

## NEUROLEPTIC MEDICATION WORSENS THE COGNITIVE DECLINE OF DEMENTIA

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**Background:** Patients with dementia who also have the non-cognitive symptoms of aggression, psychosis or sleep disturbance have a faster rate of subsequent cognitive decline than those without. The possibility that neuroleptic medication, which is often used to treat these symptoms, accounts for this phenomenon has not previously been examined.

**Method:** As part of a longitudinal study of behaviour in dementia, the cognitive function of 71 subjects with dementia was assessed every four months on at least six occasions using an expanded version of the MiniMental State Examination (MMSE) and non-cognitive symptoms were rated using the Present Behavioural Examination. Linear regression was used to establish which of the following independently contributed to more rapid decline: neuroleptic use, physical aggression, sleep disturbance, persecutory ideas, hallucinations, sex, age, duration of illness and initial level of cognitive function. Neuropathology was available in 37 cases.

**Results:** Those who took neuroleptics declined twice as fast as those who did not (MMSE decline over 20 months:  $10.3 \pm 1.5$  versus  $5.1 \pm 0.7$ ,  $p = 0.006$ ). Although cognitive decline was also greater amongst those with more severe persecutory ideas, aggression and sleep disturbance, only the use of neuroleptics and the severity of persecutory ideas independently contributed to more rapid cognitive decline. Furthermore, in 20 subjects who started neuroleptics after study entry, the rate of decline was significantly greater over the year after the start of the medication than in the previous year. Cortical Lewy body pathology did not affect these results.

**Conclusion:** The neuroleptic medication used to treat behavioural problems in dementia worsens the already poor cognitive function.

## APOLIPOPROTEIN E POLYMORPHISM, CALCIUM AND ALZHEIMER'S DISEASE

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Both, A4- $\beta$ -amyloid and apolipoprotein E (apoE) have been implicated as major factors in the pathophysiology of Alzheimer's disease. The in vitro observed neurotoxicity of  $\beta$ -sheeted  $\beta$ A4-amyloid appears to be in part mediated by a disturbance of Ca-homeostasis. The pathogenic mechanisms however of apoE is still obscure. In vitro, apoE isoforms bind to  $\beta$ A4 amyloid. Moreover, Alzheimer's disease related antigens are induced by increased intracellular Ca-levels. The present study analyses the effects of  $\beta$ A4 amyloid, apoE and their complexes on intracellular calcium concentrations as measured by FURA-2/AM image analysis. Hippocampal neurons of E18 rat pups were cultivated for between three and five weeks before measuring the intracellular calcium level. Synthetic  $\beta$ A4 amyloid (1–43 mer; Bachem; 20  $\mu$ Mol), and recombinant apoE3 isoforms (PanVERA) were used. These compounds were incubated, either alone or together, overnight at 37°C. The respective compound was added to the cells bath solution and, after being incubated for four minutes, removed by washing for a 16 minute period. After this, the next

	$\Delta$ Ca	$\overline{\Delta}$ Ca
$\beta$ A4	92%	
ApoE3	120%	
$\beta$ A4/E3	204%	270 nM

resting  $\overline{\text{Ca}} \sim 100$  nM; 3 cultures/total  $n \approx 100$  neurons

compound was applied to the same cells. In order to avoid bias due to the order of application, the application sequence was varied. Synaptic network and consecutive bursting due to rebound excitation was blocked by 10  $\mu$ Mol CNQX. A significant co-operative effect was observed for  $\beta$ A4/apoE complexes (Table 1)

We conclude that apoE plays an important role in conjunction with A4- $\beta$ -amyloid in the disturbance of Ca-homeostasis, neurotoxicity and induction of Alzheimer's disease related antigenetic changes.

## DIFFERENTIAL DIAGNOSIS OF DEPRESSION AND DEMENTIA IN GERIATRIC PATIENTS BY QUANTITATIVE MAGNETIC RESONANCE IMAGING

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The differentiation between depression and dementia in elderly patients can be complicated by the fact that some degree of cognitive dysfunction or "pseudodementia" is frequently observed in depression. In order to improve differential diagnosis, we used quantitative magnetic resonance imaging (MRI) to investigate volumes of different brain structures in patients and controls. Up to now, 13 patients fulfilling the criteria of major depression (DEP, DSM-III-R: 296.), 21 age and sex matched patients with dementia of the Alzheimer type (DAT/ NINCDS/ADRDA criteria) and 10 elderly healthy controls were investigated. Cognitive performance was evaluated on the Mini Mental State Examination (MMSE) and the Brief Cognitive Rating Scale (BCRS). 3-D MRI sequences were acquired using a Siemens 1.5T scanner. Whole brain volume (WBV), total intracranial volume (TIV), volume of the frontal and temporal lobes (FL, TL) and the volume of the amygdala-hippocampus complex (AHC) were assessed using the newly developed software NMRWin. This software provides a semiautomated user independent measure of the WBV, while measurements of the substructures need to be manually guided. Measurements were performed by two independent raters (interrater reliability:  $r = 0.95-0.96$ ,  $p \pm 0.0001$ ) on a conventional 486 PC. As would be expected, MMSE scores were significantly ( $F: 36, 98$ ,  $p \pm 0.005$ ) lower in the DAT group than in the DEP group and the controls. Accordingly, we observed highly significant differences between the DEP and the DAT group for the volumes of the frontal (right FL:  $F = 7.81$ ,  $p < 0.005$ ; left FL:  $F = 6.15$ ,  $p < 0.005$ ) and temporal lobes (right TL:  $F = 8.48$ ,  $p < 0.001$ ; left TL:  $F = 4.13$ ,  $p < 0.05$ ) as well as for the AHC volume (fight AHC:  $F = 23.83$ ,  $p < 0.0001$ ; left AHC:  $F = 30.08$ ,  $p < 0.0001$ ). The TIV did not differ between the diagnostic groups. Compared to the controls, the depressed patients performed worse on the cognitive scales. However, depressed patients and healthy controls showed no significant differences in the volumetric measurements. Our results indicate that quantitative MRI may be useful to support the clinician in the differential diagnosis of depression and dementia.

## MRI COMPUTER ASSISTED LINEAR BRAIN RATIOS, AND NEUROPSYCHOLOGY OF TREATMENT RESISTANT DEPRESSION IN THE ELDERLY

Steve Simpson, Bob Baldwin, Alan Jackson, Alistair Burns.

**Methods:** Consecutive cases of elderly DSM 111 R depression ( $n = 65$ ), and age matched normals ( $n = 24$ ), were assessed with a neuropsychology battery. Forty four of the depressed patients completed MRI. Simple computer assisted linear brain ratios were used as brain parameters of estimated atrophy. Response to treatment was evaluated prospectively, and patients were allocated to three

groups (1) Responsive to monotherapy. (2) Responsive to second line treatment. (3) Poor response to second line treatment.

**Results:** Lateral ventricular enlargement, and dilatation of the sylvian fissure was associated with poor response to monotherapy, but only infratentorial atrophy was associated with poor response to second line treatment. The neuropsychological impairment of the resistant group was most pronounced in tests of speed, and perseveration.

**Conclusion:** In late life depression the response to treatment, is adversely affected by organic brain abnormalities, characterised by diffuse atrophy, mental slowing, and impaired frontal lobe functioning.

#### WHAT ARE THE FACTORS INFLUENCING PRESCRIBING OF COGNITION ENHANCERS

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To discover 1., to what extent patients' wishes and the extent of any abnormality of brain performance influence the frequency with which cognition enhancers (CE; in Germany mainly Ginkgo biloba, nimodipine, piracetam, secale alkaloids, xanthine derivatives) are prescribed and 2., the medical practitioners' expectations of the effectiveness of such medications, we performed a representative survey (145 family physicians (FP), 14 primary care neuropsychiatrists (NP); response rate 83.2%) in southern Lower Saxony.

Two different written sample case histories were presented to these physicians in a face-to-face interview. Case one described a slight unspecific memory and concentration problem in an otherwise healthy 70 y old woman with or without expressed wish for medication, case two a moderate dementia of Alzheimer's type (Version B) or vascular type (Version A).

Regardless of the wish of the patient and type of the abnormal brain function about 70% of all participating doctors would prescribe those drugs, even though about 56% had doubts about their effectiveness. About 28% expected a positive effect on brain performance. A nearly equal proportion of doctors would continue an existing CE-drug regimen as would prescribe one.

In conclusion, the prescription of CEs is influenced less by medical criteria than by factors which concern doctor-patient relationship.

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## NR10. Schizophrenia: psychopharmacology and neuropsychology

*Chairmen:* K Aitchison, A Mortimer

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#### VISUAL FORM PERCEPTION IN SCHIZOPHRENIA: FURTHER EVIDENCE FOR A DISORDER OF SEMANTIC MEMORY

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A considerable literature has documented that patients with schizophrenia perform poorly on tests of visual perception, particularly those involving recognition of complex forms and judgements of facial expression. Left unanswered by this work is the question of

whether such deficits are neuropsychologically specific or whether they merely form part of a general pattern of poor performance in schizophrenia.

We examined aspects of visual object perception in a group of 40 patients meeting DSM IV criteria for schizophrenia. All patients were assessed using the Visual Object and Space Perception Battery (VOSP) of Warrington and James (1991), which includes tests sensitive to different kinds of visual impairment seen in neurological patients. Patients who showed poor performance in one or more aspects of the tests were subjected to more detailed 'single case' analysis using a battery of additional tests distinguishing different levels of visual analysis. All patients were also administered tests of IQ and general intellectual function.

In the group screening phase of the study the patients showed a low frequency of poor performance on basic level 'presemantic' tasks such as identifying shapes from fragmented outlines. Those who failed tended to show overall intellectual impairment. Substantially worse performance was observed with tests requiring higher level form representation, especially when these required semantic information, eg naming objects.

Single case analysis supported the view that the bulk of the deficit in schizophrenia is found on tasks which require semantic level analysis and presemantic aspects of visual analysis are spared or relatively spared in the disorder.

#### LONG-TERM RELAPSE PREVENTION WITH CLOZAPINE IN SCHIZOPHRENIA

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The atypical neuroleptic clozapine has superior antipsychotic efficacy in patients refractory to treatment with classical neuroleptics. Moreover, clozapine is used for prevention of relapse in patients who respond to clozapine as acute treatment. Unfortunately, systematic studies of relapse rates of clozapine are lacking but clinical reports on successful long-term treatment with clozapine (Povlsen et al., 1985; Kuha et al., 1986) — e.g. in terms of social and occupational re-integration — suggest that clozapine might effectively prevent schizophrenic relapse.

In this study we calculated relapse rates and mean duration of hospitalizations in 53 outpatients treated with clozapine up to 8 years. 11 patients were changed to clozapine during their first hospitalization, the remaining 42 patients were pretreated for relapse prevention over mean  $\pm$  SD 41.8  $\pm$  24.1 months with typical neuroleptics. The mean  $\pm$  SD duration of continuous clozapine treatment (including intermittent hospitalizations) was 60.3  $\pm$  22.8 months, the actual mean  $\pm$  SD daily clozapine dosage 214  $\pm$  135 mg (range 50–550). During a cumulative observation period of 2995 months in 53 patients, 40 relapses were observed under clozapine. In the 42 patients who had previous relapse prophylaxis with typical neuroleptics, the yearly relapse rate calculated from the raw data was reduced from 0.56 to 0.16 under clozapine. For statistical analysis the mirror image design was used. Using similar intraindividual observation periods (mean  $\pm$  SD 41.8  $\pm$  24.1 months) and excluding one previous hospitalization (where medication was changed to clozapine) there was still a significant superiority ( $p < 0.01$ ) of clozapine as compared to typical neuroleptics indicating a high efficacy in prevention of schizophrenic relapse.