

Care Management of Poststroke Depression

A Randomized, Controlled Trial

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Background and Purpose—Poststroke depression is a prevalent and disabling disorder, yet evidence regarding the effectiveness of treating poststroke depression is inconclusive. Our objective was to determine the effectiveness of the Activate–Initiate–Monitor care management program for the treatment of poststroke depression.

Methods—We conducted a prospective, randomized, outcome-blinded trial in 188 ischemic stroke survivors identified at the time of admission to one of 4 Indianapolis hospitals. Depression screening and enrollment occurred between 1 and 2 months poststroke. The Activate–Initiate–Monitor intervention was a care management program that included Activation of the patient to recognize depression symptoms and accept treatment, Initiation of an antidepressant medication, and Monitoring and adjusting treatment. Usual care subjects received nondepression-related education and were prescribed antidepressants at the discretion of their provider. The primary outcome measure was depression response, defined as a Hamilton Depression Inventory score <8 (remission) or a decrease from baseline of at least 50% at 12 weeks.

Results—Intervention and usual care groups did not differ on any key baseline measures. Both depression response (51% versus 30%, $P=0.005$) and remission (39% versus 23%, $P=0.01$) were more likely in the Activate–Initiate–Monitor intervention than in the usual care group. This difference in depression scores was present by 6 weeks and persisted through the 12-week assessment. Serious adverse events did not differ between the 2 groups.

Conclusion—The Activate–Initiate–Monitor care management model is significantly more effective than usual care in improving depression outcomes in patients with poststroke depression. (*Stroke*. 2007;38:998-1003.)

Key Words: randomized clinical trial ■ poststroke depression ■ outcomes ■ care management model

Poststroke depression (PSD) occurs in approximately one third of stroke survivors and is associated with diminished recovery, including less functional gain in activities of daily living and lower recovery trajectories, even when adjusting for other important covariates, including stroke type and severity.^{1–7} Like with depression that occurs after myocardial infarction, PSD is also associated with increased risk for subsequent cardiovascular events, increased mortality, and increased healthcare utilization.^{8–10}

Although the diagnosis of PSD can be complicated by overlap with stroke-related physical symptoms poststroke and by cognitive and language effects of stroke, multiple studies have documented the accuracy of various depression screening tools in stroke survivors.^{11–13} The symptom profile of PSD has also been shown to be quite similar to that of nonstroke-related depression, suggesting PSD can be diagnosed in a manner similar to depression in other settings.^{14–16}

Despite these similarities, few randomized, controlled clinical trials have been done to rigorously evaluate whether depression treatment is efficacious in improving rates of

depression remission poststroke. Although a number of these trials demonstrated improvements in depressive symptoms for treated patients, the results remain inconclusive because most trials included less than 100 subjects and few included blinded outcome assessments. A Cochrane meta-analysis of PSD treatment trials concluded evidence was insufficient to recommend treatment specifically for the remission of depression after stroke or for the prevention of depression after stroke,^{17,18} a conclusion that may impact the decision of providers to treat patients with PSD. Although studies have shown depression can be effectively treated in patients with other acute comorbid medical disorders, for example, myocardial infarction,^{19–21} it is not known whether conventional depression therapies are equally effective in treating PSD.

Given the prevalence and impact of PSD, the evidence for successful treatment of depression in patients with other acute illnesses, and the lack of definitive clinical trial evidence for the effectiveness of PSD treatment on depression remission, we conducted a randomized trial of a care management intervention versus usual care for treatment of PSD. Our

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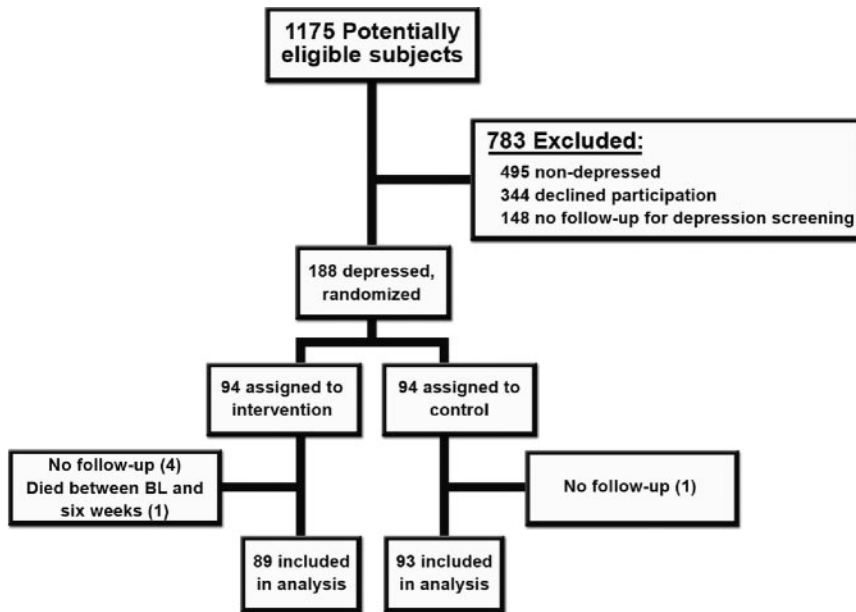


Figure 1. Flow chart of participants in the trial.

primary hypothesis was that stroke survivors receiving care management for PSD would have improved 12-week depression remission rates, defined by scores on the Hamilton Depression Inventory, compared with those receiving usual poststroke care.

Methods

Participants

Adults 18 years and older from 4 Indianapolis hospitals with ischemic stroke who had no severe language impairment, defined by a score <2 on the National Institutes of Health Stroke Scale language item,²² no severe cognitive impairment, defined by a score >3 on the modified 6-item Mini-Mental Status Examination,²³ who could speak and understand English, had a telephone, and who had a life expectancy of at least 6 months were eligible to participate. Persons with hemorrhagic stroke, active psychosis, suicidality, or substance abuse; those currently taking a monoamine oxidase inhibitor; and women pregnant at the time of stroke were ineligible. Approximately 8% of potential subjects were excluded as a result of severe aphasia and 13% resulting from preexisting dementia or failed cognitive screening. Prior treatment for depression either before or at the time of the stroke did not disqualify subjects from this study. This trial was approved by the Clarian/Indiana University Institutional Review Board, which is responsible for research oversight at all 4 study hospitals, and was monitored by a local independent Data Safety Monitoring Committee.

Study Protocol

The Activate–Initiate–Monitor trial was a prospective, randomized, outcome-blinded designed study.²⁴ We identified all potentially eligible subjects at the time of stroke hospitalization and invited them to participate in depression screening for possible study enrollment 1 to 2 months poststroke (Figure 1).

Depression Screening and Diagnosis

All potentially eligible subjects were screened with the 9-item Patient Health Questionnaire depression scale (PHQ-9), a widely used measure for detecting depression in medical populations,^{25–27} and also validated in stroke survivors.¹¹ Those endorsing either the depressed mood or the anhedonia item or those with scores ≥ 5 regardless of items endorsed were administered the structured clinical interview for *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*.^{28,29} Persons with a structured clinical

interview for *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*-determined diagnosis of major depression or minor depression were invited to participate.

Care Management Intervention and Usual Care

The Activate–Initiate–Monitor intervention was conducted by nurse care managers under the supervision of study physicians and consisted of 3 main steps: (1) Activating stroke survivors and their families to understand and accept depression diagnosis and treatment, (2) Initiating antidepressant medication; and (3) Monitoring treatment effectiveness. Activation took place at study entry and consisted of a 20-minute structured psychoeducational session. The session included discussion of depression diagnosis, symptoms, and treatment guidelines with emphasis on destigmatizing the diagnosis and reinforcing the link between symptoms and treatment. Initiation of treatment involved the study nurse recommending an antidepressant to the stroke survivor's treating physician (typically either a neurologist or primary care provider). Antidepressant recommendations followed a medication algorithm, which usually involved initial treatment with a selective serotonin reuptake inhibitor antidepressant, but also took into account previous antidepressant failures or adverse effects as well as individual subject contraindications. Monitoring of antidepressant therapy consisted of scripted bimonthly telephone calls from the nurse to assess depression symptoms, medication side effects, and adherence. The standardized medication algorithm provided for increasing the antidepressant dose after 4 weeks of treatment if symptoms were not improving. The algorithm also provided options to change medications if bothersome side effects occurred. All intervention group subjects were discussed with study physicians during weekly care management meetings. Suggested changes in antidepressant treatments were made by the care management team and communicated to the subjects by the nurse care managers. Stroke survivors randomized to usual care received an identical number of baseline and telephone sessions to serve as a control for an attention effect. Instead of depression, these sessions focused on recognition and monitoring of stroke symptoms and risks. In both groups, serious adverse events were defined as any event requiring hospitalization or an emergency department visit during the 12-week study period and were reported to the Institutional Review Board and the local Data Safety Monitoring Board as specified by the Clarian/Indiana University Institutional Review Board.

Medication Algorithm

For intervention group subjects with no prior antidepressant treatment or no history of side effects with paroxetine, study nurses

suggested initiation of 10 mg paroxetine daily for 1 week followed by an increase to 20 mg daily. If subjects had a history of side effects or lack of response to paroxetine, 50 mg sertraline daily was suggested. Intervention subjects on an antidepressant for less than 6 weeks before enrollment were continued on that medication; if they had received an antidepressant for more than 6 weeks, they were managed according to the standard algorithm. Subjects with a poor response (ie, PHQ-9 decline of less than 5 points) after 4 weeks of treatment had an increase in antidepressant dose. For subjects with <50% drop in PHQ-9 score at 6 weeks, study nurses suggested a change to 75 mg venlafaxine daily. Other antidepressants (eg, mirtazapine) were occasionally used in the event these antidepressants were ineffective, not tolerated, or contraindicated with the general intent to change class of antidepressant at 6 weeks in subjects with a lack of response to the initial treatment. Regardless of the antidepressant used, the doses were increased as needed at 4 weeks after initiation in accordance with American Psychiatric Association guidelines in an effort to obtain at least a 50% improvement in PHQ-9 score.³⁰ All antidepressant medications during the 12-week intervention period were provided to the patient without cost.

Study Timeline and Outcome Assessments

The primary study outcome was the proportion of patients who, after 12 weeks of treatment, had achieved significant depression response defined as an absolute Hamilton Depression Inventory (HAM-D) score <8 or a 50% or greater decline in HAM-D score.³¹ Prespecified secondary outcomes were depression remission defined by a HAM-D score <8 or by a PHQ-9 score <5^{25,26} and reduction in depression severity as measured by the mean change in HAM-D and PHQ-9 scores between baseline and 12 weeks.

Subjects were assessed and enrolled at study baseline (1 to 2 months poststroke) and were interviewed face-to-face at 6 and 12 weeks for depression and other outcome assessments. All study interviewers underwent standardized training and observation to ensure accuracy and reproducibility of structured clinical interview for *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* diagnoses and depression scale scores. The Cumulative Illness Rating Scale was performed at baseline as a measure of overall medical comorbidity,³² and the National Institutes of Health Stroke Scale at the time of study enrollment was used to assess stroke impairments.²² Adverse events, including medication side effects, were assessed by standardized questionnaires in bimonthly telephone calls from the care managers. Serious adverse events were defined as any event requiring an emergency department visit or hospitalization during the 12-week intervention period.

Randomization and Blinding

Subjects were randomized to the Activate–Initiate–Monitor intervention versus usual care in blocks of random sizes of 2 and 4 at each site. Site-specific randomization lists were computer-generated and treatment assignments were supplied in sealed opaque envelopes by biostatistics personnel. The nurse care manager consented subjects and revealed the randomization assignment for each subject by opening the next envelope in the sequence. This trial used a prospective, randomized, outcome-blinded design, in which all 6- and 12-week depression outcomes were assessed by a research assistant blind to treatment allocation and uninvolved in care management of subjects.²⁴

Sample Size and Statistical Analysis

Analyses were based on intention-to-treat in all randomized subjects. With 100 subjects per group, we projected 82% power to detect an odds ratio of 0.43 (translating to an approximately 20% absolute difference in response rates between the groups) using a 2-sided χ^2 test with $\alpha=0.05$. Analyses were performed using SAS Version 9.1 (SAS Inst).

Of the 188 randomized patients, 6 subjects had only baseline depression data and 6 additional subjects had baseline and 6-week data but no 12-week data. We imputed the missing 12-week outcomes using the last observation carried forward method.³³ Because there were no differences in the primary outcome assess-

ment, we present the 182 patients with at least baseline and 6-week data. All analyses were conducted according to group assignment regardless of whether patients complied with the intervention.

Baseline characteristics were reported and comparisons were made between the 2 treatment groups. Categorical data were reported as frequencies and relative frequencies (%), and differences between groups were compared with χ^2 or Fisher exact tests if the expected cell frequencies were less than 5. Continuous data were reported as the mean and SD, and the difference between groups were tested using 2-sample t tests.

Using the 12-week follow-up data, we calculated the within-subject changes in HAM-D and PHQ-9 from the baseline. Percent change of HAM-D and PHQ-9 scores from baseline to 12 weeks was also calculated to classify subjects as depression responders or remitters. Mean HAM-D and PHQ-9 scores and their pointwise 95% CIs were presented graphically for the 2 treatment groups over time. Regression models for repeatedly measured responses based on generalized estimating equations were used to accommodate the potential correlations among the measurements contributed by the same subject.

Finally, we analyzed the 12-week HAM-D score through a linear regression model adjusting for important covariates, including age, sex, race, whether the patient had a caregiver enrolled in the study, National Institutes of Health stroke severity score, comorbidity score, baseline HAM-D score, and the presence of major depression as defined by the structured clinical interview for *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*. To ensure the numeric stability of the model, we examined the variance inflation factors of the independent variables contained in the regression model. A variance inflation factors value of 10 or larger for an independent variable is usually considered an indication of multicollinearity involving the variable.³⁴ None of the variance inflation factors values were greater than 1.32 in the presented model.

Results

Of the 188 depressed subjects enrolled between April 9, 2001, and February 10, 2005, 182 (97%) are analyzed here (Figure 1); rate of study completion did not differ by treatment group. Five subjects (4 intervention and one control) had no follow up after baseline and one intervention group subject died between baseline and 6 weeks from an intracerebral and subdural hemorrhage. Six subjects (one intervention and 5 controls) had baseline and 6-week data only; these are included in the analysis using last observation carried forward methodology for the 12-week scores as described. Gender, race, age, depression diagnosis and severity, medical comorbidity, National Institutes of Health Stroke Scale score at study entry, and presence of a caregiver did not differ among the intervention and control groups (Table 1), and slightly more than one third of enrolled subjects were black. Fifty-two of the 93 control subjects (56%) took an antidepressant at some time during the 12-week study period; the majority of these prescriptions were for serotonin reuptake inhibitors.

Twelve-week depression outcomes are shown in Table 2. Intervention group subjects were more likely to have HAM-D-defined depression response at 12 weeks compared with usual care subjects (51% versus 30%, $P=0.005$). Intervention subjects also had significantly better outcomes by all other prespecified depression outcome criteria, including PHQ-9-defined depression response, HAM-D and PHQ-9-defined depression remission, and mean 12-week HAM-D and PHQ-9 scores. Figure 2 shows the mean HAM-D and PHQ-9 scores and 95% CIs by treatment groups over time, demonstrating that the depression scores separate by 6 weeks of

TABLE 1. Baseline Characteristics

	Intervention (N=89)	Control (N=93)	P Value
Demographic data			
Male	35 (39%)	48 (52%)	0.10
Race			1.0
White	54 (61%)	56 (60%)	
Black	32 (36%)	34 (37%)	
Other	3 (3%)	3 (3%)	
Mean (SD) age (years)	60 (13)	60 (11)	0.94
Caregiver enrolled*	55 (62%)	53 (57%)	0.51
Major depression†	64 (72%)	70 (75%)	0.61
Cumulative Illness Rating Scale score (comorbidity)	15.9 (5.1)	16.8 (4.7)	0.24
Baseline depression and stroke data (mean [SD] score)			
HAM-D	18.0 (5.4)	19.2 (5.9)	0.16
PHQ-9	14.0 (5.2)	14.4 (5.2)	0.54
National Institutes of Health Stroke Scale	2.5 (2.5)	2.8 (2.5)	0.32

*Percent with a family caregiver enrolled in the study.

†Major depression determined by structured clinical interview for *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* criteria.

treatment and remain significantly different at 12 weeks. Generalized estimating equations models confirmed significant group differences in both HAM-D and PHQ-9 scores at 6 as well as 12 weeks.

Even after adjusting for important covariates in the multivariate linear regression model, subjects in the intervention group had significantly lower 12-week HAM-D scores than usual care subjects ($P=0.037$). Additionally, 12-week HAM-D scores were lower in individuals with less severe depression (ie, lower baseline HAM-D scores, $P<0.001$), less medical comorbidity ($P<0.001$), older age ($P=0.003$), and

TABLE 2. 12-Week Depression Outcomes

Depression Outcome	Intervention (N=89)	Control (N=93)	P Value
HAM-D			
12-week mean (SD)	10.6 (6.9)	13.9 (7.8)	0.004
Mean (SD) change from baseline	-7.4 (7.2)	-5.4 (8.0)	0.07
Relative percent (SD) change from baseline	-39 (40)	-25 (42)	0.02
Response, n (%)*	45 (51)	28 (30)	0.005
Remission, n (%) (HAM-D <8)	35 (39)	21 (23)	0.01
PHQ-9			
12-week mean (SD)	6.0 (5.0)	9.4 (6.3)	<0.001
Mean (SD) change from baseline	-8.0 (6.2)	-5.0 (6.4)	0.002
Relative percent (SD) change from baseline	-55 (38)	-33 (43)	<0.001
Remission, n (%) (PHQ-9 <5)	43 (48)	24 (26)	0.002

*HAM-D score less than 8 or a 50% reduction in HAM-D score from baseline.

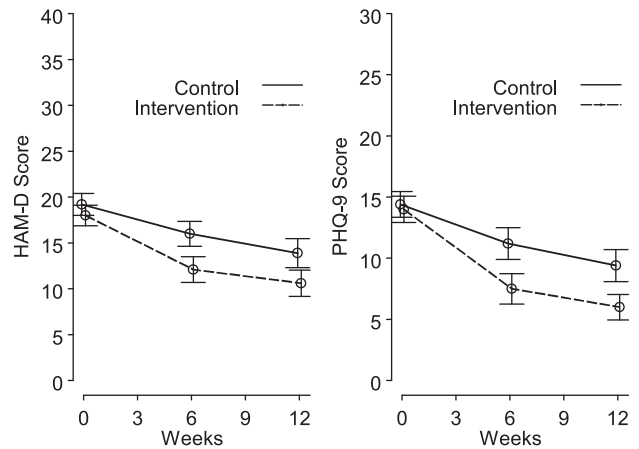


Figure 2. Change in mean HAM-D and PHQ-9 scores during the clinical trial showing significantly greater improvement in the intervention compared with the control group at both 6 and 12 weeks (all probability values ≤ 0.001). Values presented are group means at each visit with 95% CIs.

depressive diagnosis other than major depression ($P=0.03$). Gender, race, and the presence of an enrolled caregiver were not associated with 12-week HAM-D scores.

In total, 22 serious adverse events were reported in 17 subjects, but overall event rates were not significantly different between groups. There were 2 deaths in the intervention group related to secondary hemorrhagic stroke and one death in the control group resulting from myocardial infarction. Two intervention group subjects and one control subject had a seizure during the study period. During the 12-week intervention phase, 15 (16%) of intervention group subjects had antidepressant side effects bothersome enough to change medications, and 4 subjects changed medications more than once. The most common of the 39 side effects reported by these 15 subjects was sedation (14), followed by sexual (7), gastrointestinal (6), and anxiety (4) side effects.

Discussion

These data represent the largest randomized clinical trial of treatment for poststroke depression to date and demonstrate that care management of depression in patients with recent ischemic stroke results in greater remission of depression and reduction of depressive symptoms than usual care alone. The remission rate of 39% in our intervention group is comparable or superior to that reported in most antidepressant trials in nonstroke-related depression. This is important because some studies suggest depression may be more difficult to treat in patients with concomitant medical conditions.

Notably, the care management intervention proved superior to usual care despite the fact that nearly 60% of usual care subjects were also prescribed an antidepressant by their physician. Moreover, usual care subjects received an equal number of study contacts to control for the nonspecific effects of attention. For these 2 reasons, our results can be considered a conservative estimate of the treatment effect of a care management intervention for PSD. Our results also suggest that although some stroke survivors may respond to antidepressants alone, the addition of patient activation and telephone-based treatment monitoring that includes dose

adjustment and medication changes may further enhance the successful treatment of PSD. Recent evidence has shown change in antidepressant class for treatment-resistant patients may yield an additional 20% of patients with successful depression response.³⁵ Care management has also proven superior to usual care in improving depression outcomes in primary care and other populations.^{36–38} Although this is the first depression care management study demonstrating effectiveness on remission of depression poststroke, other care management studies have reported reduction of PSD symptoms (but not depression remission) in response to a family caregiver training intervention and to a comprehensive risk factor management intervention.^{39,40}

Our results are especially striking given that both groups had relatively moderate depression symptom severity overall as demonstrated by the mean baseline HAM-D score of 18 to 19. Lower overall depression severity in a clinical trial often may result in greater difficulty demonstrating separation between intervention and control groups, because more spontaneous remission can be expected in subjects with less severe depression. The Activate–Initiate–Monitor intervention was effective in subjects regardless of age or gender and was similarly effective in black and white subjects. As expected, those with less severe depression (ie, lower HAM-D scores at baseline or a depression diagnosis other than major depression) and those with less medical comorbidity were more likely to have lower 12-week HAM-D scores. Our finding that, despite a relatively high rate of exposure to antidepressants and the moderate initial depression severity, only 23% of usual care subjects had remission of their depression at 12 weeks suggests that PSD may be unlikely to spontaneously remit without treatment. Likewise, although our intervention was successful over 12 weeks, some patients may require longer treatment to achieve remission of depression. The rate of development of late-onset depression in patients who are nondepressed early after stroke is not well described, although those with more difficulties in social functioning may be particularly prone to develop late depression.^{1,41}

Antidepressant treatment was well tolerated with only 16% of intervention patients requiring a medication change during the first 12 weeks. This rate is generally comparable to other studies of antidepressant treatment in stroke survivors and in geriatric depression treatment trials.^{42,43} We did not observe a statistically significant increased risk of bleeding complications or seizures in the intervention group, although the group size, the relatively short period of follow up, and the fact that 60% of the usual care group also received antidepressant medications make statistical comparisons of medication side effects difficult. It is important to acknowledge that our subjects were slightly younger and had less physical impairment, especially aphasia and cognitive effects of stroke, than may be seen in other stroke samples. Thus, the effectiveness and tolerability of the intervention in such patients may differ from what we observed. We also did not screen patients for other concomitant mood disorders such as anxiety, which may be associated with PSD and may complicate depression treatment poststroke.

Overall, these data demonstrate that PSD can be effectively treated with standard antidepressant algorithms based on

current evidence-based guidelines for depression treatment. Our findings also suggest that PSD is as responsive to treatment as is depression associated with other serious medical conditions and that the rate of spontaneous remission of PSD in patients treated in a usual care setting is not high. Given the prevalence and impact of PSD, providers should consider active depression screening in this high-risk group and should provide guideline-adherent depression treatment, including dose and antidepressant class adjustments for stroke survivors with depression in the first few months after stroke.

Disclosures

None.

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