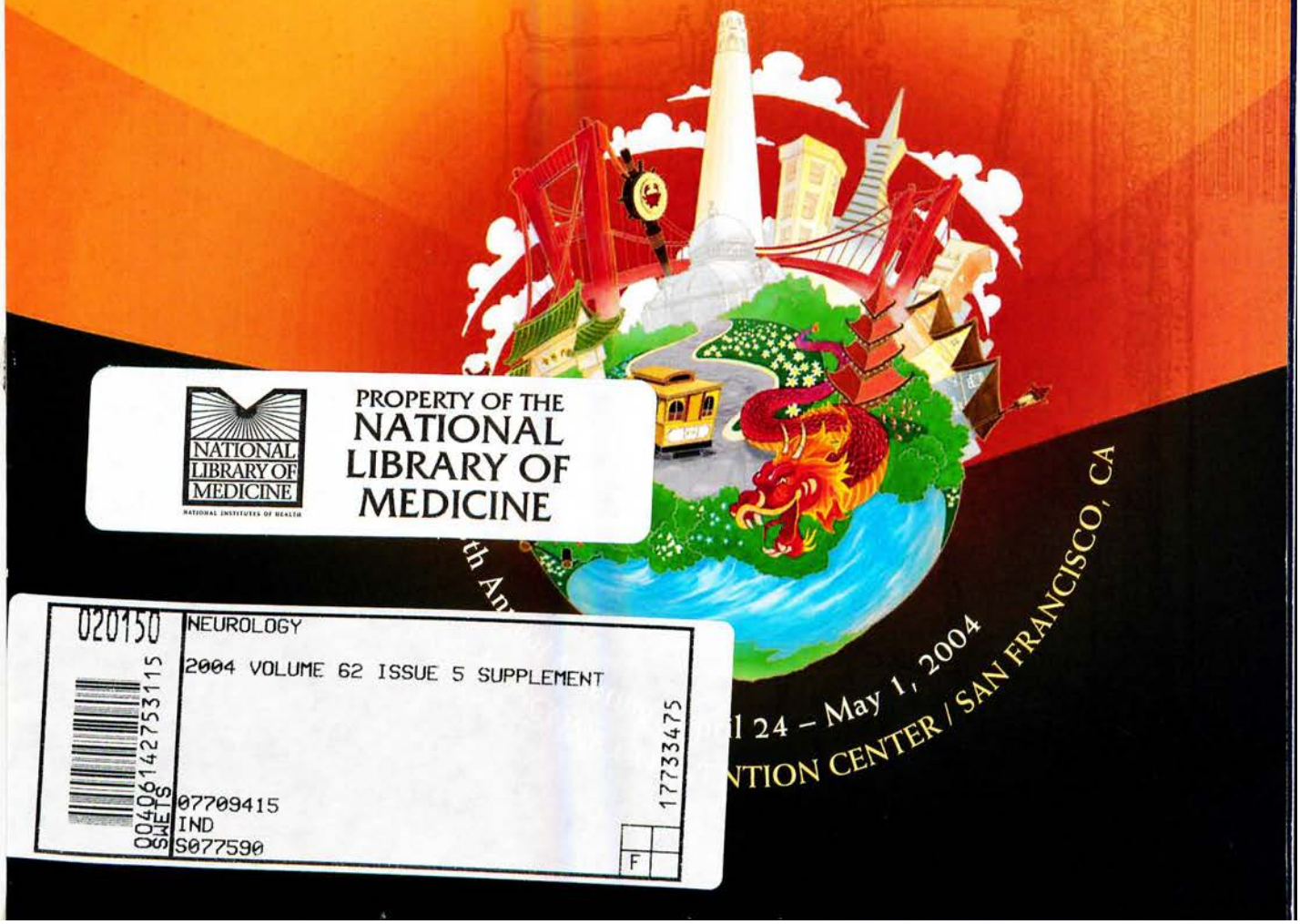
AMERICAN ACADEMY OF NEUROLOGY

56TH ANNUAL MEETING PROGRAM



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effective as CBZ and VPA. However, TPM 100 was better tolerated than TPM 200, CBZ or VPA. Discontinuations due to adverse events: TPM 100, 19%; TPM 200, 28%; CBZ, 25% and VPA, 23%.

CONCLUSIONS: Taken together, these studies demonstrate that 100 mg/day TPM is an effective dose, is at least as effective as CBZ and VPA, but is better tolerated. 100 mg/day TPM can therefore be recommended as the initial target dose for previously untreated patients with epilepsy.

Supported by: Johnson & Johnson Pharmaceutical Research & Development, L.L.C.

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P04.104

Lamotrigine Serum Concentration during Taper of Phenytoin: Time Course of Deinduction

Mary Ann Werz, Cleveland, OH, Barbara E. Swartz, Newport Beach, CA

OBJECTIVE: This study investigated the time course and dose-dependence of phenytoin taper on lamotrigine serum concentration.

BACKGROUND: Phenytoin (PHT) is a powerful inducer of lamotrigine (LTG) metabolism. Therefore, it may be difficult to achieve adequate LTG serum concentrations during adjunctive treatment with PHT. Furthermore, a transient exacerbation of seizures may occur during conversion to monotherapy dependent upon the time course of deinduction of LTG glucuronidation enzymes. Analysis of data from the published active control, conversion to monotherapy trial suggested that LTG serum concentrations doubled following withdrawal of PHT. Furthermore, LTG serum concentrations did not increase until PHT was completely stopped. Interpretation of this study is potentially limited by the rapid withdrawal of PHT in weekly decrements of 20%, as a week may be insufficient for deinduction of hepatic enzymes to reach steady-state.

DESIGN/METHODS: Patients treated with PHT with either incomplete control or unacceptable side effects were recruited for conversion to LTG monotherapy. Seven patients have thus far completed. Lamotrigine was titrated to 400 to 500 mg total daily dose over three months. PHT was then withdrawn every three weeks in decrements of one-third the initial dose. Serum concentrations were measured weekly for ten weeks. Blood draws occurred on the same day of the week and at the same time of day. PHT dose reductions were scheduled to occur immediately after a blood draw. Patients did not alter other medications during the protocol. PHT was measured at our institution using the CEDIA Phenytoin II (ROCHE) immunoassay. LTG was measured at ARUP Laboratories by HPLC.

RESULTS: Five patients were recruited who had adverse events to the prior medication and two had had incomplete seizure control. Seven of seven patients have thus far been successfully converted to LTG monotherapy. Baseline serum concentrations of LTG ranged from 3.6 to 4.5 mcg/ml, attained on 400 mg total daily dose, with PHT serum concentrations ranging from 8.7 to 27.0 mcg/ml. Decrease in PHT doses up to 67 % increased LTG serum concentrations by less than 10%. At that time PHT serum concentrations averaged 2.4 mcg/ml (range 2.2 to 2.7mcg/ml). One, two, and three weeks after PHT cessation, the average LTG serum concentration had increased 47, 82, and 109%, respectively. The range of maximal increase was 50–230%.

CONCLUSIONS: LTG serum concentrations typically double with withdrawal of PHT. The increase does not occur until PHT concentrations are under 2.5 mcg/ml. The increase then occurs quite quickly with half in the first week of complete PHT withdrawal. Complete deinduction of glucuronidation appears to require two to three weeks though our current small sample size limits complete accuracy of the time course. Epilepsy patients may require special efforts at seizure prophylaxis during taper from PHT and for several weeks thereafter.

Supported by: Investigator Initiated award from Glaxo-SmithKline

Disclosure: Dr. Werz and Dr. Swartz have nothing to disclose.

Aging and Dementia: Treatment

P04.105

Efficacy of Once-Daily Galantamine Extended-Release in Patients with Mild to Moderate Alzheimer's Disease

Henry Brodaty, New South Wales, Australia, Bing Yan, ChandrasekharRao V. Damaraju, Titusville, NJ

OBJECTIVE: To assess the efficacy of once-daily galantamine in patients with mild to moderate Alzheimer's disease (AD).

BACKGROUND: Galantamine is an acetylcholinesterase inhibitor and allosteric modulator of nicotinic cholinergic receptors. Clinical trials have shown that 16 or 24 mg/day of an immediate-release (IR) formulation (b.i.d.) improves cognition and global performance compared with placebo, maintains activities of daily living, and delays the emergence of neuropsychiatric symptoms. A once-daily extended-release (ER) formulation of galantamine was developed to enhance ease of use and potentially facilitate compliance.

DESIGN/METHODS: The efficacy of galantamine ER was evaluated in a 6-month, double-blind, flexible-dose, multicenter trial of 971 patients with mild to moderate AD (Mini-Mental State Examination [MMSE] score 10–24; AD Assessment Scale-cognitive subscale [ADAS-cog] score ≥18). Patients were randomized to receive galantamine ER (n=320), galantamine IR (n=327), or placebo (n=324) with total daily dosages escalating by 8 mg/day every 4 weeks to a maximum of 16 or 24 mg/day. Primary efficacy outcomes were change from baseline in ADAS-cog/11 scores and Clinician's Interview-Based Impression of Change-Plus Caregiver Input (CIBIC-plus) score at Week 26. Key secondary outcomes included changes from baseline in AD Cooperative Study-Activities of Daily Living (ADCS-ADL) score at Week 26.

RESULTS: Mean ADAS-cog/11 scores were significantly improved from baseline at Week 26 in galantamine ER and IR groups compared with placebo (-1.4, -1.8, and 1.3, respectively; $P<0.001$). No significant differences in treatment response were observed between the galantamine groups. The galantamine ER group also maintained daily functioning (ADCS-ADL scores) significantly better than the placebo group ($P=0.003$), consistent with previously reported results for galantamine IR. Both galantamine groups improved or maintained global functioning (CIBIC-plus scores) numerically better than the placebo group at Week 26; the difference approached statistical significance for the ER group ($P=0.086$). There was, however, an overrepresentation of subjects enrolled with mild AD (MMSE scores >22) in the placebo group, contributing to a disproportionately high placebo response rate in CIBIC-plus scores (77%). Galantamine ER was safe and well tolerated. The most frequently reported adverse events in the galantamine ER group were similar to those reported for galantamine IR, with fewer nausea and vomiting episodes during dose escalation in the galantamine ER group.

CONCLUSIONS: Galantamine ER provides treatment efficacy similar to galantamine IR for mild to moderate AD while offering the convenience of once-daily dosing and better tolerability during dose escalation.

Supported by: Janssen Pharmaceutica Products, L.P., Titusville, New Jersey.

Disclosure: Dr. Brodaty is a consultant for Janssen Pharmaceutica and has received honoraria from Janssen Pharmaceutica

P04.106

Postmenopausal Hormone Therapy and Risk of Cognitive Decline

Francine Grodstein, Boston, MA

OBJECTIVE: To examine the relation of postmenopausal hormone use to cognitive decline.

BACKGROUND: A large randomized trial of postmenopausal women over aged 65 years reported an increased risk of cognitive decline with combined estrogen and progestin treatment. However, questions remain, including the effect of estrogen alone, or of hormone therapy initiated at menopause versus many years after menopause.

DESIGN/METHODS: The Nurses Health Study is an ongoing, prospective cohort begun in 1976, comprising 121,700 nurses. Women continuously provide updated and detailed health information via biennial mailed questionnaires. This sub-study includes 13,807 participants who completed two telephone cognitive assessments, 2 years apart, between 1995–2002 when they ranged in age from 70–81 years. We tested general cognition, verbal memory, category fluency, and attention. Participation and follow-up are over 90%.

We used logistic regression to estimate multivariate-adjusted risks of substantial decline in cognitive function and linear regression to examine multivariate-adjusted mean decline, across hormone groups. Extensive data on potential confounding variables was considered including: age, education, diabetes, high blood pressure, vitamin supplements, age at menopause, body mass index, smoking, physical activity, depression, alcohol intake and NSAID use.

RESULTS: Overall, after multivariate adjustment, we found little difference in the rates of cognitive decline between current hormone users and never users. However, for long-term users of estrogen alone or combined with progestin, there were suggestions of increased risk of substantial decline on most cognitive tests (relative risks=1.25–1.72).

Rates of cognitive decline were similar between women initiating hormone use at menopause and women who never used hormone therapy. Although only 4% of hormone users initiated hormone therapy after age 65 years, the greatest decline was observed among these women: for those who began taking hormones at age 65 years or older, the relative risk of substantial decline in general cognition was 1.74 (95% CI 1.08,2.81) compared to never users, and mean difference in decline for these late initiators compared to never users was -0.43 points (95% CI -0.73, −0.12).

CONCLUSIONS: In this large cohort study, postmenopausal hormone therapy provided no cognitive benefits in older women. There may be risks in certain subgroups.

Supported by: Grants from NIH and Ellison Medical Foundation

Disclosure: Dr. Grodstein received fees as a temporary consultant from Schering-Plough and received honorarium for lectures from Novo Nordisk, Schering Plough, Wyeth-Ayerst, Pfizer, and Orion Pharma.

P04.107

Functional and Behavioral Effects of Memantine in Alzheimer's Disease

Jeffrey Cummings, Los Angeles, CA, Christopher van Dyck, New Haven, CT, Frederick Schmitt, Lexington, KY, Stephen M. Graham, Jason T. Olin, James Jin, Jersey City, NJ, Pierre N. Tariot, Rochester, NY

OBJECTIVE: The objective was to assess the effect of memantine on functional and behavioral domains in moderate to severe Alzheimer's disease (AD) patients stabilized on donepezil.

BACKGROUND: AD is a progressive, neurodegenerative illness associated not only with cognitive deficits but also with functional decline and behavioral disturbances. Memantine is a low-[illegible] for the treatment of moderate to severe AD based on demonstrated efficacy in cognition, function and global status in two trials, one of which included patients treated with ongoing donepezil therapy. This report provides further analyses of the functional and behavioral effects of memantine in moderate to severe AD patients stabilized on donepezil in this latter study.

DESIGN/METHODS: A 24-week double-blind, placebo-controlled trial was conducted in moderate to severe AD patients on a stable donepezil regimen (N=395, ITT population) and randomized to memantine or placebo. Functional abilities were assessed using the modified ADCS-ADL$_{19}$ scale and the BGP Care Dependency subscale. ADCS-ADL$_{19}$ was given at baseline, weeks 4, 8, 12, 18 and the final visit (Week 24), while the BGP Care Dependency was administered at baseline and at the final visit. Behavioral symptoms were assessed using the Neuropsychiatric Inventory (NPI), and data were analyzed at baseline, Week 12 and the final visit. The efficacy analyses were based on the ITT population, using both OC and LOCF approaches.

RESULTS: Memantine-treated patients demonstrated significantly higher functional ability (ADCS-ADL$_{19}$ or BGP Care Dependency) compared to placebo-treated patients (p=0.028, p=0.001, respectively). A by-item analysis of ADCS-ADL$_{19}$ revealed that at endpoint, abilities in grooming, being left alone, and watching television were statistically significant, in favor of memantine. NPI total score favored memantine treatment over placebo (p=0.0002). NPI domains demonstrating statistically significant improvement after 24 weeks in memantine-treated patients were agitation/aggression, irritability/lability, and appetite/eating.

CONCLUSIONS: Memantine treatment in combination with ongoing donepezil therapy is associated with less functional and behavioral deterioration in Alzheimer's disease than with donepezil therapy alone.

Supported by: Forest Laboratories, Inc.

Disclosure: Dr. Cummings received consulting fees from Forest Laboratories, Inc. Dr. van Dyck received research support from Forest Laboratories, Inc. Dr. Schmitt received research support from Forest Laboratories, Inc. Dr. Graham is an employee of Forest Research Institute. Dr. Olin is an employee of Forest Research Institute. Dr. Jin is an employee of Forest Research Institute. Dr. Tariot received research support from Forest Laboratories, Inc., received consulting fees from Forest Laboratories, Inc. and received honoraria for speaking from Forest Laboratories, Inc.

P04.108

Incidence of Presumptive Tardive Dyskinesia in Elderly Patients Treated with Olanzapine or Conventional Antipsychotics

Bruce J. Kinon, Virginia Stauffer, Christopher Kaiser, Sara Kollack-Walker, Walter Deberdt, Indianapolis, IN

OBJECTIVE: To determine the risk of developing dyskinetic symptoms in elderly patients treated with olanzapine versus conventional antipsychotics.

BACKGROUND: Incidence rates of presumptive tardive dyskinesia (TD) were compared in acutely psychotic or agitated elderly patients treated with olanzapine (OLZ) or conventional antipsychotic (CNV) drug therapy.

DESIGN/METHODS: Patients without TD were randomized to OLZ (2.5–20 mg/day; n=150) or CNV (dosed per label; n=143) therapy, and underwent a 6-week drug tapering/drug initiation period, followed by reassessment of TD. Patients remaining without TD after six weeks were treated with OLZ or CNV for up to 1 year. Primary analysis was time-to-TD incidence, defined as rating on the Abnormal Involuntary Movement Scale (AIMS) of either: A) moderate severity (≥3) in 1 body region or mild severity (≥2) in 2 or more body regions, or B) moderate severity (≥3) in 1 body region.

RESULTS: Patients in CNV group were at a greater risk for presumptive TD than patients in OLZ group (criteria A or B, p<.05). Incidence of presumptive TD that persisted for at least 1