Preventing Depression After Stroke: Results From a Randomized Placebo-Controlled Trial

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Objective: We designed this study to determine whether the daily treatment of nondepressed acute stroke patients with sertraline reduced the incidence of depression at follow-up.

Method: 111 patients with recent stroke (< 2 weeks; *International Classification of Diseases*, Tenth Revision criteria) were randomly assigned to treatment with placebo (N = 56) and sertraline (N = 55, 50 mg once daily) in this double-blind, placebo-controlled 24-week clinical trial. Subjects were recruited from the 2 largest teaching hospitals of Western Australia between June 2002 and June 2004. The primary endpoint of interest was development of clinically significant depressive symptoms as assessed by a Hospital Anxiety and Depression Scale-depression subscale score of 8 or above, or as diagnosed by the treating physician during 24 weeks.

Results: There was no significant difference in the incidence of depressive symptoms during 24 weeks of treatment (16.7% [8/48] sertraline vs. 21.6% [11/51] placebo, rate ratio = 0.8, 95% CI = 0.3 to 2.1, p = .590). The trial medication was discontinued by 51.8% (29/56) of patients assigned placebo and 47.3% (26/55) assigned sertraline (p = .634), most often because of perceived side effects or because the treating physician introduced an antidepressant medication.

Conclusions: Twenty-four–week treatment with 50 mg of sertraline once daily initiated within 2 weeks of onset of acute stroke is not a significantly more effective strategy to prevent 6-month depression than usual care plus placebo among nondepressed stroke patients. New pharmacologic and nonpharmacologic strategies need to be developed to reduce the health and financial burden associated with depression after stroke.

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Stroke is a leading cause of morbidity and mortality in Western societies.[1] The long-term outcome of stroke patients is variable, but, as a group, only 40% are alive after 5 years.[2] Among the survivors, one third remain significantly disabled.[3] The results from observational studies suggest that depression is one of the factors that contributes to hinder recovery and increase mortality after stroke,[4–6] raising the possibility that, by preventing poststroke depression, one might also improve the general health outcome of patients.

Poststroke depression is common, affecting approximately 1 in every 3 survivors.[7] Surprisingly, however, only a small proportion of patients with depression are correctly diagnosed and treated.[8] There is preliminary evidence that treatment with antidepressants is associated with remission or partial improvement of depressive symptoms in stroke patients,[9] although the clinical relevance of those findings remains unclear.[10] A small number of trials have also investigated the effectiveness of antidepressant treatment in preventing depression after stroke. Anderson et al.[11] summarized their findings as follows: data were available for 479 patients, with only 5 of the 10 studies identified reporting data on the number of subjects who met criteria for depression at the end of the intervention. However, meta-analysis was not possible, and no firm conclusions could be drawn from the published data because of methodological shortcomings. They recommended that future trials should recruit participants early (within 4–6 weeks of onset of stroke), follow-up for at least 6 months, limit the number of outcomes measured (preferably use a binary outcome such as the presence or absence of depression at follow-up), and report on adverse events.[11]

We designed this randomized, double-blind, placebo-control trial to determine whether sertraline, a selective serotonin reuptake inhibitor started within 2 weeks of onset of stroke and continued for 24 weeks among patients without clinical evidence of depression, reduced the incidence of depression after 24 weeks.

METHOD

Participants

Subjects were recruited from the 2 largest teaching hospitals of Western Australia (Royal Perth Hospital and Sir Charles Gairdner Hospital, Perth, Western Australia) between June 2002 and June 2004. Acute ischemic or hemorrhagic strokes were diagnosed according to accepted guidelines (*International Classification of Diseases*, Tenth Revision). After informed consent was obtained, the trial medication was introduced within a period of up to 2 weeks after the stroke symptoms became apparent. None of the participants had alcohol dependence at the time of the assessment. We excluded patients with severe communication difficulties (aphasia or limited ability to communicate in English), unstable medical condition as determined by the treating physician, severe cognitive impairment (Mini-Mental State Examination [MMSE][12] score < 10), and depression (Hospital Anxiety and Depression Scale [HADS]-depression subscale [HADS-D] score > 7),[13,14] as well as those taking antidepressants (within 4 weeks of stroke) or who had a prior history of clinically significant adverse reactions to sertraline.

Treatment Allocation and Blinding

Subjects were allocated to 24-week treatment with placebo or sertraline (fixed daily dose of 50 mg at night) according to a computer-generated random list of numbers that was maintained centrally and independently by the pharmacist at the Royal Perth Hospital. Placebo and sertraline were purchased from the Royal Perth Hospital pharmacy. The lists were produced in random blocks of 8, 10, or 12 subjects to minimize the risk of unbalanced treatment groups and nonblinding. Placebo and sertraline were delivered in capsules that had the same size, shape, color, smell, and weight. Both the research team and participants were unaware of treatment allocation until the final endpoint was collected from the last participant enrolled into the study. Only 1 breach of protocol was recorded: treatment allocation was disclosed upon request from the treating physician and Ethics Committee after a participant developed seizures. Treatment was discontinued at the end of week 24.

Assessment Procedures and Instruments

The research nurse (A.W.) approached potential participants for consent and eligibility screening. Subjects were assessed at baseline (day 0, day in which the medication was initiated ± 2 days) and again 12, 24, 36, and 52 weeks after randomization.

Demographic and clinical information was systematically gathered at baseline with questions from section A of the Cambridge Examination for Mental Disorders of the Elderly (CAMDEX-R).[15] Hazardous or harmful drinking was defined as the use of 4 or more units of alcohol per day on a regular basis. Participants were considered physically active if they reported regularly engaging in any form of physical activity for 3 hours or more per week.

We used the HADS to ascertain mood at all timepoints, with an HADS-D subscale score of 8 or more indicating the presence of clinically significant depression. The research nurse read aloud all HADS items to participants, who then chose their most appropriate rating. In addition, the research nurse read aloud a checklist of perceived adverse events associated with the use of the trial medication to participants at weeks 12 and 24. The checklist (yes/no) included symptoms such as nausea, diarrhea, dyspepsia, insomnia, tremor, dry mouth, headache, skin rash, somnolence, sweating, agitation, dizziness, sexual dysfunction, and other. The MMSE and the Modified Rankin Scale (MRS)[16] were rated by the research nurse and provided measures of cognitive function and disability at baseline and at weeks 24 and 52. All participants were invited to return for assessment regardless of whether or not they were compliant with the treatment protocol.

Outcomes of Interest

The major endpoints of interest of this trial were the presence of clinically significant depressive symptoms as defined by an HADS-D score of 8 or more or prescription of an antidepressant by the treating physician at 24 weeks (primary endpoint of interest) or 52 weeks (secondary endpoint of interest). From the point of view of this study, these endpoints represent "intention to prevent depression failure." Other secondary outcomes of interest included changes in the HADS-D, MRS, and MMSE scores between baseline and weeks 24 and 52. The frequency of adverse events attributed to the trial medication, compliance with treatment (pill count), and prescription of antidepressants between baseline and week 52 were also recorded.

The Ethics Committees of the Royal Perth Hospital and Sir Charles Gairdner Hospital approved this study. All subjects provided written informed consent to participate.

Analysis of Data

The data were analyzed with the statistical package Stata, release 9.0 (StataCorp LP, College Station, Tex.). Analysis was by intention to treat. Descriptive statistics included frequencies, means, standard deviation of the mean, and ranges. Student t test was used to assess

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Table 1. Demographic and Clinical Characteristics of Participants With Diagnosis of Stroke at Study Entry According to Treatment Allocation Group

Variable	Placebo (N = 56)	Sertraline (N = 55)	p
Age, mean (SD), y	67.1 (13.0)	67.9 (13.4)	.728
Male, %	62.5	67.3	.598
Married or cohabiting, %	60.7	65.4	.605
Born in Australia/New Zealand, %	58.9	72.7	.126
Physically active, %	60.7	69.1	.355
Ever smoked, %	55.4	69.1	.136
Still smoking, %	38.7	26.3	.272
Hazardous/harmful drinking, %	10.7	16.4	.384
Diabetes, %	21.4	16.4	.496
Hypertension, %	42.9	52.7	.298
Previous heart attack, %	9.1	16.4	.252
Previous stroke, %	12.5	20.0	.284
Previous nervous illness, %	7.1	9.1	.707
No. of medications, median	5	5	.202
HADS-D score, mean (SD)	3.0 (2.4)	3.3 (2.3)	.601
MMSE score, mean (SD)	24.6 (4.3)	24.9 (3.9)	.694
MRS score, median	3	3	.370
MRS score > 3 (moderate/severe disability), %	21.4	32.7	.180

Abbreviations: HADS-D = Hospital Anxiety and Depression Scale-depression subscale, MMSE = Mini-Mental State Examination, MRS = Modified Rankin Scale.

between-group differences in age, MMSE scores, and HADS scores. We used the Mann-Whitney rank test (z statistic) to investigate between-group differences in the MRS. Frequency distribution of binary outcomes, such as being depressed or not, were tested using the χ^2 method of Pearson or, in the case of low expected cell numbers, the Fisher exact test (FET). Analysis of variance for repeated measures was used to investigate changes in HADS ratings over time. We used exponential regression (hazard ratio [HR]) to determine the difference in the cumulative proportion of participants prescribed an antidepressant over time according to treatment group. The respective 95% confidence interval (95% CI) of the HR was also estimated. Alpha was set at 5%, and all tests were 2-tailed.

RESULTS

A total of 981 patients were admitted to one of the study hospitals with diagnosis of acute stroke during the study period, of which 344 were identified as potentially eligible. Of those, 111 (32%) provided informed consent to participate (153 did not consent and 80 were discharged before they could be approached by the research nurse). The mean age of participants was 67.5 years (SD = 13.2; range, 21 to 88 years), and 64.9% were men. They all lived independently in the community (alone or with others) prior to the stroke. Seven subjects had a hemorrhagic stroke and 104 an ischemic stroke. Table 1 summarizes participants' baseline demographic and clinical information according to treatment allocation.

Primary Endpoint: Clinically Significant Depressive Symptoms at the End of the Treatment Period

By the end of the 24-week trial, the proportion of participants who were depressed (HADS-D score of 8 or more, or diagnosed with depression by the treating physician) was 21.6% (11/51) among patients assigned placebo and 16.7% (8/48) among those assigned sertraline (rate ratio [RR] = 0.8, 95% CI = 0.3 to 2.1, p = .590) (Table 2).

We also conducted completers (compliant with study protocol and not treated with antidepressant by a general practitioner) and last-observation-carried-forward (LOCF) analyses to investigate the primary endpoint of interest for this study (diagnosis of depression based solely on HADS scores). There was no difference between treatment groups in the frequency distribution of patients with depression in the completers (FET, p = 1.000) and LOCF analyses (FET, p = 1.000).

Secondary Endpoints of Interest

There was no significant difference between the groups in the way their HADS-D scores changed between baseline and week 24 (Table 2). Of the available 50 (placebo) and 44 (sertraline) patients followed up for 52 weeks, 30.0% (N = 15) and 22.7% (N = 10), respectively, met the study criteria for depression (RR = 0.8, 95% CI = 0.3 to 1.8, p = .506). Analysis of variance for repeated measures showed that the intervention had no obvious impact on the evolution of HADS-D scores from baseline to week 52 (including measurements at 12, 24, and 36 weeks) (F = 0.07, df = 1, p = .796). There was also no interaction between time and treatment group (F = 0.97, df = 4, p = .425).

Six controls and 11 patients in the sertraline group were not contactable by the end of week 52. Table 2 reports the proportion of patients who discontinued the trial medication and were prescribed an antidepressant drug during the 24-week treatment period. A large proportion of subjects in both treatment groups discontinued the use of the trial medication, most often due to perceived side effects or because the treating practitioner introduced an antidepressant medication (Tables 2 and 3). There was no significant difference between patients treated with placebo and sertraline in the hazard of being prescribed an antidepressant during follow-up (HR = 0.58, 95% CI = 0.26 to 1.27, p = .168) (Figure 1). Treatment with sertraline was not superior to placebo on cognitive and disability outcomes or mortality (Table 2). All participants who took the medication for 24 weeks consumed at least 85% of the prescribed tablets (i.e., they were all considered compliant).

DISCUSSION

In this study, treatment of nondepressed acute stroke patients with 50 mg of sertraline for 24 weeks failed to significantly reduce the point prevalence of clinically significant depressive symptoms at 24 and 52 weeks compared to

Table 2. Clinical Outcomes of Participants With Diagnosis of Stroke According to Treatment Allocation Group

Outcome	Placebo	Sertraline	p[a]
Primary endpoint			
Depressed at week 24, N/N (%)[b]	11/51 (21.6)	8/48 (16.7)	.536
Secondary outcomes of interest			
Change in HADS-D score between week 24 and baseline, mean (SD)	–0.2 (3.1)	–0.1 (2.4)	.794
Increase greater than 50% on HADS-D score between baseline and week 24, N/N (%)	10/51 (19.6)	13/47 (27.7)	.347
Depressed at week 52, N/N (%)[c]	15/50 (30.0)	10/44 (22.7)	.426
Change in HADS-D score between week 52 and baseline, mean (SD)	0.1 (3.1)	–0.7 (2.9)	.199
Prescribed antidepressant between baseline and week 24, N/N (%)	8/56 (14.3)	4/55 (7.3)	.234
Discontinued trial medication by week 24, N/N (%)	29/56 (51.8)	26/55 (47.3)	.634
Reasons for discontinuing medication by week 24, N/N (%)			.827
Became depressed	2/29 (6.9)	2/26 (7.7)	
Perceived side effects	9/29 (31.0)	11/26 (42.3)	
Medical advice	12/29 (41.4)	6/26 (23.1)	
No reason given	4/29 (13.8)	5/26 (19.2)	
Not contactable	2/29 (6.9)	2/26 (7.7)	
Change in MMSE score between week 24 and baseline, mean (SD)	2.6 (3.9)	2.6 (3.0)	.979
Change in MMSE score between week 52 and baseline, mean (SD)	2.7 (3.5)	3.3 (2.8)	.517
MRS score > 3 (moderate/severe disability at week 24), N/N (%)	0/56 (0)	0/55 (0)	
MRS score > 3 (moderate/severe disability at week 52), N/N (%)	1/50 (2.0)	0/44 (0)	1.000
Dead by week 52, N/N (%)	1/52 (1.9)	2/48 (4.2)	.606

[a]Probability according to Pearson's χ^2 statistic or Student t test.
[b]Presence of clinically significant depressive symptoms established by a HADS-D score ≥ 8 at week 12 or 24 or prescription of an antidepressant by the treating physician.
[c]Presence of clinically significant depressive symptoms established by a HADS-D score ≥ 8 at week 12, 24, 36, or 52 or prescription of an antidepressant by the treating physician.
Abbreviations: HADS-D = Hospital Anxiety and Depression Scale-depression subscale, MMSE = Mini-Mental State Examination, MRS = Modified Rankin Scale.

placebo. Sertraline use also had no significant impact on disability or cognitive function at 1 year.

These findings should be interpreted in light of the design of the study and in the context of previously published data on this topic. First, our definition of depression was based on accepted cut points for the HADS-D[14] and the clinical impression of the treating general practitioner. Although this approach reflects what happens in real clinical practice to poststroke patients, we accept that its validity may be questioned. We have previously shown that the diagnosis of depression in Western Australian general practices has high positive but low negative predictive values.[17] This finding would suggest that the cases of depression identified by the general practitioner are likely to have been "true cases." Moreover, the prevalence of depression after stroke observed in our study was very similar to that reported by Burvill et al.[18] in this community and consistent with published estimates worldwide.[7]

Second, our study may not have been sufficiently powered to reliably detect the anticipated reduction in the rate ratio of depression among treated patients. Our results showed a lower incidence of depression (21.6% [placebo] and 16.7% [sertraline]) at 6 months compared with the reported 33% by Hackett et al.[7] and lower point estimate of reduction in the relative risk (RRR) of depression of only 20% (95% CI = –76% to 64%). One reason for the lower rate of depression observed in our patients was that 32% of patients assigned placebo and 18% of subjects assigned sertraline were started on antidepressants by their physician during the treatment period (Figure 1). This may have been due, at least in part, to Hawthorne effect. Reasons for the lower than expected treatment effect of sertraline included the higher proportion of crossovers to active antidepressant treatment in the placebo group (32% [16/50]) than the sertraline group (18% [8/44]) and a high proportion of discontinuation of the trial medication among participants. These factors are likely to have compromised statistical power for efficacy, and our sample size was probably not sufficiently large to reliably determine whether the observed treatment effect of a 20% RRR was a real or chance finding (the same rationale applies to the hazard of being prescribed an antidepressant). However, a post hoc analysis based on available data for subjects who used the trial medication for 24 weeks revealed that 500 people would need to be treated with sertraline to avoid 1 case of depression by the end of 6 months. This finding suggests that treatment with sertraline is unlikely to be a cost-effective approach to prevent depression after stroke.

Other preventive trials have produced similar results. Palomäki et al.[19] treated 71 stroke patients with 60 mg per day of mianserine or placebo for 1 year and found that there was no between-group difference in the prevalence of depression at 0, 2, 6, 12, and 18 months (prevalent cases of depression were included in the sample). Likewise, Robinson et al.[9] treated poststroke rehabilitation patients with placebo (N = 17), fluoxetine (N = 23, up to 40 mg), or nortriptyline (N = 16, up to 100 mg) for 12 weeks. Subjects were recruited 6 months after the stroke, and prevalent cases of depression may have been included in

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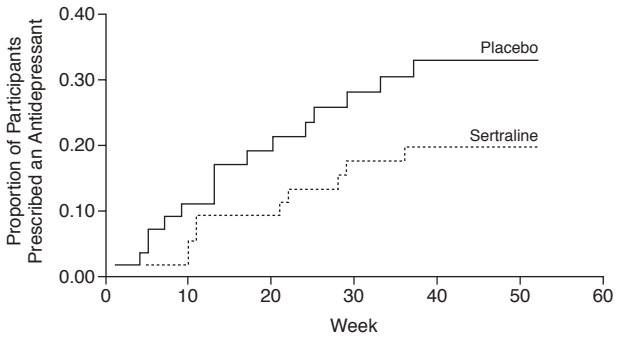
Table 3. Proportion of Participants With Diagnosis of Stroke Reporting Side Effects Associated With the Trial Medication

Side Effect	Placebo, N/N (%)	Sertraline, N/N (%)	p[a]
Reported at week 12			
Nausea	4/44 (9.1)	11/48 (22.9)	.073
Diarrhea	2/44 (4.5)	6/48 (12.5)	.176
Dyspepsia	3/44 (6.8)	10/48 (20.8)	.054
Insomnia	5/44 (11.4)	6/48 (12.5)	.867
Tremor	0/44 (0.0)	6/48 (12.5)	.027
Dry mouth	13/44 (29.5)	12/48 (25.0)	.624
Headache	8/44 (18.2)	7/48 (14.6)	.641
Skin rash	3/44 (6.8)	1/48 (2.1)	.346
Somnolence	6/44 (13.6)	8/48 (16.7)	.686
Sweating	1/44 (2.3)	2/48 (4.2)	1.000
Agitation	2/44 (4.5)	4/48 (8.3)	.679
Dizziness	5/44 (11.4)	3/48 (6.2)	.473
Sexual dysfunction	0/44 (0.0)	0/48 (0.0)	
Other	5/44 (11.4)	6/48 (12.5)	.867
Reported at week 24			
Nausea	1/31 (3.2)	2/30 (6.7)	.612
Diarrhea	1/31 (3.2)	1/30 (3.3)	1.000
Dyspepsia	1/31 (3.2)	3/30 (10.0)	.354
Insomnia	1/31 (3.2)	1/30 (3.3)	1.000
Tremor	0/31 (0.0)	7/30 (23.3)	.005
Dry mouth	6/31 (19.3)	6/30 (20.0)	.949
Headache	3/31 (9.7)	3/30 (10.0)	1.000
Skin rash	0/31 (0.0)	1/30 (3.3)	.492
Somnolence	2/31 (6.4)	4/30 (13.3)	.425
Sweating	2/31 (6.4)	4/30 (13.3)	.425
Agitation	1/31 (3.2)	7/30 (23.3)	.026
Dizziness	2/31 (6.4)	3/30 (10.0)	.614
Sexual dysfunction	0/31 (0.0)	2/30 (6.7)	.229
Other	5/31 (16.1)	2/30 (6.7)	.425

[a]Probability according to Fisher exact test.

Figure 1. Cumulative Proportion of Participants With Diagnosis of Stroke Prescribed an Antidepressant According to Treatment Group[a]



[a]Hazard ratio (exponential regression) = 0.58 (95% CI = 0.26 to 1.27), $\chi^2 = 1.90$, df = 1, p = .168.

the sample. There was no difference between the study groups in the prevalence of depression at any timepoint. Narushima et al.[20] later reported that poststroke patients treated with nortriptyline were more likely to develop a depressive episode once the medication was discontinued after 3 months but, again, the number of patients available was small (13 patients treated with nortriptyline, 13 treated with fluoxetine, and 15 treated with placebo), and no conclusions could be firmly drawn from the study.

Rasmussen et al.[21] randomly assigned poststroke patients to 12-month treatment with either placebo (N = 67) or sertraline (N = 70, up to 150 mg, mean daily dose of 62.9 mg, 78.6% treated with 50 mg). There was no significant difference between the groups after 12 months of treatment. More recently, Niedermaier et al.[22] reported the results of a placebo-controlled trial of mirtazapine (up to 45 mg/day) for the prevention of depression after stroke (N = 70). People treated with mirtazapine were 11 times (95% CI = 2.1 to 105.9) less likely to become depressed during the subsequent 1 year than placebo-treated controls. The study was open-label, and the allocation of participants was not random (alternate assignment).

Studies investigating depression in later life found that poor response to treatment is associated with increasing severity of cerebrovascular disease.[23] If this is the case, one might expect poststroke depression not to respond as well to treatment as depression not associated with a somatic illness. Indeed, a systematic review of available studies found that there was no evidence that antidepressant treatment was associated with remission of depressive symptoms after stroke.[10] Finally, the recently published results of the National Institute of Mental Health Collaborative Depression Study indicate that pharmacologic antidepressant treatment may not be sufficient to avoid the recurrence of depression in people at high risk.[24] These observations are consistent with the findings of our study and would argue against the systematic use of antidepressant drugs to prevent depression after stroke.

This study has strengths that merit comment. The procedures for randomization and blinding were rigorously adhered to, participants were recruited into the trial during the acute phase of the stroke (maximum of 2 weeks), and all participants were free of depressive symptoms at the time they started taking the trial medication. In addition, standard criteria for the diagnosis of stroke were used, key outcomes were clearly defined, and adverse events were systematically recorded. Importantly, subjects continued being followed up regardless of whether or not they were compliant with the trial medication. This process enabled us to carry out intention-to-treat analyses using real rather than statistical follow-up data (such as LOCF).

One of the potential limitations of the study includes the use of a fixed dosage of sertraline, although a previous study using up to 150 mg of the drug was also unable to demonstrate a significant difference of outcomes in relation to placebo.[21] We also acknowledge that the study sample may not adequately represent the population of stroke patients: they are likely to have had less severe and debilitating strokes than people who did not join the study. This factor could potentially have led to a "healthy participant" bias, with participants being less likely than

nonparticipants to become depressed or develop significant morbidity at follow-up. The low mortality rate observed among study subjects would be consistent with such a possibility. On the other hand, one might argue that a preventive strategy can only work for those who remain alive. Finally, the relatively poor compliance with the trial medication may raise questions as to the validity of our results (i.e., excessively negative), although our rates are entirely consistent with the adherence rates to antidepressant treatment reported by several other studies in clinical practice (up to 52% noncompliance at 3 months).[21,25] Therefore, we would suggest that our approach to the analyses of the data was conservative, particularly because poor compliance indicates that this type of "prevention" is not acceptable to a large proportion of stroke patients, regardless of whether they were being treated with placebo or sertraline. Of note, a number of new drugs are often introduced after stroke (such as warfarin, aspirin, clopidogrel), which may increase the reluctance of patients to add yet another medication to their treatment regimen, particularly when this medication is seen as being of no immediate clinical relevance.

In summary, 24-week treatment with 50 mg of sertraline once daily initiated within 2 weeks of onset of acute stroke was not a significantly more effective strategy to prevent depression than usual care plus placebo among nondepressed stroke patients. New pharmacologic and nonpharmacologic strategies need to be developed to reduce the health and financial burden associated with depression after stroke.

Drug names: clopidogrel (Plavix and others), fluoxetine (Prozac and others), mirtazapine (Remeron and others), nortriptyline (Pamelor, Aventyl, and others), sertraline (Zoloft), warfarin (Coumadin, Jantoven, and others).

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