Poststroke Depression: An Examination of the Literature

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Objective: To examine literature on poststroke depression (PSD).

Data Sources: More than 200 articles related to stroke and depression were selected from a computer-based search spanning 1985 to 1995.

Study Selection: All relevant articles on PSD. Articles in foreign languages, case studies, anecdotal reports, book chapters, and reviews were excluded.

Data Extraction: Summary findings were independently reviewed by the authors.

Data Synthesis: PSD remains a frequent sequela of stroke; its prevalence remains uncertain because of continued methodologic problems in defining subject groupings and in utilizing psychiatrically normed assessment tools with neurologically impaired individuals, and because of the poor specificity/sensitivity of neuroendocrine markers in determining a diagnosis. The etiology of PSD appears to be complex and not fully understood. Although there has been much research on PSD, this review highlights the sparsity of available literature on its treatment.

Conclusion: The review points out the further need for more carefully designed studies of PSD that examine both assessment and treatment.

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More than 15 years ago, Labi and colleagues described depression as the most common untreated disability secondary to stroke. Poststroke depression (PSD) continues to be an area of significant research interest. A search of the Medline and Psychlit databases for the years 1985 to 1995, using the parameters “poststroke and depression” and “poststroke depression,” uncovered 225 papers that were published in English. Fifty of the manuscripts were unique to Medline, 39 articles were unique to Psychlit, and 69 articles were common to both databases. Despite this abundance of research, considerable gaps remain in our understanding of PSD, especially with regard to such issues as its diagnosis, its neuroanatomic correlates, and its treatment.

Interest in PSD stems from the fact that stroke is a major cause of disability, i.e., more than 600,000 individuals sustain a new stroke each year and there are more than two million stroke survivors living in the United States. Stroke continues to be the most common diagnostic group among inpatient rehabilitation patients occupying more than one third of the beds. Furthermore, PSD has been found to negatively affect length of stay and functional outcomes. PSD has also been associated with increased risk for subsequent mortality. Thus, although innovations in the acute management of stroke have resulted in a decrease in its mortality rate and, to some extent, the magnitude of its impairments, little has been done to improve the quality of life of those who survive as that quality relates to depression. Consequently, many who survive the acute event will live lives that are compromised by depression.

This review will examine the diagnostic issues related to PSD, the variability in the reported prevalence of PSD, the neuroanatomic correlates of PSD, and the psychopharmacological and psychological treatment of PSD.

The Prevalence of PSD: A Minor or Major Sequela of Stroke?

In 1986, we reviewed extensively the early research on the prevalence of PSD and factors associated with its reported variability. Although PSD continues to be the subject of a significant amount of investigation, little research has been done that increases our understanding of, or accounts for, the variability in its reported prevalence. Reported PSD prevalence rates range from as low as 25% to as high as 79%. Despite this variability, it is clear that a many individuals are debilitated by depression after stroke. Methodologic factors accounting for this variability include differing subject selection, methodologic problems with instrumentation, and limited utility of biochemical markers traditionally used in diagnosing depression. Each of these issues will be briefly discussed.

Subject Selection

Whether PSD is primarily associated with right or left brain damage is an issue that remains unresolved, since researchers often fail to separate the reported incidence of PSD in individuals after right and left cerebral strokes. Criteria for selection of patients in previous studies have differed widely and may also account, in part, for the variability in prevalence rates. For example, studies vary in the subsets of the stroke patients sampled (e.g., inpatient versus outpatient), in the time since the onset of the stroke (e.g., acute versus chronic), in the neuroanatomy of the stroke (e.g., cerebral versus noncerebral involvement, unilateral versus bilateral damage), in the inclusion and/or exclusion of individuals with global aphasia and/or concomitant dementia, and in the inclusion and/or exclusion of patients with prior psychiatric/substance abuse histories or other central nervous system diseases. These sampling differences limit the generalizability of present findings to other patient subgroups.

Instrumentation

Perhaps the most serious limitation of the PSD literature relates to the issue of diagnostic accuracy when standardized psychiatric assessment techniques, (i.e., structured clinical interviews, self-report scales, and biochemical markers) are applied to neurologically impaired individuals. Traditional psychiatric
criteria for determining a mood disorder relies heavily on patients' reports of specific symptoms in combination with depressed mood as indicators of depression. Implicit in this approach is the assumption that patients are aware of their situation, are capable of providing an accurate report of their mood, and do not have coexisting medical/neurological conditions that could either "mimic" targeted symptomatology or be interpreted more parsimoniously. When evaluating stroke patients, these basic assumptions must be reevaluated. Awareness cannot be assumed because stroke patients have been found to minimize and/or exaggerate their poststroke-related physical, cognitive, and affective changes in function. Indeed, individuals may be aware of some of their impairments yet minimize or exaggerate others. Thus, awareness is not a dichotomous variable but rather one that should be viewed along a continuum of impairment. This variability in awareness can bear directly on the accuracy of self-reports incorporated into traditional psychiatric assessment. In addition, when stroke patients have aphasia or severe dementia, they are often unable to provide accurate self-reports of their internal mood state. Hence, mood must be inferred from behavioral observations of these individuals or from data that are systematically gathered from others familiar with the patient's affective states. It is our observation, along with that of other investigators, that multiple sources of information are crucial to the diagnosis of PSD, yet they are not routinely or systematically pursued in making a psychiatric diagnosis. Given the problems inherent in the self-reports of stroke patients, a systematic multidimensional approach to the collection of information about the patients' mood is clearly needed.

The validity of any psychiatric assessment is also clouded by the nature of the assessment tools used in making a diagnosis of PSD. Both traditional psychiatric criteria, ie, DSM-IV, and psychological measures of mood rely heavily on the specific somatic complaints in combination with depressed mood as indicators of depression. For example, five of the nine symptoms required for a DSM-IV diagnosis of a major mood disorder (ie, fatigue or loss of energy, weight loss or gain and/or appetite changes, insomnia, psychomotor changes, concentration difficulties) are somatic in nature. Similarly, 11 items on the Beck Depression Inventory and 8 items on the Hamilton Rating of Depression are somatic in nature. These symptoms are just as likely to reflect behavioral/neurological impairments, the effects of age, or the impact of the person's immediate environment (eg, the effects of hospitalization) as they are to reflect the person's altered mood. For example, impairments in memory, attention, and abstraction may frequently underlie the patients' complaints of concentration difficulties after a stroke. Thus, a positive response to a question related to concentration could be mistakenly attributed to depression as opposed to an underlying cognitive impairment. Similarly, increased fatigue after a neurological insult could be misinterpreted as adhonia, a symptom of depression, rather than be viewed as hypoarousal, a secondary impairment to the stroke. Thus, as a result of the over-representation of somatic symptoms in traditional psychiatric criteria, there is potential for the misdiagnosis of mood disorders. Several authors have argued for the creation of more sensitive criteria for the diagnosis of PSD. This belief is based in part on recent evidence that somatic symptoms are unreliable indicators of PSD. In fact, some investigators have found that somatic symptoms are sensitive indicators of a mood disturbance in poststroke individuals, whereas others have found the opposite to be true. Indeed it has been reported that "... somatic symptoms were neither specific to PSD nor added incremental validity over nonsomatic symptoms for diagnosing PSD. ..." Furthermore this methodologic issue has been highlighted by recent research indicating that stroke patients are unreliable reporters of their mood.

A third issue that limits accuracy in diagnosing PSD is the lack of a systematic way to assess the impact of neurobehavioral syndromes and cognitive changes on the validity of depressive symptoms reported by patients. How severe do impairments such as hypoaorusal alterations in affective regulation (ie, euphoria, pathological laughter, or crying), and difficulties with prosodic expression have to be for the person's self-report to be unreliable? Two examples illustrate how neurobehavioral syndromes complicate the diagnosis of depression. First, hypoaorusal is a common sequella of PSD, as we have found in our work; it is not, however, correlated with depression in stroke patients. Second, alterations in affect expression, ie, excessive tearfulness and constricted affect, are indicative of depressed mood in non-neurologically impaired individuals. In stroke patients, these same behaviors are more likely to be attributable to a neurologically based lability or to a prosodic deficit. Unlike neurologically impaired individuals, a stroke patient's external affective behaviors may not match his or her internal mood. Recently, Starkstein and colleagues provided additional support for the independence of a prosodic deficit and PSD. Of the stroke patients they examined, 49% had prosodic deficits unrelated to depression. Depressed patients, as well as nondepressed patients, showed similar patterns of prosodic deficits. Thus, neurobehavioral sequelae of stroke, taken together or separately, complicate the diagnosis of PSD and directly affect the validity of PSD diagnostic statements.

Biochemical Markers of PSD

In non-brain damaged individuals, the Dexamethasone Suppression Test (DST) is a neuroendocrine marker of melancholia that has acceptable levels of sensitivity and specificity. Following the administration of dexamethasone, depressed individuals do not show suppressed plasma cortisol levels; nondepressed individuals do. Because the DST does not rely on the person's self-report of symptoms or of his/her mood, it has been suggested as an alternative approach to diagnosing PSD. Unfortunately, research reports wide variability in both sensitivity and specificity of this diagnostic tool when it is used to assess poststroke individuals. In poststroke inpatients, reported sensitivities are as low as 0% and as high as 75%. The DST's specificity is also quite varied and ranges from 70% to 95% for rehabilitation inpatients. Harvey and colleagues found that 75% of their sample had abnormal DSTs 1 week after stroke while 50% had an abnormal DST 3 weeks after stroke. Although individuals with abnormal DSTs had higher scores on the Hamilton Rating of Depression, none met DSM-III criteria for depression. The authors suggest that abnormal DSTs at 3 weeks after stroke might be predictive of future depression. Thus, it is difficult to interpret these data with regard to the utility of the DST in diagnosing PSD during the acute phase of poststroke recovery.

Studies of outpatients are even more confusing with respect to the relative merits of the DST as an indicator of PSD. In our study of a group of poststroke outpatients, we found the DST's sensitivity was 15% and its specificity was 67%. We concluded the DST was not a useful measure in the diagnosis of PSD. A similar conclusion was reached by Dam and colleagues. In contrast, Aström and colleagues reported that the DST is useful, (sensitivity = 70%, specificity = 96%) in diagnosing depression in chronic, but not acute, strokes. Thus, the DST does not appear to be a useful adjunct to the diagnosis of PSD. It remains to be seen whether other neuroendocrine markers, eg, thyrotropin releasing hormone or corticotropin releasing hormone, will be effective in diagnosing poststroke depression.
CEREBRAL LATERALITY AND PSD

Our understanding of the relation between the neuroanatomic loci of brain damage and the incidence of PSD is an unresolved issue. During the late 1970s and early 1980s, several researchers reported a clear-cut relation between laterality of brain injury and PSD, with the preponderance of research supporting PSD as an impairment associated with left brain damage. In subsequent attempts to replicate these earlier studies, some researchers reported reverse findings, i.e., PSD more commonly observed following right brain damage, whereas others failed to demonstrate any association between the laterality of brain damage and PSD.

PSD may reflect a more complex phenomenon than merely the neuroanatomic loci of brain damage. Schwartz and colleagues found PSD to be independent of lesion location, more severe in persons with right hemisphere lesions and correlated with functional disability, lesion size, and previous history of depression. In contrast, Downhill and Robinson found that coexisting depression and impairments in cognition were more likely to be observed in individuals with left hemisphere strokes.

Within the last 5 years, cerebral blood flow studies have been used to further examine PSD. These advanced imaging techniques have supported the notion that PSD is, indeed, a more complex phenomenon than anticipated. Using this imaging technique, Grasso and colleagues reported a reduction in blood flow to the area of the mesial temporal cortex of the affected hemisphere in depressed stroke patients. Reduced blood flow was strongly correlated with the severity of depression observed in these individuals. Yamaguchi and colleagues found that individuals with lesions in the left frontal and/or right parieto-occipital regions were more likely to be depressed. In another study by Stern and colleagues, lesion location within a hemisphere was found to be a more sensitive indicator of PSD than side of brain damage. More specifically, patients with lesions in the left parietal/occipital, left inferior frontal, right superior frontal, and right temporal lobe were more likely to be depressed than individuals whose strokes affected other areas of the brain.

Over the past decade, Robinson and colleagues have refined their understanding of the neuroanatomic correlates of PSD. In more recent investigations, they report a relation between PSD and lesion location primarily in patients with typical occipital asymmetry. In patients with left hemispheric lesions, PSD is found primarily in those without a history of depression. Additionally, these researchers have reported that PSD and a generalized anxiety disorder are associated solely with cortical lesions, whereas depression alone is associated with subcortical lesions. In patients with right hemispheric strokes, depression is associated with lesions involving the parietal cortex and a family history of psychiatric disturbance. Finally, this research team has concluded that catastrophic reaction is a subtype of PSD.

THE TREATMENT OF PSD

Given the prevalence of PSD and the amount of research focused on delineating its neuropathology, there is a surprising dearth of research focused on treatment of PSD. As in other depressive disorders, there are two traditional approaches to the treatment of PSD, one being antidepressant medication and the other being psychotherapy. When severe depressive reactions fail to respond to more traditional approaches, electroconvulsive therapy is considered. A review of the PSD literature suggests that there have been few studies on the efficacy of the various approaches to intervention and no published research on the relation among treatment efficacy, patient characteristics, and the medical economics of intervention. Literature pertinent to these domains of treatment are highlighted below.

Psychopharmacological Interventions

Treatment of PSD with antidepressant medication is often effective. However, drug therapy must be carefully evaluated to avoid polypharmacological interactions and potential adverse side effects of a particular antidepressant on a patient’s comorbidities. Nortriptyline, a tricyclic antidepressant, was among the early choices of antidepressants reported to be successful in the treatment of PSD. Indeed, Lipsey’s study documenting the benefits of this medication is one of the few randomized clinical trials in the literature. Balunov and colleagues compared the effects of amitriptyline to that of a tranquilizer (Seduxen) in individuals after stroke and a comparison group of individuals who received no treatment. They reported that amitriptyline was more effective in reducing depression, as measured by the Hamilton Rating Scale of Depression. Nortriptyline has also been reported to be an effective treatment of both emotional lability and depression after stroke. Andersen and colleagues compared the effects of two tricyclic antidepressant regimens (imipramine plus mianserin vs. desipramine plus mianserin) in 20 poststroke individuals whose Hamilton Rating Scale of Depression scores were 15 or above. A combination of imipramine plus mianserin was found to be superior to that of desipramine plus mianserin.

Other antidepressant medications have been evaluated. In a randomized trial, Reding and colleagues found that Trazadone was useful in the treatment of PSD. In a 6-week double-blind, placebo control study, the effects of the drug Citalopram, a selective serotonin reuptake inhibitor, were examined in a sample of 66 stroke patients. It was found to significantly reduce depression, as measured by the Hamilton Rating Scale of Depression. Support for alterations in levels of serotonin in depressed stroke patients can be found in work by Bryer and colleagues. They found that depressed stroke patients exhibit lower concentrations of 5-hydroxyindolacetic acid (5-HIAA) in their cerebrospinal fluid when compared with either nondisabled stroke patients or nondepressed individuals without a stroke. Since 5-HIAA is a serotonin metabolite, this study again points to altered levels of serotonin in poststroke depressed individuals and suggests that more recently developed serotonin reuptake inhibitors, eg, Prozac, Paxil, etc, are worthy of clinical trials as treatment for PSD.

An alternative pharmacologic approach to treatment of PSD has been the use of psychostimulants. In a comparison study of the relative effectiveness of two differing psychostimulants, ie, Dextroamphetamine and Methylphenidate, both drugs were equally effective in the treatment of PSD. Of the patients tested, 82% reported improved mood, with 47% showing "marked or moderate" improvement. Lazarus and colleagues compared the psychostimulant methylphenidate to the antidepressant nortriptyline. An equivalent rate of remission of depressive symptoms was observed in both treatment groups (53% methylphenidate, 43% nortriptyline); however, the response to treatment was more rapid in the individuals administered methylphenidate (average response time = 2.4 days for methylphenidate vs. 27 days for nortriptyline). Earlier studies by this same research team and by others described a reduction in depression following treatment with methylphenidate in 70% to 80% of patients (n = 10/study). Unfortunately the validity of these studies is compromised by a lack of adequate comparison groups, absence of randomization, and small sample sizes. While there is growing evidence to support the use of various antidepressant medications and psychostimulants in the treatment of PSD, further research is needed to identify the specific characteristics.
of patients who respond best to either of these types of medications and whether there are benefits in using antidepressants and psychostimulants in combination.

Use of Electroconvulsive Therapy

Electroconvulsive therapy (ECT) has been viewed as an approach to treatment of depression, particularly in severely depressed individuals who fail to respond to traditional approaches. The efficacy of ECT in the treatment of PSD has been explored in two retrospective studies. The first study, conducted by Murray and colleagues, found that 14 of 193 (7%) individuals had been treated with ECT for PSD between 1969 and 1981. The authors report improved mood in 12 of the 14 patients (86%), with only one patient experiencing an adverse effect as a result of treatment. In contrast, Currier and associates reviewed charts covering a 10-year period from 1982 to 1991 and found only 70 depressed poststroke individuals who had been treated with ECT. The authors report improvement in 95% of the cases, and conclude that ECT is a "generally well-tolerated and effective treatment." Despite this positive interpretation by the authors, significant side effects were observed in 60% (12 of 20 patients) of the cases, i.e., 7 patients suffered relapses despite their maintenance on antidepressant medication, 5 developed ECT-related medical complications and 2 pts experienced postinterictal confusion or amnesia. Given the prevalence of complications, we do not believe that the data reported support Currier and his colleagues’ conclusion. Thus, although data from retrospective studies appear to support the efficacy of ECT in poststroke individuals, we do not believe that the data support Currier and his colleagues’ conclusion. Thus, although data from retrospective studies appear to support the utility of ECT in the treatment of PSD, side effects of this intervention appear to be frequent. Therefore, a clinical trial examining the efficacy of ECT in poststroke individuals is indicated.

Psychotherapeutic Interventions

Given the high prevalence of PSD and the attention focused on pharmacological management, it is curious that minimal effort has been directed to the study of psychotherapy, either alone or combined with antidepressant medication as a treatment modality for PSD. Psychopharmacological treatment of PSD using the older tricyclics, while often effective, is frequently contraindicated in patients with stroke because of age considerations and coexisting medical problems. More than 10 years ago, we compared the effectiveness of cognitive psychotherapy, Nortriptyline, or a combination of both in the treatment of PSD and found that many patients either refused to take these earlier types of antidepressant or stopped taking medications because of their side effects (unpublished data). Although it is not known whether the refusal rate for antidepressants is any different from that for any other type of medication (eg, anticoagulants, antihypertensives, etc.), it is a still a factor to consider when contemplating available therapeutic options. Unfortunately, only one study on the effectiveness of these newer forms of antidepressant medications (eg, Prozac, Zoloft, and Paxil) has included poststroke individuals. These drugs, however, appear to offer the potential for effective treatment of PSD with minimal side effects.

Given the aforementioned considerations, psychotherapy frequently becomes the only viable intervention for PSD treatment. An obvious benefit is that the intervention can help depressed individuals learn new coping and social skills, thus increasing their sense of control over their current mood and their environment and helping prevent the recurrence of depressive episodes.

The paucity of research on psychological interventions for PSD may reflect the inherent difficulty clinicians face when attempting to apply traditional psychotherapies to individuals who are cognitively compromised after stroke. We have reported a successful adaptation of Beck’s cognitive-behavioral psychotherapy to the treatment of PSD. Focused principles of cognitive therapy have also been developed as guidelines for successful application of this approach to the treatment of PSD. Clearly, further systematic investigation of the relative utility of psychotherapy alone or in combination with psychopharmacological agents is needed to advance our understanding of the treatment of PSD.

SUMMARY

This review of the literature on PSD has examined an extensive body of research. PSD remains a frequent sequela of stroke, but its actual prevalence remains unknown. This is due in large part to continued methodologic problems in the literature that stem from a lack of clarity regarding such issues as subject selection, tools used for assessment, and an apparent lack of specificity and sensitivity of traditional neuroendocrine markers of depression in individuals after stroke. While studies published in the early 1980s indicated a clear-cut relation between PSD and lesion location, the neuroanatomic correlates of PSD are more complex than initially anticipated. Thus, the early work of Robinson and colleagues relating PSD to laterality of brain damage has evolved as more recent research has illustrated the importance of intrahemispheric loci of the lesion rather than the laterality of brain damage in the etiology of PSD. In addition, the extent of coexisting cognitive deficits and histories of psychiatric illness appear to play important roles in the presence and severity of the depression observed after stroke. Finally, this review has highlighted that treatment of PSD remains a relatively underexamined domain. Although a variety of antidepressant medications and psychostimulants appear to be effective in reducing the severity of PSD, these studies are short term, pay inadequate attention to the specific patient characteristics of those who respond to treatment, and fail to examine the long-term efficacy of these medications. Clearly, the cost benefits of ECT have not been adequately demonstrated in poststroke individuals. Furthermore, the demonstration that psychotherapy is a useful intervention for PSD, either alone or in combination with other therapeutic approaches, remains a challenge for future researchers.

In summary, this review points out how much research has been done within the past decade, but we believe that little new information has been learned about PSD, which in turn has resulted in little forward movement in the field. Consequently much remains to be learned about the diagnosis and treatment of PSD.

Acknowledgments: The authors appreciate the constructive comments of Steven Flanagan, MD, and Jennifer Bogdany on earlier versions of this manuscript.

References