A Randomized, Placebo-Controlled, Double-Blind Efficacy Study of Nefiracetam to Treat Poststroke Apathy

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Background: To evaluate the efficacy of treatment with nefiracetam compared to placebo in poststroke apathy. *Methods:* A parallel group, randomized, placebo-controlled, double-blind two-center trial in patients with recent stroke and apathy was conducted in 2 tertiary teaching hospitals in Perth, Western Australia, between March 2010 and October 2014. Consenting patients hospitalized with stroke were screened for participation at the time of hospitalization and, if diagnosed with apathy 8-36 weeks later, they were randomized to 12 weeks of 900 mg/day nefiracetam or placebo. The primary efficacy parameter was change in apathy at 12 weeks defined by the 14-item Apathy Scale (AS). *Results:* Of 2514 patients screened, only 377 (15%) were eligible for the study after the first screening, 233 declined further participation, and 144 were assessed for apathy at 8-36 weeks post stroke to confirm eligibility. Twenty patients out of 106 with a complete psychiatric assessment had apathy (19%). Of this sample, 13 patients were randomized. Overall, the AS score decreased by a mean of 7.0 points (95% CI = –14.6 to .6), but there was no significant between-group difference at week 12 (mean paired *t*-tests, $P > .14$). *Conclusions:* Treatment with nefiracetam did not prove to be more efficacious than placebo in ameliorating apathy in stroke. The main limitation was the very small sample randomized, highlighting the limitations of conducting drug trials for behavioral problems among stroke patients. Pharmacological studies of apathy in stroke will require a large multicenter study and a massive sample of patients.
Key Words: Stroke—apathy—depression—nefiracetam.

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Introduction

Apathy is a frequent complication of stroke, affecting about one third of patients with acute stroke lesions. A recent meta-analysis suggests that poststroke apathy may be even more frequent than poststroke depression.[1] Poststroke apathy is associated with reduced cognitive function, depression, and increased disability and dependency on activities of daily living (ADLs).[2,3] Robinson et al[4] conducted a double-blind, placebo-controlled study using the nootropic nefiracetam as treatment for poststroke depression, with apathy as a secondary outcome. In that study, patients were randomized to 600 or 900 mg of nefiracetam, or identical placebo. There was no significant outcome for depression, but a secondary analysis showed that nefiracetam 900 mg/day decreased apathy scores. Nefiracetam was well tolerated and did not produce more adverse events than placebo.[4]

Given the promising effect of nefiracetam on poststroke apathy, we designed and conducted a parallel group, randomized, placebo-controlled, double-blind two-center trial in patients with acute stroke and apathy. Participants were randomized to receive placebo or nefiracetam 900 mg/day. We hypothesized the active treatment group to show significant improvements in apathy, as measured by the Apathy Scale (AS)[5] over a period of 12 weeks.

Patients and Methods

Trial Design

This was a 12-week, randomized, controlled, double-blind efficacy study of nefiracetam for the treatment of poststroke apathy. A consecutive series of patients admitted to the stroke units of 2 university hospitals from March 2010 to October 2014 were assessed for eligibility during the first 2 weeks following an acute stroke (the "screening period"). Eight weeks after the stroke, consenting participants completed baseline evaluations and were randomized to treatment with placebo or nefiracetam (900 mg/day in divided doses). Patients were treated in a double-blind fashion for 12 weeks, with follow-up assessments every 4 weeks. The study protocol was approved by the Human Research Ethics Committee of Fremantle Hospital (FH) and Royal Perth Hospital (RPH), and written informed consent was obtained for each participant and next of kin. The trial was registered with the ClinicalTrials.gov, registration number NCT00273676.

Participants

A total of 2514 admissions to the stroke units at FH and RPH were screened for potential participation, and 13 participants were randomized between July 2010 and March 2013 (see Fig 1: Consort diagram).

Inclusion criteria were as follows: (1) age greater than 40 years and less than 90 years; (2) clinical and neuroradiological findings consistent with either a hemispheric, brainstem, or cerebellar stroke, regardless of a history of previous strokes; (3) meeting criteria for apathy 8 weeks after stroke, based on a score of 14 or higher on the AS[5]; (4) being capable of taking oral medication and able and agreeable to undergo clinical assessments; and (5) being cared for by a reliable spouse, caregiver, or case manager responsible for ensuring the administration of medication.

Exclusion criteria were as follows: (1) meeting DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, 4th Edition) criteria for major depression at the 8-week assessment; (2) stroke occurring after rupture of an intracranial aneurysm, arterial-venous malformation, or as a complication of head injury, intracranial tumor, or a neoplastic process; (3) presence of prestroke dementia, as assessed with the Informant Questionnaire on the Cognitive Decline in the Elderly,[6] or any other neurodegenerative condition; (4) severe language comprehension deficits (patients unable to complete part I of the Token Test[7] were excluded as they are unable to provide reliable responses to the instruments assessing psychopathology); (5) comorbid alcohol or drug abuse, as defined by meeting DSM-IV criteria for alcohol abuse or dependence within the 12 months prior to enrollment; (6) presence of severe medical comorbidity that may compromise 12-month survival; and (7) current use of neuroleptics or drugs reported to affect apathy (i.e., anticholinesterase inhibitors, bupropion). Finally, inclusion criteria for informants were as follows: (1) a score on the Mini Mental State Exam (MMSE) of 28 or higher and (2) in regular contact with the patient (3 or more times per week for at least 9 hours/week).

Study Assessments and Outcome Measures

Men and women admitted to the Stroke Units at FH and RPH and their caregivers were contacted by research personnel within the first 2 weeks after the stroke (screening period), and all the data were gathered by means of structured interviews conducted by research staff trained by the investigators (please see below). Detailed *medical history* was obtained at screening, including demographic data and medications taken during the 2 weeks before the stroke. The functional impact of chronic medical conditions was assessed using the *Cumulative Illness Rating Scale*. All stroke patients at FH and RPH were assessed with Magnetic Resonance Imaging (MRI) during the acute stroke period, and this information guided the inclusion or exclusion of participants. Assessment of neurological deficits and functional and cognitive status included the following instruments:

The first author completed a physical and neurological examination of all consenting participants at screening, baseline, and at the end of the intervention phase (i.e., 12 weeks later). Results of the neurological examination were recorded using the *National Institutes Health Stroke Scale*.[8] Functional impairment was assessed with the *Functional Independence Measure* (FIM) and the *Functional Assessment Measure* (FAM),[9] and global cognitive function was assessed with the *Modified Mini-Mental State Exam* (3MS).[10]

Psychiatric diagnoses of major or minor depression and other Axis I disorders were made 8 weeks after stroke by a psychiatrist or trained senior research officer using the *Mini International Neuropsychiatric Interview* (MINI). The MINI is a semistructured interview whose reliability and validity in neuropsychiatry have been demonstrated in previous publications.[11-16] Consenting patients meeting the inclusion or exclusion criteria were randomized to 1 of 2 treatment groups (placebo or nefiracetam) and started treatment on the day of randomization. The study medication was centrally and independently controlled by the FH pharmacy. Prior to receiving study drug, patients and caregivers were evaluated on the following instruments to determine baseline values.