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Production of nitric oxide and proinflammatory cytokines by cultured microglia stimulated with heparan sulphate proteoglycan.

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Heparan sulphate proteoglycan (HSPG) belongs to a family of molecular chaperons that are detected in the b-amyloid protein (Ab) containing lesions of Alzheimer's disease including activated microglia. HSPG is a complex macromolecule consisting of a protein core to which polysaccharide chain (HS) is covalently attached. HSPG appears very early during plaque evolution and is presumably involved in Ab deposition and fibrillogenesis. The effects of HSPG have previously not been investigated in cultured microglia. We therefore examined by RT-PCR and specific immunoassays the production of nitric oxide (NO) and proinflammatory cytokines by cultured primary murine microglia stimulated with different concentrations of HSPG for up to 48 h. We demonstrate that HSPG induced production of tumour necrosis-alpha (TNF-a) and interleukin-6 (IL-6) as well as release of high nitrite (NO2-) levels with increased mRNA accumulation of inducible nitric oxide synthase (iNOS) in a dose- and time-related fashion. On the contrary, heat denatured HSPG or HS alone failed to induce both NO production and cytokine release. These data suggest that HSPG, and particularly its core protein, may contribute to chronic microglial activation detected in senile plaques with production of proinflammatory cytokines and free radicals implicated as a causative factor in neurodegeneration associated with Alzheimer's disease.
Supported by Ricerca Finalizzata 2000 of the Italian Ministry of Health.

P 2181

Effects of central amyloid-beta on learning, glial activation, neuronal degeneration and apoptosis in rats

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Amyloid-beta (AB) accumulates in Alzheimer's disease (AD) brains, and it is thought that AB deposition is a primary cause of the neuronal death and the cognitive impairment occurring in AD patients. Therefore, reduction of AB deposits might constitute a promising strategy to treat or prevent AD.

Here we investigated the in vivo effects of AB fragments 1–28 and 1–40 injected into the rat hippocampus: (1) Effects of bilateral AB28 and AB40 injections on the retention of a passive avoidance learning task (PAL): comparison with control and water-injected (Sham) rats; (2) Effects of unilateral AB28 injections on neuronal degeneration and glial (microglia, astrocytes) activation; (3) effects of unilateral AB40 injections on PAL retention and on neuronal loss and apoptosis.
AB injections impaired learning improvement from the acquisition to the retention PAL sessions ($p<0.01$ vs. sham). These amnesic effects of AB being more evident for the 1–40 fragment. The central administration of AB induced a significant neuronal loss in the hippocampal CA1 area ($p<0.05$ vs. sham), as well as significant increases in the number of profiles immunoreactive for ED1 ($p<0.05$) and for GFAP ($p<0.05$) in the hippocampus. Finally, central AB increased the expression of apoptotic figures in the rat hippocampus and brain cortex ($p<0.05$).
Our results indicate that central AB impairs learning and induces glial activation, neuronal degeneration and apoptosis in the rat brain.

P 2182

The locus caeruleus in Alzheimer's disease: a Golgi and electron microscope study

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We studied the fine structure of locus caeruleus of ten early cases of Alzheimer's disease in correlation to normal controls. PHF were abundant in the majority of neurons of the locus caeruleus whereas neuritic plaques were rare. Large number of neurons demonstrated a poverty of the rough endoplasmic reticulum and a marked dilatation of the cisternae of the smooth endoplasmic reticulum as well as fragmentation of the cisternae of the Golgi apparatus. Mitochondrial alterations, such as accumulation of osmiophilic material, fragmentation of the cristae and vacuolization were frequently seen. Axonal dystrophy was observed in substantial number of neurons. Loss of dendritic spines and abbreviation of the dendritic arborisation were also seen in the majority of the round and elongated neurons of the locus caeruleus. Unattached spines were rare. Morphological alterations of the axo-somatic, axo-dendritic and axo-axonic synapses were seen in extend and described in detail. Extensive astrocytosis was seen in all parts of the locus caeruleus in correlation with normal controls. Microglial activation and neuronophagia was minimal in correlation with other parts of the brain stem.
Morphometric estimation of the mitochondria, the Golgi apparatus and the synapses in correlation with normal controls emphasised the substantial changes of those organelles in early cases of Alzheimer's disease.

P 2183

Dopamine system in Alzheimer's disease and mild cognitive impairment

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It is well known that monoaminergic systems innervate cholinergic cells can affect the release of acetylcholine in the cerebral cortex. With regard to this, previous reports suggest a deregulation of these systems in neurodegenerative diseases such as Alzheimer's disease (AD), especially in term of dopaminergic deficit. Dopamine receptors have been identified in human and rat peripheral blood lymphocytes (PBL) and there is evidence that human lymphocytes synthesize catecholamines. In the present study we investigated changes in the PBL acetylcholine and Dopamine systems in AD and mild cognitive impairment (MCI) by measuring tyrosine hydroxylase and Dopamine beta-hydroxylase immunoreactivity as well as choline acetyl-transferase and acetylcholine esterase immunoreactivity. The study was carried out on 10 AD patients and 10 MCI subjects. Eight healthy subjects, matched for age, were used as a control population.
The mean value of Dopamine beta-hydroxylase immunoreactivity was significantly higher in AD patients with respect to MCI and control subjects (0.16+/–0.008, 0.127+/–0.01, 0.117+/–0.006, respectively; $P<0.0001$). By contrast, the immunoreactivity for choline acetyl-transferase was slightly decreased in AD patients as compared with MCI and controls (0.054+/–0.016, 0.069+/–0.024, 0.071+/–0.008). No significant differences were found between patients and controls on tyrosine-hydroxylase and acetylcholine esterase. These data suggest that monoaminergic systems are impaired in AD and that PBL may represent a simple and useful tool to identify this impairment probably also in the early stage of the disease.

P 2184

Apolipoprotein-E genotype and psychiatric symptoms in Alzheimer's disease

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Introduction Although the epsilon 4 allele of Apo-E is a well-known risk factor for late-onset Alzheimer's disease (AD), the relationship between Apo-E allele status and non-cognitive symptoms is less clear in AD patients. Psychiatric disturbances are very common in these patients and often worsen their functional disability. Therefore, it is interesting to evaluate any phenotypic aspect of Apo-E allele status. We examined the relationship between Apo-E allele status and psychiatric symptoms in AD patients.
Methods Apo-E genotype was determined in 121 AD patients (diagnosed according DSM-IV criteria). The clinical dementia rating scale was used to rate the severity of dementia. The presence of behavioural disturbances, depression and psychotic symptoms was assessed using the neuropsychiatric inventory and the geriatric depression scale.
Results The following Apo-E genotypes were observed: 4/4 (n=5), 4/3 (n=45), 4/2 (n=4), 3/3 (n=61), 2/2 (n=6). Depression was found in 38% of the demented subjects, 28.1% of them had psychotic symptoms, and 25.6% had behavioural disturbances. After adjusting for age, sex, education and severity of dementia, we found a significant risk for psychosis (OR 5.3; 95% CI 1.8–16.2) in patients carrying the epsilon 4 allele; no significant relationship was found between either the epsilon 3 allele or the epsilon 2 allele and any of the non-cognitive symptoms assessed.
Conclusion Our results suggest that differences in ApoE allele status influence the phenotypic expression in AD patients. In particular, the epsilon 4 allele was found to be a significant risk factor for psychosis.

P 2185

Proinflammatory cytokines in the CSF of Creutzfeldt-Jakob-disease

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Introduction Creutzfeldt-Jakob-disease (CJD) is a neurodegenerative disease within the central nervous system (CNS).
The starting-point for this investigation was the analysis of the potential role of cytokines following neurodegeneration.
Methods Cerebrospinal fluid and serum samples were collected in the framework of the German CJD surveillance study. Concentrations of the interleukins (IL): IL-1β, IL-6, IL-8, IL-12 and tumour necrosis factor-α (TNF-α) were determined using commercially available ELISA-test kits.
Tests were conducted in patients with following diagnosis: CJD (n=10), inflammatory diseases (n=11), epilepsia (n=12), of various dementia (n=17) and healthy controls (n=13).
Results No measurable amounts of IL-1β, IL-12 and TNF-α could be detected in CSF. IL-6 was detectable in CSF without significant difference between groups.
The investigation of IL-8 showed a significant elevation in CJD (median 24.86 pg/ml, min 4.81 pg/ml, max 54.12 pg/ml) compared to: inflammatory diseases (median 19.81 pg/ml, min 1.80 pg/ml, max 74.23 pg/ml), epilepsia (median 8.58 pg/ml, min 4.82 pg/ml, max 12.04 pg/ml), dementia (median 17.38 pg/ml, min 3.01 pg/ml, max 45.69 pg/ml).
Conclusions Only one of five investigated proinflammatory cytokines were elevated in the CSF of CJD. These new findings may be interesting in view of pathophysiological processes involved in CJD following neurodegeneration. A potential utility of IL-8 in diagnosis has to be investigated further. The mechanisms of elevation of IL-8 in CJD are unknown, but an isolate elevation in CJD compared to other dementia suggests a specific role in prion diseases.

P 2186

Creutzfeldt-Jakob disease: correlation of MRI and clinical findings

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Introduction Creutzfeldt-Jakob disease (CJD) is a fatal disease with characteristic neurological features such as rapid progressive dementia, myoclonus, ataxia, and pyramidal and extrapyramidal signs. Although the definite diagnosis of CJD requires neuropathology, the patients often present with a typical EEG and typical cerebrospinal fluid findings such as elevated levels of 14-3-3 proteins. Lately the MRI showing an increase of signal in the basal ganglia on T2-weighted images has also been discussed as a valuable tool in diagnosing CJD, however, until now, this characteristic finding has not yet been correlated with the clinical features.
Material and methods We studied 239 patients containing 155 ascertained CJD cases for their neurological symptoms and MRI findings. An investigator blinded for diagnosis assessed the MRI.
Results surprisingly, among the CJD cases, patients without signal increase of the basal ganglia were shown to have a higher frequency of extrapyramidal disturbances (83% vs. 70%). Differences that are more striking were shown for symptoms such as depression, sensory disturbances and akinetic mutism, which were more frequent among cases without signal, increase as well. Patients with typical MRI findings seemed to have a more aggressive disease course with rapid progressive dementia in an early stage and a shorter disease duration (median 6.7 months and 9 months respectively).
Discussion These results suggest distinct CJD phenotypes distinguished by neuroradiology. These phenotypes have still to be examined in regard to pathological lesion patterns and prevailing genotype.

P 2187

Difference of depressive symptoms in patients with vascular dementia and Alzheimer's disease

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Background Depressive symptoms frequently accompany both vascular dementia (VAD) and Alzheimer's disease (AD). In VAD they are related to damage of frontal-subcortical networks, while in AD genesis of depressive symptoms are unclear.
Objective One-year follow-up of VAD and AD patients, including comparison of depressive symptoms and cognitive decline.
Design/Methods 39 VAD (NINDS-AIREN criteria) and 34 AD (NINDS-ADRDA criteria) patients have been followed up for one year. At the beginning two groups were similar due to dementia severity (MMSE), which was mild. Depressive symptoms were analysed according to Hamilton depression scale.
Results At the beginning incidence (per 100 person-year) of depressive symptoms was 30.6% among VAD and 13.4% among AD patients (p. 0.05). Despite equal antidepressant regime, depressive symptoms persisted in 58% of VAD while in 62.2% of AD patients' improvement was significant. At follow up prevalence of depressive symptoms in VAD patients increased up to 46.4% and in AD group – up to 16%. Comparison of cognitive decline and depressive symptoms in AD patients did not reveal any correlation. VAD patients treated with antidepressants revealed reduced rate of cognitive decline, in comparison to untreated patients. Reduced rate of cognitive decline was similar among antidepressant responder and non-responder patients.
Conclusions Persistent depressive symptoms are prominent for VAD. Similarity of reduced cognitive decline in antidepressant effective and ineffective patients suggests that cognitive decline in VAD is caused by multiple neurotransmitter systems damage. Even in the absence of antidepressant's effect, in VAD patients they could be used for slowing of cognitive decline.

P 2188

Optimisation of the diagnosis of Alzheimer's disease and other dementias (OPDAL) – a survey on carers in Europe

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Introduction The OPDAL program was initiated to provide guidelines for physicians and other health care professionals for the disclosure of the diagnosis of Alzheimer's disease or other dementia disorders to the patient and the family. The aim of this survey was to collect opinions from carers about the procedure for diagnostic disclosure, about the information presently provided to patients and family carers, and about the information sought by carers.

Methods A total of 323 carers, mainly spouses (56%) or sons and daughters (31%) from 11 countries participated in the survey and completed the 42-item questionnaire.
Results In 46% of the cases, the physician had disclosed the diagnosis to the family, and not to the patient, and many family carers did not know how to inform the patient. Drug treatment was initiated in 62% of patients in whom an AD diagnosis was established. While most carers were informed about dosing (76%), fewer were informed about efficacy (46%) and side effects (59%). A large part of the carers (46%) found that the information provided to them was insufficient and in many cases, (29%) there was no regular contact with any physician after the diagnostic disclosure.
Conclusions The results highlight the need to develop and implement 1) structured guidelines to health care professionals for the information and education of family carers and patients; 2) written information to patients and carers on a number of issues concerning diagnosis and treatment.

P 2189

The incidence and risk factors for new-onset dementia within one year after ischemic stroke

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Background and Purpose Dementia after stroke may be caused by vascular lesion, but pre-existing degenerative changes can also influence its development. The patients after stroke with co-existing Alzheimer-type pathology need appropriate treatment. The aim of the study was to evaluate the incidence of pre-stroke and new onset dementia within one year after stroke.
Methods We evaluated pre-stroke dementia in 250 patients with ischemic or hemorrhagic stroke using the informant questionnaire on cognitive decline in the elderly (IQCODE). Post-stroke dementia was assessed in 220 patients three months after stroke and in 194 patients one year after stroke by means of the neuropsychological tests and/or IQCODE. The DSM-IV definition for dementia was used.
Results Dementia was found in 31.4% of stroke patients three months after stroke and in 32.6% of patients one year after stroke. Nine patients (4.6%) who did not fulfil DSM-IV criteria for dementia 3 months after stroke were found to be demented 9 months later. Twelfth percent of stroke patients had significant impairment of cognitive functions detected by IQCODE on admission suggesting pre-stroke dementia.
Logistic regression analysis showed that older age, higher IQCODE score on admission and lower Barthel index on discharge from the hospital but not CT findings increased the risk of new-onset dementia.
Conclusions The results suggest dementia appears in about 20% of patients within one year after stroke. About one-tenth of stroke patients have pre-existing dementia. Older age, cognitive decline before stroke and functional disability on discharge are independent contributors to the risk of dementia after stroke.

P 2190

Healthcare utilization and costs due to common medical co-morbidities are increased in community-dwelling patients with Alzheimer's disease

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Introduction Co-morbid conditions and healthcare costs were analysed for patients with Alzheimer's disease (AD) in a Medicare-Managed Care Organization (MCO), and implications for disease management programs were derived.
Methods A retrospective analysis was conducted of administrative data for AD patients (3517) and age-gender-matched controls (17,480) selected from a Medicare-MCO. The prevalence of AD and 16 co morbid conditions identified using diagnostic classifications from the Charlson co-morbidity index were determined.
Results The prevalence of AD in the MCO was 3.9%. Annual healthcare costs were $3706 higher for AD patients than controls. Costs for co-morbid conditions were higher for AD patients: compared with controls with the same conditions. Costs were $5389 higher for patients with AD and congestive heart failure (CHF), $7410 higher for AD and diabetes with chronic complications, and $4404 higher for AD and diabetes without complications. Increased healthcare costs for AD patients were attributable to greater utilization of inpatient and skilled nursing facilities.
Conclusion Costs for AD patients in a Medicare-MCO were 1.6 times higher than for controls and significantly higher for 13 of 16 co-morbid conditions examined, including CHF and diabetes. Much of these costs appeared to be related to potentially avoidable hospitalisations. These findings demonstrate the need for early identification and improved care management and treatment of patients with AD who also have multiple co-morbidities in order to improve the quality of care and potentially reduce healthcare costs in frail elderly.
Supported by Pfizer outcomes research.

P 2191

Epidemiology of dementia in Tirana – Albania

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Dementia is a syndrome caused by brain diseases, usually with a chronic and progressive course, characterized by the impairment of the cognitive functions and the deterioration of previously acquired intellectual abilities that interferes with social or occupational functioning.
The scientific purpose of the study was to estimate the prevalence of dementia in the city of Tirana.
We have chosen the persons in a randomised way from the municipal register in a determined geographic area of Tirana City. We found 3550 people over 60 years old registered in that area.
The study had two phases:
Phase I: The people were screened at their home by a team of residents of neurology. Every group of residents conducted the interview according to questionnaire (MMSE) and made a simple neurological objective examination. The people, who resulted positive, passed at the phase two.

Phase II: In this phase the target persons were investigated by a senior of the Clinic of Neurology, University Hospital Centre "Mother Theresa", Tirana-Albania, who made the correct diagnosis according to the specific clinical and radiological criteria of dementia. The ICD 10 diagnostic criteria for dementia are applied.
The data were elaborated in the Neuroepidemiology Unit of the Clinic of Neurology.
The study lasted about 6 months.
During the first phase of the study, we screened 3521 people (from 3550 over 60 years old persons from the municipal registers). There were 380 positive (7.75%; 4.83% for males and 11.45% for females) (P<0.001).

P 2192

Genetic vascular risk score for sporadic Alzheimer's disease: relationship with mini mental state examination performances

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Introduction Recent evidences suggest a strong association between cardiovascular genetic risk factors and sporadic Alzheimer's disease (sAD). We analysed the distribution of methylenetetrahydrofolate reductase (MTHFR), angiotensin-converting enzyme (ACE), endothelial nitric oxide synthase (eNOS), and apolipoprotein E (APOE) gene polymorphism, all vascular genetic risk factors, and sAD.
Methods We studied 142 sAD patients (65% women, mean age±SD of 72.0±9.7) with probable AD, and 142 healthy individuals matched for age, sex, and geographical distribution (mean age±SD of 73.3±7.6). Subjects were genotyped for the following gene polymorphisms: MTHFR (C677T), ACE (I/D), eNOS (G894T), and APOE. A genetic vascular risk score (VRS – ranging from 0 to 8), clustering the allele distribution of the 4 polymorphisms, were calculated.
Results No significant differences were detected in genotype or allele frequencies for MTHFR, ACE, and eNOS polymorphisms between cases and controls. The frequency of the e4 allele (cases 20.0%, controls 7.0% – p<.0001) and e4-containg genotypes was significantly higher in sAD (cases 40.0%, controls 13.2% – p<.0001). Regression analyses showed a significant negative relationship between the genetic VRS and the score obtained on the mini mental state examination (MMSE) (r–0.19, p.008).
Conclusion Our data suggest that MTHFR, ACE, and eNOS genotypes do not contribute to genetic susceptibility in Italian sAD, and confirm APOE as a major genetic risk factor for AD. Furthermore, our data suggest that a "vascular" polygenic trait, could affect cognitive performances in sAD patients.

P 2193

Quantitative EEG changes during cognition tasks in patients with cognitive impairment.

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The linear changes of ongoing quantitative EEG were studied in elderly subjects with cognitive impairment during five different conditions: two resting conditions (eyes open and eyes closed) and three cognition tasks (verbal, non-verbal and fluency). Separate analysis of all frequency bands took place. 21 subjects, mean age 75.4 years (SD=7.2) were divided into 4 matched groups: Controls, subjects with subjective memory complaints, subjects with Mild Cognitive Impairment (MCI), subjects with Alzheimer's disease (AD).
The eyes closed resting condition: AD patients showed significant power differences in all frequency bands compared to controls. No statistical difference was detected between other groups and controls. The eyes opened resting condition: only AD patients demonstrated a statistically significant lack of normal EEG reactivity in comparison with the controls (p<0.01). The verbal and non-verbal tasks: MCI and AD patients had comparable significant low reactivity of theta and alpha bands. The MCI subjects showed significant increase in beta 2 and gamma frequencies (p<0.01) when compared to controls. Performance of fluency task showed no significant EEG spectral value differences between the groups. Cognition tasks during ongoing qEEG-registration can be used to reveal significant abnormalities even in cases of subtle cognitive impairment, i.e. in MCI patients.

P 2194

SPECT studies in vascular dementia

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The diagnosis of vascular dementia is very difficult, but new diagnostic methods have made it easier.
The study was performed in 37 patients aged 48–85, mean 67. SPECT and CT were carried out in all patients. The CT showed two and more ischemic lesions in the brain. In the group of patients with dementia classified according to the criteria of DSM-IV, ICD-10, MMS and Hachinsky Ischemia Scale. SPECT was performed with APEX SP 6 HR, produced by Elscint, using a complex of 99m-Tc-ECD.
Results Many hypodense lesions were found in all patients with dementia, especially in the temporal and frontal lobes. These results were compared with CT results. Both examinations showed lesions in the same localisation. However, the hypodense lesions in SPECT were bigger than the lesions in CT. SPECT revealed many ischemic lesions, which were invisible in CT.
Conclusions 1. SPECT is a more sensitive examination than CT in the diagnosis of vascular dementia.
2. SPECT should be the primary examination in the diagnosis of vascular dementia if the results of CT are negative.

P 2195

Isotopic studies in fronto-temporal dementia

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Introduction 80% of people over 60 years of age suffer from at least one of the diseases connected with ageing of the organism. Often several diseases appear simultaneously quickly leading to death. Of the diseases connected with ageing, dementia syndromes have the most serious effect on personality and social status. Especially Alzheimer's disease with its progressive brain damage deprives man of his most human values of psychical and emotional life, ending with death of a patient.

Objectives In CT investigation there is distinct disappearance of frontal pieces. In SPECT investigation considerable degree of handicap ECD perfusion in frontal and temporal lobes localization, often on both sides.
Methods Studies were performed by using CT – SHIMADZU SCT-7000T and SPECT – gamma camera APEX SP 6 HR. Patients were examined for two tests: Mini Mental State Scale and Hamilton Depression Scale.
Material 11 patients between 49 to 74 years (mean 61.5). Control group: 9 patients aged between 51 and 72 years (mean 61.5). All of these patients were estimated of melting stupefactions by means of psychological tests, Mini Mental State Scale and Hamilton Depression Scale and screening tests to measure the level of depression in patients of higher age.
Results In neuroimaging of dementia syndromes, most often lesions are found in frontal lobe and hippocampus. Our MRI studies showed lesions in the frontal and temporal lobes in two cases. These results and further investigations revealed a considerable hypo-perfusion in frontal and temporal lobes. Both methods, SPECT and PUSG-Doppler, permit the estimation of cerebral blood flow (CBF) for each arterial supply area. However, small disturbances of brain perfusion ascertained by SPECT are not revealed by PUSG-D. PUSG-D as cheap, non-invasive method and easily accessible investigation should find use as diagnostic method for patients with CBF disturbances, especially in dementia syndromes.
Conclusions 1.In fronto-demential syndromes with frontal lobe atrophy character it is necessary to perform SPECT study for the purpose of settlement of the final diagnosis.
2. Brain SPECT-ECD is the choice study in fronto-temporal dementia.

P 2196

The value of visual EEG in patients with dementia of different origin

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Methods Standard-EEG-recordings from 40 patients with probable dementia, mild/moderate dementia and severe dementia of different origin were studied. The Mini Mental State Examination (MMSE) classified the severity of mental impairment. Thereby the patients were divided in three groups. Group I: 13 patients with MMSE score between 30–24; Group II: 16 patients with MMSE score between 24–17; Group III: 11 patients with MMSE score 16–0.
The EEGs were visually assessed on the following criteria: 1) Dominant alpha frequency (rhythm) occipital; 2) Dominant theta frequency (rhythm) occipital; 3) Other slow frequencies occipital; 4) Presence of theta and/or delta activity local or diffusely spread; 5) Left/right asymmetry; 6) Spikes, sharp waves, triphasic waves; 7) Generalized, bilateral synchronous paroxysmal Delta activity = bursts, short and long runs of Delta; 8) Effect of eye opening; 9) Suppression periods. There also was an overall classification of EEG in normal, slightly abnormal, moderately abnormal and abnormal.
Results Normal EEGs were predominant in group I. No normal EEG was seen in group III. In group III even light and moderately abnormal EEGs were absent. With increasing severity of dementia, there also was an increase of EEG abnormalities. If a normal EEG is seen in a patient who seems to be severely demented, the diagnosis of dementia should be questioned and other causes of dementia should be carefully considered.
Beside the appearance of some theta and delta waves, no other pathological EEG pattern was found in cases with mild dementia. With increasing severity of dementia, there was an increase of theta and delta waves in the occipital regions, an increase of generalized paroxysmal delta activity and also an increase of spikes, sharp and triphasic waves. Suppression periods were only seen in severely demented patients.
Visually analysed EEG appeared to be a cheap and useful tool in the estimation of the severity of dementia.

P 2197

Executive functions and declarative memory in patients with Alzheimer's disease

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Introduction Memory impairment is a hallmark of Alzheimer's disease. Executive functions are more preserved at the beginning. We correlated these two functions to see to what extent they are independent so that adequate cognitive treatment measures can be applied.
Methods We examined 11 patients with early or moderate Alzheimer's disease, 7 females and 4 males, age 59 to 84 years (mean 70.4), all right handed, mean education 14.2 years, with Mini Mental State Examination (MMSE), Wisconsin Card Sorting Test (WCST), Rey Auditive Verbal Learning Test (RAVLT) and Rey Complex Figure (RCF). Statistical analysis was done with Pearson correlation test.
Results MMSE score correlated significantly only with RAVLT evocation and recognition ($p<0.05$). Also, there was significant correlation between RAVLT evocation and recognition ($p<0.05$) and RAVLT evocation and RCF evocation after 3 minutes ($p<0.05$). WCST measures of number of categories achieved and perseverative responses did not correlate neither between each other nor with other variables.
Conclusion MMSE, RAVLT evocation and recognition and RCF evocation after 3 minutes are all measuring retrorolandic memory function can be used in monitoring the dementia progression. WCST measures are independent variables and measure prefrontal function that is less severely damaged in early Alzheimer's disease and can be used in cognitive treatment to alleviate memory problems.

P 2198

Motor activity in patients with vascular dementia or dementia of Alzheimer's type

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Introduction There is evidence that enhanced motor activity in dementia improves cognitive symptoms (Tappen et al. 2000). There is only little information about motor activity in demented patients. **Aim** of the study is the development of a method to assess daily motor activity in patients with vascular dementia (VD) or dementia of Alzheimer's type (DAT).
Methods Within 14 days all patients (10 males, median age 77 years, 10 females, median age 76 years) wore a step counter from 9 a.m. to 12 a.m. and 4 p.m. to 6 p.m. The patients suffered from moderate dementia according to the Mini Mental State Examination (MMSE, Folstein).

Results Daily mean steps in DAT-patients were 7448 (SD: 620, corresponding 3700 meters), in VD-patients 5720 (SD: 740, corresponding 2700 meters). DAT-patients produced more steps than VD-patients: $t=2.9$, $p<0.05$.
Conclusion In DAT and VD different brain regions are involved. While DAT-patients suffer from degeneration of the endorhinal system, in VD-patients, among other regions, motor areas and are involved.

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Motor reaction time in patients with dementia of Alzheimer's type and in vascular dementia

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Introduction Motor reaction time in patients with dementia of Alzheimer's type (DAT) and with vascular dementia (VD) is prolonged. Reaction time consists of the interval between stimulus and recognition (motor initiation time) and of the interval between recognition and motor reaction (motor reaction velocity). Aim of the present study is the differentiation of reaction time into motor initiation time and motor reaction velocity in patients with DAT and with VD.
Methods 16 patients (8 DAT, mean age: 69 years, 8 VD, mean age: 67 years) took part in the study. All patients suffered from a moderate dementia (MMSE, Folstein). EMG recordings were made from the forearm of the dominant hand. The time between onset of the visual stimulus and EMG activation and the latency between onset of EMG-activity and pushing the reaction key were registered.
Results The mean latency between stimulus onset and EMG activation was in DAT-patients: 1742 ms (SD: 120 ms) and in VD-patients: 1789 ms (SD: 110 ms; $p>0.1$, n.s.). The movement-time between EMG onset and pushing the reaction key was in DAT-patients: 125 ms (SD: 28 ms) and in VD-patients: 173 ms (SD: 43 ms; $p<0.05$).
Conclusion There were no significant differences between stimulus onset and EMG activation in DAT- and VD- patients. But a significantly prolonged motor latency occurred in VD-patients. We conclude that DAT-patients suffer from cognitive functions, while VD-patients suffer from a cerebro-vascular disease, which influences both cognitive and motor functions.

P 2200

Cognitive deficits in Parkinson's disease

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Introduction Patients with Parkinson's disease (PD) manifest a wide spectrum of cognitive deficits during the course of their illness.
Methods Twenty non-medicated PD patients (H&Y stage 1, mean age=44.7±1.6); 20 PD medicated patients (H&Y stage 2, mean age=52.3±2.5, mean dose of levodopa=725±92.5 mg); and 20 medicated PD patients (H&Y stage 3, mean age=62.3±3.2, mean dose of levodopa=950.5±125mg) were included in the study. Age and IQ matched groups of normal controls were also included in this study. Attention, visual memory, problem-solving abilities were investigated with tests from the Cambridge Neuropsychological Test Automated Battery (CANTAB).
Results The visual recognition memory problems are evident in PD medicated patients (H&Y stage 3). Paired associated learning was spared in all three groups. In contrast, on a test of spatial working memory, significant impairment was found in both medicated PD groups, in particular in those patients with more severe clinical deficits. However, all three PD groups were impaired on the test of shifting ability. In a series of problems based on "Tower of London" test medicated patients need significantly longer thinking time about planning the solution, but the accuracy solution deficits were only evident in those patients with more severe PD (H&Y stage 3).
Conclusions This study suggests that parallel to the motor decline there is a considerable cognitive decline related to the stage of the disease.

P 2201

Features of clinical and differential diagnosis in early onset of Alzheimer's disease and vascular dementia

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P 2202

TCD in dementia syndromes

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Ageing and dementia 2

P 3109

Use of the MOSES and NPI/NH to assess the effects of olanzapine treatment in patients with Alzheimer's disease-associated psychosis

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This pilot study was conducted to compare changes in dementia measured with the Multidimensional Observation Scale for Elderly Subjects (MOSES) and the Neuropsychiatric Inventory-Nursing Home version (NPI/NH) scales.

Elderly patients (n=41 for all measures) with psychosis associated with Alzheimer's disease (AD) received olanzapine (1.0–7.5 mg/d) for 10 weeks. The MOSES scale was used to assess functional impairment, the NPI/NH total score was used to assess psychopathology, and the sum of the NPI/NH *Delusions* and *Hallucinations* subscores (Psychosis Total) was used to assess changes in psychosis.

Following treatment with olanzapine, mean LOCF change scores showed significant improvement on the Psychosis Total (–9.73±6.43; p<.001), MOSES (–14.59±14.96, p<.001), and NPI/NH total (–36.54±21.67, p<.001). Pearson correlation analyses showed a significant correlation between baseline MOSES and NPI/NH total scores (r=0.5472, p<.001). Correlation between endpoint MOSES and NPI/NH total scores approached, but did not achieve, significance (r=0.2925, p=.06). No other significant baseline-, endpoint-, or change-score correlations were seen among the MOSES, NPI/NH total, or Psychosis Total scores.

These data indicate that olanzapine effectively reduced levels of psychosis and overall impairment in elderly patients with AD. The MOSES and NPI/NH scales may be useful indices of impairment, but external consistency between them is low.

P 3110

Donepezil in advanced Alzheimer's disease: Improvements in cognition and quality of life. Results of the 2nd German post marketing surveillance study

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Introduction Donepezil is approved for the symptomatic treatment of mild to moderate Alzheimer's disease (AD) in over 50 countries. Here we report results from the second German post marketing surveillance study, in which patients were observed while switched from other antidementia treatments (i.e. nootropics) to Donepezil. The tolerability and efficacy of Donepezil in advanced AD patients (mini-mental state examination [MMSE] score ≤10) were evaluated in comparison with patients in milder stages of the disease.

Methods 913 patients were enrolled. Cognition was evaluated by the MMSE. Quality of life (QoL) was assessed by the investigators on a three-point scale (improved/unchanged/worsened). Tolerability was evaluated by adverse event (AE) reports.

Results A baseline MMSE was documented for 906 patients; 76 had a baseline MMSE of ≤10 ("severe" cohort, mean baseline MMSE 7.3). The "moderate" cohort (MMSE 11–18) comprised 377 patients (mean MMSE 15.0) the "mild" cohort (MMSE ≥19), 453 patients (mean MMSE 22.3). After 3 months of Donepezil therapy, MMSE score improved by +3.0 points in the "severe" cohort ("moderate": +2.8, "mild": +1.5). QoL was judged "improved" in 65.3% of the "severe" cohort ("moderate": 68.9%, "mild": 71.2%). Donepezil was very well tolerated. AEs were reported in 6 patients (7.9%) of the "severe" cohort ("moderate": 6.6%; "mild": 10.4%).

Conclusions In a routine clinical setting reflecting daily life conditions, Donepezil showed at least the same improvements in cognition and QoL in advanced to severe Alzheimer patients as in patients with mild to moderate AD. Donepezil was very well tolerated across all severity cohorts.

P 3111

Further understanding the meaning of "clinical benefit": Results from the pre-randomisation phase of the Donepezil AWARE Study

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Background Alzheimer's disease (AD) patients who show no apparent improvement after 3–6 months are often discontinued from cholinesterase inhibitor therapy. However, due to the degenerative nature of AD, these patients may still experience therapeutic benefits.
Objective To determine the extent to which donepezil-treated AD patients show clinical benefit, based on criteria requiring evidence of improvement.
Design AWARE (Aricept WAshout and REchallenge) consists of 3 phases: 1) 24-week, pre-randomisation, open-label phase; 2) 12-week, randomised, double-blind, placebo-controlled phase; 3) 12-week, single blind Donepezil treatment phase.
Methods (pre-randomisation phase) All patients received Donepezil 5 mg/day for 28 days, then 10 mg/day. Clinical benefit was assessed at Weeks 12, 18, and 24. Patients classified as showing "no clinical benefit" exhibited decline or no change from baseline on the MMSE and the physician was not sufficiently certain of clinical benefit to warrant continued treatment (assessed by formal questionnaire); these patients were randomised into the double-blind phase.
Results 817 patients (mean MMSE, 20.7) were enrolled. After 24 weeks, 51% of patients were rated as showing "clinical benefit", (MMSE mean change from baseline, 2.3); 25% were rated as showing "no clinical benefit", (MMSE mean change from baseline, –1.8). 24% discontinued; 15% due to adverse events.
Conclusions The proportion of patients showing "clinical benefit" within 24 weeks was high. Patients who declined or showed no change continued in the double-blind phase of AWARE. Although these patients were rated stringently in this 24-week phase as showing "no clinical benefit", they may still prove to benefit from long-term treatment with Donepezil.

P 3112

Donepezil improves cognition in patients with vascular dementia

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Background Evidence to suggest that patients with vascular dementia (VaD) may benefit from treatment with cholinesterase inhibitors is accumulated.
Objective Evaluation of the efficacy and tolerability of the acetyl cholinesterase inhibitor Donepezil in patients with probable or possible VaD.
Design A randomised, double-blind, placebo-controlled, 24-week, parallel group study (Study 307).
Methods A diagnosis of probable or possible VaD according to NINDS-AIREN criteria was required for inclusion. Patients with a prior diagnosis of Alzheimer's disease were excluded. Patients were randomised to receive placebo, Donepezil 5 mg/day or Donepezil 10 mg/day (5 mg/day for first 28 days). Efficacy assessments included the ADAS-cog. Results are reported for intent-to-treat observed cases.
Results 603 patients were enrolled (199 placebo, 198 Donepezil 5 mg/day, 206 Donepezil 10 mg/day); 425 (70%) had probable VaD and 30% had possible VaD. At Week 24, both Donepezil-treated groups showed significant improvements in cognitive function compared with placebo (ADAS-cog mean change from baseline score effect size: Donepezil 5 mg/day, –1.86, $P=0.002$; Donepezil 10 mg/day, –2.37, $P<0.001$). Donepezil was well tolerated in this population (of whom 89% had co-morbid cardiovascular disease), with low withdrawal rates due to adverse events (placebo, 11.1%; Donepezil 5 mg/day, 11.1%; Donepezil 10 mg/day, 21.8%) and a similar incidence of cardiovascular adverse events across all treatment groups (placebo, 18.1%; Donepezil 5 mg/day, 20.7%; Donepezil 10 mg/day, 20.4%).
Conclusions Donepezil-treated patients with probable or possible VaD demonstrated significant cognitive improvements compared with placebo-treated patients. Donepezil was also well tolerated in this population, which has a high incidence of cardiovascular disease.

P 3113

Donepezil provides cognitive and global benefits in patients with vascular dementia

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Background As evidence suggests that vascular dementia (VaD) is associated with a cholinergic deficit, patients with VaD may benefit from cholinesterase inhibitor therapy.
Objective Evaluation of the efficacy and tolerability of Donepezil in patients with probable or possible VaD.
Design A randomised, double-blind, placebo-controlled, 24-week study (Study 308).
Methods A diagnosis of probable or possible VaD according to NINDS-AIREN criteria was required for inclusion; patients with a prior diagnosis of Alzheimer's disease were excluded. Patients were randomised to receive placebo, Donepezil 5 mg/day or Donepezil 10 mg/day (5 mg/day for first 28 days). Results are reported for intent-to-treat observed cases.
Results 616 patients were enrolled (193 placebo, 208 Donepezil 5 mg/day, 215 Donepezil 10 mg/day); 76% had probable VaD and 24% had possible VaD. Both Donepezil-treated groups showed significant improvements in cognition compared with placebo (ADAS-cog mean change from baseline score effect size at Week 24: Donepezil 5 mg/day, –1.60, $P=0.006$; Donepezil 10 mg/day, –2.12, $P<0.001$). Greater improvements in global function were observed with both Donepezil groups than with the placebo group (% patients showing improvement on the CIBIC-plus at Week 24: placebo, 26%; Donepezil 5 mg/day, 44%, $P=0.006$; Donepezil 10 mg/day, 35%, $P=0.08$; overall treatment $P=0.011$). Donepezil was well tolerated in this population, with low withdrawal rates due to adverse events (placebo, 8.8%; Donepezil 5 mg, 10.1%; Donepezil 10 mg, 16.3%).
Conclusions Donepezil is an efficacious and well-tolerated treatment for patients with probable or possible VaD, and may have an important role in the management of these patients.

P 3114

Donepezil improves cognition both in patients with probable and those with possible vascular dementia

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Background Patients with vascular dementia (VaD) appear to benefit from treatment with cholinesterase inhibitors. However, little is known about the responses to therapy in patients with probable VaD compared with possible VaD.
Objective A comparison of the effects of Donepezil in patients with probable versus those with possible VaD.
Design A combined analysis of two randomised, double-blind, placebo-controlled, 24-week, parallel-group studies (with identical protocols) in patients with probable or possible VaD.
Methods Patients with probable or possible VaD (classified according to NINDS-AIREN criteria) were randomised to receive placebo, Donepezil 5 mg/day, or Donepezil 10 mg/day (5 mg/day for first 28 days). Efficacy measures included the ADAS-cog. Results are reported for week 24 intent-to-treat observed cases.
Results 1219 patients were enrolled; 73% had probable VaD and 27% had possible VaD. In probable VaD patients, significant cognitive improvements compared with placebo were observed in both Donepezil groups (ADAS-cog LS mean change from baseline: placebo, –0.23, n=228; Donepezil 5 mg/day, –1.79, P=0.001, n=235; Donepezil 10 mg/day, –2.91, P<0.001, n=210). Similar results were observed in possible VaD patients (ADAS-cog LS mean change from baseline: placebo, 0.23, n=82; Donepezil 5 mg/day, –2.12, P=0.003, n=82; Donepezil 10 mg/day, –1.17, P=0.07, n=88).
Conclusions Placebo-treated patients with probable VaD maintained levels of cognition over 24 weeks, whereas patients with possible VaD showed minimal decline. Compared with placebo, Donepezil significantly improved cognition both in patients with probable and those with possible VaD, indicating that Donepezil is an effective treatment for the cognitive symptoms of both possible and probable VaD.

P 3115

Benefits of Donepezil treatment in patients with very mild Alzheimer's disease

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Introduction The efficacy and tolerability of Donepezil was evaluated in patients with very mild Alzheimer's disease (AD).
Methods A 24-week, randomised (Donepezil: placebo, 2:1), double-blind study included patients with probable AD (DSM-IV and NINCDS/ADRDA criteria), a mini-mental state examination (MMSE) score of 21–26, and a global clinical dementia rating of 0.5 or 1. Patients received placebo or Donepezil 10 mg/d (5 mg/d for the first 42 days, 10 mg/d thereafter). The Alzheimer's disease assessment scale-cognitive subscale (ADAS-cog) and the MMSE were used to assess treatment-related benefits on cognition. Efficacy analysis was based on the least squares mean change from baseline determined using last observation carried forward analysis of the intent-to-treat population.
Results Baseline demographics, including age, gender, and time to diagnosis, were similar in Donepezil- (n=96) and placebo-treated patients (n=57). Mean (SD) MMSE scores at baseline were 24.3 (1.3) and 24.1 (1.7) for the placebo and Donepezil groups, respectively. ADAS-cog scores were improved from baseline at all visits for Donepezil- compared with placebo-treated patients, with significant treatment differences observed at Weeks 12 (1.9; p=.025) and 24 (2.3; p=.008), and at endpoint (2.3; p<.003). Drug-placebo differences on the MMSE significantly favoured Donepezil at Week 6 (1.4; p=.017), 12 (1.2; p=.035), and 24 (1.4; p=.030), and at endpoint (1.8; p=.002). Withdrawal due to adverse events was low (placebo, 8.8%; Donepezil, 15.6%).
Conclusion: Donepezil treatment improved cognition and was well tolerated in patients with very mild AD. These results further support initiating Donepezil therapy early in the disease course.

P 3116

Sustained Donepezil treatment is associated with lower healthcare costs and utilization in community-dwelling patients with Alzheimer's disease

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Introduction The impact of Donepezil therapy on healthcare costs associated with Alzheimer's disease (AD) in a large population of community-dwelling elderly individuals was evaluated.
Methods A retrospective case-control analysis was conducted on 204 AD patients with prescriptions for Donepezil and 12 or more months of enrolment in a Medicare-managed care organization (MCO) following the date of the first prescription. A control group of 204 patients with 12 or more months of plan enrolment following the diagnosis of AD was selected. Healthcare costs were calculated for cases and controls during the 12-month follow-up period, adjusting for age, gender, comorbid conditions, and complications of dementia.
Results Annual adjusted costs for medical services and prescription drugs were $3891 lower for patients taking Donepezil compared with controls. Adjusted costs were $4192 lower for patients on longer-term therapy (270 or more days supply of Donepezil) and $3579 lower for patients on shorter-term therapy (less than 270 days supply) when compared with controls. Reduced inpatient costs were responsible for 74% of these savings.
Conclusion Donepezil was associated with a significant reduction in costs for patients with AD in this community-dwelling population. Patients receiving longer-term Donepezil therapy incurred the lowest costs, largely attributable to differences in utilization of inpatient services. The lower healthcare costs associated with Donepezil therapy are likely to be the result of improved cognitive functioning and associated improvements in medical management of co-morbidities and complications associated with AD.
Supported by Pfizer Outcomes Research.

P 3117

Galantamine, a novel drug with unique dual mode of action reduces depression in Alzheimer's disease

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Introduction Galantamine, a novel treatment for Alzheimer's disease (AD) is an allosteric modulator of the nicotinic acetylcholine receptors. A multicenter clinical trial recently performed in Germany investigated the potential influence of nicotinic stimulation on other neurotransmitter systems such as serotonin. The efficacy of galantamine in AD patients with behavioural and psychological disturbances was investigated with a focus on depression.
Methods 245 patients with predominantly mild AD were eligible to receive galantamine 16mg/day or 24mg/day over 6 months. The Neuropsychiatric Inventory (NPI) and "test for early detection of dementia with distinction from depression" have assessed depression (TFDD). The NPI evaluates non-cognitive symptoms including depression. A cut-off >4 points (frequency x severity) was judged for relevant depressive symptoms. Using the TFDD, depression is judged by the physician and in addition by the patient on an 11- item numerical rating scale from "0" (not at all depressed) to "10" (severest depression imaginable). More than 8 points of combined physicians' + patients' evaluation indicate a relevant depressive disturbance. The TFDD correlates with the Geriatric Depression Scale (r=0.73).
Results The NPI depression score (ITT) showed 63% less depressive patients (N=10) after 6 months galantamine treatment versus baseline (N=27). Comparable results emerged from the TFDD: from 41 patients with baseline depression (17.1% of total study population) only 19 patients were still above 8 points at month 6 demonstrating a mean reduction of 54% in depressive symptoms.
Conclusion In this patient population with mild AD, it could be demonstrated for the first time that galantamine has an impact on depression. The substantial reduction in depressive symptoms may indicate that galantamine provides an antidepressive efficacy possibly mediated by serotonin.

P 3118

Galantamine reduces behavioural and psychological disturbances and related caregiver burden in Alzheimer's disease patients

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Background Up to 90% of all Alzheimer's disease (AD) patients develop behavioural and psychological disturbances often escalating in the patient's institutionalisation and the need for caregiver's treatment, respectively. Galantamine (Reminyl®), a novel cholinergic treatment with a unique dual mode of action may delay the onset or improve these non-cognitive symptoms.
Objective To evaluate Galantamine treatment for behavioural disturbances, psychological symptoms, and associated caregiver distress in community dwelling AD patients.
Methods In a 3-month, open-label, Swiss multicenter Phase IV study mild-to-moderate AD patients were treated with galantamine up to 24mg (bid.). The efficacy was assessed upon completed 3-month treatment (observed cases [OC]) with the Neuropsychiatric Inventory (NPI) for primary outcome, the Clinical Global Impression (CGI) for secondary outcome, safety and tolerability monitoring.
Results From 124 patients (mean age 75.2 years, 55.6% women) receiving galantamine (intention-to-treat safety analysis), 91 patients completed the study per protocol (OC efficacy analysis) demonstrating significant improvements in NPI versus baseline (p=0.004) with mean total NPI scores (±SE) reduced from 14.93 (±1.17) to 11.25 (±1.16) after 3 months. Eleven out of 12 NPI domains were improved, the most frequent and severe symptoms being irritability, apathy, depression, agitation, and anxiety improved by 19–38%. The total NPI caregiver burden was significantly reduced at Month 3 (p=0.004) and according to CGI ratings eighty-eight percent of all patients improved or were unchanged. There were mostly gastrointestinal adverse events.
Conclusion In this general clinical setting Galantamine treatment was well tolerated, significantly improved the behavioural disturbances and reduced the behaviour-related caregiver burden.

P 3119

Effect of Donepezil on EEG spectral analysis in Alzheimer's disease

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Introduction EEG spectral analysis (EEG-SA) allows a detailed and quantitative analysis of waveform changes in Alzheimer's disease (AD). Although there have been studies investigating the correlation of EEG-SA and clinical findings in AD, the effect of treatment with anticholinesterase drugs on EEG findings has not been investigated so far.
Material & Methods Eighteen patients with AD entered the study. All patients were given Donepezil 5 mg/day and after 2 months 10 mg/day. Folstein Mini Mental State Examination (MMSE) and EEG's were obtained at baseline and at the end of the 2nd and 6th month. EEG-SA evaluations were done in temporal and centro parietal derivations.
Results Pre-treatment MMSE scores were 16.28±5.03. At the end of the 6th Month MMSE scores increased to 17.87±7.36 but this difference was not significant. Delta amplitudes were reduced and amplitudes in all other frequency ranges increased (p<0.005) in the temporal derivations. In the centroparietal derivations tetha, alpha and beta amplitudes increased (p<0.005) but delta amplitudes remained unchanged. Tetha amplitudes increased in both derivations (p<0.005).
Conclusion We have shown that in AD treatment with Donepezil led to some improvement in cognitive functions and caused a positive effect by decreasing delta amplitudes and increasing alpha and beta amplitudes in EEG-SA. Tetha amplitudes increased despite treatment.
This is the first study investigating the effect of cholinergic treatment on EEG-SA in AD. Our results support other studies showing a modulator role of the cholinergic system on EEG and point to the utility of EEG-SA in the follow-up of treatment in AD.

P 3120

Changes of quantitative EEG after Donepezil treatment in Alzheimer's disease

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Introduction Though symptomatic improvements after treatment of Donepezil is well documented in Alzheimer's disease (AD), the electrophysiological change have not yet been elucidated. Among the parameters of quantitative electroencephalography (q-EEG), high frequency activity, especially gamma rhythm, may play a role in normal cognitive function including the integration of sensory processing, association, coupling or selective attention, which are characteristically impaired in AD.
Methods In order to define the profile of q-EEG changes including gamma rhythm after Donepezil treatment, we followed 17 AD patients for 12 weeks. We analysed the spectra power taken from 16 derivations by averaging twenty-2-sec epoch in normal controls and AD patients. After logarithmic transformation of spectra power, statistical test was done and the effect of Donepezil treatment on q-EEG profile was analysed during follow up period.
Results Before medication of Donepezil, AD patients had a significantly lower alpha spectra power as well as a significant higher delta spectra power, compared with normal control. After medication of Donepezil in AD patients, compared to base-line q-EEG, gamma spectra power was significantly increased, whereas theta spectra power was significantly reduced. Compared to absolute power, relative power was more sensitive in detecting change of EEG after Donepezil treatment
Conclusions This study suggests that Donepezil significantly change theta and gamma spectra power in q-EEG, and the increase in gamma rhythm may be correlated with the clinical improvements after Donepezil treatment.

P 3121

Donepezil in dementia with Lewy bodies

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The objective of this six-month, open-label, prospective study was to assess the clinical efficacy of Donepezil in dementia with Lewy Bodies (LBD). LBD is characterized by cognitive decline with fluctuating course, visual hallucinations and other psychotic manifestations, and parkinsonism.
Method 19 patients with LBD – diagnosed according to McKeith et al (1996) diagnostic criteria – 8 male and 11 female, of 76.3 years mean age, were treated with Donepezil, 5 mg per day, dose which could be increased to 10 mg per day after the first month. Most patients were under concomitant medication. Efficacy of Donepezil was assessed using the MMSE for cognitive performance, the NPI for neuropsychiatric symptomatology and the UPDRS for parkinsonism, at baseline and at the end of the 1st, 3rd and 6th month.
Pre- and post-treatment mean scores for all scales were compared using paired t-test.
Results By the end of the 6th month the MMSE mean 1.4 points raised score and the NPI total score was reduced by 26% ($p<0.01$). Reduction in mean scores for separate NPI items was: for hallucinations 57%, for delusions 48%, for agitation 41%, for apathy 59%. Parkinsonian symptomatology improved slightly.
Medication was generally well tolerated.
Conclusion Donepezil seems to be a safe and effective alternative treatment for LBD, significantly improving cognition, psychotic and behavioural symptoms. The degree of improvement noted in our study was similar to that seen with neuroleptics, a class of medications by definition problematic in LBD due to poor tolerability.

P 3122

Donepezil is well tolerated in patients with vascular dementia: a comparison of tolerability in vascular dementia patients and Alzheimer's disease patients

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Background Donepezil is an effective and well-tolerated treatment in Alzheimer's disease (AD) patients. Donepezil is also effective in vascular dementia (VaD) patients. However, VaD patients have high levels of co-morbid disease and their tolerability profile may therefore differ from that of AD patients.
Objective A comparison of the tolerability of Donepezil 5 and 10 mg/day in patients with VaD and patients with AD enrolled in randomised, double-blind, placebo-controlled trials.
Methods Incidences of adverse events (AEs) across placebo and Donepezil 5 and 10 mg/day groups were compared using data from two 24-week studies in patients with probable or possible VaD, and similar studies in patients with AD.
Results The proportions of VaD patients with AEs were: Donepezil 10 mg/day, 93% (n=421); Donepezil 5 mg/day, 90% (n=406); and placebo, 88% (n=392). The equivalent figures in AD patients were: Donepezil 10 mg/day, 83% (n=642); Donepezil 5 mg/day, 65% (n=821); and placebo, 62% (n=874). The majority of AEs in both VaD and AD patients were of mild intensity. Withdrawals due to AEs were low: 19% and 11% from the VaD Donepezil 10 and 5 mg/day groups, 10% from the VaD placebo group; 14% and 6% from the AD Donepezil 10 mg/day and 5 mg/day groups, 6% from the AD placebo group.
Conclusions VaD placebo- and donepezil-treated groups showed a higher incidence of AEs than corresponding AD groups, indicating that VaD patients are generally "sicker" than AD patients. However, these results nevertheless demonstrate that Donepezil is well tolerated in VaD and AD patients.

P 3123

Greater improvement in cognition and activities of daily living with Donepezil compared to Galantamine in a direct head to head trial in Alzheimer patients

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Introduction Although Donepezil and Galantamine have been studied previously in clinical trials, no direct comparison of these agents in the same trial population has been reported to date.
Methods Patients with mild to moderate AD were randomised to open-label Donepezil (up to 10 mg qd) or Galantamine (up to 12 mg bid) for 12 weeks, according to product labelling. Primary study objectives were to assess tolerability and physicians and caregivers satisfaction with treatment (reported in accompanying abstract). Secondary assessments explored

effects of treatment on cognition using the ADAS-cog (modified 13-item) and the MMSE, and on Activities of Daily Living (ADL) using the Disability Assessment for Dementia (DAD). Trained independent raters blinded to study treatment and adverse events assessed the cognitive measures.
Results A total of 120 patients were enrolled from 4 countries. 64 patients were treated with Donepezil (mean age =73.8, mean baseline MMSE±SD=18.3±3.3) 56 patients with Galantamine (mean age =75.1, mean baseline MMSE±SD=18.4±3.7). Significantly, greater improvements in cognition and ADL were observed for Donepezil compared with Galantamine for the MMSE at endpoint (Week 12 LOCF); for the 13-item modified ADAS-cog at both Week 12 and endpoint; and the DAD at Weeks 4, 12 and endpoint (all P-values <0.05).
Conclusions Cognitive and ADL assessments revealed greater improvement for patients treated with Donepezil compared with Galantamine. In contrast to Donepezil, the necessity of having to titrate Galantamine to a therapeutic dose may contribute to these results.

P 3124

Donepezil compared to Galantamine in Alzheimer's disease: Better physician and caregiver satisfaction/ease of use ratings in a multinational randomised trial

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Introduction Donepezil and Galantamine have been evaluated previously in clinical trials but no direct comparison of these two cholinesterase inhibitors in the same trial has been reported to date.
Methods Patients with mild to moderate AD were randomised to open-label Donepezil (up to 10 mg qd) or Galantamine (up to 12 mg bid) for 12 weeks according to approved product labelling. Tolerability was assessed by reporting of adverse events (AEs). Physicians and caregivers completed questionnaires to rate satisfaction with treatment and ease of use of the medication in daily practice.
Results 120 patients were enrolled from 4 countries. 64 patients were treated with Donepezil (mean age=73.8, mean baseline MMSE±SD=18.3±3.3); 56 patients were treated with Galantamine (mean age=75.1, mean baseline MMSE±SD=18.4±3.7). Both treatments were well tolerated, but a greater proportion of patients receiving Galantamine (46.4%) reported gastrointestinal AEs compared with Donepezil (25.0%). Six (9.4%) Donepezil-treated and 12 (21.4%) Galantamine-treated patients reduced their dose or discontinued treatment temporarily due to AEs. Both physicians and caregivers reported significantly higher total satisfaction/ease of use scores with Donepezil compared with Galantamine at Weeks 4 and 12 and at study endpoint (Week 12 LOCF) (all P-values <0.05).
Conclusions Both treatments were well tolerated, with more gastrointestinal AEs reported for Galantamine compared with Donepezil. Physician and caregiver total ease of use/satisfaction scores were significantly better for Donepezil versus Galantamine in the first reported head-to-head study of these two agents.

P 3125

Effects of Cerebrolysin on brain bioelectrical activity and cognition in humans

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Effects of Cerebrolysin, a peptide preparation with potential neurotrophic activity, on brain bioelectrical activity and on cognitive performance were investigated in neurorehabilitation patients with traumatic brain injury (TBI), in senile dementia patients (SD) and in healthy elderly subjects. TBI and SD patients received repeated i.v. Injections (30 ml/day; 20 infusions/4 weeks) of Cerebrolysin, while a single oral dose (30 ml) of the Cerebrolysin solution were administered to control subjects.
Cerebrolysin increased average alpha activity ($p<0.05$ in O1 and P3 electrodes of TBI patients) and induced a generalized decrease in slow delta activity ($p<0.05$ in F7 and P3 electrodes of TBI and SD patients). In elderly controls, Cerebrolysin also increased alpha activity ($p<0.05$ in O1 electrode) and decreased slow delta activity from 1 to 6 hours after drug intake. Cerebrolysin improved cognitive performance scores with respect to baseline values in SD (MMSE, $p<0.05$; ADAS, $p<0.05$), TBI (SKT reversal naming, $p<0.05$) and control subjects (ADAS memory items, $p<0.01$).
Our results indicate that Cerebrolysin might be a useful neuroprotective treatment in patients with brain damage of traumatic or degenerative cause and in elderly people with age-associated memory impairment.

P 3126

Galantamine improves behavioural disorders and reduces caregiver distress in patients with mild-to-moderate Alzheimer's disease

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Background Controlled clinical trials with Galantamine in over 3200 Alzheimer's disease (AD) patients have demonstrated its broad range of efficacy and tolerability. We investigated the efficacy and safety of Galantamine and its potential to reduce caregiver distress in an ambulant setting.
Methods Patients with mild-to-moderate AD receiving at least one dose of Galantamine were included in the analyses. Dose titration ranged from 8mg/day to 16mg/day or 24mg/day. The 6-month treatment outcome vs. baseline was assessed by Alzheimer's disease Assessment Scale (ADAS-cog-11), Neuropsychiatric Inventory (NPI), physicians Clinical Global Impression (CGI), and General Health Questionnaire (GHQ, evaluating caregivers' emotional distress).
Results 149/245 patients in this open-label trial (mean age 72 years, 59% female, 92% "mild" AD) responded with significant improvements in cognition at month 6 versus baseline (ADAS-cog $_{\text{baseline}}$=24, mean change –1.9, $p\leq0.001$). Almost 1/4 of all patients improved their mean ADAS-cogs by –10.2 points. NPI scores demonstrated significant improvements from week 12 ($p\leq0.01$) with 69% responders at month 6, although the patients entered with very low baseline scores (mean 9.9, severity x

frequency). The decrease in behavioural symptoms corresponded with a significant reduction in caregiver distress (mean –0.5, $p \leq 0.05$). GHQ significantly improved from week 12 ($p \leq 0.001$) onward. At month 6, the caregivers' distress was significantly reduced by 27%. The responder rate was 78%. The CGI showed 65% patients improved after 12 weeks and 83% were improved or unchanged after 6 months. Galantamine was well tolerated.

Conclusion Galantamine demonstrated significant benefits on cognition, behavioural symptoms, and caregiver distress also in mild AD and may thereby be favourable for both, patients and caregivers even in the early stages of the disease.

P 3127

Front temporal dementia with motor neuron disease: A case report with fasciculation's and no bulbar palsy after five years onset.

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Introduction Dementia with motor neuron disease (MND) has been described as a new clinic pathologic entity, characterized by profound breakdown in personality and social conduct, a dynamic spontaneous speech, higher cortical function impairment and clinical manifestations of MND. Pick's disease, frontal lobe degeneration and front temporal dementia with MND consist of the three subtypes of frontal dementia.

Methods/Results We studied a 60 years old male, hospitalised in the Psychiatric Department, five years after the onset of the disease. Patient's clinical spectrum included psychomotor retardation, behavioural disorders, aggressiveness, poor verbal fluency and severe memory and orientation disorder. Primitive reflexes and fasciculation's on biceps and deltoids were noted during physical examination.

Routine blood tests, B 12, folic acid, homocysteine, thyroid hormones and EEG were normal. Brain MRI showed prominent front temporal atrophy. EMG showed neurogenous diagram with fasciculation.

Conclusion Front temporal dementia with MND is a rare disease characterized by presenile onset and 2–3 years survival. In our patient clinical and laboratory studies advocate for the above diagnosis. The specific feature is the long duration of the illness and the lack of bulbar or other manifestations of MND with the exception of fasciculation's. A few reports exist in the world bibliography and furthermore investigation is required in order to determine specific criteria for a secure diagnosis.

P 3128

Therapeutic efficacy of Nootropil on cognitive disturbances in patients with chronic ischemic cerebrovascular disease (CICVD)

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P 3129

Exercise and dementia

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