Poststroke Depression: A Biopsychosocial Approach

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Poststroke depression (PSD) is a form of geriatric depression that is associated with various negative outcomes. This article reviews existing research concerning the etiology, treatment, and prevention of PSD with particular emphasis on the development of a biopsychosocial conceptualization of PSD etiology and treatment. Existing intervention trials are reviewed. A behavioral model of PSD treatment is presented based on a biopsychosocial understanding of PSD that highlights the potential utility of the lesion location hypothesis in the early poststroke period and the behavioral and social changes that may be linked to depression in the postacute period after stroke.

Introduction

Approximately 600,000 people in the United States have stroke each year, leaving approximately 3 million stroke survivors currently living in the Unites States [1]. Stroke leads to significant cognitive, physical, and functional limitations [2,3], and is the leading cause of long-term disability in the United States [1]. A substantial number of stroke survivors also experience depression, and there is considerable evidence that depression in stroke survivors is associated with excess disability. Although estimates of the prevalence of depression after stroke vary depending on sampling criteria, measurement methods, and sampling time frame, most estimates of the prevalence of poststroke depression (PSD) are approximately 30% to 40% [4–6]. Moreover, patients with PSD have greater neurologic and cognitive impairment [7,8], greater limitations in activities of daily living [9], slower recovery [10,11], and may have greater risk for mortality than stroke patients without depression [12]. In short, depression among patients with stroke increases the probability of negative outcomes associated with stroke, and should be a major focus of treatment. Furthermore, preliminary evidence suggests that reductions in depressive symptoms among patients with stroke can lead to better long-term outcomes [10,13].

In this article we 1) review hypotheses concerning the etiology of PSD and present a biopsychosocial model of PSD; 2) review evidence concerning the utility of current treatment and prevention approaches for PSD; and 3) present a conceptualization for additional research into behavioral interventions for PSD based on the biopsychosocial model of PSD.

Etiology, Treatment, and Prevention of Poststroke Depression

Most research on PSD has focused almost exclusively on strictly biomedical hypotheses regarding the etiology of PSD and on pharmacologic approaches to its treatment. Etiologic studies have focused primarily on the lesion location hypothesis [14]. The lesion location hypothesis as proposed by Robinson et al. [15] argues that depression is more common after left frontal and subcortical strokes than after strokes in other brain regions. Evidence supporting this hypothesis has not been consistent [16,17]. A comprehensive meta-analysis by Carson et al. [18] revealed no empirical support for the notion that depression after stroke is associated with the cerebral hemisphere involved (*ie*, right vs left), or with the particular location within each hemisphere (*ie*, anterior vs posterior). Recent studies and reviews since that meta-analysis have continued to show mixed results [19,20].

In light of the strong biomedical emphasis in existing conceptualizations of PSD, it is not surprising that pharmacologic treatments have surfaced as the first choice for combating PSD. To date, controlled treatment studies have primarily focused on the efficacy of antidepressants for reducing depressive symptoms in patients with stroke [21–27]. Table 1 contains a summary of published randomized clinical trials aimed at reducing depression among patients with stroke. Antidepressant efficacy for treatment of PSD has been reported in double-blind, randomized, placebo-controlled studies with tricyclic antidepressants [21,25] and selective serotonin reuptake inhibitors (SSRIs) [22,23]. Although tricyclic antidepressants have consistently shown efficacy, SSRIs have produced mixed results.

Table 1. Randomized clinical pharmacologic trials aimed at reducing depression after stroke*

Study	Drug/dosage	Sample size, *n*	Treatment duration	Outcome measures for PSD	Treatment response†	Mean Δ (SD)
Andersen et al. [23]	Citalopram, 40 mg/d, vs placebo	33/33	6 wk	HDRS	59%/28%	8(6)‡/4.8(4.6)
Wiart et al. [22]	Fluoxetine, 20 mg/d, vs placebo	16/15	45 d	MADRS	62.5%/33.3%	16.6(8.1)‡/8.4(7.8)
Fruehwald et al. [26]	Fluoxetine, 20 mg/d, vs placebo	26/24	12 wk	HDRS	69.2%^{E}/75%^{E}	23.3(12)^{E}/19.1(12)^{E}
			18-mo open-label follow-up		81.8%^{E‡}/27.8%^{E}	22‡(17.2)^{E}/8.8(12)^{E}
Lipsey et al. [25]	Nortriptyline, 100 mg/d, vs placebo	14/20	6 wk	HDRS	Support efficacy of nortriptyline over placebo^{E§}	NR
Rampello et al. [27]**	Reboxetine, 4 mg/d, vs placebo	16/15	16 wk	HDRS	Significant treatment response for the reboxetine group§	Pre: 24.06(1.52)/24(1.31); Post: 9.26(2.15)§/22.73(2.4); no dropouts $^{T/E}$
Robinson et al. [21]	Nortriptyline, 100 mg/d, vs fluoxetine, 40 mg/d, vs placebo	16/23/17	12 wk	HDRS	63%^{T§}/9%^{T}/24%^{T}	Pre: 22.5(8.5)^{E}/20.4(4.7)^{E}/17.5(6.2)^{E}; Post: 9(5.5)^{E§}/18.5(7.6)^{E}/12.2(4.7)^{E}
Miyai and Reding [28]	Desipramine, 100 mg, vs trazodone, 100 mg, vs fluoxetine, 20 mg	13/6/5	4 wk	HDRS	Each drug multiplied by time^{E¶}; ns between groups	6(3)^{E}/8(3)^{E}/5(NR)^{E}
Lauritzen et al. [24]	Imipramine, 150 mg, plus mianserin, 30 mg, vs desipramine, 150 mg, vs mianserin, 30 mg	10/10	6 wk	HDRS	NR	10(6.4)/7.2(4)

*Results reported using intention-to-treat (^{T}) analysis unless otherwise specified (^{E}efficacy)
†> 50% reduction in symptoms
‡$P < 0.05$
§$P < 0.01$
¶$P < 0.001$
**Included only patients meeting criteria for "retarded depression"
HDRS—Hamilton Depression Rating Scale; MADRS—Montgomery-Asberg Depression Rating Scale; NR—not reported; ns—not significant; PSD—poststroke depression

Robinson et al. [21], in a study comparing nortriptyline (tricyclic antidepressant), fluoxetine (SSRI), and placebo reported a significant decrease in depressive symptoms with nortriptyline over placebo and fluoxetine, but no significant differences between fluoxetine and placebo. Additionally, Fruehwald et al. [26] found no significant differences between fluoxetine and placebo after the initial 12-week treatment period. However, at 18-month follow-up, the fluoxetine group had significantly lower rates of depression than the placebo group.

Psychostimulants also have received attention in the treatment of PSD. Although randomized controlled trials are currently lacking, retrospective studies have reported significant reductions in depressive symptoms in patients with PSD after treatment with psychostimulants [29–31].

The results from studies listed in Table 1 indicate that although many stroke patients benefit from antidepressant trials, there is a substantial percentage of patients who do not respond to antidepressant trials and remain depressed after treatment. Others have been critical of the existing antidepressant literature in PSD. Notably, Hackett et al. [32•], in an extensive meta-analysis of the PSD pharmacologic literature, cited the lack of uniform methodology among the studies to date, which may temper conclusions drawn regarding the clinical significance of pharmacologic treatment benefit in patients with stroke. They note that although many treatments seem to reduce depressive symptoms after stroke, the clinical significance of these changes is unclear.

Pharmacologic treatment studies of PSD also have increased understanding of the disorder in other ways. First, treatment studies have shown potential heterogeneity within PSD. For example, a double-blind study by Rampello et al. [33] classified depressed subjects as "retarded depressed" (characterized by symptoms of lethargy) or "anxious depressed" (characterized by symptoms of anxiety) and randomly assigned them to citalopram (SSRI) or reboxetine (noradrenergic reuptake inhibitor). Although both treatments have shown efficacy in patients with PSD [23,27], the study showed that the SSRI compound was more efficacious than reboxetine in patients with "anxious depression," whereas the patients classified with "retarded depression" and treated with the noradrenergic reuptake inhibitor compound had significantly better outcomes than those treated with citalopram. Therefore, patients with PSD may present with different subtypes of depressive symptoms that may determine the best pharmacologic treatment. Although these results seem promising and raise interesting hypotheses concerning optimal treatment matching, they require replication with other samples. Second, some PSD treatment studies have shown that there often is considerable spontaneous remission of PSD in the early postacute phase [23,26]. Andersen et al. [23] reported that approximately 50% of patients who began treatment 2 to 6 weeks after stroke recovered from depression regardless of whether they received the active treatment or placebo. In a second study [26], approximately 75% of patients receiving placebo showed a significant treatment response at 12 weeks (compared with 69% in the active treatment).

As the negative impact of PSD on recovery from stroke has become more apparent, interest in the prevention of PSD has grown. Table 2 lists randomized trials that have attempted to decrease the frequency of depression in patients with stroke. Of five published randomized trials, three present either lower rates of depression or lower mean depression scores in treated patients as compared to control subjects [34–36]. One trial found significantly lower rates of depression with efficacy analyses, but not intent-to-treat analyses [37], and the final study showed no significant differences in depression between treatment and control groups [38]. However, methodologic differences between the studies may hinder the conclusiveness of their findings as a whole. For example, the time between the stroke and the initiation of intervention ranges from 1 day after stroke to 6 months after stroke.

The relatively large percentage of nonresponders in most studies suggests that alternative approaches to treatment and prevention may be needed as an adjunct to pharmacologic approaches or as stand-alone treatments in some patients. Yet, despite the potential value of nonpharmacologic treatments in PSD, many of these have not been rigorously studied [32,39]. Several treatments have shown encouraging preliminary results. For example, a 2-week, 10-session treatment of repetitive transcranial magnetic stimulation (rTMS) was compared with sham rTMS treatment over the same period. Beneficial treatment effects were reported in the group receiving rTMS [40]. Although there have been no randomized controlled studies to date, electroconvulsive therapy (ECT) also has been successfully used in the treatment of PSD [41,42]. In a retrospective study, 95% of study subjects had a moderate or marked response to the treatment, and 63% had not relapsed when measured 4 months later [41].

In terms of psychotherapy, cognitive behavior therapy (CBT) also has been used to treat patients with PSD [43–46]. Hibbard et al. [43] recommended modifications of CBT according to empirically derived principles developed from research on patients with PSD that purportedly increase the utility of CBT in treating PSD. Case studies and uncontrolled studies have reported the usefulness of CBT for patients with PSD [44,45]. However, the only randomized, controlled trial of CBT for PSD [46] did not show significant benefits of CBT over the no-treatment condition. Controlled studies examining nonpharmacologic attempts to prevent PSD have included leisure rehabilitation, occupational therapy, and an education and counseling intervention after stroke, but none of these efforts significantly decreased the frequency of PSD in participants [47–49].

The inconsistent support for the lesion location hypothesis and the modest efficacy of antidepressants

Table 2. Randomized studies on prevention of PSD

Study	Drug/dosage	Sample, *n*	Time between stroke and treatment initiation	Treatment duration	Outcome measure	Depression occurance rate
Rasmussen et al. [34]	Sertraline, 50 to 100 mg/d, vs placebo	70/67	Within 6 wk of stroke	12 mo	HDRS	≈ 10%*/ ≈ 30%
Niedermaier et al [35]	Mirtazapine, 30 to 45 mg/d, vs no treatment	35/35	1 d after stroke	NR	HDRS	5.71%*/40%
Palomaki et al. [38]	Mianserin, 60 mg/d, vs placebo	50/50	< 1 mo after stroke	1 y	HDRS	ns
Narushima et al [37]	Nortriptyline, 100 mg/d, vs fluoxetine, 40 mg/d, vs placebo	15/17/16	Within 6 mo after stroke	12 wk	HDRS	$7.7\%T^{ns}$, $^{E*}/20\%T^{ns}$, $^{E*}/33.3\%^{T}$
Grade et al. [36]	Methylphenidate, 30 mg/d, vs placebo	10/10	Admission to rehabilitation unit	3 wk	HDRS	Treatment group scored significantly lower on HDRS*; rates of depression NR

*$P < 0.05$

E—efficacy analysis; HDRS—Hamilton Depression Rating Scale; NR—not reported; ns—not significant; PSD—poststroke depression; T—intention-to-treat analysis

beyond placebo effects may highlight limitations in the current conceptualization and treatment of PSD. Moreover, the limited benefit of CBT may highlight the need for greater modification of existing psychotherapy approaches to treat PSD, particularly in light of the significant cognitive impairment that often co-exists with PSD. We address each of these below by outlining one potential biopsychosocial model of PSD and a treatment approach that not only reflects this model, but has also been used successfully with cognitively impaired patients.

Limitations of a Strictly Biomedical Approach to Poststroke Depression

The inconsistent results in lesion location research coupled with the limited efficacy of antidepressant trials may be linked to psychosocial factors associated with PSD. One hypothesis is that the correlates of depressive symptoms may change over time. For example, in a study by Astrom et al. [50], depression was associated with left hemisphere lesions during the acute rehabilitation phase. However, at 3 months, depression was associated with the severity of impairment in activities of daily living, and at 12 months depression was associated with social contact and integration. The biomedical variables (*eg*, lesion location) that may be associated with the onset of depression in the period immediately after stroke may not be as influential several months after stroke when psychosocial factors may play a greater role in maintaining depression. The apparent heterogeneity observed in PSD may be linked to time since stroke. Consistent with Astrom et al. [50], Tateno et al. [51•] have noted potential heterogeneity in PSD such that depression shows stronger associations with lesion location in the acute (or subacute) poststroke period (early-onset PSD), but that postacute-phase PSD (late-onset PSD) reflects a psychosocial syndrome with links to physical disability and social impairment. Despite the initial cause of PSD in the acute phase, psychosocial factors may maintain depression over time, or may lead to new cases of late-onset depression in the postacute phase.

Although the current biomedical conceptualizations and treatment of PSD have proven useful to some extent, the limitations of these purely biological approaches may lie in their inability to account for and modify psychosocial consequences of stroke. For example, Robinson et al. [21] observed that patients who responded to nortriptyline (*ie*, reductions in depressive symptoms) did not show similar improvements in social functioning. Therefore, biopsychosocial hypotheses that take into account the biomedical aspects and psychosocial consequences of stroke may be more effective in understanding and treating PSD over time.

The literature reviewed suggests that the correlates of PSD may change over time, and psychosocial factors in PSD have not been adequately addressed in treatment and prevention studies. Based on these findings, we present a dynamic biopsychosocial model of PSD and have outlined how this model can be linked to existing treatment and prevention packages that may be useful in PSD.

Biopsychosocial Approach to Poststroke Depression

Early-onset PSD may be linked to disruption of neural circuits responsible for mood regulation such as the frontal-subcortical circuits [52,53]. Yet, patients who do not show depression in the acute/subacute period still may show significant risk for depression over time because of stroke-related physical and cognitive impairment, which disrupt social and behavioral functioning. Moreover, for patients with early-onset PSD, the initial causes of depression (*ie*, possible frontal-subcortical dysfunction) may not be the same factors that maintain and exacerbate this depression over time (*ie*, social withdrawal and behavioral deactivation).

There is empirical support for the notion that depression is linked with left frontal lesions in the acute/subacute phase as compared to the postacute phase, and is stronger among inpatients than among community-dwelling stroke survivors [19]. However, Nys et al. [54] suggest that early PSD may be more reactive to cognitive and functional deficits. Singh et al. [20] found that although inferior frontal lesions were predictive of depression in stroke patients at 3 month follow-up, functional dependence remained a stronger predictor of depression than neuroantomical indices.

An adequate biopsychosocial model of PSD should highlight not only early (subacute) -onset PSD and its possible neuroanatomical correlates, but also other sequelae of stroke (*eg*, functional limitations in mobility, activities of daily living, and cognitive impairment), which may disrupt behavioral and social functioning and subsequently lead to a later phase PSD. Although functional and cognitive limitations have been linked to depressive symptoms in stroke [8,9,20,21], there has been little emphasis on potentially modifiable mediators between these limitations and depression that may be targeted in treatment. Potential behavioral consequences linking biomedical aspects of stroke to depression include failure to resume social activities [55], lower levels of social contact and activity [50], social withdrawal [56], and decreased participation in pleasurable events [57]. These psychosocial consequences of stroke show clear associations with depression after stroke and represent potentially modifiable aspects of PSD that could be addressed in treatment. These poststroke changes also fit well with behavioral conceptualizations of late-life depression, which have proven useful in various geriatric samples including patients with Alzheimer's disease (AD) [58], patients receiving geriatric medical rehabilitation [59], and patients in nursing homes [60].

Behavioral models of depression among frail older adults highlight the notion that biomedical events may disrupt behavioral regularity and reduce the availability of positive reinforcement and the frequency of response contingent reinforcement [61]. In the current context, the sequelae of stroke, including functional limitations and cognitive impairment, may disrupt behavioral regularity and lead to reduced engagement in pleasant events and increased social withdrawal. Development and utilization of behavioral treatments that address these behavioral issues may be effective in reducing depression after stroke in the postacute period. In terms of treatment strategies, these behavioral correlates of PSD may be more amenable to intervention, whereas the modifiability of biomedical aspects of stroke (*ie*, functional and cognitive impairment) may be limited to a large extent by the natural course of recovery.

Current Status of Psychosocial Treatments

Although the pharmacologic studies listed in Table 1 indicate the potential need for adjunct psychosocial and behavioral interventions, there have been few systematic attempts to develop nonpharmacologic treatment packages for PSD (Table 3). Kneebone and Dunmore [39] recommend that investigators seek to develop treatments for PSD that are more appropriate for individuals with PSD. That is, consideration should be given to substantial rates of cognitive impairment, functional limitations, and communication difficulties that patients with stroke often show. It is their contention that the usefulness of standard psychotherapy approaches may be limited in addressing PSD because the cognitive and communication impairments often experienced by patients with stroke would likely limit the extent to which the patient can engage in the treatment process. This may partially explain the lack of treatment response observed in the randomized trial of CBT for PSD described above [46]. Therefore, an effective treatment approach would need to account for these factors and be sensitive to the potential limitations that may be involved in verbally mediated treatment approaches with aphasic and cognitively impaired patients with stroke.

Although tailored treatments for PSD have not been systematically developed, behavioral treatments have been successfully standardized and used in populations with similar cognitive and functional limitations [58,59]. These treatments hold promise for circumventing the cognitive and communication difficulties that stroke patients experience by incorporating a caregiver into the treatment process and instructing the caregiver in treatment methods. This allows a cognitively impaired or moderately aphasic patient to potentially benefit from these treatments because the caregiver implements the treatment on a daily basis.

Teri et al. [58] adapted two behavioral treatments for depression among older adults with AD. As mentioned above, their treatment approach was unique in that the patient and caregiver were involved in treatment sessions. The caregiver was trained in behavioral methods aimed at reducing depression, including problem-solving techniques and scheduling of pleasant events for the patient with AD. The pleasant-event treatment condition focused on teaching Lewinsohn's behavioral model of depression [62], which emphasizes increasing pleasant events and positive interactions as one method to decrease depressive behavior and symptoms. The problem-solving treatment was a more flexible approach aimed at systematic problem solving related to depressive behavior. Seventy-two patient-caregiver dyads were randomly assigned to one of these conditions or to wait-list and typical care conditions. Sixty percent of patients in the active treatment conditions showed clinically significant improvement compared with 20% in the control conditions.

At a conceptual and practical level, this treatment fits well with the biopsychosocial model of PSD because it can be used to address behavioral changes that occur after stroke by including an explicit focus on increasing pleasant events and social interaction. It is also advantageous in that, in contrast to traditional CBT, it reduces the cognitive demands placed on the patient by incorporating the patient's caregiver who can learn to implement the treatment methods. Its efficacy among patients with significant cognitive impairment (*ie*, AD) provides some indication that the cognitive impairment observed in PSD may not be a significant barrier to successful outcomes. This is further supported by a study by Lichtenberg [63] that used a conceptually similar treatment approach among geriatric rehabilitation patients. In this study, geriatric patients received a similar pleasant-event treatment based on Lewinsohn's model [62] during the course of their rehabilitation stay. Thirteen patients received the behavioral treatment from a doctoral level psychologist, and an additional 13 patients received the same treatment from occupational therapists trained to implement the treatment. Eleven patients received typical rehabilitation care. Over the course of their rehabilitation stay (mean length of stay, 13 days), 69% of patients in the active treatments showed declines of at least one standard deviation on the Geriatric Depression Scale, compared with only 25% of patients in the usual care condition.

These related treatment approaches have shown efficacy and fit well conceptually and practically among patients with stroke. Yet, to date, there has been no application of these approaches in a stroke population. However, the treatment approach developed by Teri et al. [58], for the treatment of depression in patients with AD is likely to be a feasible treatment for depression among patients with stroke for several reasons including 1) similarity in the patient characteristics, 2) the importance of using close caregivers in the treatment process, and 3) the context in which the treatment is given.

Table 3. Randomized studies using nonpharmacologic treatments to reduce depression after stroke*

Study	Treatment (dosage)	Sample, *n*	Treatment duration	Outcome measures for PSD†	Treatment response	Mean Δ (SD)
Jorge et al. [40]	Left prefrontal rTMS vs sham rTMS (10 sessions)	10/10	2 wk	HDRS	30%/0%	7.3 (NR)‡, 38% reduction vs NR, 13% reduction
Lincoln and Flannaghan [46]	CBT vs attention placebo vs standard care (mean number of 1-hr sessions over 3 mo = 9.85, SD = 2.31)	39/43/41	3 mo	BDI, WDI	ns between groups	NR

*Efficacy analyses reported
†> 50% reduction in symptoms
‡$P < 0.001$
BDI—Beck Depression Inventory; CBT—cognitive behavior therapy; HDRS—Hamilton Depression Rating Score; PSD—poststroke depression; NR—not reported; ns—not significant; rTMS—repetitive transcranial magnetic stimulation; WDI—Wakefield Depression Inventory

First, patients with AD and with stroke show similar clinical characteristics including significant cognitive impairment and limitations in their instrumental and basic activities of daily living. These represent changes from previous levels of functioning, and in depressed patients are likely to be closely linked to behavioral deactivation in which the patients no longer participate or engage in activities that they once enjoyed and which provided their lives with a certain degree of behavioral regularity. Second, patients with AD and stroke are unlikely to be able to consistently attend to, organize, and carry out complex treatment activities because of their associated impairments in attention, memory, and executive functioning. This highlights the necessity of caregiver involvement in treatment in both of these patient populations. Third, the context in which the treatment given is similar in AD and stroke populations. These populations share demographic similarity in that most individuals with these problems are olden than 65 years. In the behavioral approach described above, behavioral regularity is disrupted by a biomedical process in AD and stroke. AD and geriatric stroke patients share similarity in that the resumption of behavioral regularity is likely to be aimed at resuming leisure and social activities, rather than formal employment. This provides a common treatment context and goal. Lastly, research has suggested that the context of the familial relationships may be important in each of these groups because each has shown high levels of caregiver burden associated with caring for individuals with these conditions [64]. Furthermore, caregivers of AD and stroke patients also have shown high levels of psychologic distress and depression [64,65]. In the published efficacy trial of the Teri et al. [58] behavioral treatment, caregivers showed reductions in their own depressive symptoms in the active treatment conditions. These findings highlight not only the similarity of these two geriatric populations, but also the appropriateness and need for such a treatment intervention for the patient and the caregiver.

Problem-solving therapy may be an alternative treatment approach that may prove effective in treating PSD. Rather than seeking to work around core cognitive deficits in depression (by incorporating caregivers into the treatment process), this approach seeks to directly address the cognitive dysfunction that often accompanies depression in geriatric patients. Alexopoulos et al. [66] noted that executive dysfunction is common in late-life depression and often takes the form of difficulties in planning, goal-directed behavior and modification of plans in response to feedback from the environment. By using a problem-solving therapy, they hoped to address this deficit in depression and thereby improve depressive symptoms. This treatment was efficacious in treating depressive symptoms in geriatric patients with executive dysfunction. Although relatively untested in moderately to severely impaired patients, it may be particularly applicable to PSD given the frequency of coexisting depression and executive dysfunction seen in older stroke patients. Moreover, Vataja et al. [67] found that stroke patients with depression and executive dysfunction had more severe depression, poorer social functioning, and poorer activities of daily living functioning than depressed stroke patients without executive dysfunction. As such, problem-solving therapy may be another avenue for addressing modifiable behavioral and social changes after stroke that may be important for later onset PSDs.

Conclusions

In this review we have attempted to describe one biopsychosocial model of PSD and related treatment approaches. To date, much of the etiology and treatment research has de-emphasized the role of psychosocial factors and treat-

ment in PSD. However, our intention is not to suggest that current conceptualizations of and treatments for PSD are without merit. In light of the biological and psychosocial correlates of PSD, it seems likely that a combination of antidepressants and psychotherapy may be the most effective approach to treating PSD. Although combination treatment trials have not yet been published in PSD, there is considerable evidence that this may be the optimal treatment for more general adult and geriatric depression [68•]. This review was intended to broaden the discussion of PSD, its potential heterogeneity, and a broader range of intervention options for this debilitating syndrome. There is considerable need for additional research into biopsychosocial aspects of the etiology, treatment, and prevention of PSD.

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