symposium on 'Assessing the effects of Alzheimer's disease treatment'.

The challenges that Alzheimer's disease (AD) presents to patients, carers and physicians are well documented, and appreciation of how these individual challenges affect patients and carers is helping to drive drug development into new realms of efficacy. In this session, we aim to provide an update on several areas that are key to managing the wide-ranging and progressive effects of AD.

In the first presentation, Philip Scheltens will discuss the role of biomarkers in current and future practices of diagnosis and treatment in AD. Following this, David Wilkinson will summarise the latest data for the NMDA receptor antagonist, memantine, in the treatment of AD. This presentation will cover established data such as symptomatic benefits and meaningful clinical worsening analyses, and will also consider future development options for memantine. The last of our speakers, Nathan Herrmann, will then focus on the important area of behavioural symptoms in AD, the problems faced, and the current best practices for management.

We hope that you will find today's symposium informative, and we look forward to hearing your perspectives on the issues covered, during the final question and answer session.

SS02.2 – Assessment of Alzheimer's disease treatment: The role of biomarkers

Philip Scheltens

VU University Medical Center, Amsterdam, Netherlands

Alzheimer's disease (AD) is associated with the accumulation of amyloid plaques (containing beta-amyloid, Aβ) and neurofibrillary tangles (abnormally twisted bundles of hyper-phosphorylated tau protein). Knowledge of the pathology underlying AD has helped to drive the development of new disease evaluation and treatment approaches, including the use of biomarkers.

Based upon current pathological understanding, the most frequently used biomarkers for AD evaluation are Aβ, and tau (total or phosphorylated) in the cerebrospinal fluid (CSF). The CSF of AD patients generally contains reduced levels of Aβ42 and elevated levels of tau, and many studies have shown that Aβ42 and total tau levels are sensitive markers for the identification of AD. However, although their levels may reflect the extent of neuronal damage and degeneration present, specificity in discriminating AD from other dementias is limited. Phosphorylated tau seems to have greater specificity for AD, as it displays normal levels in other dementias. A combination of these markers has potential as a useful evaluation tool in dementia—particularly when combined with brain imaging techniques.

Aside from diagnosis, changes in biomarker levels over time could help to track disease progression. For example, MRI can identify changes in total brain volume, as well as volume changes in specific areas such as the hippocampus. Other imaging techniques (e.g., MR spectroscopy,

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FDG-PET) can help to identify changes in brain metabolism.

A mixed approach, using biochemical markers and imaging analyses, both for diagnosis and tracking disease, may be informative in assessing AD evolution, including the functional, and potential disease-modifying effects of pharmacotherapy.

In preclinical investigations, the NMDA receptor antagonist, memantine, has been shown to reduce the levels of total Aβ, and protect against the neurotoxic and apoptotic effects of Aβ deposition. Furthermore, a preliminary clinical study in 11 AD patients revealed a statistically significant reduction in phosphorylated tau after 1 year of memantine treatment. Most recently, multimodal imaging has been employed to assess the effect of memantine on AD evolution. In a randomised, double-blind, placebo-controlled pilot study, MRI and PET imaging showed that 1 year of memantine treatment produced less reduction in glucose metabolism in all brain regions, and less hippocampal atrophy than placebo. These findings correlate with the functional, and potential disease-modifying effects of memantine, respectively. Further studies are evaluating the effect of memantine on the rate of brain atrophy.

SS02.3 – Memantine in Alzheimer's disease: Symptomatic treatment and beyond

David Wilkinson

Moorgreen Hospital, Southampton, United Kingdom

The symptoms experienced in Alzheimer's disease (AD) vary between patients, as well as over time, but characteristically involve a progressive decline in aspects of cognition, function and behaviour. These symptoms gradually reduce patient independence and, consequently, create a significant increase in carer burden.

In individual clinical trials, memantine has demonstrated benefits in overall ratings of cognition, function and behaviour in moderate to severe AD – an effect further supported by meta-analyses and pooled data. Single-item analyses have also been performed to illustrate the specific benefits of memantine. In patients with moderate to severe AD, memantine produced cognitive improvements in the SIB subscales of memory, language, praxis, and visuospatial ability. Memory impairment is usually the first sign of AD, eventually progressing to affect patients' ability to perform activities of daily living (ADLs). However, communication and language are also important, and the disintegration of language skills in the later stages of AD reduces patients' ability to interact, communicate and deal with everyday activities. Memantine's favourable effects in all these key cognitive areas are, therefore, meaningful outcomes for the patient. In the assessment of function, memantine produced significant benefit in ADCS-ADL_{19} items including grooming, toileting, and 'makes conversation'. Thus, there is good evidence that memantine impacts on basic ADLs, as well as higher level functions. In terms of specific behavioural effects, memantine has been associated with significant benefits on individual NPI items of agitation/aggression, irritability/lability, delusions, and appetite/eating changes.

Memantine has also been investigated in analyses of the prevention of clinical worsening – a clinically relevant and realistic treatment outcome in a progressive neurodegenerative disorder such as AD. Post hoc analyses were performed on pooled data from six, 6-month, placebo-controlled memantine studies of patients with moderate to severe AD whose clinical condition concurrently worsened on the cognitive, global and functional domains. Results showed that memantine was statistically significantly superior to placebo at preventing the concurrent clinical worsening of patients in all three domains. This effect is particularly relevant for patients with moderate to severe AD, who are most in need.

In summary, memantine has proven beneficial in specific areas of cognition, function and behaviour in moderate to severe AD. Taken together with data showing that memantine can also prevent clinical worsening and significantly reduce caregiver burden, this gives memantine a clinically meaningful profile of specific benefits.

SS02.4 – Managing behavioural problems in Alzheimer's disease

Nathan Herrmann

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Behavioural problems emerge throughout the course of Alzheimer's disease (AD), becoming more frequent as the disease progresses, and representing some of the most distressing aspects of the condition for both patients and caregivers. Indeed, the frequency of behavioural symptoms correlates with the level of caregiver distress, is associated with caregiver depression, and also has a marked socio-economic impact. Symptoms such as severe agitation are often the trigger for a transfer to institutional care—a change in circumstance that represents a significant increase in healthcare

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costs. Consequently, effective management of these symptoms is critical.

The management of behavioural symptoms can involve non-pharmacological means such as behavioural therapy and sensory enhancement (e.g., music, massage). In addition, caregivers may also receive various forms of support, including psychotherapy or provision of respite care. Regarding pharmacotherapy, management options may include pharmacotherapy with psychotropics (antidepressants, antipsychotics, anticonvulsants) or anti-dementia agents (cholinesterase inhibitors, memantine). However, antipsychotic agents can produce side effects such as extrapyramidal symptoms (EPS), sedation, lowered blood pressure, and QT prolongation, and have been associated with a 1.7-fold increase in mortality. Furthermore, some antipsychotics may produce cognitive decline, and increase the risk of cerebrovascular adverse events. Consequently, warnings against the use of atypical antipsychotics in dementia have been issued by most health regulatory agencies. There is clearly an increase in the need for alternative treatment options.

Acetylcholinesterase inhibitors such as donepezil have shown beneficial effects on some behavioural disturbances in AD. In addition, the NMDA antagonist, memantine, produced additional behavioural benefits in patients with moderate to severe AD who were already receiving stable treatment with donepezil. The memantine/donepezil group showed significant benefits over the placebo/donepezil group in total NPI score, and in individual items of agitation/aggression, irritability/lability, and appetite/eating changes. The behavioural impact of memantine was investigated further in a sub-population of behaviourally disturbed patients (i.e., patients with agitation/aggression and psychosis at baseline), using pooled data from three studies of moderate to severe AD. In this patient population, memantine produced significant stabilisation or improvement of behavioural symptoms, as well as beneficial effects on cognition, function and global outcomes. Memantine also had significant effects on the prevention of behavioural symptom emergence in patients without agitation/aggression at baseline.

It is evident that effective management of behavioural symptoms is critical in order to prolong the safety, dignity and quality of life of the AD patient, alongside the relief of caregiver burden, and reduction of considerable social and economic costs. Therefore, treatments such as memantine represent a new option for the pharmacotherapy of behavioural symptoms.

SS03 – Pfizer, Inc. Satellite Symposium

Alzheimer's disease: Developing the next generation of treatment

SS04 – Eli Lilly and Company Satellite Symposium

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