The Efficacy of Antidepressants for the Treatment of Post-Stroke Depression

Lesley Taylor

Palo Alto University

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In the United States, over 795,000 strokes occur every year, and it is a leading cause of long-term disability (American Heart Association, 2017). Post-stroke depression (PSD) is a common neuropsychiatric complication with prevalence rates ranging between 39% to 52% during the first 5 years after stroke (Robinson & Jorge, 2015). Although the majority of strokes occur in adults who are age 65 and older, 34% of strokes occur in individuals under 65-years-old (Centers for Disease Control and Prevention, 2017). The negative effects of PSD include increased disability, cognitive impairments, mortality, and decreased functional rehabilitation and quality of life (Paolucci, 2008; Robinson & Jorge, 2015). Additionally, research indicates that PSD is associated with increased suicidality, especially in women and young patients (Pompili et al., 2015).

Diagnosis and treatment of PSD is complicated by its complex etiology and related post-stroke impairment. Diagnosis can be difficult due to cognitive and communication impairments, such as aphasia, and changes in facial expression, (Hackett, Kohler, O'Brien, & Mead, 2014; Paolucci, 2008). In addition to psychosocial factors, physiological factors related to brain damage, such as lesion location and biochemical dysfunction, may contribute to PSD (Robinson & Jorge, 2015). Therefore, PSD is considered to be a bio-psycho-social disorder (Ayerbe, Avis, Wolfe, & Rudd, 2013; Robinson & Jorge, 2008).

Antidepressants (ADs) are one of the main treatments for PSD and contribute to improving biochemical dysfunction. Selective serotonin reuptake inhibitors (SSRIs) are the most recommended because they are generally well tolerated (Paolucci, 2008). However, other classes of ADs are shown to be effective and may have advantages for treating co-occurring conditions (Cravello, Caltagirone, & Spalletta, 2009; Rampello et al., 2005) or in situations

where SSRIs are not tolerated (Robinson et al., 2000) or contraindicated (Ducros, 2012). For example, noradrenaline reuptake inhibitors (NARIs) have been effective in treating PSD characterized by psychomotor retardation (Rampello et al., 2005). Serotoninergic and noradrenergic reuptake inhibitors (SNRIs) have been effective in treating PSD and emotional unawareness, alexithymia (Cravello et al., 2009). In addition, research indicates that tricyclic antidepressants (TCAs) have a higher response rate for treating PSD than SSRIs (Robinson, 2000). Therefore, effective treatment of PSD may involve selecting ADs most suitable for the individual.

PSD is a complex disorder with multiple causes. Effective treatment for depression includes antidepressants, which are especially effective for individuals after stroke. Antidepressants are effective as demonstrated by several studies because they help improve neurochemical dysfunction.

Post-Stroke Depression

The *Diagnostic and Statistical Manual of Mental Disorders* (5th ed.; DSM-5; American Psychiatric Association [APA], 2013) defines depression as a depressed mood or anhedonia for more than two weeks, plus four or more symptoms that affect daily life, such as weight loss or gain, sleep problems, reduced concentration, and fatigue. However, Hackett et al. (2014) proposes that in busy, resource challenged settings tools other than *DSM-5* may be appropriate to screen and measure post-stroke depression. These tools include the nine-item Patient Health Questionnaire (PHQ-9; Kroenke, 2001), the Hamilton Depression Rating Scale (HAM-D; Hamilton, 1960), and the Beck Inventory Depression Inventory (BDI; Beck, 1961). Although a lack of consistency and arbitrary cut-offs are cited as possible confounding factors in depression studies (Ayerbe, et al, 2013; Chen, Guo, Zhan, & Patel, 2006), Deng et al., 2107), Hackett et al.,

2014; Paolucci, 2008), researchers also indicate that different assessment scales did not impact AD treatment results (Chen, 2006; Deng 2017). In addition to being resource efficient, depression rating scales are critical as they can take a granular approach to symptoms and improvements. This enables researchers and healthcare professionals to make decisions with increased precision regarding optimal treatments and efficacy for individuals with PSD.

Antidepressant Treatment

Different ADs work in similar ways, typically by increasing target neurotransmitters that are implicated in depression (Kalat, 2013). For patients post-stroke, research indicates that ADs may be effective in preventing PSD (Robinson & Jorge, 2015) and in facilitating functional recovery (Adams & Robinson, 2012). Considering the bidirectional aspect of depression and recovery (Robinson & Jorge, 2015), this may further support the usage of ADs. Yet, some studies produced conflicting results regarding both prevention and function (Paolucci, 2008), thus, limiting routine use of ADs in post-stroke care.

Early intervention is critical for both depression and functional recovery post-stroke, so timing of treatment is important. Guidelines from America and Europe suggest screening for PSD within 6 weeks after stroke. Once PSD diagnosis is confirmed, AD treatment for 6 months is recommended (Hackett et al., 2014). Additional recommendations include evaluating AD efficacy at 6 weeks and modifying treatment if the patient has not responded (Deng et al., 2017). Research indicates that AD usage may be most effective during the 6 to 9-month post-stroke period. (Gao et al., 2017). This research supports a time-based approach to treating PSD.

Due to the adverse effects of PSD, effective treatment is essential. However, current research on efficacy and timing of ADs is conflicting and limited. Chen et al. (2006) conducted a meta-analysis of 16 randomized placebo-controlled trials including 1320 patients to determine

the efficacy of ADs to treat PSD. Studies were included when a single AD was compared with placebo and when depression was confirmed by the *DSM* or other validated rating scale. Both English and Chinese literature were reviewed for inclusion. The primary outcome measurement was response rate, which was defined as remission or reduction in depression rating scale scores from baseline to endpoint.

SSRIs were evaluated in 12 studies. TCAs were evaluated in two, and other antidepressants were evaluated in three studies. Treatment duration ranged from 4 to 26 weeks. For treatment groups, dropout rates ranged from 0% to 39%; pooled response rates were 65.18%. Depression scores significantly improved post-treatment in patients who received an AD versus placebo. However, the authors commented that significance was not reached when treatment response was identified as full remission of depression rather than reduction of symptoms. Longer treatment duration resulted in greater improvements of depressive symptoms. Chen et al. (2006) concluded that patients with PSD experienced significant improvements in depressive symptoms with AD treatment and that effectiveness increased with longer treatment.

However, although ADs are shown to be effective compared to placebos, less research has been conducted comparing different classes of AD medications. In a meta-analysis of randomized controlled trials, Deng et al. (2017) found that NARIs were the most effective at reducing HAM-D scores, followed by TCAs, psychotherapy with ADs, and SSRIs. However, since different ADs have different side effects, they are not all equally appropriate regardless of their efficacy at reducing depressive symptoms.

SSRIs

SSRIs are the most recommended AD for PSD treatment since they are generally well tolerated (Paolucci, 2008). They are also the most researched. In recent meta-analyses, SSRI

studies were included in 53% (Hackett et al., 2008), 66% (Deng et al., 2017) and 75% (Chen et al, 2006) of all pharmacological interventions. In patients post-stroke, SSRIs are effective at improving cognition, physical recovery, activities of daily living, as well as treating depression (Robinson & Jorge, 2015).

The association between serotonin and mood is well established, and research confirms its role in PSD. In one study (Gao, Zhu, Zhang, & Wang, 2008), patients with PSD compared to without had significantly lower serotonin levels. Furthermore, in a neuroimaging study, a 6-month SSRI treatment improved depressive symptoms and N-acetyl aspartate/creatine (NAA/Cr) and Choline/creatine (Cho/Cr) ratios in individuals with PSD. These studies support the role of SSRIs in ways other than simply increasing serotonin levels and decreasing depressed mood.

However, recent research indicates that SSRIs may not be the the most effective treatment for reducing depressive symptoms compared to other ADs (Deng et al, 2017). Other research indicates that SSRIs were less effective (Robinson, et al, 2000) or equally as effective (Fruehwald, Gatterbauer, Rehak, & Baumhackl, 2003) as placebo for reducing depressive symptoms at 3 months. This may be explained when conservative measurements evaluate efficacy, such as intention-to-treat. Also, high-touch interventions during the immediate post-stroke period may be psychologically protective for some individuals.

SNRIs

Depression and emotional unawareness, alexithymia, are common after stroke, so evaluating the efficacy of antidepressants that treat both conditions is important. Cravello et al. (2009) compared the effects of the SNRI venlafaxine with the SSRI fluoxetine on patients with PSD and alexithymia. The 8-week, open-label study included 50 patients with PSD with and without alexithymia. Patients were randomized to either fluoxetine or venlafaxine treatments,

starting on the lowest dosage. Dosage was reevaluated at 4 weeks and adjusted accordingly. Depression was confirmed with the *DSM* (4th ed.; DSM-IV; APA, 2000) and assessed with the HAM-D. Alexithymia was assessed with the Toronto Alexithymia Scale-20 (TAS-20; Bagby, 1994). HAM-D and TAS-20 measurements were repeated at 1, 2, 4, 6, and 8 weeks.

Individuals in both the fluoxetine and venlafaxine groups reported mild side effects but did not discontinue treatment. After 8 weeks, HAM-D scores had significantly reduced with similar improvements for both treatment groups**.** However, patients in the venlafaxine group also improved on alexithymic symptoms regardless of a baseline diagnosis of alexithymia. The authors commented that venlafaxine efficacy may be dose dependent because 76% of patients had increased to 150-mg a day from the baseline dose of 75-mg a day. Cravello et al. (2009) concluded that the results further support the hypothesis that alexithymia is associated with noradrenergic dysregulation and that SNRIs may be an effective treatment for PSD with alexithymia.

TCAs

TCAs are not usually a first choice AD due to side effects (Deng et al., 2017; Paolucci, 2008). However, they have been found to be more effective than either ADs in combination with psychotherapy or SSRIs alone in reduction or remission of depression and should be considered if other ADs are not effective (Deng et al., 2017)

Robinson et al. (2000) evaluated the effectiveness of the TCA, nortriptyline, versus the the SSRI, fluoxetine, in PSD and recovery. The double-blind randomized controlled trial included 104 patients post-stroke who were assigned to receive nortriptyline, fluoxetine, or placebo for 12 weeks. Patients with and without depression were enrolled to control for recovery unrelated to depression. The HAM-D was used to assess response-to-treatment and

improvement between baseline and endpoint. Other measures evaluated anxiety, impairment of activities of daily living (ADLs), cognition, and social functioning. Results showed that nortriptyline had a significantly higher response rate than either fluoxetine or placebo for treating PSD and improving anxiety. However, ADL improvements depended on the measurement used. There were no differences shown for either cognitive or social functioning for nortriptyline, fluoxetine, or placebo groups. However, in the fluoxetine group, drop out rates and mean HAM-D scores were significantly higher than nortriptyline or placebo at 12 weeks. In addition, 10 of the 12 patients in the fluoxetine group lost more than 10 pounds and most drop outs stated gastrointestinal symptoms as the reason for withdrawal.

NARIs

NARIs are a newer class of ADs that inhibit the reuptake of noradrenaline and may be appropriate for patients who do not respond to other ADs or need treatment for co-occurring conditions. Rampello et al. (2005) evaluated the effectiveness and tolerability of the NARI, reboxetine, on patients with PSD characterized by psychomotor retardation. Although SSRIs are widely used, patients with psychomotor retardation show less response to these antidepressants. In this double-blind randomized controlled trial, 31 patients were assigned to either reboxetine or placebo groups for 16 weeks. Upon completion, HAM-D and BDI depressions scores were reduced for both groups, however, this was statistically greater in the reboxetine group. In addition, symptom improvements in psychomotor retardation were significant in the reboxetine group only. This study shows that reboxetine may be an effective and well-tolerated treatment for PSD characterized by psychomotor retardation.

Research Limitations

It is important to note that research on PSD and AD treatment may be limited by study characteristics. In a systematic review of PSD (Ayerbe, et al., 2013), the majority of research was conducted in hospital or rehabilitation settings (86%) and with follow-up of a year or less (78%). All studies in the review had a mean age between 60 – 78-years-old. Furthermore, AD research often excludes individuals with cognitive impairment, communication deficits, and/or previous psychiatric illness (Chen et al., 2006; Deng et al., 2017; Hackett et al., 2014). These limitations may prevent generalization for treating PSD in different individuals.

Conclusion

PSD is a complex bio-psycho-social disorder with multiple causes. ADs typically reduce depressive symptoms by improving biochemical dysfunction, however, there is also some evidence that ADs prevent depression and improve function. Because of the negative effects and bidirectional component to depression and disability, further research into this association should be investigated.

Although SSRIs are the most recommended and researched AD, they are not always the most effective. Some research indicates higher dropout rates, lower efficacy, and serious side effects, like significant weight loss, that may make them inappropriate for some individuals, especially geriatric patients who are physically ill. Alternatives to SSRIs, such as SNRIs, TCAs, and NARIs, are shown to be more effective for treating some co-occurring conditions and may be considered for SSRI-resistant depression. Therefore, it may be equally important to identify the most suitable AD for the specific individual, taking into consideration underlying causes, problematic side effects, poly-drug interactions, and adherence issues.

Variability in research methods and inclusion criteria may prevent generalization of findings to the broader post-stroke population. Excluding individuals with cognitive disabilities,

communication problems, and/or prior psychiatric disorders may especially affect individuals most at risk for developing PSD. Furthermore, the focus of research on the short-term effects of ADs in individuals over 60-years-old, may not apply to younger stroke patients coping with long-term physical disability, lack of social support, and depression. Research in this area is severely lacking and much more is needed.

Although few studies have focused on nonpharmacological treatments, growing research in this area shows promise. ADs show efficacy in treating PSD at the neurochemical level, but this is a single component for a complex bio-psycho-social disorder. A research-based, multimodal, and integrated approach to post-stroke care deserves to be explored. This approach may offer additional psychological and physical health benefits as individuals transition from high-touch medical settings to home, then navigate their new life after stroke.

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