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MECHANISM FOR THE PROTECTIVE EFFECT OF PYRROLIDINE DITHIOCARBAMATE AGAINST OXIDATIVE STRESS IN AD: INDUCTION OF THE NRF2-ARE PATHWAY

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Background: Oxidative injury is central in the pathogenesis of Alzheimer's disease (AD). An endogenous defence system against oxidative stress is induced by binding of nuclear factor E2-related factor 2 (Nrf2) to the antioxidant response element (ARE). The Nrf2-ARE pathway is activated in response to reactive oxygen species to trigger the simultaneous expression of numerous protective proteins. We have previously demonstrated the potential of the Nrf2-ARE pathway as a therapeutic target in AD; in transgenic (APP/PS1) mice the Nrf2-ARE pathway is attenuated at the time of amyloid beta deposition, Nrf2 over-expression protects against amyloid beta toxicity, and Nrf2 gene delivery attenuates cognitive decline in APP/PS1 mice. Pyrrolidine dithiocarbamate (PDTC) scavenges reactive oxygen species and transports copper inside cells. We have previously shown that PDTC ameliorates cognitive dysfunction in APP/PS1 mice via inhibition of active glycogen synthase kinase-3b (GSK-3b). The fact that GSK-3b regulates nuclear translocation of Nrf2 suggests that the protective effect may be mediated by the Nrf2-pathway. This study aims to exploit the Nrf2-ARE pathway therapeutically by assessing the potential of PDTC to induce Nrf2 in *in vitro* and *in vivo* models of AD. **Methods:** Neuronal cultures from wildtype and Nrf2 knock-out (KO) mice were used to assess the ability of PDTC to protect neurons against amyloid beta toxicity. Western blotting was used to study Nrf2-pathway induction by PDTC *in vitro*. To assess the effect of PDTC *in vivo*, APP/PS1 mice were treated with PDTC in the drinking water for 10 months. Western blotting, qRT-PCR and measurement of oxidative stress were carried out to assess the protective effect and induction of the Nrf2-pathway. The copper content of the brain was measured with ICP-MS. **Results:** The finding that PDTC protects against amyloid beta toxicity in wildtype, but not in Nrf2-KO neurons suggests that the Nrf2-pathway is implicated in its protective action. PDTC also induces the expression of Nrf2-controlled proteins. Treating mice with PDTC increases the copper content of the brain and reduces oxidative stress. **Conclusions:** Considering that the Nrf2-pathway is impaired in AD, induction of this endogenous defence mechanism by molecules such as PDTC can be harnessed to combat neurodegeneration.

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COST-EFFECTIVENESS OF DONEPEZIL 23 MG IN THE TREATMENT OF MODERATE TO SEVERE ALZHEIMER'S DISEASE FROM A US PAYOR PERSPECTIVE

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Background: Efficacy for donepezil has been demonstrated in patients with mild, moderate and severe Alzheimer's disease (AD). Treatment with the FDA approved, once-daily 23 mg tablet showed improved efficacy in moderate and severe AD when compared with continued treatment with 10 mg/day. This analysis estimated, from the perspective of a US payor, the cost effectiveness and budget impact of donepezil 23 mg tablets compared with 10 mg tablets in moderate to severe AD. **Methods:** A Markov cohort model was developed to project 10-year health-related outcomes, costs, quality-adjusted life years (QALYs), and cost-effectiveness of donepezil 23 mg versus 10 mg among US AD patients with MMSE scores of 0-16. Patients progressed at 6-month cycles through health states defined by AD severity (mild, moderate, severe), setting (community, nursing home), and death. Treatment efficacy and discontinuation were based on an analysis

of a subpopulation of the Phase 3 clinical trial, and transitions and health state utilities were based on published data. Pharmacy costs were estimated from 2009 national AWP, and medical costs incurred by AD patients by stage and setting were estimated from the published literature. Treatment was continued for 18 months, and costs and outcomes were discounted at an annual rate of 3%. **Results:** Compared with patients using donepezil 10 mg, those on 23 mg were estimated to spend less time over 10 years with severe AD and in the costly nursing home setting. In addition, they were predicted to have greater absolute and quality-adjusted survival. Overall, donepezil 23 mg added 0.06 QALYs at a cost of \$3,306, producing a 10-year incremental cost efficacy ratio (ICER) of \$53,748 per QALY gained and a \$0.018 per-member per-month (PMPM) cost for a million-member plan. **Conclusions:** From the payer perspective, donepezil 23 mg was cost effective at the generally accepted US willingness to pay threshold of \$50,000/QALY when used to treat moderate to severe AD. The budgetary PMPM impact of adding donepezil 23 mg to a managed care formulary was limited. If worldwide, rather than US-based, estimates of efficacy for moderate to severe AD are used, the 10-year ICER increases to \$69,675/QALY.

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THE EFFECTS OF NEU-P11 ON MEMORY PERFORMANCE IN NAN3 INDUCED POSTERIOR CINGULATE CORTEX HYPOMETABOLISM

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Background: Posterior cingulate cortex hypometabolism is implicated in mild cognitive impairment (MCI) and early stage Alzheimer's disease (AD). Neu-P11 is a novel melatonin-serotonin receptors agonist in development insomnia and neurodegenerative disorders. The memory performance sparing effects of Neu-P11 were assessed in a rat model of posterior cingulate cortex hypometabolism. Memory performance was assessed by the step-down inhibitory avoidance task. **Methods:** Adult male rats (10 per group) were given a morning training session of the step-down inhibitory avoidance task. Latency to step-down, placing the four paws on a metal grid, was measured. Immediately upon stepping down, the animals received a 3.0-s, 0.4-mA foot shock. The test session was procedurally identical except that no foot shock was given. Rats received a microinjection of sodium azide (NaN₃) into the posterior cingulate cortex 1-1.5 h after the training session and then two injections of either Neu-P11 (50mg/kg, IP) or vehicle at 2 h and 6 h after NaN₃ microinjection. Non-treated rats were used as controls. Aretention test was carried out 24 h after training. Data were compared using a one-way ANOVA. **Results:** Microinjection of NaN₃ produced a significant decrease of step-down latency in the step-down inhibitory avoidance task compared tonon-treated rats. NaN₃- treated rats who received 2 injections of Neu-P11 presented a significant increase of step-down latency during the test session compared with those receiving vehicle ($P < 0.05$). **Conclusions:** Neu-P11 exerts a significant protective effect against memory performance decline following posterior cingulate cortex hypometabolism in rats. Further research on the potential use of Neu-P11 in amnesic MCI and prodromal AD is warranted.

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CORNEL IRIDOID GLYCOSIDE IMPROVES MEMORY ABILITY AND MICROENVIRONMENT FOR CENTRAL NERVE REGENERATION IN FIMBRIA-FORNIX TRANSECTED RATS

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Background: Cornel iridoid glycoside (CIG) is a main component extracted from a traditional Chinese herb *Cornus officinalis*. Our previous study found that CIG improved neurological function and promoted neurogenesis and angiogenesis in cerebral ischemic rats. The aim of this study was to investigate the therapeutic benefit of CIG in treating AD and explore the underlying molecular mechanisms in the rat model with fimbria-fornix transection (FFT). **Methods:** CIG (20, 60 and 180