Double-Blind Treatment of Apathy in Patients with Poststroke Depression Using Nefiracetam

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Nefiracetam is a novel pyrrolidone-type nootropic compound shown in preliminary trials to increase blood flow and improve patient outlook and energy following stroke. Of 137 stroke patients with major depression, 70 also met published diagnostic criteria for apathy (51.1%) and were randomly assigned either to placebo or 600 mg or 900 mg of nefiracetam per day, and received at least 4 weeks of treatment. Using the group with at least 4 weeks of treatment as the intention-to-treat sample with last observation carried forward, repeated measures analysis of variance of Apathy Scale scores demonstrated a significant time-by-treatment interaction. Patients taking 900 mg nefiracetam had a significantly greater change in Apathy Scale scores compared to 600 mg of nefiracetam or placebo. Future studies should assess whether apathy without depression may respond to this novel treatment.

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Apathy is a mental disorder characterized by lack of motivation. Marin[1] has defined apathy as a syndrome manifested by an absence of feeling or emotion, impaired cognitive function and reduced goal directed activity. Apathy occurs in a variety of neurological disorders including stroke,[2] Parkinson's disease,[3] trauma[4] and Alzheimer's disease.[5] Although the syndrome has not been defined by DSM-IV criteria, both Marin[1] and Starkstein[5] have suggested diagnostic criteria to define this condition. Abnormalities in aspects of emotion, cognition, motor function, and motivation have been suggested as the basis for the development of specific diagnostic criteria for apathy.

We have been studying apathy in patients with stroke since 1993.[2] The identification of apathy thus far has been based primarily on severity of scores on apathy rating scales.[2] We developed an apathy rating scale[2] based on a modified version of the scale proposed by Marin.[6] The Marin scale was modified to provide a more brief assessment. This modified version has been shown to be both reliable[7] and valid.[5] Using a cutoff

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score of 12 on our Apathy Scale, we found that 18 of 80 consecutive patients (22.5%) admitted to the hospital with an acute cerebrovascular lesion met this criterion for apathy. Of the 18 patients with apathy, half had associated major or minor depression. Poststroke apathy was also significantly associated with older age, cognitive impairment, and impairment in activities of daily living as well as lesions of the internal capsule.[2]

Although there is a strong association of apathy with depression, the distinction between depression and apathy is not difficult because of the symptoms in emotional, cognitive, psychomotor, and autonomic functions are very different between the two disorders (e.g., apathy is characterized by loss of emotion while depression is characterized by intense sadness of emotion.)[8] Furthermore, depression distresses patients while apathy distresses caregivers.

In spite of a growing interest in apathy, published treatment studies have been limited to anecdotal case reports generally utilizing dopamine agonists or stimulant medications.[9–12] Nefiracetam is a novel pyrrolidone-type nootropic agent which has been demonstrated in animal studies to enhance aminergic, glutaminergic, and cholinergic neurotransmission by stimulating α=4, β=2 type neuronal nicotinic acetylcholine receptors, activating protein kinase C, and reducing magnesium block of the NMDA receptor.[13–19] In addition, nefiracetam increased brain-derived neurotrophic factor (BDNF) expression as well as regional blood flow and glucose utilization after sustained cerebral ischemia in rats.[20,21] This compound was first administered to humans in Japan as a potential treatment for poststroke cognitive impairment. Preliminary results published in Japanese language journals, however, showed an effect of treatment on outlook (i.e., optimism about the future) and interest (i.e., desire to undertake new activities), but no significant change in cognitive impairment.[22]

The current study was therefore undertaken as part of a phase II trial of nefiracetam for treatment of poststroke depression[23] and, secondarily, apathy utilizing multisite enrollment and double-blind placebo-controlled methodology. This study thus represents a secondary analysis which was powered for assessment of depression, not for apathy. The hypothesis was that apathy, as well as depression would improve more following nefiracetam treatment, 900 mg/day, compared with placebo.

METHODS

Participants

A multisite (28 sites) trial of nefiracetam utilizing double-blind methodology was conducted from 1999–2001. All sites obtained institutional review board approval and all participants provided informed consent. Patients who lacked the capacity to consent based on comprehension deficit or severe cognitive impairment were excluded. This was based on clinical assessment by the treating neurologist. The study included 159 patients within 3 months of stroke who met DSM-IV diagnostic criteria for "depression due to stroke with major depressive-like episode." Exclusion criteria included prior nonstroke-related brain injury, other psychiatric or neurological disease such as Alzheimer's or Parkinson's disease, existence of other life-threatening illness, comprehension deficit that would preclude a verbal interview, allergic response to nefiracetam, and taking any other psychotropic medications with the exception of small doses of benzodiazepines or related insomnia medications. Patients were randomly assigned to one of three treatment arms including 600 mg nefiracetam (n=55), 900 mg nefiracetam (n=48), or identical placebo (n=56), given in three identical 150 mg capsules twice daily. Patients were evaluated prior to entry into the study and followed-up at 4 weeks, 9 weeks, and 12 weeks. Scores on the Hamilton Depression Rating Scale (HAM-D) were the primary outcome variable. After 12 weeks, the study was completed and nefiracetam was discontinued. The patient disposition is shown in the flow chart in Figure 1. This secondary analysis of intention-to-treat data included all of the 137 patients who had initial assessment and at least 4 weeks of follow-up.

Diagnosis

All patients included in the study were diagnosed with apathy using the diagnostic criteria suggested by Starkstein et al.[5] Based on the interviewer rated findings from the Apathy Scale (clinician version), all patients with a diagnosis of apathy had loss of motivation (a score of 2 or 3 on item 7 [Are you inspired to accomplish things?]) and at least one symptom indicating decreased function from each of the three symptom clusters: emotion (a score of 2 or 3 on items 10 [Are you indifferent to things?] or 13 [Are your emotions gone?]); behavior (a score of 2 or 3 on items 4 [Do you have energy to do things?] or 9 [Do you need prodding to get going?]); or cognition (a score of 2 or 3 on items 1 [Are

you interested in learning?] or 2 [Do activities interest you?]).

The modified Apathy Scale is an interviewer-rated, 14-item scale that has been shown to be reliable and valid in the stroke population.[2] Scores range from 0 to 42 with higher scores indicating greater severity. The interviewers' ratings represented a clinical judgment based on information provided by the patient and a family member.

Psychopathological Evaluation

In addition to the Apathy Scale, all patients were administered the modified Present State Examination,[24] a semistructured mental status exam designed to allow DSM-IV-TR[25] diagnoses of depression due to stroke with major depressive-like episode, minor depression (DSM-IV-TR, research criteria), or anxiety disorder due to stroke with generalized anxiety. Patients were also administered the HAM-D (17-item)[26] and the Beck Depression Inventory (BDI).[27] Each of these instruments has been shown to be reliable and valid in assessing patients with stroke.[28,29]

Prior to beginning the study and halfway through the study (to prevent rater drift), all study raters were trained in the use of all of these instruments. All raters were shown 5 videos of patient interviews and asked to rate their responses. An interview rater was not permitted to participate in the study until their interrater reliability exceeded 80% agreement based on intraclass correlation with the ratings made by an experienced rater (i.e., RGR).

FIGURE 1. Flow Chart of Patient Treatment Protocol

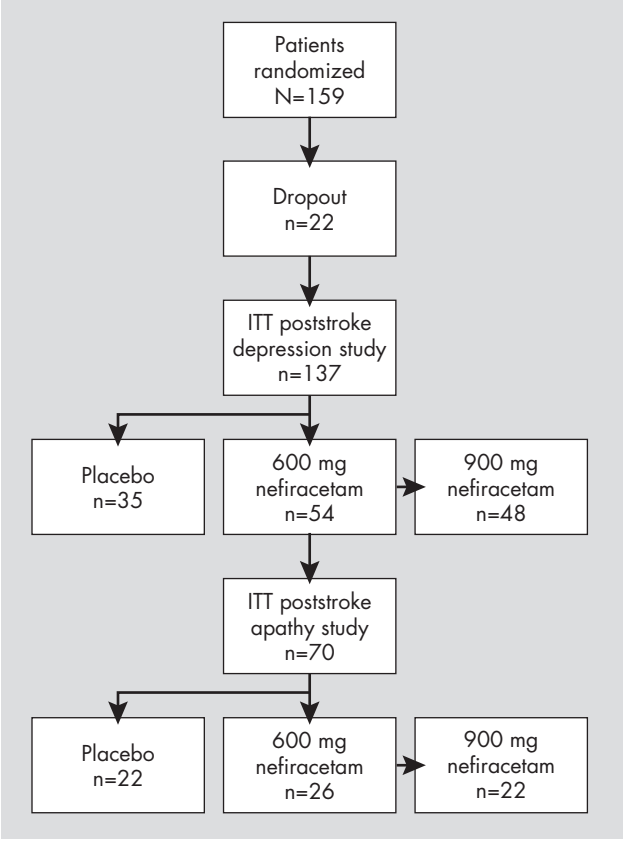


Chart includes treatment assignment and the number of patients who maintained treatment protocol for the first 4 weeks or more of the poststroke major depression study. Of the 159 enrolled, this group of 137 in the depression study and 70 in the apathy study constituted our intention-to-treat (ITT) sample.

Neurological and Cognitive Examinations

Patients were administered the Modified Mini-Mental State test (3MS) for assessment of cognitive impairment.[30] Scores range from 0 to 100 with lower scores indicating greater impairment. The Functional Independence Measure[31] assessed activities of daily living in the domains of self-care, mobility, communications, sphincter control, locomotion, and social cognition. Scores range from 0 to 100 with lower scores indicating greater impairment. The NIH Stroke Scale[32] measured severity of neurological impairment in level of consciousness, visual fields, facial palsy, motor function, ataxia, sensory impairment, language, dysarthria, extinction, and distal motor function. Higher scores indicate greater severity of stroke-related impairment. Each of these scales has been demonstrated to be reliable and valid in a stroke population.[31,32]

Statistical Analysis

The data were compared across groups using means, standard deviations, and analysis of variance. The intention-to-treat population of 137 had at least 4 weeks of data. Longitudinal data were analyzed using a repeated measures analysis of variance. Missing data points were estimated using last observation carried forward. Frequency distributions were evaluated using chi-squared or Fisher's exact test. Statistical significance was based on a two-tailed p value less than 0.05.

RESULTS

Background Characteristics

Figure 1 shows patient disposition. A total of 159 patients were randomized and 158 given placebo or ne-

firacetam (600 mg or 900 mg). A total of 44 patients dropped out and 115 completed the 12-week protocol while 137 represented our intention-to-treat population who had 4 or more weeks of treatment. Of the 22 patients who dropped out prior to completing 4 weeks, three (13.6%) met criteria for apathy compared with 70 of 137 completers (51.1%) who met criteria for apathy (Fisher Test, two-tailed, p=0.001). The background characteristics and impairment scores of the apathetic and nonapathetic patients are summarized in Table 1. There were no statistically significant differences in the background characteristics or mean scores on the HAM-D, or on the neurological and cognitive impairment measures. The background characteristics of the 22 dropouts compared to the 137 intention-to-treat patients showed no significant differences in age, gender, ethnicity, handedness, NIH Stroke Scale scores, cortical lesions, subcortical lesions, HAM-D scores, or Apathy Scale scores.

The background characteristics and impairment scores of the patients diagnosed with apathy, divided into the three medication treatment arms, are shown in Table 2. There were no statistically significant differences in any of the demographic variables. Similarly there were no statistically significant differences in the HAM-D, Functional Independence Measure, 3MS, or Apathy Scales among the three groups. The patients all had moderately severe depression and apathy, but only mild-to-moderate severity of impairment in cognitive function and activities of daily living.

There were no significant differences among the three treatment groups in severity of stroke based on the NIH Stroke Scale, or the frequency of lesions affecting the frontal cortex, basal ganglia, thalamus, or internal capsule.

TABLE 1. Background Characteristics and Baseline Variables Scores Among Patients With Major Depression With and Without Coexisting Apathy

	Apathetic n=70	Non-apathetic n=67
Age (mean, SD)	66.3 (11.8)	65.3 (12.8)
Sex (female)	45.7%	47.1%
Race (white)	92.9%	85.3%
Education (mean, SD)	11.4 (2.8)	12.0 (3.2)
HAM-D (mean, SD)	22.6 (4.1)	22.1 (3.2)
FIM (mean, SD)	89.7 (27.1)	90.2 (23.0)
3MS (mean, SD)	81.5 (13.0)	77.5 (17.2)

HAM-D=Hamilton Depression Rating Scale; FIM=Functional Independence Measure; 3MS=Modified Mini Mental State Exam

Drug-Related Side Effects

The frequency of adverse events comparing 900 or 600 mg of nefiracetam or placebo is shown on Table 3. There were no significant differences between the groups in the frequency of adverse events.

Intention-to-Treat Analysis

Apathy scores for the three treatment groups over the course of the treatment trial are shown in Figure 2, panel A. Repeated measures analysis of variance (ANOVA) of Apathy Scale scores showed both a significant effect for time (F=9.4, df=3, 65, p=0.0001) and a significant time × treatment group interaction (F=2.3, df=6, 128, p=0.050). Patients receiving 900 mg/day of nefiracetam showed a significantly greater decrease in Apathy Scale scores during the 12-week trial compared to patients receiving placebo (time × treatment group interaction: F=4.0, df=3, 65, p=0.01). The time by treatment group interaction for 600 mg/day versus placebo was nonsignificant (F=1.3, df=3, 65, p=0.29). The time by treatment interaction for 900 mg versus 600 mg was nonsignificant (F=1.45, df=3, 65, p=0.23). The absolute risk reduction for 900 mg nefiracetam versus placebo was 0.18 (95% CI 0.02–0.34) while 600 mg nefiracetam versus placebo was 0.04 (95% CI=0.04–0.11).

Furthermore, considering remission as a 75% decrease in apathy scale scores, four of 22 patients in the 900 mg nefiracetam group, one of 26 patients in the 600 mg nefiracetam group and none of the 22 patients in the placebo group had remission of symptoms (χ^2=6.7, df=2, p=0.031). Thus, apathy remission was significantly more frequent in the 900 mg nefiracetam group compared with the placebo and 600 mg nefiracetam groups.

TABLE 2. Demographic Characteristics and Baseline Variables Scores Among Apathy Patients Within Treatment Groups

	Placebo n=22	Nefiracetam 600 mg n=26	Nefiracetam 900 mg n=22
Age (Mean, SD)	64.7 (11.9)	63.9 (11.1)	70.5 (11.9)
Sex (female)	53.6%	42.3%	31.9%
Race (white)	90.9%	92.3%	95.4%
Education (mean, SD)	11.3 (2.7)	11.4 (3.2)	11.4 (2.6)
HAM-D (mean, SD)	21.6 (3.2)	22.6 (3.9)	23.5 (4.8)
FIM (mean, SD)	88.8 (27.3)	95.1 (27.6)	84.3 (26.4)
3MS (mean, SD)	79.7 (12.3)	86.0 (10.1)	78.2 (15.6)
AS (mean, SD)	19.3 (4.8)	20.3 (5.0)	21.2 (5.7)

HAM-D=Hamilton Depression Rating Scale; FIM=Functional Independence Measure; 3MS=Modified Mini Mental State Exam; AS=Apathy Scale

In the assessment of depression, a repeated measure analysis of HAM-D scores did not show a significant time by treatment group interaction, suggesting that the differential treatment effect on apathy scores was not simply due to an improvement in depression scores (Figure 2, panel B). In addition, we compared change on HAM-D and Apathy Scale scores (i.e., initial minus 12-week scores). There was a significant difference between the 900 mg, 600 mg, or placebo groups in change of Apathy Scale scores (i.e., apathy 900 mg group =7.5±8.5; 600 mg group =3.5±6.6; placebo group =2.0±7.0, p=0.038). This was not the case for change in HAM-D scores (i.e., 900 mg group =14.0±8.2, 600 mg group = 12.8±7.1, placebo group =12.7±7.9, ANOVA, p=0.82).

Since apathy has manifestations in cognition as well as emotion, we examined correlations between the change in Apathy Scale scores from beginning to end of treatment and HAM-D or 3MS scores (HAM-D score, Spearman ρ=0.28, p=0.0018 and 3MS (cognition) score (Spearman ρ=−0.12, p=0.15). Although this finding does not support the hypothesis that apathy effects cognition, this is a global score and some aspects of cognition may have improved with Apathy Scale scores.

TABLE 3. Adverse Events Reported by Patients Taking Nefiracetam Compared With Placebo

System	Placebo	Nefiracetam 600 mg	Nefiracetam 900 mg
General symptoms (%)	26.7	20.5	17.9
Gastrointestinal (%)	20.0	22.7	28.2
Cardiac (%)	13.3	6.5	7.7
Vascular (%)	8.9	6.8	5.1
Musculoskeletal (%)	20.0	13.6	15.4
Nervous system (%)	31.1	27.3	25.6
Respiratory (%)	11.1	6.8	7.7
Skin (%)	20.0	15.9	17.9

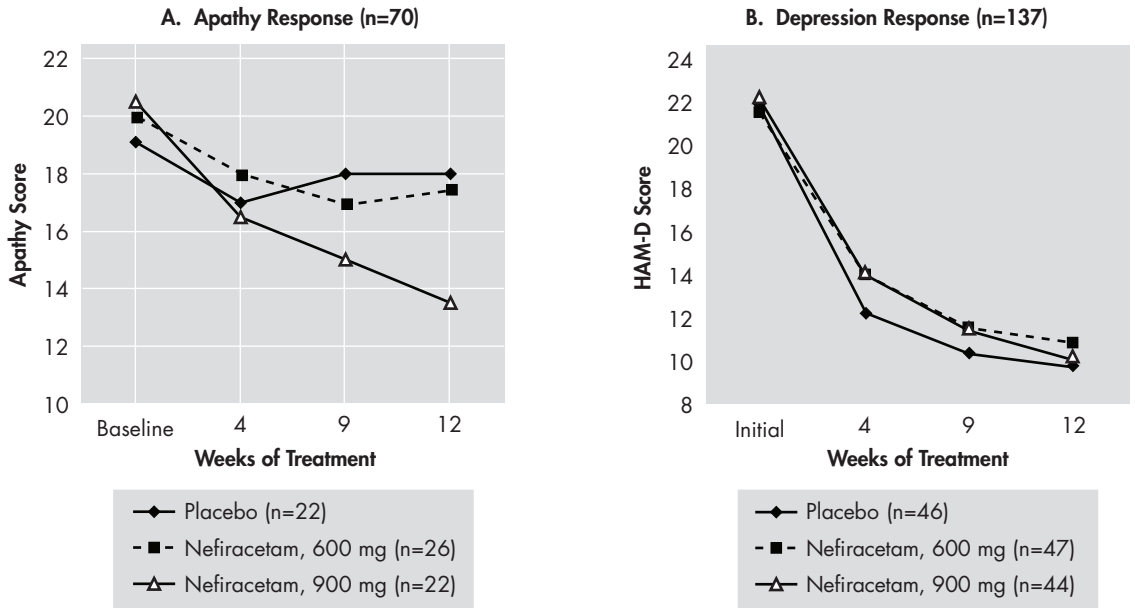
Imaging Analysis

We examined treatment response in patients with subcortical compared to cortical involvement,[33] (i.e., cortical: 900 mg, n=10; 600 mg, n=14; placebo, n=13; and subcortical: 900 mg n=4; 600 mg, n=3; placebo, n=7) and there was no significant treatment × lesion location × time interaction.

DISCUSSION

This randomized, double-blind study demonstrated that, among patients who met diagnostic criteria for

FIGURE 2. Intention-to-Treat Analysis of Patients Meeting Diagnostic Criteria for Apathy



Patients completing 4 or more weeks of treatment as measured by the Apathy Scale (A) and the 137 patients included in the poststroke major depression trial (B). Patients who received 900 mg/day of nefiracetam had significantly greater reduction in Apathy Scale scores over 12 weeks than patients treated with placebo or 600 mg nefiracetam (time × treatment interaction; F=2.3, df=6, 128, p=0.050). There was not a significant time × treatment interaction using the Hamilton Depression Rating Scale. Note that all depression groups improved without specific response to Nefiracetam compared with placebo.

both apathy and major depression, 900 mg of nefiracetam administered over 12 weeks of treatment significantly improved apathy scores compared with patients who received placebo or a lower dose (600 mg) of nefiracetam. On the other hand, 900 mg of nefiracetam was not different from placebo as a treatment for depression, suggesting that the differential effect of active versus placebo effect on apathy was different than the active versus placebo effect on depression. Finally, nefiracetam and placebo had few similar side effects.

This is the first trial, of which we are aware, that has demonstrated a significant treatment effect among patients with a diagnosis of apathy using double-blind, placebo controlled methodology. The first issue which must be addressed, however, is whether this response is simply due to an improvement in depressive symptoms. First, clinicians can readily distinguish between apathy and depression because depression involves feelings of sadness, sometimes with agitation, decreased sleep and appetite, hopelessness, self-blame, and suicidal thoughts. Apathy is characterized by lack of motivation and blunted emotional responses without the former symptoms. Second, the strongest argument for this being a specific effect on apathy is that active versus placebo treatment showed no difference on depressive symptoms, but a very significant differential effect on apathy symptoms. Thus, the treatment effect on apathy cannot be explained based on the treatment effect on depression.

There is a growing literature consisting of case reports and small series of patients who were treated for apathy with a variety of psychoactive agents.[4] Psychostimulants and dopaminergic agonists may modestly improve arousal and speed of information processing, reduce distractibility, and improve some aspects of motivation and executive function.[34,35] However, the magnitude and temporal course of their therapeutic effect is still controversial.[36] Amantadine, a drug with pharmacologic effects on dopaminergic, cholinergic and NMDA receptors, could also have some efficacy in the treatment of motivational deficits.[37–39] Finally, there is some empirical evidence that cholinesterase inhibitors such as donepezil may improve motivation and general well being of patients with traumatic brain injury[40–42] and may improve apathetic symptoms among patients with dementia.[43] Thus, other drugs besides nefiracetam may be effective treatments for poststroke apathy.

Although the mechanism of apathy is unknown, Kalivas et al.[44] has postulated that the rostral cingulate, nucleus accumbens, ventral pallidum, and ventral tegmental areas constitute a core circuit in which motivational state is dependent upon the pattern of information in the core circuit. Limbic structures such as the amygdala, hippocampus, and frontal cortex modulate the core circuit based on the motivational and emotional significance of the internal and external input to these limbic structures. This hypothesis is consistent with the findings of Okada et al.,[45] using xenon inhalation methods, who found that 20 patients with apathy following stroke had significantly reduced regional cerebral blood flow in the right dorsal lateral frontal and left frontotemporal regions compared with 20 patients without apathy. In a more recent study of 29 patients with apathy and subcortical stroke, the same group of investigators reported a significantly prolonged latency and decreased amplitude of the P3-Novelty component of the auditory event-related potential in the frontal cortex.[46] It is plausible that hypoactivity in frontal and temporal lobe regions, and therefore reduced input to the core circuit, may be reversed by the enhanced aminergic, glutaminergic, and cholinergic neurotransmission produced by nefiracetam. Other mechanisms could, of course, be proposed.

Finally, the limitations of the study should be acknowledged. First, this was a secondary analysis and the study was primarily designed to assess response of poststroke depression to nefiracetam. Second, of the 159 patients randomized to the three treatment arms, 22 patients (13.8%) dropped out during the first month of the trial. Although there was a significantly lower frequency of apathy among dropouts than continued participants, there were no significant differences in demographic or baseline impairment variables between patients who remained in the study and those who dropped out. Although it is unlikely that this influenced our findings, attrition-related bias cannot be ruled out. Third, all patients enrolled in the study had major depression as well as apathy. Based on prior literature, about half of all stroke patients with clinically significant apathy would be expected to have depression.[2] We do not know, however, whether the response to nefiracetam was applicable only to patients with apathy plus depression or whether these findings apply to patients with apathy without associated depressive disorder. Fourth, we lacked sufficient power to examine whether apathy was associated with specific impairments such as cognitive function or specific lesion location. Finally, because this was a 12-week treatment trial without prolonged follow-up, we do not know

whether the improvement in apathy symptoms continued after discontinuation of the drug.

In conclusion, apathy has received increasing attention because of its effect on emotion, behavior, and cognitive function. The current study is the first randomized double-blind treatment trial to be conducted among a large group of stroke patients with coexistent apathy and depression, and our results suggest that nefiracetam may be an effective treatment for this clinically important condition. Further studies in patients with apathy without associated depression are needed to determine the specificity of nefiracetam as treatment of apathy and whether treatment of apathy significantly improves long-term outcome and recovery.

This study was conducted between January 2000 and June 2001. It was sponsored by Diiachi Pharmaceutical and Prestwick Pharmaceuticals. Dr. Robinson was a study design consultant and a member of the Data Monitoring and Safety Board for Prestwick Pharmaceutical and Diiachi Pharmaceuticals. This work represents the independent data analysis and manuscript preparation by the authors. Drs. Jorge and Starkstein have no disclosures. Dr. Robinson was a study design consultant to Hamilton Pharmaceuticals who initiated a trial of nefiracetam following stroke, with apathy scale score as the primary outcome variable, in March 2003 and abandoned in December 2003. Dr. Clarence-Smith was the CEO of Prestwick Pharmaceuticals and was involved in the design and conduct of the treatment trial.

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