Curr Neurol Neurosci Rep (2013) 13:318
DOI 10.1007/s11910-012-0318-z

STROKE (HP ADAMS JR, SECTION EDITOR)

Use of Antidepressant Medications To Improve Outcomes After Stroke

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Published online: 14 December 2012

Abstract Interest in the use of antidepressants after stroke has been renewed by better knowledge of poststroke depression, but mainly by the capacity of some of them to promote functional recovery of nondepressed subjects. Recombinant tissue plasminogen activator thrombolysis within the first few hours after the stroke is currently the only validated treatment able to improve the spontaneous—and most of the time incomplete—recovery of neurological functions after stroke. However, we have learned from research over the last decade, in part based on the considerable improvement of neuroimaging techniques, that spontaneous recovery of neurological functions is associated with a large intracerebral reorganization of the damaged human brain. The question of whether lesioned-brain plasticity can be modulated by external factors such as pharmacological antidepressant agents is now being addressed with the aim of improving recovery and reducing the final disability of patients. Poststroke depression is known to be frequent and deleterious for patient outcome. We review the interest in the use of antidepressants after stroke in classic but often neglected poststroke depression and we strongly underline the action of some antidepressants in promoting functional recovery of nondepressed patients after stroke.

Keywords Stroke · Recovery · Depression · Antidepressants · Fluoxetine · Brain plasticity · Motor function · Monoaminergic drugs

This article is part of the Topical Collection on *Stroke*

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Introduction

Recovery from stroke remains a worldwide major issue for public health policies. Clinicians have long recognized that most stroke survivors recover over time, albeit to differing degrees. Recombinant tissue plasminogen activator thrombolysis within the first 4.5 h after the stroke is currently the only validated and registered treatment able to improve the spontaneous—and most of the time incomplete—recovery of neurological functions after stroke. Recovery after a stroke has long been a puzzling question for clinicians and scientists as it is well known that neurons, when destroyed after ischemia, are not restored despite some very localized neurogenesis. In the past two decades, we have learned from modern neuroimaging techniques, mainly PET scanning and MRI, that the human brain is able to spontaneously reorganize after a stroke; recruitment of remote functional areas, overactivation of primary cortices, and changes in cortical maps are now known as the physiological basis of clinical recovery of neurological functions. Spontaneous lesioned-brain reorganization has been shown to be a rational basis for spontaneous recovery of neurological functions. The question of whether lesioned-brain plasticity can be modulated by external factors such as pharmacological agents is now being addressed with the aim of improving recovery and reducing the final disability of patients. These rely on induced functional changes in a damaged intracerebral network. The pharmacological agents require extensive validation. Preclinical studies mainly using small-animal models have shown that monoaminergic drugs can modify functional recovery [1–3]. This is particularly the case for some antidepressant drugs. From this approach, selective serotonin reuptake inhibitors (SSRIs) were tested and their suspected positive action in the recovery process was recently proved in patients in the FLAME trial.

Depression is also a major issue for stroke patients. It is a common poststroke complication affecting approximately one third of patients and is likely to interfere with the

patient's neurological condition. The highest rates of incident depression are reported early in the first month after stroke and, although the incidence may decline over time and there may be a general trend toward improvement of symptoms, poststroke depression may persist in a significant proportion of individuals. The diagnosis of poststroke depression is not easy most of the time as the interpretation of clinical symptoms is more difficult in the context of stroke. There appears to be less emphasis on feelings of low self-esteem, guilt, and self-blame when depression accompanies stroke, whereas there is more emphasis on hypochondrial concerns, lethargy, and behavior disturbances. Two main possible explanations for the association between physical illness and depression can be proposed. The first is a negative mood reaction to the physical consequences of the stroke. The second possible explanation is a neurotransmitter imbalance as a result of cerebral damage caused by the stroke [4–6••]. Epidemiologic observational studies have provided a realistic approach for assessing stroke depression prevalence risk factors and predictors. Robinson [7] showed that the mean prevalence of depression among inpatients in acute or rehabilitation settings was 19.3 % and 18.5 % for major and minor depression, respectively, whereas in outpatient studies, the mean reported prevalence was 23.3 % for major depression and 15 % for minor depression. Moreover, persistent depression was detected in more than half (55 %) of the individuals identified as depressed during inpatient rehabilitation after stroke [8]. Some risk factors associated with increased risk of poststroke depression have been isolated as female sex, past history of depression or psychiatric illness, persistent neurological deficit, and cognitive impairment. Prior treatment of depression and the need for assistance with activities of daily living may be the factors most predictive of risk. Predictors of persistent depression include lower levels of prestroke social activity, greater severity of stroke, and lower levels of function at the baseline [9–17]. These aspects have been extensively developed in a recent and remarkable review by Salter et al. [6••].

We will review two main aspects regarding the use of antidepressants in patients with stroke:

1. Interest in the use of antidepressants in patients with stroke and depression with regard to the potential interference between depression and recovery
2. Interest in the use of antidepressants in patients with stroke but without depression, which appears to be a new promising approach for treatment of stroke patients

Antidepressants in Poststroke Depression

At least one third of stroke patients will experience depression. The question of the links between poststroke depression and recovery has a major impact on patient care. Most of the time neurologists find it difficult to diagnose poststroke depression. Linguistic difficulties in aphasic patients with left hemispheric lesions, neglect and its cognitive consequences in patients with right hemispheric lesions, and preexisting memory disturbances often prevent or delay an appropriate diagnosis of depression. On the other hand, poststroke depression has to be differentiated from the initial mood consequence of the acute neurological deficit and according to the fourth edition of the *Diagnostic and Statistical Manual of Metal Disorders* it is difficult to make the diagnosis of poststroke depression in the very acute phase before 2 weeks. Finally, the scales used in this context are not designed for stroke patients, and most of the time the diagnosis relies on the conviction of th clinician. So the studies mentioned in this article must be interpreted with regard to those difficulties. However and despite the limitations, it is possible to address three main questions:

1. Does poststroke depression reduce poststroke recovery?
2. Are antidepressants active in poststroke depression?
3. Can antidepressants improve stroke outcome in patients with depression?

Poststroke Depression Has a Negative Impact on Functional Recovery

Depression after stroke may have a negative impact on recovery. Although patients with poststroke depression often experience significant recovery, functional ability may remain at a lower level than in nondepressed patients, despite rehabilitation interventions. Goodwin and Devanand [17] demonstrated that co-occurrence of stroke and depression is associated with greater physical limitations than either condition on its own. Physical impairment and poststroke depression appear to act upon each other, and each influences the recovery of the other. Van de Port et al. [18] published the results of a prospective cohort study (n=205) which demonstrated that mobility decline was experienced by 21 % of participants between 1 and 3 years after stroke. Significant predictors of this decline in mobility status were level of activity, cognitive problems, fatigue, and depression. So, it can be said that poststroke depression has a negative impact on functional recovery. As a consequence, early identification and treatment of poststroke depression may serve to enhance functional recovery. Moreover, poststroke depression interferes with cognitive performances and depression may appear to be associated with definitive cognitive decline, whereas cognitive disturbances may be most of the time mainly the transient consequences of depression.

Antidepressants and Treatment of Poststroke Depression

Drug therapy for depression is based on the notion that depression is associated with an imbalance and underactivity of the cerebral noradrenergic and serotonergic systems. In a meta-analysis of 16 studies examining the use of antidepressants in individuals with poststroke depression, Chen et al. [5] reported a significant treatment response regardless of the definition of response used by the authors of individual studies. In addition, treatment was associated with a significant reduction in depressive symptoms on all scales used to assess outcome. Chen et al. [5] also identified a relationship between the duration and benefit of treatment. Pooled analysis of studies with treatment durations of 1 and 2 weeks revealed no significant treatment effects. However, from 3 weeks onward, demonstrated effects were, generally, of increasing significance. In an updated Cochrane review, Hackett et al. [4] included 12 studies examining the use of pharmacological interventions for the treatment of poststroke depression. Like the review of Chen et al. [5], Hackett et al. [4] included trials examining a variety of agents initiated at a variety of times after stroke and for various intervals. Using pooled analysis where possible, the authors concluded that use of pharmacotherapy was globally associated with a significant, positive treatment effect. Within drug categories, there is strong evidence that heterocyclic antidepressants improve depression after stroke. Side effects in elderly patients mean that these medications should be used with caution in that population. On the basis of the results of meta-analyses, there is also strong evidence that SSRIs are effective in the treatment of poststroke depression. On the other hand, regarding the use of selective noradrenaline reuptake inhibitors (SNRIs), there is only moderate evidence that reboxetine is effective in reducing retarded poststroke depression and there is an absence of evidence regarding the effectiveness of venlafaxine, an SNRI, for treatment of poststroke depression. Finally, the GABA compound nefiracetam and the psychostimulant methylphenidate showed only moderate evidence of improving depression symptoms [19–30].

Antidepressants and Stroke Outcome in Patients with Depression

As mentioned earlier, depression has a negative impact on recovery of neurological function and thus the appearance of poststroke depression is believed to adversely affect the rate of recovery and rehabilitation of stroke survivors. A study by Gainotti et al. [31] demonstrated that treatment with fluoxetine was associated with an improvement in functional recovery in addition to recovery from depression; a finding which is supported by other studies [20, 30, 32–34]. Although several studies also documented the effectiveness of treatment with nortriptyline in terms of physical function, Miyai and Reding [32] noted that trazodone and fluoxetine improved self-care function and depression after stroke, whereas nortripyline improved only depression. In addition, the effect of the timing of treatment on the recovery of activities of daily living requires further investigation. Although most studies have examined the effectiveness of treatment initiated more than 1 month after stroke, some of them [30, 33] focused on treatment beginning in the first month following the stroke. Gonzalez-Torrecillas et al. [30], in an open-label study, demonstrated that early treatment, initiated within 4 weeks of the index event, was associated with significant improvements in physical, cognitive, and neurological function by the end of the 6-week treatment period. Similarly, Narushima et al. [33] reported a significantly greater improvement in physical function over the active treatment period (12 weeks) for patients with early initiation of treatment (within 4 weeks of stroke) than for patients whose treatment started later. Recently, a secondary analysis of data collected as part of the Activate–Initiate–Monitor (AIM) study demonstrated that individuals who reported improvement of depressive symptoms were more likely to be independent at 12 weeks after stroke than those who did not improve over the same period [35]. It is now admitted that there is strong evidence for pharmacological treatment of depression and improved functional recovery after stroke being closely associated.

Antidepressants for Recovery from Stroke in Nondepressed Patients

If it is true that depression will occur in about one third of patients with stroke, as a consequence, it is also obvious that two thirds of them will not experience poststroke depression. The question of the use of antidepressants in this category of nondepressed patients with stroke needs to be addressed as we have strong arguments showing that some antidepressants may act directly on the damaged neuronal networks and may modulate spontaneous poststroke intracerebral reorganization. This question of whether lesioned-brain plasticity can be modulated by external factors such as pharmacological agents is now being addressed with the aim of improving recovery and reducing the final disability of patients. Preclinical studies mainly using small-animal models have shown that monoaminergic drugs can modify functional recovery. This is particularly the case for noradrenergic, dopaminergic, and serotoninergic drugs, which have been shown to facilitate cerebral postlesional reorganization, whereas other drugs such as neuroleptics and benzodiazepine would prevent it. From this approach, SSRIs were tested in small clinical trials and their suspected positive action in the recovery process was recently shown in the FLAME trial with fluoxetine [1, 36••]

SSRIs and Motor Recovery After Stroke

Small Trials

Few clinical trials with serotonin reuptake inhibitors have been reported. They have all included small numbers of patients; all have produced results that suggest a positive effect on recovery after stroke. In an early trial, fluoxetine and maprotiline were tested against placebo for 3 months in patients with hemiplegic stroke enrolled 1–6 months after the stroke [34]. The patients in the fluoxetine group (n=16] had a better outcome than those in the maprotiline group or the placebo group. Acler et al. [37] confirmed this finding in ten patients in the active-treatment group versus ten in the placebo group. In a double-blind, placebo-controlled crossover trial, Zittel et al. [38] investigated the effects of a single dose (40 mg) of citalopram in eight patients with chronic stroke. Dexterity was significantly improved.

Proof of Concept

In a double-blind, placebo-controlled study by our group [39], by combining clinical motor testing and functional MRI motor assessment in patients recovering from post-stroke hemiplegia (n=8), we showed that a single dose (20 mg) of fluoxetine improved hand motor function and was correlated with an overactivation of motor cortices on functional MRI. In a subsequent double-blind, placebo-controlled trial in healthy individuals, transcranial magnetic stimulation showed that the intake of a single dose of the serotonin reuptake inhibitor paroxetine was associated with hyperexcitability of the primary motor cortex, whereas long-term intake was associated with hypoexcitability of the brain motor cortices. Serotonin reuptake inhibitors increase interneuron-facilitating activity in the primary motor cortex. This study demonstrated that, in recovering stroke patients, a single dose of 20 mg transiently improved motricity and acted directly in overactivating motor cortices through a fluoxetine-induced change of cortical excitability [40].

FLAME Trial

The FLAME trial [36••] was designed to test the efficacy of fluoxetine in motor recovery of patients with ischemic stroke as hemiplegia and hemiparesis are the commonest deficits caused by stroke. The FLAME trial investigated whether fluoxetine would enhance motor recovery if given soon after an ischemic stroke to patients who had motor deficits.

In this double-blind, placebo-controlled trial, patients from nine stroke centers who had experienced an ischemic stroke, had hemiplegia or hemiparesis, had Fugl-Meyer motor scale (FMMS) scores of 55 or less, and were aged between 18 and 85 years were eligible for inclusion. Patients with depression were excluded. Patients were randomly assigned, using a computer random-number generator, in a 1:1 ratio, to fluoxetine (20 mg once per day, orally) or placebo for 3 months starting 5–10 days after the onset of stroke. All patients had physiotherapy. The primary outcome measure was the change on the FMMS between day 0 and day 90 after the start of administration of the drug or placebo. Participants, carers, and physicians assessing the outcome were masked to group assignment.

Analysis was done for all patients for whom data were available (full analysis set): 118 patients were randomly assigned to fluoxetine (n=59) or placebo (n=59), and 113 were included in the analysis (57 in the fluoxetine group and 56 in the placebo group). Two patients died before day 90 and three withdrew from the study.

FMMS score improvement at day 90 was significantly greater in the fluoxetine group [adjusted mean 34.0 points (95 % confidence interval 29.7–38.4)] than in the placebo group [24.3 points (95 % confidence interval 19.9–28.7); p=0.003]. The drug was well tolerated. Moreover the number of independent patients (modified Rankin scale 0–2 after 3 months of treatment) was higher in the fluoxetine group. The number of depressions occurring during the 3-month treatment period was lower in the fluoxetine group.

The mechanism of action of fluoxetine needs to be discussed. An effect of fluoxetine on mood is likely even in nondepressed people. However, we do not think that fluoxetine acted only through antidepressant mechanisms in this study. As mentioned earlier, a single dose of fluoxetine improved hand motor function and increased activity in the motor cortex compared with placebo in patients recovering from stroke, showing a specific motor effect, whereas a mood effect is unlikely after a single dose. However, a fluoxetine-mediated attention and/or a fluoxetine-mediated motivation effect cannot be excluded and needs to be investigated in further studies.

Nevertheless, the FLAME trial has limitations. The number of patients included was small. Those who were included were selected for motor deficit and did not represent the general population of stroke patients. Second, treatment was stopped after 90 days, and we have no idea of the long-term development of patients' motor function and whether the treatment effect persisted in the months after treatment was stopped. However, the effect of fluoxetine seems to be strong and clinically relevant, and the data from the trial show a global coherence.

The FLAME trial shows that in patients with ischemic stroke and moderate to severe motor deficit, the early prescription of fluoxetine with physiotherapy led to enhanced motor recovery after 3 months.

Long-Term Effects

In a subsequent study with citalopram, a population of poststroke depressed patients were treated for 3 months. Patients treated with antidepressants had better recovery from disability by 1 year after stroke (i.e., 9 months after antidepressants were stopped) than patients who did not receive antidepressant therapy. This effect was independent of depression and suggests a permanency of effect of the drug [41].

Ongoing Clinical Trials

Clinical investigations for recovery of patients with stroke using serotoninergic, dopaminergic, or noradrenergic drugs (most of them are antidepressant drugs) will continue, as those treatments (if validated) can bring about a new approach for our patients and new hope. The FLAIR phase III trial with fluoxetine in the USA and the LIFE phase IIb trial with the SNRI levomilnacipran in Europe are beginning now.

Antidepressants and Depression Prevention in Stroke Patients

Given the negative impact of poststroke depression on stroke recovery, early initiation of antidepressant treatment in stroke patients to prevent the development of poststroke depression has been investigated [42–45]. Overall, individual studies offer conflicting evidence with regard to prevention of poststroke depression through pharmacological intervention.

However, there appears to be a positive trend toward protection against depression associated with prophylactic treatment. As mentioned earlier, in the FLAME trial, the number of depressions occurring during the 3-month treatment period was lower in the fluoxetine group than in the placebo group.

There is now some evidence that early initiation of antidepressant therapy in nondepressed stroke patients is associated with reduced risk of the development of poststroke depression. However, systematic prescription is not recommended yet. Further study is required to assess both the duration of treatment and optimal timing for the initiation of therapy.

Other Antidepressants or Psychostimulants

Inconsistent but sometimes positive arguments can be found for the action of other drugs. Reboxetine inhibits the reuptake of noradrenaline. Ten chronic stroke patients receiving a single dose of 6 mg reboxetine were studied in a double-blind, placebo-controlled crossover design by Zittel et al. [46]. Grip strength, dexterity, and hand-tapping speed were evaluated before drug ingestion, 3 h after drug intake, and after a single session of physiotherapy aimed at improvement of hand function. In addition, motor excitability changes were investigated using transcranial magnetic stimulation. Reboxetine induced a significant improvement of tapping speed and grip strength. The dexterity and transcranial magnetic stimulation results remained unchanged.

On the other hand, moclobemide an inhibitor of monoamine oxidase A when compared with placebo (600 mg/day for 6 months), did not enhance the regression of aphasia following an acute stroke [47].

Methylphenidate produces an increase in dopamine signaling through multiple actions. As mentioned earlier, a prospective, randomized, double-blind, placebo-controlled trial with 21 patients early after stroke indicated that the combination of methylphenidate and physical therapy over a period of 3 weeks improved motor functions [28] and decreased depression. A subsequent neuroimaging study by Tardy et al. [29] confirmed these findings regarding motor function.

Summary of Clinical Trials

Currently, antidepressants can be considered as part of the treatment of many patients with stroke. The level of evidence differs for patients with poststroke depression and patients with stroke but no depression.

In poststroke depressed patients (one third of patients approximately), a review of the literature provides strong evidence in three main aspects: poststroke depression has a negative impact on functional recovery; pharmacological treatment has an effect on poststroke depression (mainly heterocyclic drugs and SSRIs); antidepressants improve stroke outcome in patients with depression.

In stroke patients with no depression, the field is now open for a new therapeutic strategy in stroke management with monoaminergic drugs, especially serotoninergic drugs and also noradrenergic and dopaminergic components. Some of them are not antidepressants but others clearly are. This is the case for SSRIs and fluoxetine. Currently, and other than the FLAME trial, there is only limited evidence supporting or refuting the use of centrally acting drugs to enhance the effects of neurorehabilitation. Many reasons can be underlined to explain the difficulties encountered by the investigators in published clinical trials with negative findings: recruitment of patients (25–40 screened on enrollment), heterogeneity in stroke types, size, location of lesion, concomitant neurological symptoms (within-subject variability in recovery), standardization of rehabilitation programs, dose of the drug, specific chemical formulation of the drug under study (D-amphetamines or DL-amphetamines), time of prescription, duration of the treatment, etc. Most

studies were performed in well-selected small patient groups and rather serve as a proof-of-principle investigation. The interpretation is sometimes further complicated by conflicting results. The FLAME trial with fluoxetine appears to be the first trial showing an efficacy in a target population of ischemic stroke patients. Despite its limited aspects, it shows that with an appropriate clinical trial design, it will be possible to demonstrate the capacity ot incapacity of monoaminergic drugs to modify the natural history of stroke and its outcome.

No regulatory agency will grant approval for use of such drugs until evidence is also provided by properly powered, formal, phase III clinical trials. Such trials would likely have to evaluate effects in the long term, and consider effects on function and disability.

Pharmacotherapy Mechanisms of Monoaminergic Drugs

The observed effects of a single dose can be explained by short-term plasticity. The mechanisms might include alleviation of metabolic depression, stimulation of sensorimotor pathways, increase in cortical excitability, and partial reestablishment of interhemispheric inhibition between both primary motor cortices [29, 39, 40]. In analogy with amphetamine, monoaminergic drugs can increase the signal-to-noise ratio, i.e., the ratio between task-dependent activity and tonic activity. If this is applied to poststroke recovery, drugs could increase adaptive brain activity in a compensatory network. More specifically, dopamine through attention and reward may reinforce associative learning, and the effects of dopamine drugs might be mediated through dopamine projections to cerebral areas related to these functions. Noradrenaline modulates saliency of sensory inputs, attention, and memory. One additional hypothesis is that a primary function of the serotoninergic system of the brain is to facilitate motor output ,which underlines the fact that drug intake would be more efficient when paired with training [48]. Further, serotonin enhances arousal and vigilance and enhances energetic supply by stimulating glycogenolysis. Serotonin is also involved in spatial memory acquisition, learning, consolidation, short-term facilitation (enhancement of transmitter release), storage of long-term memory in *Aplysia* sensorimotor synapses, and long-term facilitation (growth of new synaptic contacts between sensory and motor neurons and facilitation of synaptic strength), growth factor gene expression, declarative memory, and the associated hippocampal neurogenesis in animals and humans [49, 50]. All monoamines (norepinephrine, dopamine, serotonin), and acetylcholine, may drive long-term potentiation, optimize activity-dependent learning in humans, and possibly relearning after stroke. Finally, even though there is no ongoing current development, amphetamine takes part in postlesional remodeling of motor areas through noradrenergic modulation.

Conclusions

Antidepressants are useful in the care management of patients with stroke. This is particularly the case in post-stroke depressed patients. Poststroke depression needs to be carefully detected and treated in order to optimize recovery of neurological functions. However, a new aspect of antidepressant use (mainly SSRIs) is emerging. The SSRI fluoxetine has been demonstrated to improve motor recovery of patients with hemiplegic stroke through a direct neuronal mechanism related to cortical excitability changes. The modulation of brain spontaneous postlesional reorganization by monoaminergic antidepressants opens up a new field in stroke care through a neuronal nonvascular target.

Disclosure No potential conflicts of interest relevant to this article were reported.

References

Papers of particular interest, published recently, have been highlighted as:
•• Of major importance

1. Loubinoux I, Chollet F. Neuropharmacology in stroke recovery. In: Cramer SC, Nudo RJ, editors. Brain repair after stroke. Cambridge: Cambridge University Press; 2010. p. 183–93.
2. Goldstein LB. Influence of common drugs and related factors on stroke outcome. Curr Opin Neurol. 1997;10:52–7.
3. Liepert J. Pharmacotherapy in restorative neurology. Current Opin Neurol. 2008;21:639–43.
4. Hackett ML, Anderson CS, House A, Xia J. Interventions for treating depression after stroke. Cochrane Database of Systematic Reviews 2008, Issue 4. Art. No.: CD003437. doi:10.1002/14651858.CD003437.pub3.
5. Chen Y, Patel NC, Guo JJ, Zhan S. Antidepressant prophylaxis for poststroke depression: a meta-analysis. Int Clin Psychopharmacol. 2007;22(3):159–66.
6. •• Salter K, Bhogal S, Teasell R, Foley N, Speechley M. Post-stroke depression. The evidence-based review of stroke rehabilitation (EBRSR) Version 15. http://www.ebrsr.com/uploads/Depression-SREBR-15_1.pdf. *Exhaustive review of the relationships between stroke and depression*.
7. Robinson RG. Poststroke depression: prevalence, diagnosis, treatment and disease progression. Biol Psychiatry. 2003;54:376–87.
8. Farner L, Wagle J, Engedal K, Flekkoy KM, Wyller TB, Fure B. Depressive symptoms in stroke patients: a 13 month follow-up study of patients referred to a rehabilitation unit. J Affect Disord. 2010;127(1–3):211–8.
9. Astrom M, Adolfsson R, Asplund K. Major depression in stroke patients: a 3-year longitudinal study. Stroke. 1993;24(7):976–82.
10. Berg A, Psych L, Palomaki H, et al. Poststroke depression—an 18-month follow-up. Stroke. 2003;34(1):138–43.
11. Paolucci S, Gandolfo C, Provinciali L, Torta R, Toso V. The Italian multicenter observational study on post-stroke depression (DESTRO). J Neurol. 2006;253:556–62.
12. Paolucci S, Gandolfo C, Provinciali L, Torta R, Sommacal S, Toso V. Quantification of the risk of post-stroke depression: the Italian

multicenter observational study DESTRO. Acta Psychiatr Scand. 2005;112:272–8.
13. Hackett ML, Anderson CS. Frequency, management, and predictors of abnormal mood after stroke: the Auckland Regional Community Stroke (ARCOS) study, 2002 to 2003. Stroke. 2006;37:2123–8.
14. Hackett ML, Anderson CS. Predictors of depression after stroke: a systematic review of observational studies. Stroke. 2005;36:2296–301.
15. Bour A, Rasquin S, Aben I, Boreas A, Limburg M, Verhey F. A one-year follow-up study into the course of depression after stroke. J Nutr Health Aging. 2010;14:488–93.
16. Carota A, Berney A, Aybek S, et al. A prospective study of predictors of poststroke depression. Neurology. 2005;64:428–33.
17. Goodwin RD, Devanand DP. Stroke, depression, and functional health outcomes among adults in the community. J Geriatr Psychiatry Neurol. 2008;21:41–6.
18. Van de Port I, Kwakkel G, van WI, Lindeman E. Susceptibility to deterioration of mobility long-term after stroke: a prospective cohort study. Stroke. 2006;37:167–71.
19. Robinson RG, Schultz SK, Castillo C, Kopel T, Kosier JT, Newman RM, Curdue K, Petracca G, Starkstein SE. Nortriptyline versus fluoxetine in the treatment of depression and in short-term recovery after stroke: a placebo-controlled, double-blind study. Am J Psychiatry. 2000;157:351–9.
20. Finklestein SP, Weintraub RJ, Karmouz N, Askinazi C, Davar G, Baldessarini RJ. Antidepressant drug treatment for post stroke depression: retrospective study. Arch Phys Med Rehabil. 1987;68:772–6.
21. Lauritzen L, Bendsen BB, Vilmar T, Bendsen EB, Lunde M, Bech P. Post-stroke depression: combined treatment with imipramine or desipramine and mianserin. A controlled clinical study. Psychopharmacology (Berl). 1994;114:119.
22. Robinson RG, Jorge RE, Clarence-Smith K. Double-blind randomized treatment of poststroke depression using nefiracetam. J Neuropsychiatry Clin Neurosci. 2008;20:178–84.
23. Kucukalic A, Bravo-Mehmedbasic A, Kulenovic AD, Suljic-Mehmedika E. Venlafaxine efficacy and tolerability in the treatment of post-stroke depression. Psychiatr Danub. 2007;19:56– 60.
24. Choi-Kwon S, Choi J, Kwon SU, Kang DW, Kim JS. Fluoxetine improves the quality of life in patients with poststroke emotional disturbances. Cerebrovasc Dis. 2008;26(3):266–71.
25. Choi-Kwon S, Han SW, Kwon SU, Kang DW, Choi JM, Kim JS. Fluoxetine treatment in poststroke depression, emotional incontinence, and anger proneness: a double-blind, placebo-controlled study. Stroke. 2006;37:156–61.
26. Wiart L, Petit H, Joseph PA, Mazaux JM, Barat M. Fluoxetine in early post-stroke depression: a double-blind placebo-controlled study. Stroke. 2000;31:1829–32.
27. Fruehwald S, Gatterbauer E, Rehak P, Baumhackl U. Early fluoxetine treatment of post-stroke depression—a three-month double-blind placebo-controlled study with open-label long-term follow up. J Neurol. 2003;250:347–51.
28. Grade C, Redford B, Chrostowski J, et al. Methylphenidate in early poststroke recovery: a doubleblind, placebo-controlled study. Arch Phys Med Rehabil. 1998;79:1047–50.
29. Tardy J, Pariente J, Leger A, et al. Methylphenidate modulates cerebral post-stroke reorganization. Neuroimage. 2006;33:913–22.
30. Gonzalez-Torrecillas JL, Mendlewicz J, Lobo A. Effects of early treatment of poststroke depression on neuropsychological rehabilitation. Int Psychogeriatr. 1995;7:547–60.
31. Gainotti G, Antonucci G, Marra C, Paolucci S. Relation between depression after stroke, antidepressant therapy and functional recovery. J Neurol Neurosurg Psychiatry. 2001;71:258–61.
32. Miyai I, Reding MJ. Effects of antidepressants on functional recovery following stroke: a double-blind study. J Neurol Rehabil. 1998;12:5–13.
33. Narushima K, Chan KL, Kosier JT, Robinson RG. Does cognitive recovery after treatment of poststroke depression last? A 2-year follow-up of cognitive function associated with poststroke depression. Am J Psychiatry. 2003;160:1157–62.
34. Dam M, Tonin P, De Boni A, et al. Effects of fluoxetine and maprotiline on functional recovery in poststroke hemiplegic patients undergoing rehabilitation therapy. Stroke. 1996;27:1211–4.
35. Schmid AA, Kroenke K, Hendrie HC, Bakas T, Sutherland JM, Williams LS. Poststroke depression and treatment effects on functional outcomes. Neurology. 2011;76(11):1000–5.
36. •• Chollet F, Tardy J, Albucher JF, Thalamas C, Berard E, Lamy C, Bejot Y, Deltour S, Jaillard A, Niclot P, Guillon B, Moulin T, Marque P, Pariente J, Arnaud C, Loubinoux I. Fluoxetine for motor recovery after acute ischaemic stroke (FLAME): a randomised placebo-controlled trial. Lancet Neurol. 2011;10(2):123–30. *First trial demonstrating the positive effect of SSRI fluoxetine on motor deficit of patients with ischaemic stroke*.
37. Acler M, Robol E, Fiaschi A, Manganotti P. A double blind placebo RCT to investigate the effects of serotonergic modulation on brain excitability and motor recovery in stroke patients. J Neurol. 2009;256(7):1152–8.
38. Zittel S, Weiller C, Liepert J. Citalopram improves dexterity in chronic stroke patients. Neurorehabil Neural Repair. 2008;22:311–4.
39. Pariente J, Loubinoux I, Carel C, et al. Fluoxetine modulates motor performance and cerebral activation of patients recovering from stroke. Ann Neurol. 2001;50:718–29.
40. Gerdelat-Mas A, Loubinoux I, Tombari D, et al. Chronic administration of selective serotonin reuptake inhibitor (SSRI) paroxetine modulates human motor cortex excitability in healthy subjects. Neuroimage. 2005;27:314–22.
41. Mikami K, Jorge RE, Adams HP Jr, Davis PH, Leira EC, Jang M, Robinson RG. Effect of antidepressants on the course of disability following stroke. Am J Geriatr Psychiatry. 2011.
42. Robinson RG, Jorge RE, Moser DJ, Acion L, Solodkin A, Small SL, Fonzetti P, Hegel M, Arndt S. Escitalopram and problem-solving therapy for prevention of poststroke depression: a randomized controlled trial. JAMA. 2008;299(20):2391–400.
43. Hackett ML, Anderson CS, House A, Halteh C. Interventions for preventing depression after stroke. Cochrane Database of Systematic Reviews 2008, Issue 3. Art. No.: CD003689. doi:10.1002/14651858.CD003689.pub3.
44. Narushima K, Kosier JT, Robinson RG. Preventing poststroke depression. A 12-week double-blind randomized treatment trail and 21-month follow-up. J Nerv Ment Dis. 2002;190:296–303.
45. Palomaki H, Kaste M, Berg A, Lonnqvist R, Lonnqvist J, Lehtihalmes M, Hares J. Prevention of poststroke depression: 1 year randomised placebo controlled double blind trial of mianserin with 6 month follow up after therapy. J Neurol Neurosurg Psychiatry. 1999;66:490–4.
46. Zittel S, Weiller C, Liepert J. Reboxetine improves motor function in chronic stroke: A pilot study. J Neurol. 2007;254:197–201.
47. Laska AC, von Arbin M, Kahan T, et al. Long-term antidepressant treatment with moclobemide for aphasia in acute stroke patients: a randomised, double-blind, placebo-controlled study. Cerebrovasc Dis. 2005;19:125–32.
48. Jacobs BL, Fornal CA. Serotonin and motor activity. Curr Opin Neurobiol. 1997;7:820–5.
49. Lim CM, Kim SW, Park JY, Kim C, Yoon SH, Lee JK. Fluoxetine affords robust neuroprotection in the postischemic brain via its anti-inflammatory effect. Neurosci Res. 2009;87:1037–45.
50. Li WL, Cai HH, Wang B, et al. Chronic fluoxetine treatment improves ischemia-induced spatial cognitive deficits through increasing hippocampal neurogenesis after stroke. J Neurosci Res. 2009;87:112–22.