Research Project

Pharmacologic treatment options for post-stroke depression focused on selective serotonin reuptake inhibitors vs. tricyclic antidepressants

Submitted by

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We hereby recommend that the research project prepared under our supervision by Brooke Gates entitled Pharmacologic treatment options for post-stroke depression focused on selective serotonin reuptake inhibitors vs. tricyclic antidepressants will be accepted as partial fulfillment for the degree of Master of Physician Assistant.

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Abstract

Background and Purpose**:** Post-stroke depression (PSD) affects 20 to 50 percent of patients within one year after stroke. Depression is considered to be the most common emotional outcome of stroke. PSD is often not detected or inadequately treated. There is little evidence in the literature to guide health-care providers in regard to selection of pharmacological treatment. This study will focus on the efficacy and safety of selective serotonin reuptake inhibitors (SSRIs) versus tricyclic antidepressants (TCAs) in the treatment of PSD. Methodology: An evidence-based systematic review of the current literature was conducted utilizing multiple electronic databases to identify randomized, controlled trials of the treatment of PSD. MESH terms used were poststroke depression, cerebrovascular accident AND depression, stroke AND depression, antidepressant treatment after stroke. Results: 22 articles were selected for review. 14 out of those were randomized-controlled trials (RCTs) that were closely reviewed for recommendations regarding treatment of PSD. The class of drug with the largest number of RCTs was SSRIs, followed by the TCAs, and other antidepressants. TCAs and SSRIs appear to be equally effective in the treatment of PSD; however, a Grade A recommendation can be made in favor of SSRIs due to improved tolerability and significantly reduced side effect potential. In addition, the drug with the most RCTs supporting its use in PSD was fluoxetine. Conclusion: SSRIs prove to have the greatest amount of clinical data to support their use and appear to be the preferred treatment option for PSD. Further trials with larger sample sizes and longer duration of treatment are needed to provide specific treatment recommendations to practitioners.

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Introduction

Approximately 700,000 Americans suffer a stroke or cerebrovascular accident (CVA) each year, making it the third leading cause of death, and a leading cause of long-term disability.[1] The number of stroke survivors is increasing because of improvement in the management of acute stroke. This has resulted in greater numbers of stroke survivors who will suffer from significant residual physical and psychological impairments.[2] Depression is an important complication following the event of a stroke. The Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition (DSM-IV) classifies poststroke depression as a "mood disorder due to a general medical condition.[3]" Poststroke depression (PSD) affects twenty to fifty percent of patients within one year after stroke, with a mean duration of three months to greater than two years.[4] Depression is considered to be the most common emotional outcome of stroke.[5] PSD is often not detected or inadequately treated by healthcare professionals.[6] The challenge of accurately diagnosing depression after stroke is a concern of healthcare providers. Further, the presentation may be complicated by speech and cognitive disturbances secondary to stroke.[2]

In addition to being a significant cause of increased morbidity and mortality, poststroke depression is associated with increased physical disability, loss of independence, and increased rates of institutionalization. [7, 8, 9, 10] Ostir, et al reported that high depressive symptoms are associated with poorer recovery, and that high positive affect will be associated with improved recovery one year post-event in adults aged 65 and older.[9] Depression following CVA has been shown to increase mortality for more than five years following the event.[11] Most cases of PSD occur

within the first two years following a stroke, with the peak prevalence estimated at three to six months.[2] Poststroke depression occurs in approximately one-third of all ischemic stroke survivors and has been linked to decreased functional outcome, slower recovery, and decreased quality of life.[7]

Several randomized-controlled trials (RCTs) provide evidence for a direct relationship between poststroke depression and increased mortality rate.[7, 11-13] Ostir, et al proposed three mechanisms to explain the relationship between depression and increased mortality. First, depressive symptoms generally decrease a person's motivation for rehabilitation, especially related to a decrease in diet and exercise. Second, depression may also be indirectly related to recovery through decreased social interaction. Patients experiencing low levels of social support may have a decreased likelihood of adhering to medical advice and treatment. Third, depressive symptoms associated with disease may be related to a real or perceived inability to adapt to environmental demands.[9] Alternatively, another study suggested that sociodemographic characteristics, rather than emotional health, may be responsible for the differential functional ability patterns between depressed and non-depressed subjects.[9]

The mechanism by which stroke leads to depression remains highly controversial. Some studies suggest that depression is a product of patients facing the disability itself.[9, 14] Other researchers hypothesize that a direct biological mechanism related to damage in a particular area of the brain causes depression, or that the disruption of neural circuits involved in mood regulation by the ischemic brain lesions directly cause the depression. Others conclude that increased patient age,

female gender, large lesion location, and high degree of physical disability contribute to the highest incidence of depression in patients following stroke.[15,16] Another study found that crying behaviors soon after stroke, a younger age, and severe disability are the highest predictors of PSD in patients with first-ever stroke.[17] An additional finding emerged from a study which examined depression at three months poststroke in elderly patients. The study found that an organic brain lesion may be responsible for depression in the acute stroke stages, but the cause of PSD at three months post-event seemed to correlate more with the patient's individual reaction to their physiological impairments and had no relation to lesion location.[5]

There is a great debate across the literature regarding the neurobiology behind poststroke depression and numerous studies attempting to find a correlation between the onset of PSD and a specific lesion location in the brain. The consensus in the current literature proves that none of the above stated theories are absolute. It is remarkable that the literature contains far more studies on the content and prevalence of PSD than studies on treatment of this condition. For this reason, this research study will examine only those studies identifying the treatment options for poststroke depression.

Poststroke depression continues to be a significant area of concern for patients, families and practitioners. The prevalence of post-stroke depression is undeniably high and on the rise due to the increasing age of today's population. The main objective of this research paper is to outline the efficacy and safety of the pharmacologic treatment options for poststroke depression, according to the most recent medical literature available. Furthermore, there is little evidence in the

literature regarding evidence-based guidelines for clinical practitioners to reference in regard to selection, timing, and duration of treatment when faced with this increasingly common medical dilemma. This paper will attempt to provide clinical treatment recommendations, compounded from highly supported studies for practitioners to reference when confronted with patients experiencing poststroke depression.

Literature Review

Throughout the literature, there are references to numerous assessment scales used to measure or rate depressive symptoms, none of which are specific to PSD. The most frequently used scales are the Hamilton Rating Scale for Depression (HDRS), the Geriatric Depression Scale (GDS), Mini Mental State Examination (MMSE), the Beck Depression Inventory (BDI), the Montgomery Asbery Depression Rating Scale (MADRS), Functional Independence Measure (FIM), and the Zung Self-Rating Depression Scale (ZDS).[2] (see Raw Data, Appendix A.)

Currently, there is no accepted standard on which scale is best to accurately measure depression following stroke.[18] This fact contributes to the difficulty experienced by clinicians when faced with the diagnosis of PSD. The HDRS scale has been used most frequently in screening for PSD mostly due to its simplicity and quick completion time.[19] The HDRS depends on information provided by the patient for further evaluation by a third party. This method is beneficial compared with other rating scales because evaluation by a third party is crucial. Further, rating scales that rely on the patient's response to verbal, written and non-verbal material raise concerns regarding the validity of the assessment due to the potential neurological,

psychological and communicative complications of stroke in these patients. The Beck Depression Inventory (BDI) has also shown to be a useful tool for assessment of PSD because of its low reliance on somatic symptoms.[20] To be complete, the numerous tools that are used to identify patients with poststroke depression have been mentioned. It is agreed across literature that the inconsistencies with these depression scales may alone contribute to the enormous difficulty of accurately recognizing and treating PSD. The ongoing debate regarding rating scale selection in PSD is beyond the scope of this study and will not be further examined.

SSRIs

The total number of RCTs found in the literature for treatment with SSRIs was ten. This number includes those studies comparing more than one drug and/or drug class. These studies were further broken down by specific drug tested in the study. The drugs included in the individual SSRI studies include: fluoxetine (Prozac®),[12, 21] citalopram (Celexa®),[22] and sertraline (Zoloft®).[23] The final portion of this section will include two studies in which researchers used a combination of two drugs, an SSRI and another antidepressant, to compare their effectiveness in head-to-head trials.[24, 25]

Wiart et al used a multicenter, double-blind, placebo-controlled study to examine the efficacy and tolerance of fluoxetine in the treatment of PSD.[12] Thirty-one patients were randomized to receive either 20 mg per day fluoxetine or placebo for six weeks. The patients were evaluated by several different depression rating scales, the MMSE, FIM, and MADRS. At endpoint, the fluoxetine-treated patients scored higher on the MADRS scale versus those treated with placebo; and therefore

had a greater response rate (62.5% versus 33.3%, respectively). The safety of antidepressant treatment has been disputed considerably across the literature. This study found no differences in motor function, cognitive activity, or functional improvement and no significant side effects, except for one patient with a moderate and transient elevation of transaminases. According to this study, the overall safety and tolerability are better in SSRIs than in tricyclic antidepressants. This study stated that although significant elevations in transaminases are rarely seen in clinical trials using depressed patients from the general community, poststroke patients may be at greater risk because of polymedication. The study was in agreement with a larger population based, case-controlled study and concluded that fluoxetine appears to be effective and well-tolerated treatment.[26] Limitations to this study included small sample size, short duration of treatment, and exclusion of aphasic patients.

Another RCT was conducted to evaluate the efficacy and safety of early treatment with SSRI, fluoxetine in patients with PSD.[21] Fifty patients were enrolled in this study within two weeks following the event of stroke. Individuals were to receive three months of treatment with either 20 mg per day of the drug or placebo. There were no side effects detected in either group in the study. The unique finding with this study was that no benefits in fluoxetine could be seen in the initial 3 months of treatment, but were noted at the 18 month follow-up. This finding may be explained by the possibility for a high rate of recovery from depressive symptoms in the early rehabilitation period, due in part to the increased level of therapeutic efforts during the early phase. This study additionally concluded that SSRIs are generally well-tolerated in patients with PSD.

Murray et al conducted a RCT to compare sertraline to placebo in PSD patients with minor depression.[23] Subjects were recruited from four Swedish stroke centers, 123 patients were enrolled in this 26-week trial. Patients were enrolled at a range from three days to one year after stroke. The group treated with sertraline (n=62) ranged from a dosage of 50 to 100 mg per day. At the end of the treatment period, there were a total of 69 patients remaining. The dropout rates were similar among the treatment and placebo group. The explanation for the high rate of drop out was most likely due to the long duration of treatment for this particular study. Although the long duration of treatment may have led to increase numbers of drop out, this is an advantage for this particular study compared to the majority of trials with short durations of treatment. The results revealed better outcome with sertraline at six weeks and better quality of life at week twenty-six ($p<0.05$). No serious side effects were seen.

Finally, a RCT, comparing a single SSRI with placebo in PSD patients was conducted by Anderson et al in 1994.[22] This study was designed to evaluate the effectiveness of citalopram in treatment of depression, within the first year following stroke. Sixty-six patients were enrolled in the trial; half were treated with 10 to 40 mg of citalopram, and the other half with placebo. Citalopram significantly out-scored the placebo group in comparison of HDRS depression scale at three and six weeks ($p<0.05$).

A non-RCT conducted by Gainotti et al, looked retrospectively at a cohort of 49 depressed and 15 non-depressed patients with stroke who were followed up for other research purposes between June 1994 and July 1997. These patients were under

the care of physicians, some of whom were interested in treating poststroke depression and some of whom were not. Twenty-four of the depressed patients with stroke had been treated, whereas the other 25 had not received antidepressant drugs. Twenty-three out of 24 patients received the SSRI fluoxetine with doses ranging between 20 and 40 mg per day. This study is unique because it included non-depressed, depressed but treated, and non-treated depressed subjects. The study showed that the non-treated depressed patients following stroke presented the lowest rate of functional recovery, compared to depressed but treated patients who had a recovery rate similar to the non-depressed subjects.[6]

An open-label, non-placebo controlled study, demonstrated findings to suggest that left stroke may be a predictor of SSRI treatment resistance.[27] Forty-five patients completed this eight week study. It found the improvement of depressive symptoms and cognitive level after SSRI treatment was statistically different in patients with left stroke in comparison to patients with right stroke ($p<0.001$). Muller et al demonstrated that low doses of paroxetine and citalopram are equally effective to treat pathological crying, following stroke and other neurological diseases ($p<0.001$).[28] This study also confirms a low side effect profile for SSRIs in treating PSD.

The following two RCTs were combination studies completed to evaluate the effectiveness of an SSRI with another antidepressant drug. Dam et al designed a 12-week study to evaluate the effects of SSRI (fluoxetine) compared to maprotiline (a tetracyclic antidepressant) on recovery in poststroke hemiplegic patients undergoing rehabilitation therapy.[25] Researchers recruited 52 patients with CT-scan confirmed

ischemic strokes. The greatest improvement in functional recovery was seen in the group treated with 20 mg per day of fluoxetine. Maprotiline was found to have the lowest effect on improvement; it was also thought to actually hinder recovery ($p<0.05$). The conclusion of this study postulated that long-term treatment with fluoxetine increases serotonergic transmission, therefore stimulating motor function and possibly restoring processes that commonly occur following stroke.

Another RCT, combination study was designed to predict the response of SSRI (citalopram) and NARI (reboxetine) in poststroke depressed patients.[24] Seventy-four poststroke patients affected by anxious or retarded depression were selected. Retarded depression can be defined as a state of clinical depression in which the patient demonstrates qualities of lethargy, slow initiation to action, and hypokinesia. Anxious depression is the opposite of retarded, and presents clinically different with symptoms of insomnia, anxiety, restlessness, and hostility. Citalopram led to a score reduction only in the clinical subscale specific to anxious depression, whereas reboxetine specifically reduced the score relative to symptoms of retarded depression. An interesting finding in this study is the recommendation to classify PSD patients according to their clinical features, and to use this classification as a predictor of the clinical response to various classes of antidepressants. Lastly, the study concluded that citalopram or other SSRIs and reboxetine may be the first choice treatment in PSD because of their good efficacy and low risk of side effects.

TCAs

The total number of RCTs found in the literature for treatment with TCAs was six. Four studies out of the six are in comparison with SSRIs and will be discussed in

the section to follow. The drug included in all of the individual TCA studies was nortriptyline.[29, 30] In fact, there was very little evidence noted in the literature with any of the other TCAs.

Kimura et al enrolled 47 patients in a double-blind, placebo-controlled study to examine the response of cognitive function to treatment with nortriptyline or placebo.[30] There were no significant differences in regard to lesion location, type of stroke, or neurological deficits between patients in the two groups. Twenty-one randomly assigned patients began nortriptyline at a dose of 20 mg per day and were titrated up to 100 mg per day. The most impressive finding in this study showed that for the first time, a treatment trial was able to demonstrate evidence that patients with stroke had partially reversible cognitive dysfunction when their depressive symptoms were successfully treated. Another finding revealed that improved cognitive function was correlated to mood improvement and not nortriptyline itself. Unexpectedly, one-third of the patients who responded to treatment with positive cognitive improvement were in the placebo group.

Another RCT was designed to compare recovery in activities of daily living (ADL) in poststroke depressive patients who responded to antidepressant treatment compared with those who failed recovery.[29] They found no significant difference between nortriptyline compared to placebo in the six-week trial. However, researchers did discover patients whose depressive disorder remitted at follow-up had significant greater recovery on ADL functions compared with patients whose depression did not remit.

SSRIs vs TCAs

TCAs and SSRIs are the most frequently tested drugs in the literature for treatment of PSD; as a result, it is not surprising that there have been several head-to-head studies conducted to compare the two classes. In the literature search performed for this study, there were four RCTs comparing these two classes of antidepressants.[11, 13, 31, 32] In each of these studies, the drugs compared were nortriptyline (TCA) versus fluoxetine (SSRI).

Jorge, et al assessed whether antidepressant treatment would reduce poststroke mortality over nine years of follow-up. This study included 104 randomly selected patients who were assigned to receive a 12-week, double-blind course of nortriptyline, fluoxetine, or placebo early in the recovery period after a stroke. Of the 104 patients, 48% had died by the 9-year follow-up period. Of the 53 patients who were given full-dose antidepressants, 68% were alive at follow-up, compared with only 36% of the 28 placebo-treated patients. Regression analysis, showed the beneficial effect of antidepressants remained significant both in patients who where depressed and in those who were non-depressed at enrollment. This finding is one of the most significant from the current literature review and is particularly relevant to the current research question. This same study suggested continuing treatment with antidepressives for prolonged periods may affect platelet function and progression of atherosclerosis and may also have an effect on the autonomic changes that make patients prone to severe cardiac arrhythmias.[11]

Another placebo-controlled, double-blind study was the first RCT in the literature to compare the use of nortriptyline vs. fluoxetine for the treatment of PSD.[13]

This study entered 104 poststroke subjects into a study to compare nortriptyline to fluoxetine in the treatment of poststroke depression. This study recommended against the use of fluoxetine dosed 10 to 40 mg per day in poststroke patients due to an average weight loss of 15 pounds (8% of initial body weight) over 12 weeks of treatment that was not seen with nortriptyline or placebo. Overall, this study indicated better efficacy and fewer side effects in nortriptyline than fluoxetine in the treatment of PSD.

Another study was designed to document the effects of early treatment of PSD with either fluoxetine or nortriptyline.[33] The 37 patients in the treatment groups were not randomized to receive the medication. Side effects experienced in both patient populations were mild; only two patients (one in each treatment group) dropped out of the study secondarily to side effects. After six weeks of treatment, the results showed that early treatment with either fluoxetine at 20 mg per day or nortriptyline at 75 mg per day significantly improved patients' mood, neurological function, as well as cognitive and functional ability (Evidence level 2B).

Narushima and colleague Robinson designed a RCT to determine the effect of early versus late antidepressant treatment on recovery in activities of daily living in PSD patients.[34] In some clinical studies the early administration, within the first three months following stroke, has been shown to prevent PSD. This study intended to predict if the same was true in regard to preventing functional deficits in ADL. The functional impairments in 62 patients were evaluated with the Functional Independence Measure (FIM). The results demonstrated greater remission of functional impairments in the early treatment group. Although patients in this study

were treated with nortriptyline, fluoxetine or placebo, it did not compare efficacy of one drug to another. Despite this fact, the study provided new evidence that early treatment in patients with PSD is crucial. An earlier study also conducted by Narushima and colleagues, used nortriptyline and fluoxetine to determine if cognitive recovery after treatment of PSD continues greater than two years.[31] Cognitive function, once PSD is effectively treated, was determined to remain stable over the next two years. This study made no recommendations regarding the efficacy or safety of these two medications in their study population.

The following sections regarding stimulant medications and Noradrenaline Reuptake Inhibitors (NARIs) are not directly involved in the core research of this study, as the focus is to compare the most widely used medications to treat PSD, SSRIs and TCAs. However, it is worth mentioning these two categories of treatment options as they do appear to have some degree of efficacy and are present in a fair amount of research studies.

NARIs

There are two studies in the literature that address the class of NARIs for use in the treatment of PSD. Both of these articles are RCTs with the drug reboxetine; one of them is a comparative study with another drug, citalopram, an SSRI.[24] This study is mentioned in the section regarding treatment with SSRIs as above. NARIs are a newer class of antidepressants. Reboxetine has been available in Europe and Canada for over 20 years; it is not currently on the market in the United States. However if it does become available, researchers anticipate positive results. It has neither affinity for serotonin or dopamine uptake site nor for muscarinic, histaminic,

or alpha adrenergic receptors, therefore the risks for side effects especially in the elderly population could be greatly reduced.

Rampello, et al designed a double-blinded, placebo-controlled study comparing reboxetine to placebo.[35] This study was designed to evaluate treatment of PSD with reboxetine in a subset of PSD patients classified by "retarded" depression. The author designed this study to compare treatment in two different subsets of PSD, anxious and depressed, based on the belief that each responds differently to treatment. Reboxetine was administered to 31 patients at 4 mg twice daily for 16 weeks. The result of this study showed statistically significant reduction in depressive symptoms compared to placebo ($p<0.01$). Although this drug is not currently available in the United States, it may give doctors and future researchers hope when examining treatment options for PSD.

Stimulant Medications

Stimulant medications have been utilized in PSD, but large-scale randomized clinical trials are still needed. In the literature review, there was one RCT found regarding PSD treatment with methylphenidate.[36] There were three additional studies found that had variable, non-RCT designs.[37-39] No studies were found in the literature for treatment with stimulants dated later than 1998. Clearly, these drugs have lost appeal due to the concern of use in elderly patients at greater risk for adverse drug reactions.

The first known RCT to examine the effect of methylphenidate in early poststroke recovery was completed in 1998 by Grade et al.[36] Methylphenidate acts by directly stimulating the release of dopamine and norepinephrine, as well as

blocking catecholamine reuptake. Twenty-one stroke patients were enrolled in this three-week treatment trial with methylphenidate (5 mg titrated to 30 mg) or placebo. The results showed patients with poststoke depression treated early with methylphenidate responded better than with placebo. In this study, methylphenidate produced a low number of side effects to patients in the treatment group. Although this study appears to offer a safe recommendation for methylphenidate in the treatment of PSD, one must consider the limitation of small sample size in this study.

Masand et al described a five-year retrospective trial with seventeen stroke patients treated by a psychiatric consultation with either dextroamphetamine or methylphenidate.[39] Side effects were experienced by a small amount of patients with both medications. Patients treated with dextroamphetamine experienced confusion and tachycardia, and those treated with methylphenidate suffered from increased agitation. Those who tolerated the medications were able to complete the trial with marked improvement in depressive symptoms. No difference was seen in the effectiveness of methylphenidate versus dextroamphetamine. Again, this study must be scrutinized due to its design and small sample size. Another study investigated the use of the stimulant methylphenidate in a depressed, elderly stroke population.[38] Ten individuals were enrolled in this study; they were started on a dose of 2.5 mg or 5 mg and were slowly increased to as much as 40 mg per day. A total of eighty percent of the subjects showed either a full or partial response to the medication. The incidence of side effects was low in the population treated.

Non-Pharmacologic Options

Additional non-pharmacologic options remain for patients with strong

contraindications to some of the antidepressants used for treatment, i.e. various cardiac conditions, most commonly cardiac arrhythmias. Psychotherapy has shown to be effective in helping the patient and family adjust to loss of function and various impairments related to stroke.[19] A small RCT conducted in 2003, showed cognitive behavioral therapy to be ineffective in treating PSD.[40] Although cognitive behavioral therapy has proven in the literature to be effective for treating depression in the general population and in the elderly, it has not been proven to have any significant effect on poststroke depression. Additional therapeutic measures for patients who suffer from PSD have been noted in the literature. Patients have responded well to early initiation into a rehabilitation programs, and have benefited from increased attention and encouragement from family members and medical staff.[19]

Methodology

An evidence-based systematic review of the current literature was conducted utilizing multiple databases to identify randomized, placebo-controlled trials (RCT) examining the pharmacologic treatment options for PSD. A review of the literature was conducted utilizing the following computer databases: PubMed, Medline, CINAHL, Expanded Academic ASAP, PsycINFO, Ovid, and First Search databases from 1990 to the present. The search was done using the keywords of poststroke depression, treatment AND poststroke depression, stroke AND depression, cerebrovascular accident AND depression, antidepressant treatment AND poststroke depression.

Articles were individually reviewed and selected for inclusion based on the quality of methodology and randomization of each individual study; emphasis was on RCTs. Articles used in analysis preparation of this paper were dated no earlier than

1990. Non–English-language journals, abstracts, unpublished observations, manuscripts and personal communications were excluded. There were no restrictions on the basis of age, gender, ethnicity, or other patient characteristics. Patients in the studies analyzed had no history of depressive disorders or other psychiatric disturbances previous to stroke. Depression was defined individually by each study included in this review according to specific DSM IV criteria and other tools used to assess level of depression. For purposes of this study, stroke will include both acute and chronic CVA including varying degrees of severity, but will exclude transient ischemic attacks (TIA). Each article was assigned a numerical (1 through 5) and alphabetical (A through D) reference based on the evidence-based medicine guidelines for rating the evidence level of an article (Table 1).

Table 1: Evidence-Based Medicine Evidence Rating Guidelines

Levels of Evidence	
1	Systematic Reviews, RCTs
2	Systematic Reviews of cohort
3	SR of case-control studies
4	Case series
5	Expert opinion without explicit critical appraisal
Grades of Recommendation	
A	Consistent Level 1 studies
B	Consistent level 2 or 3 studies or extrapolations from level 1 studies
C	Level 4 studies or extrapolations from level 2 or 3 studies
D	Level 5 evidence or inconsistent or inconclusive studies at any level

Data extracted from the Oxford Centre for EBM Levels of Evidence[41]

Specific pharmacologic agents included selective serotonin reuptake inhibitors (SSRI), tricyclic antidepressants (TCA), psychostimulant antidepressants, and noradrenaline reuptake inhibitors (NARI). Based on a preliminary evaluation of the

available literature, there was a significant amount of research studies focused on SSRIs and TCAs. Therefore, this literature review focused on studies including the comparison of these two classes of antidepressants as they relate to the treatment of PSD.

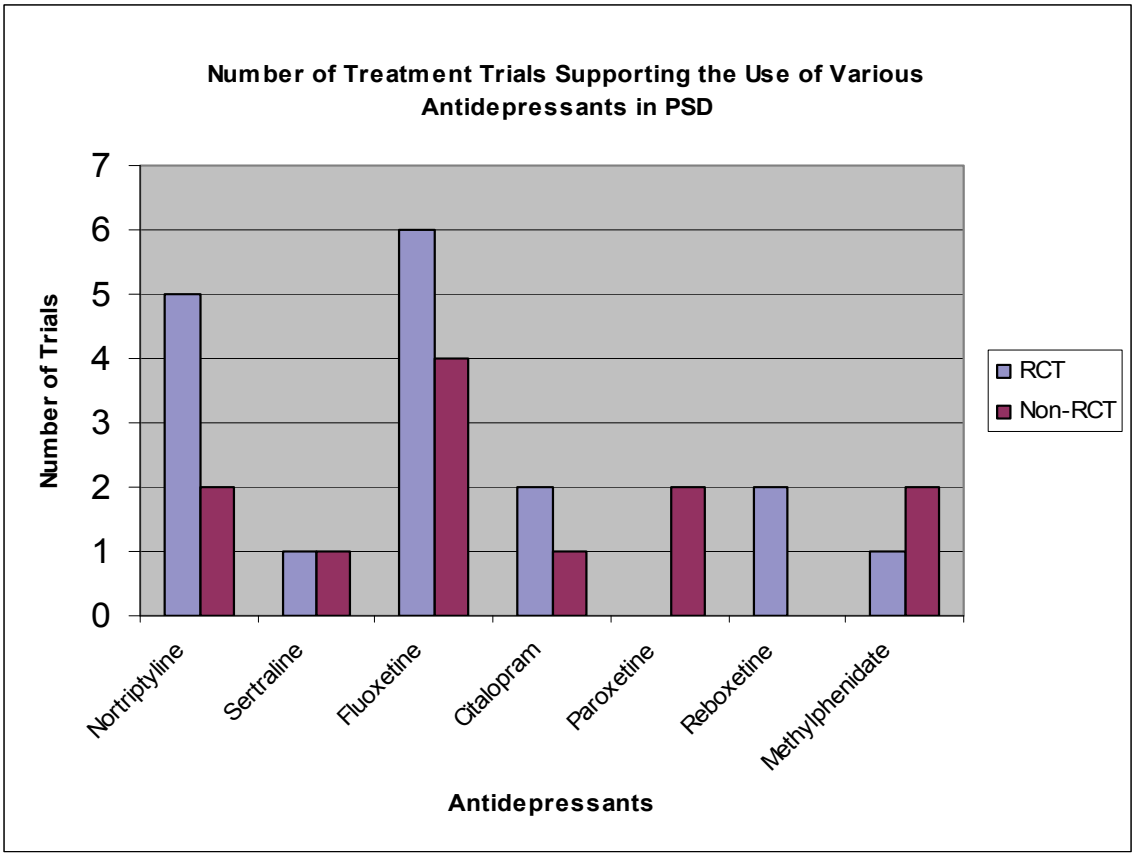
Results

Twenty-two pharmacological articles were selected for review; 14 were RCTs, 8 other (see Appendix A: Raw Data). In the RCTs, a cumulative total of 847 patients were finally selected for review. Analysis revealed the mean age of patients in the studies ranged from 58 to 77 years, with an overall age of 66.4 years. The average time from onset of acute stroke to enrollment in the research studies was less than 12 months. Among the 14 RCT treatment trials, some comparing more than one drug to placebo; 10 trials used SSRI, 6 trials tested TCA, and 4 studies examined other antidepressants. The SSRIs included: fluoxetine, citalopram, and sertraline; TCAs included: nortriptyline; and other antidepressants included: reboxetine (a NARI-noradrenaline reuptake inhibitor), methylphenidate (a psychostimulant), and maprotiline (a tetracyclic antidepressant). The doses included in each study can be found in Appendix A and are specific to each individual study. The average duration of treatment in the trials ranged from 6 weeks to 26 weeks. Due to the variability in design, methods, and rationale of each RCT selected for review, outcome data will not be pooled. Figure 1 demonstrates the results of treatment trials found in the literature to support the use in treatment of PSD.

Overall fourteen articles examined in this EBM review qualified as Level 1 randomized-controlled trials. The remaining eight were classified as Level 2 and

Level 3 evidence. This study was designed to examine the studies with the highest level of evidence. Based on Level I evidence, the articles reviewed demonstrated that 53% supported treatment with SSRIs, 29% with TCAs, and 18% with others. Therefore, a grade A recommendation suggests that stroke patients suffering from depression respond better to SSRIs.

Figure 1



Discussion

Based on a complete review of the available literature regarding treatment of poststroke depression, it was determined that several treatment options exist for patients with PSD. Comparison of the data extracted from the studies outlined above, showed variable recommendations for the pharmacologic treatment of PSD. This

research study was designed to focus on RCTs; there were a total of fourteen trials found in the current literature. Of these fourteen, Table 2 demonstrates the distribution of the studies which demonstrated clinical evidence to support various antidepressants. It is apparent with careful examination of the literature that SSRIs are more commonly prescribed today for treatment of PSD than are the TCAs. There is more evidence in the literature to support the use of fluoxetine. In addition, it is probably the most widely accepted and prescribed SSRI overall, and is also possibly the safest and most economical. Therefore based on Level 1 evidence, a grade A recommendation suggests that stroke patients suffering from depression respond better to SSRIs, specifically fluoxetine.

Table 2: Comparison of the Number of RCTs Supporting Antidepressants in PSD

Drug Class	Name	Number of RCTs	Reference Number
TCA	Nortriptyline	5	11, 13, 29, 30, 32
SSRI	Sertraline	1	23
	Fluoxetine	6	11, 12, 21, 25, 31, 32
	Citalopram	2	22, 24
OTHER	Reboxetine	2	24, 35
	Methylphenidate	1	36

Many of the treatment trials examined in this review terminated treatment at six weeks. Although most patients were shown to have improvement in depressive symptoms, this does not provide an absolute recommendation for duration of treatment. Many patients withdrawn from treatment at this stage may experience relapse. From an intuitive conclusion of the literature, it should be recommended that

PSD patients whom are started on antidepressants maintain treatment for at least four to six months, followed by a slow withdrawal.

Although SSRIs are currently the mainstay of treatment for PSD, some patients may not be able to tolerate these medications or may not experience relief of their symptoms. In this clinical situation, practitioners must consider additional treatment options and must be aware of the side effects and contraindications to their use. The side effects experienced by the majority of subjects in the treatment trials were mild; see Table 3 for a comparison of these side effects. The potency varies between the specific drugs in the class of SSRIs. Paroxetine and sertraline were the most potent, while citalopram is the newest and most selective.[42] The SSRI with the longest half-life was fluoxetine and this fact may increase the risk of potential side effects. In some studies SSRIs have been associated with increased risk of bleeding by altering the process of platelet aggregation. It is still under debate if the possibility exists for SSRIs to increase risk of hemorrhage. Citalopram (SSRI) has been shown to have the lowest affinity to affect platelet aggregation.[43] This important issue must be considered when treating any patient with an antidepressant following stroke. Aspirin and other platelet inhibitors should not be used in combination with SSRIs in high-risk patients in order to decrease this potential risk. There are several known contraindications to some medications listed in the literature, it is important to screen patients before starting any medication to rule out this possibility. Contraindications to nortriptyline (TCA) include history of cardiac arrhythmia, heart block, narrow angle glaucoma, and orthostatic hypotention.[2] TCAs inhibit the uptake of noradrenaline and serotonin; they have muscarinic cholinergic and histaminergic

receptors.[42] For this reason, TCAs have a high potential to cause numerous anticholinergic effects including constipation and urinary retention. Orthostatic hypotension is another known probable side effect which can increase the risk of falls in the stroke patient. In comparison, SSRIs do not produce any anticholinergic or histaminergic side effects, they should not be used in combination with MAO inhibitors, but otherwise have no contraindications. SSRIs are highly protein bound, and they have interaction with the cytochrome P450 pathway which may result in increased drug interactions.[42]

Table 3: Comparison of Side Effects Experienced by Subjects in RCTs

Drug Class	Name	Side Effects
TCA	Nortriptyline	sedation, gastrointestinal discomfort
SSRI	Sertraline	dry mouth, diarrhea, nausea
	Fluoxetine	nausea, confusion, moderate and transient ↑ in transaminases, weight loss
	Citalopram	nausea, insomnia, weight gain
OTHER	Reboxetine	dry face, constipation, increased perspiration, insomnia
	Methylphenidate	none mentioned

Limitations of study

Although recognized computer bibliographic databases were used, it is possible that articles that would have met the criteria were missed. This study excluded all abstracts of non-published studies and those containing non-English text. Many of the studies included small sample sizes and short duration of treatment. This research study excluded patients with a history of depression previous to stroke; this may have led to an incomplete picture of the entirety of PSD experienced by patients,

and those that must still be treated in the health care system. It was impossible to entirely pool the outcome data from the studies due to the vast amount of variables included in each study. These variables include the following: variance of study design, methods, and number of subjects enrolled in the study, duration of treatment, variance of time following stroke to enrollment in the study, inconsistent methods of diagnosing PSD, and the various diagnostic tools and depression scales that were used. In addition, the information collected and analyzed in this review was not blinded from the author or advisor, therefore, not protecting against bias.

Conclusion

The approach to diagnosing and treating PSD has proven to be exceedingly difficult based on the numerous inconsistencies in the literature. Clearly the conflicting studies regarding the safety, duration of treatment, and drug of choice to treat poststroke depression indicate the need for further research in this area. The first step is to make sure the patient is stable and ensure they are receiving the best possible care for other disabilities and emotional disturbances they may experience in the acute post-stroke period. Effective treatment of PSD depends on an accurate diagnosis. Diagnosis of this common condition still relies mainly on the clinical history and physical exam, and when necessary by the use of a selected depression scale. Emotional disturbances are common after a stroke and may not be related to poststroke depression. In general, the diagnosis of PSD should be considered in any patient following stroke with loss of energy, loss of appetite, sleep disturbances, alteration of mood, agitated state, or suicidal thoughts. It is important in the poststroke period, to accurately evaluate the patient's physical and mental state and

assess their ability to maintain activities of daily living.

The comprehensive review of the literature revealed that there are, to date, no RCTs investigating any of the newer antidepressants for the treatment of PSD; venlafaxine (Effexor®), or duloxetine (Cymbalta®). There was also no research found on escitalopram (Lexapro®), a newer SSRI. The anticipation for new antidepressant medications with fewer side effect risks and drug interactions is expected to provide newer, safer treatment options for patients with PSD. Evaluation in the early poststroke period may identify patients with PSD symptoms, but there are no clear guidelines regarding when to screen or make the diagnosis of PSD. Antidepressants should be chosen with careful attention to patient specific condition, side-effect risks, and drug interactions with concurrent medication. Initial doses of any medication when starting in an elderly patient must be small and side effects should be closely monitored by the clinician.

Based on Level I evidence, the articles reviewed demonstrated that 53% supported treatment with SSRIs, 29% with TCAs, and 18% with others. Therefore, a grade A recommendation suggests that stroke patients suffering from depression respond better to SSRIs. Further trials with larger sample sizes and longer duration of treatment are needed to accurately provide specific treatment recommendations to practitioners in regard to optimal duration of treatment, and the safety and efficacy of medications in high risk patients. In summary, this literature review provides consistent evidence to support the use of SSRIs, specifically fluoxetine, in the treatment of poststroke depression.

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Appendix A: Raw Data

Author, Year	#	Study Design	Anti-depressant(s)	Drug Class	Dosage	Duration of tmt	Purpose of study	Side effects	Results	Evidence	Assessment tool
RCTs:											
SSRIs											
Murray et al, 2005[23]	123	Randomized, DB, placebo controlled	Sertraline (Zoloft) v. placebo	SSRI	50-100 mg/day	26 wks	Compare Sertraline v placebo in PSD pts w/ minor depression	No serious SE's. Dry mouth, diarrhea, nausea	Better outcome with sertraline at 6 wks and better QoL in sertraline pts ($p<0.05$)	1A	Montgomery-Asberg Dep Rating Scale, EDS
Fruehwald et al, 2003[21]	50	Randomized, DB, placebo controlled	Fluoxetine (Prozac) v. placebo	SSRI	20mg/d	3 mos	Efficacy & safety of early tmt with Fluoxetine	No serious SE's.	Fluoxetine was safe and well-tolerated. Advantages obvious at 18 mo follow-up, not after first 3 mos ($p<0.01$)	1A	BDI, HDRS and CGI
Wiart et al 2000[12]	31	DB, RCT controlled	Fluoxetine v. placebo	SSRI	20mg/d	6 wks	Eff and tolerance of Fluoxetine in tmt of early PSD	Nausea, confusion, moderate and transient ↑ of transamina se	Fluox=placebo (at 6wks) But endpoint- Fluox improved depression in 60-75% of pts($p=0.05$)	1A	MADRS, MMSE
Anderson et al, 1994[22]	66	RCT, Double-blind, placebo-controlled	Citalopram v. placebo	SSRI	20mg/d (age<66) 10mg/d (older pts)	6 wks	Eff and saf of citalopram in tmt of PSD	mild and transient SE's	Citalopram signif> placebo at 3 and 6 wks. ($p<0.05$)	1A	HDRS

Dam et al, 1996[25]	52	Randomized, placebo-controlled	Fluoxetine v. Maprotiline v. placebo	SSRI v. Tetracyclic	Fluox-20mg/d, Maprotiline-150mg/d	3 mos	Eval effects of AD's on motor/ functional capacities of stroke pts undergoing PT.	Fluox-nausea, vomiting Maproiline-sedation	Fluoxetine>Maprotiline and placebo. Maprotiline may hinder recovery in PSD pts in rehab. ($p<0.05$)	1A	HDRS, BI
Rampello et al, 2004[24]	74	Randomized, DB	Citalopram (Celexa) v. Reboxetine	SSRI v. NARI	20mg/d; 4mg/d	16 wks	Predict response to citalopram & reboxetine in PSD pts	Citalopram-nausea, insomnia, weight ↑. Reboxetine-dry mouth, constip,↑persp.	Both showed good safety & tolerability. Citalopram ↑ efficacy in anxious depressed. Rebox ↑ efficacy in retarded depressed ($p<0.0001$)	1B	BDI and HDRS
TCAs											
Chemerinski et al, 2001[29]	23	Randomized, DB	Nortriptyline v. placebo	TCA	Titrated to 100mg/d	6 wks	Compare recovery in ADL in pts who responded to AD treatment of PSD vs. pts who failed therapy	None mentioned	No signif diff btwn Nortriptyline v. placebo.	1A	HDRS, JHFI

Kimura et al, 2000[30]		DB, placebo controlled trial	Nortriptyline v. placebo	TCA	Titrated to 100mg/d	6 wks	Examine the response of cognitive fx to tmt with nortriptyline or placebo	None mentioned	Nortriptyline> placebo. Showed pts had partially reversible cognitive fx when depression was successfully treated.	1A	HDRS, MMSE
SSRI vs. TCA											
Narushima K, Robinson R, 2003[32]	62	DB, randomized placebo-controlled	Fluoxetine v. Nortriptyline v. placebo	SSRI v. TCA	Fluox-titrated 40mg/d. Nortrip-titrated 100mg/d	12 wks	Effect of early v late tmt on recovery in ADL	Fluox- GI symptoms, insomnia, Nortrip-sedation, GI symptoms	Both the early & late group showed improvement in FIM scores during 3mos. But imp in early gp was signif > than late gp ($p<0.05$)	1A	FIM
Narushima et al, 2003[31]	17 Dep, 42 Non-Dep	DB, placebo controlled	Fluoxetine v. Nortriptyline v. placebo	SSRI v. TCA	Fluox max 40mg/d, Nortripyline max 100mg/d	3 mos	Examine how long cognitive imp. lasts after tmt of PSD. Also compare dep v. non-dep pts with similar stroke lesions.	None mentioned	Pts w/ early & sustained remission of dep=rapid imp of cognitive fx, maintained over 2yrs. Non-dep pts=no change in cognitive fx over 2yrs ($p<0.01$)	1B	MMSE, HDRS

Jorge et al, 2003[11]	104	Randomized, DB, placebo controlled	Fluoxetine v. Nortriptyline v. placebo	SSRI v. TCA	Fluox max 40 mg/d, Nortript max 100mg/d	12 wks	Assess whether anti-dep treatment would ↓ mortality over 9 yrs of followup	None mentioned	Tmt w/ Fluoxetine or Nortriptyline for 12 wks during 1st 6mos poststroke signif ↑ survival in both dep & non-depressed pts	1A	HDRS
Robinson et al, 2000[13]	104	DB, RCT	Fluoxetine v. Nortriptyline	SSRI v. TCA	Nortript-max 100mg/d Fluox-max 40mg/d	12 wks	Compare Nortipt v. Fluox in tmt of PSD in short-term recovery after stroke	Fluox- wt loss, nausea, diarrhea	Nortriptyline signif> Fluoxetine or placebo in improving anxiety and ADL in PSD ($p<0.05$)	1A	HDRS, FIM, MMSE
NARIs											
Rampello et al, 2005[35]	31	DB, placebo controlled	Reboxetine v. placebo	NARI	4mg BID	16 wks	Eval effic & safety of reboxetine in pts w/ "retarded" PSD	Dry face, constip, ↑perspir,in somnia	Reboxetine= signif reduction in HDRS and BDI scores compared to placebo ($p<0.01$)	1A	BDI and HDRS
Stimulant											
Grade et al, 1998[36]	21	Prospective, randomized DB, placebo-controlled	Methylphenidate v. placebo	psych o-stimul ant	5mg increased to max 30mg	3 wks	Determine efficacy and safety of methylphenid ate in acute stroke rehab	No serious SE's	Methylphenidat e > placebo. Appears to be safe and effective ($p<0.028$)	1B	HDRS, ZDS, MMSE, FIM

Non-RCTs:

Spalletta et al, 2003[27]	45	Open-label prospective study without placebo control	Fluoxetine v. Sertraline	SSRI v. SSRI	20-40mg/d, 50-100mg/d	56 days	Dtr if L sided stroke is a RF for SSRI treatment resistance	None mentioned	Improvement of symptoms after SSRI was statistically diff in pts with L stroke compared to R. R>L improvement ($p<0.001$)	3B	MMSE, HDRS
Paolucci et al, 2001[26]	290	Case-control study	Fluoxetine (120pts) v. paroxetine (16 pts) v. Other AD (9pts)	SSRI	Fluox-max 40mg/d, Paroxetine- max 20mg/d	not specified	Evaluate specific influence of PSD on both functional and rehab reults in stroke inpatients	Fluox-insomnia, nausea. Paroxetine-nausea, dry mouth.	No diff - all showed improvement in depressive symptoms and rehab ($p<0.001$)	3B	HDRS, VADS
Gainotti et al, 2001[6]	49	Retrospective cohort design. Analysis by Multivariate analysis of variance	Fluoxetine	SSRI	20-40mg/d	Pts from June '94-July'97	Evaluate effects of PSD and AD therapy on the improvement of functional recovery	None mentioned	Improved recovery in the (Fluoxetine) treated v. non-treated group ($p<0.01$)	2B	HDRS
Muller et al, 1999[28]	26	Open study	Paroxetine v. Citalopram	SSRI v. SSRI	10-40mg/d	6 wks	Compare AD tmt of pathological crying after brain injury	Nausea. No other major SE's.	Rapid onset (1-3days) and highly signif improvement of emotionalism in both groups ($p<0.001$)	3C	HDRS

Gonzalez et al, 1995[33]	37	Open, non-placebo controlled comparative trial with randomized controls	Fluoxetine v Nortriptyline	SSRI v. TCA	Fluox-20mg/d Nortript-max 75mg/d	6 wks	Response of early AD tmt effects on level of neuro, functional, and cognitive recovery	No serious SE's	Fluoxetine=Nortriptyline for early tmt of PSD. Signif imp in mood, neuro fx, & cognitive ability (p=0.001)	2B	MADRS, HDRS, BI, MMSE
Lazarus et al, 1994[37]	58	Retrospective study	Methylphenidate v. Nortriptyline	Psych ostim v. TCA	Methyl-10mg/d or higher. Nortrip-25-125mg/d	4 wks	Compare effect of stimulant v. TCA in tmt of PSD	Methyl-Irreg heart beat, tachycardia Nortrip-nausea, sedation	Methylphenidate =Nortriptyline in efficacy. Methy- had ↑response rate (p<0.001)	3C	DSM-III-R
Lazarus et al, 1992[38]	10	Prospective study	Methylphenidate	Psych ostim	10-40mg/d	3 wks	Eval efficacy and SE's of Methylphenidate for tmt of PSD	shortness of breath, nausea, irritability, insomnia	80% showed full or partial ↓ in depressive symptoms	3C	HDRS, MMSE
Masand et al, 1991[39]	17	Retrospective study	Dextroamphetamine v. Methylphenidate	Psych ostim	Dextro-5-20mg/d Methyl-5-15mg/d	5 yrs	Eval psychostim tmt for PSD	Dextro-confusion, tachycardia Methy-agitation	Dextro=Methyl	3C	DSM-III-R

RCT-Randomized-Controlled Trial, SSRI- Selective serotonin reuptake inhibitors, NARI-Noradrenaline reuptake inhibitors, TCA- Tricyclic Antidepressants
DB-double-blind, PSD-poststroke depression, ADL-activities of daily living, AD-antidepressant, QoL-Quality of life
BDI-Beck Depression Inventory, HDRS-Hamilton Depression Rating Scale, EDS-Emotional Distress Scale, CGI-Clinical Global Impression(Scale),
FIM-Functional Independence Measure,VADS-Visual Analogue Dysphoria Scale, MMSE-Mini Mental State Examination,
JHFI-Johns Hopkins Functioning Inventory, MADRS-Montgomery-Asbery Depression Rating Scale,
ZDS- Zung self-rating Depression Scale, BI- Barthel Index, HAM-D-Hamilton Rating Scale for Depression

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