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POST-STROKE DEPRESSION: PATHOLOGLOGY, DIAGNOSIS AND TREATMENT STRATEGY

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Abbreviations:

PSD- Post stroke depression,
WHO- World Health Organization,
DSM- Diagnostic and Statistical Manual of Mental Disorders,
BDI- Beck Depression Inventory,
HADS- Hospital Anxiety and Depression Scale,
HDRS- Hamilton Depression Rating Scale,
ZSDS- Zung Self-Rating Depression Scale,
HPA- hypothalamic pituitary-adrenal,
CT- computed tomography

ABSTRACT

Post stroke depression is most commonly faced psychiatric challenge, causing severe disability. Post stroke depression (PSD) occurs in nearly one-third patients either during acute/chronic stroke period. It's often under-diagnosed. A good diagnosis must be done within one month after stroke, based on self-reporting tools, followed by observer-rated interview. Mechanism is multifactorial, presently best supported by biopsychosocial model. Upcoming approaches are genetic based and cytokine theory. About 10% PSD patients face mortality. There is a huge negative biological and psychosocial impact of PSD. Currently, pharmacological and non-pharmacological way-outs are used to manage the PSD. However, precise and timely done evaluation aided by proper therapy and utmost care is also required, under the supervision of a multidisciplinary health team.

INTRODUCTION: A sudden injury (often with consequent multiple loss of function), followed by a recovery phase, characterizes stroke. Injury tends to be focal. This leads to a broad spectrum of neuropsychiatric complications including emotional, behavioral, and cognitive disorders [1]. Stroke is second leading cause of disability after cancer. The most common psychiatric complication which occurs after the stroke is depression (**Fig. 1 and 2**). There are three main reasons for people at increased risk of PSD namely-

a. They often suffer sudden, multiple loss of events (loss of physical function, employment, change in social status),

b. They may lose the neurological capacity to process these loss events,

c. Stroke may affect areas of the brain directly involved in control of mood [2].

It is prevalent in 20-80% cases. This variation is due to differences in diagnostic criteria, patient selection and time elapsed since stroke [3, 4]. It is often under diagnosed and undertreated. Post stroke depression (PSD) is clinically important due to its impact on stroke survivors and their family's life, socially, biologically and psychologically. It is associated with negative outcomes in terms of increased distress, disability, morbidity, suicidal thoughts, mortality and poor rehabilitation [5].

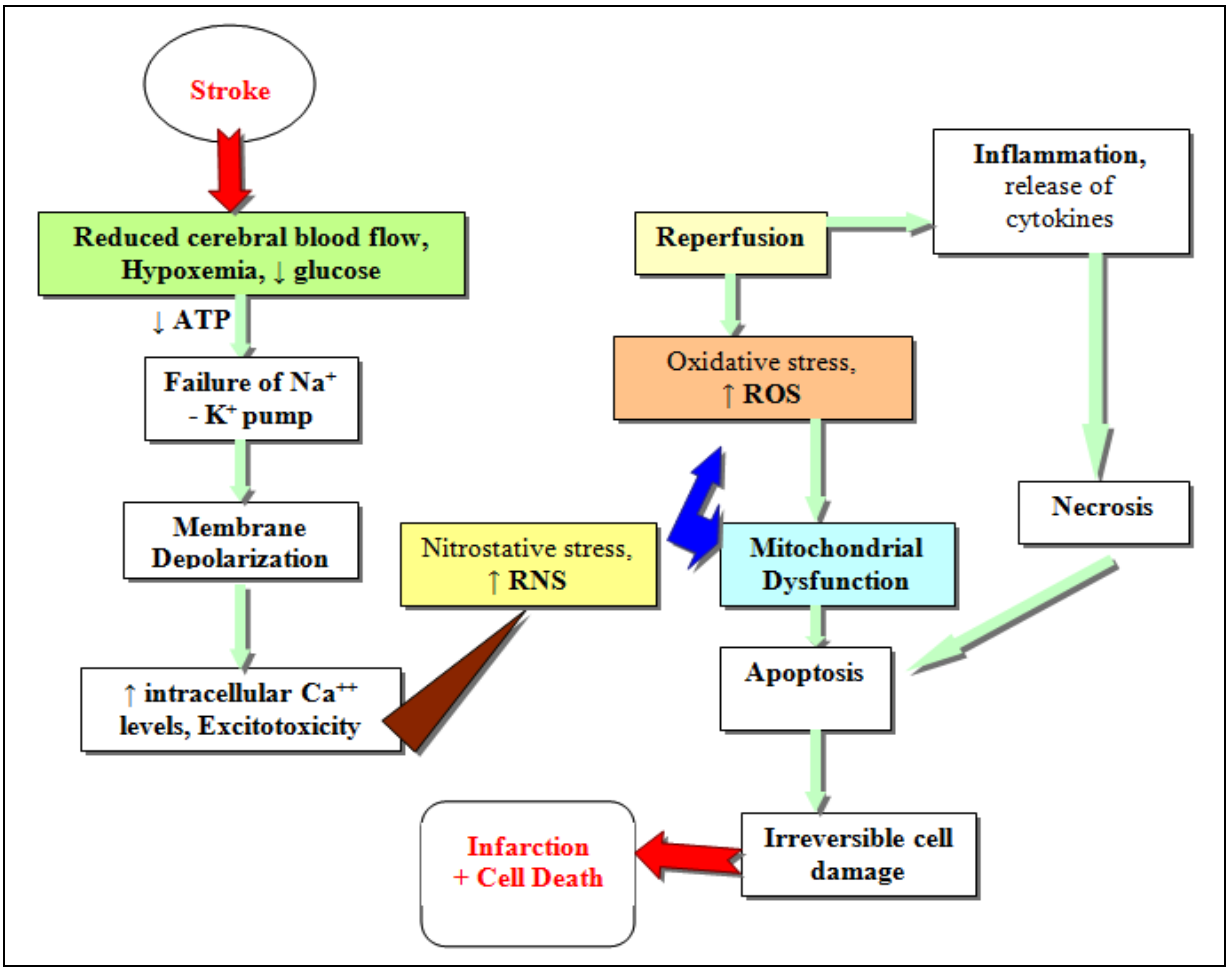

FIG. 1: DIAGRAMMATIC REPRESENTATION OF THE STROKE INJURY AND MAJOR INTER-MEDIATING PATHWAYS. ADENOSINE TRI PHOSPHATE (ATP), REACTIVE NITROGEN SPECIES (RNS), REACTIVE OXYGEN SPECIES (ROS)

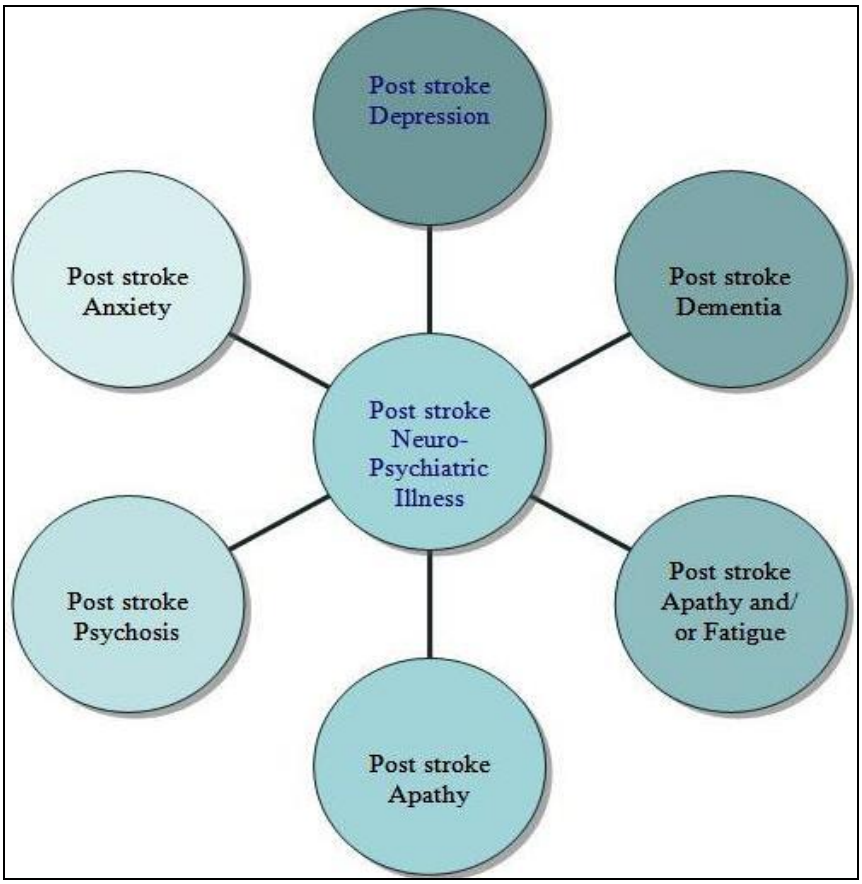

FIG. 2: VARIOUS NEUROPSYCHIATRIC COMPLICATIONS OCCUR DURING STROKE

Epidemiology: On an average, one third of stroke survivors experience depression on short or long term basis. Usually, mood disorders, depression in particular develops after stroke persisting for a long periods, but may develop in acute period. Stroke and depressive disorders both affect people of middle age, more often, old people [1, 5]. There exists a complex relationship between depression and stroke, in which stroke may predispose, precipitate or perpetuate depressive disorders. PSD varies widely in frequency as it depends on a) whether patients examined in hospital (acute stroke units, general hospitals wards or rehabilitation centers) or community settings which may lead to an important selection bias in epidemiological data. Patients with less and more severe strokes may be included in community-based surveys and samples gathered mainly from stroke units, respectively, b) whether it is reported during the acute post- stroke period or many months later to stroke, c) other factors- age of the patients taken, differing criteria for patients selection (e.g., exclusion of those with pre- existing diseases, previous stroke, communication disorders or cognitive impairment), various diagnostic methods employed and their applicability (self-reported measures or observer-rating scales) and diagnostic criteria used. Also much of the work published is limited to depression following cerebral infarction, while the data related to depression after hemorrhagic stroke is scanty [6]. There are considerable variation in frequency of PSD between individual studies and different population settings. In acute period (less than one month after index event), the frequency of PSD was observed as 30, 33 and 36% in rehabilitation,

population-and hospital-based studies, respectively [7]. A similar rate of 17-52% on an average was estimated thereafter 3-6 months and 1 year after stroke [8]. At 1-6 months post stroke, PSD rate was higher in rehabilitation settings (approximately 36%) comparatively. PSD rates were estimated to be 27-55%, 62% and 40% in rehabilitation, community-based studies and outpatient clinics, respectively [9, 10]. Depression is considered as a heterogeneous group of conditions. The mostly frequently recognized expressions of PSD are major depression (10-32%) and minor depression (40%) [11, 12, 13]. Generally, it has now been accepted that both types occur in equal/ nearly equal ratio, particularly in reference to inpatient or those in rehabilitation settings [14].

DSM-IV Criteria of Classification: The American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders (4th edition- DSMIV) enlists the following symptoms and subsequent criteria for the diagnosis of depression (same for PSD, which is also the most preferred method, presently) [3].

Symptoms:

1. Depressed mood most of the day, occurring most days (subjective or observed)
2. Markedly diminished interest or pleasure most of the day, nearly every day
3. Significant weight/ appetite change
4. Insomnia/ hypersomnia
5. Psychomotor agitation or retardation (as observed by others)
6. Loss of energy/ fatigue
7. Feeling inappropriate guilt/ worthlessness
8. Diminished ability to concentrate/ indeciviness recurring thoughts of death/ suicide plans

Criteria: Major depression- Presence of 5 or more above symptoms (including at least one of either depressed mood or decreased interest/pleasure) for a period of minimum 2 weeks.

Minor depression- Presence of 5 or more than 2 symptoms (including at least one of depressed mood or decreased interest/pleasure) for a period of minimum 2 weeks.

The symptoms due to an underlying medical condition/ mood-incongruent delusion or hallucinations are excluded.

Diagnosis: Recently, the acknowledgment of PSD has increased, but still remains under-documented. Approximately, 80% of cases are under-diagnosed by non-psychiatric clinicians. Early diagnosis includes ability to recognize and timely possible treatment so as to bring positive results in the effective management [15].

The factors liable to make PSD diagnosis difficult include- communication difficulties, impairment of facial, emotional expression, disturbance in vegetative functions; deficits in limited patients self report, impaired cognition, poor insight and aphasia, emotionalism, anosognosia, fatigue, apathy, agnosia, apraxia and intellectual decline are some of the limitations. Besides, stroke itself may be the cause of poor concentration, psychomotor retardation, or lack of energy, sleep disturbances and loss of appetite, all these depressive symptoms [2, 16, 17, 18].

Differentiating, cognitive decline and apathy (depressive syndromes) between post stroke patients secondary to depression is difficult. Differential diagnoses include organic brain syndrome, side effects of medication, sepsis and hypothyroidism [3]. Subsequent to PSD diagnosis, it has been suggested to follow a two step-approach, ideally, based on valid, reliable assessment tools and identified optimum cut-off points (highest sensitivity and specificity) [17, 19, 20] as mentioned below-

- For the presence of depression, a large number of patients should be screened through administration of self-report tools.
- Among above, such patients should be further evaluated through observer-rated interview (comparatively, lengthier and comprehensive).

DSM IV is the maximally used and preferred method as described above. Various standardized tests are used to screen patients, to determine their disease severity, monitor the change in symptomology and response to therapeutic interventions, but these should not used for diagnosis in isolation. They are broadly categorized as self-reporting and observer-rated scales, as mentioned below (**Table 1**).

TABLE 1: SUMMARIZING DIAGNOSTIC AND SCREENING INSTRUMENTS USED IN ASSESSING PSD

SELF-REPORTING TOOLS	OBSERVER-RATED SCALES
Reported by patient (self)	Reported by psychiatric (trained interviewer)
Requires less resources and time; more easily approachable; less reliable; patient compliance better	Needs much time and source; less feasible; more accurate; imposes burden on patients
Examples of tests: Beck Depression Inventory (BDI), Hospital Anxiety and Depression Scale (HADS), Patient Health Questionnaire, Center for Epidemiologic Studies Depression, Geriatric Depression Scale, Visual Analogue Mood Scale, Visual Analogue Self-Esteem Scale.	Examples of tests: Hamilton Depression Rating Scale (HDRS), Zung Self-Rating Depression Scale (ZSDS), Montgomery-Asberg Depression Rating Scale, PSD Rating Scale, Signs of Depression Scale, Stroke Aphasic Depression Questionnaire, Aphasic Depression Rating Scale.

Complete patients history, examination and families reports are important. The normal exclusion of symptoms due to an underlying medical condition is waived in PSD [21]. Emphasis are made that patients must be evaluated for depression in the first month after stroke and thereafter monitored at regular intervals, particularly those with risk factors associated with PSD development [19]. PSD diagnosis depends mainly on clinical examination, which latter be supplemented by objective data (selected scales) and subjective data (interview with the patient and/ or family) [6].

Risk Factors: In a prospective study of [22] examined the contributions of neurobiological, functional and psychosocial factors to PSD. A population-based cohort of 80 patients with acute stroke was assessed for a period of 3 years for the presence of depression, functional ability and social network. Left anterior brain lesion, dysphasia and living alone were found to be the most important predictors of immediate major PSD. After 3 months and 3 years post-stroke, the most important predictors for depression were dependent in daily activities and generalized cerebral atrophy [23]. Determination of risk factors associated with mood disorders after stroke is critical to identifying high-risk groups, enabling better preventive measures and treatment approaches to be established [6].

Pathophysiological Mechanisms: DSM- IV classification implies that PSD occurs thorough a direct biological mechanism, the nature of the mechanism linking depression and stroke still remains debated since decades in the literature. Researchers have proposed two hypotheses.

- According to the first group, there is a "biological mechanism" in which ischemic insults directly affect neural circuits (producing changes in brain functioning) involved in mood regulation [11, 24, 25]. In1977, no. of PSD patients exceeded physically ill patients, also suffering from major depression, favouring biological theory. In 1981, PSD is caused by specific brain lesions [6, 25]. A correlation between PSD severity and proximity of anterior border of the lesion

on CT (computed tomography) scan to the frontal pole in the left hemisphere and not in the right hemisphere supported the link between PSD, and left anterior cortical and left basal ganglia lesions [26]. Disruption of mood-regulating neural circuits by specific ischemic lesions, describes a similar process i.e. vascular depression [27, 28, 29]. An MRI study conducted on 275 patients implied PSD association with lesions of left side prefronto subcortical circuits [27]. From last 2 decades many researchers have supported/ opposed the lesion approach [30, 31, 32].

- The second group supports a "psychosocial mechanism" where PSD is thought to be caused by social and psychological stressors (generated secondarily to losses which occur post stroke) associated with a stroke [5]. Psychosocial hypothesis (late 1990's) opposed biological hypothesis. There's different symptom profile of PSD and vascular depression, although the pathophysiology for both is the same as per biological argument. PSD is not lesion-specific, implied by the fact that PSD and functional depression have similar symptoms and therapy. PSD is multifactorial [5]. It was found during a meta-analysis carried on 48 studies that PSD is not linked to the location of stroke lesion [33].

The pre-eminent role of monoamines in depression- primarily the serotonin system and secondarily the norepinephrine system is supported by various evidences [34, 35]. It was supposed that depressive symptoms are mediated by the serotonergic input arising from dorsal and caudal raphe nuclei to the hypothalamus, amygdala, hippocampus, striatum, brain-stem and neocortex, which may by anatomical/biological changes occurring after stroke. Depression, especially PSD is correlated with adrenergic receptor sensitivity changes or noradrenergic neurons (arising mainly in the locus coeruleus and in the lateral tegmental brain stem) dysfunction [36, 37].

Recently, the composition of the neurochemical environment has been much focused upon. Craft and De Vries hypothesized that acutely after stroke the pathophysiologic processes occur, which are linked to the PSD etiology. There's a relation between stroke and dysregulation of hypothalamic pituitary-adrenal (HPA) axis and neuroinflammation [38]

Recently, a third hypothesis concerning etiology of PSD "cytokine mechanism" by Spalletta *et al*. has emerged employing proinflammatory cytokines [IL-1beta, IL-18 and TNF-alpha] increased concentration post-stroke leads to depressive disorders [39]. Firstly, they noted that levels of 5-hydroxy-indole-acetic acid (a serotonin metabolite) decreased in PSD patients in comparison to non-depressed stroke patients, significantly. Then they showed a linking inflammatory response in brain ischemic injury and depressed mood disorders. Acute cerebral ischemia is followed by over expression of IL-1, -6 and -18, and TNF (proinflammatory cytokines).

Cytokines may stimulate the HPA axis, causing a rise in adrenocorticotropic hormone and cortisol levels, and an increased bioaminergic-metabolism (serotonin, norepinephrine and dopamine) in the limbic and hypothalamic areas [40]. Therefore, through proinflammatory cytokines over expression followed by indoleamine 2, 3-dyoxigenase enzyme (mainly serotonin) up regulation, infarcts of the paralimbic regions of the frontal and temporal lobes can lower concentration of neurotransmitter leading to occurrence of depressive symptoms [39]. There is a link between proinflammatory cytokines and depressive disorders, highlighted by many evidences [41, 42, 43].

The latest hypothesis is "genetic predisposition for PSD", based on findings from a genomic studies of stroke patients with major depression. It was implicated by Ramasubbu and coworkers that expression of major depression post stroke is associated with the 5-HTTLPR genotype (short allele of the serotonin transporter gene promoter region) by functional polymorphism in 26 stroke patients with major depression and in 25 non-depressed stroke patients of similar genetic backgrounds. Genomic development in PSD, further supported 5-HTTLPR genotype mediation in major depression after stroke [44]. In progress of PSD a crucial result comes from the complex relation between genetic and non-genetic factors, added upon by environmental or biological factors (stress or stroke lesions) or both, influencing individual genetic susceptibility [45].

DSM IV categorizes stroke as one of those few diseases that directly lead to depression [46]. Conclusively, mechanism of PSD is still elusive, best explained by biopsychosocial model. Majorly, PSD is multifactorial, biological or psychological independently or interactively with mainly biological shortly after stroke and psychological later on.

Impact and Consequences of PSD: The most serious outcome of PSD is mortality caused by it. There is more than 10% possibility of mortality calculated in 2400 PSD patients in the first three years after stroke [44]. Apart from it, it deteriorates life span and more importantly life's quality and poses an obstacle in the recovery and rehabilitation course. The outcomes are mainly recognized as the biological and psychosocial after effects outlined (**Table 2**). There is noted fall in the levels of 5-HT because of reduced monoamine synthesis (caused by enzyme inhibition during ischemia) PSD resulting in change of mood, appetite and sleep. In spite of all the attempts and efforts made, contributions done and betterment achieved still PSD patients are liable to face psychosocial problems. Beside these the other difficulties are those related to depression like arterial hypertension, cardiac complications, negligible response to treatment, increase in suicidal tendency, other worsening situations and negative effect may be imposed on life of patients family members and caregiver too. Cost of healthcare services can be heavy; also prolonged inpatient stay has been reported [47, 48, 49, 50, 51, 52].

TABLE 2: IMPACT AND CONSEQUENCES OF PSD

Biological Impact	Psychosocial Impact
Reduced cerebral outflow	Increased disability, loss of independence, impairment causing grief
Lesions particularly occurring in left frontal lobe/basal ganglia	Poor self esteem
Changed cortical receptor activity	Limited social interaction
Varying amounts of cerebrospinal fluid neurotransmitter metabolites	Poor relationship/financial phase
Alterations in electrophysiology	Less involvement in rehabilitation and failure to work back

Therapeutic Strategies:

1. **Pharmacolological Therapy:** As per patient compliance, either of nortriptyline/sertraline is preferred as the first antidepressant drug of choice. SSRI is better than TCA, as the former is relatively much safer, has quicker onset of action is a good anxiolytic (7-10 days), important for elderly patients. In TCA class, nortriptyline (20-100 mg/day) is recommended and among SSRIs, sertraline is preferred followed by citalopram. Sertraline 50 mg/day increased to 100 mg/day, in 2weeks. After a period of 4-6 weeks, therapy is either stopped if it shows negligible response or else, continued for a minimum time of 6 months as it is effective; thereafter it is gradually withdrawn or carried on if there is reoccurrence of symptoms.

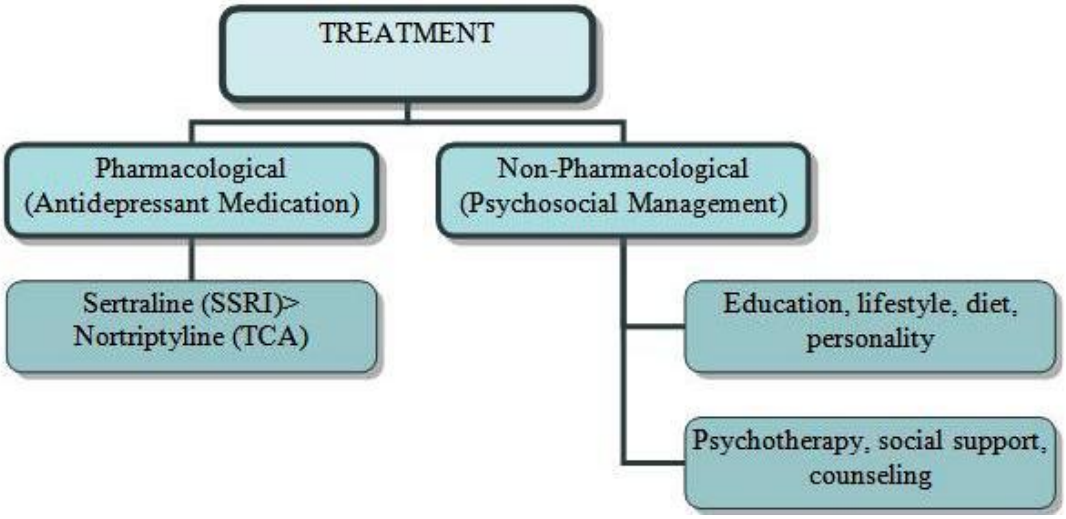

FIG. 3: **TREATMENT STRATEGY FOR PSD**

Among TCAs, nortriptyline is the well-studied and better drug in comparison to fluoxetine and placebo [26, 53, 54, 55]. Imipramine and desipramine did not show much improvement in PSD [56]. In SSRIs class, fluoxetine is the Ist and most-tested moiety [57, 58, 59]. Sertraline is the IInd most studied drug and citalopram (most selective SSRI) is IIIrd [50, 60]. Paroxetine, escitalopram and fluvoxamine (SSRIs) have not been studied against PSD. Trazodone is superior than placebo and reboxetine (an SNRI) than citalopram in lowering depressive symptoms [50]. Venlafaxine (an SSNRI) is effective in depression but not studied in [61].

Milnacipran (an SSNRI), mirtazapine (a serotonin antagonist and norepinephrine agonist), methylphenidate (a psychostimulant) have shown to be effective in prevention of PSD but maprotiline (a monoamine oxidase inhibitor) proved to be non-effective [62, 63, 64]. Duloxetine (an SSNRI), bupropion (a dopamine and norepinephrine reuptake inhibitor) and selegline have not been tested. To prevent PSD nortriptiline, fluoxetine, sertraline, trazodone, maprotiline, methylphenidate, mianserin, piracetam and indeloxazine were used [50]. Detection methodology and analysis of PSD plus the time duration of antidepressant therapy was non-uniform. Pharmacological treatment did show improvement but not in regard to remission. In reality, data seemed to be insufficient to establish the use and effectiveness of pharmacotherapy for PSD [7, 65].

2. Non-pharmacological Therapy:

- Education- knowledge concerning depression (PSD) must be provided to the patient, patient's family and career.
- Reestablishment of sleep-wake cycle.
- Diet, Exercise- having nutritious, balanced meals in optimum amount and proper time, as advised plus following a scheduled plan of physical activities.
- Behavioral strategies

There is a significant role of pharmacotherapy and psychosocial interventions in the treatment and prevention of PSD (Fig. 1). The lacunae in achieving this goal are of prime concern. The weak points in this regard are as follows:

1. Either condition is not noticed/ treatment is considered to be unimportant.
2. Safety concern over the pharmacological therapy in elderly patients with respect to

medical co morbidity and concomitant polytherapy.

3. Pharmacological approach is unable to change the factors such as extreme environmental stressors and a lack of social help, which are generally taken care of by a psychological way-out.

CONCLUSION: First of all, there is utmost need to analyze precisely and carefully to determine certain aspects associated with PSD- epidemiology, etiology, and pathophysiology. Secondly, better assessment through timely recognition, diagnosis and monitoring using best available screening tools and, newer and safer means of treatment may facilitate rehabilitation, improve patient's recovery, social reintegration practices, satisfaction to life, self-care skills, overall adding upon quality of life. Lastly, there's immense stress being laid upon increasing awareness among public as well as health professionals, to achieve the goal with the help of training and education being provided to-caregivers, policy makers, patients, their families, medical persons.

This highlights the potential of therapeutic (psychosocial and pharmacological) interventions and importance of a multidisciplinary health team, encouraging large, well-designed multicenter studies to be conducted in homogenous stroke populations which can prevent the complications related to PSD, in future.

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