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## **Pharmacological & Non-Pharmacological Interventions For Stroke Induced Depression: A Review**

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### **ABSTRACT**

Post stroke depression (PSD) is a mood disorder in which depression and anhedonia results from stroke. Stroke is a neurological deficit of cerebrovascular cause which persist either beyond 24hrs or is interrupted by death within 24hrs. Depression is a common mental disorder characterized by depressed mood, loss of interest, Feeling of guilt, disturbed sleep, decreased appetite. Development of PSD may result from the mental distress associated with physical disability. There is no reliable and universal treatment for PSD despite its debilitating effects on quality of life in stroke patients. Most of the antidepressant influences the serotonergic, adrenergic and dopaminergic systems with the aim of accelerating serotonin, dopamine and nor-epinephrine. The different therapeutic approaches to treat PSD include Antidepressants, psychotherapy, surgical therapy, Transcranial magnetic stimulation, acupuncture, music therapy. In this review we are compiling different treatment options available for post stroke depression.

**Keywords:** post stroke depression, antidepressant, psychotherapy, Transcranial magnetic stimulation, acupuncture, music therapy

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## INTRODUCTION

Post-stroke depression (PSD), a mood disorder which is primarily characterized by depression and anhedonia caused by stroke. The depressive symptoms gradually increase during the first 6 months, ease slightly at approximately 12 months, and worsen again during the second year after the stroke<sup>1</sup>. Post stroke depression is the most commonly occurring neuropsychiatric consequence of stroke, in one third of stroke patients. Post-stroke depression increases stroke morbidity and mortality and therefore, identification and evaluation of the efficacy and safety of treatments of post-stroke depression are vital to decrease the health care burden and costs of this patient population. The different therapeutic approaches to treat PSD include Antidepressants, psychotherapy, surgical therapy, Transcranial magnetic stimulation, acupuncture, music therapy<sup>2</sup>. Minor depression is usually seen in 30% of patients following stroke. In few cases, depression becomes chronic and can persist more than 3 years following stroke<sup>3</sup>. A predominantly high burden is caused by stroke to the patients as well as the caretakers<sup>4</sup>. Development of PSD may result from the mental distress associated with physical disability. The Monoamine theory states that depression is associated with low levels of 5-Hydroxy Triptamine, Nor-epinephrine and Dopamine. In severely depressed patients increased level of stress hormone, cortisol was found. This increased cortisol level impairs neuroplasticity and cellular resilience and down regulates glucocorticoid receptors<sup>5</sup>. There is no reliable and universal treatment for Post stroke depression despite its debilitating effects on quality of life in stroke patients. Most of the antidepressant drugs influences the serotonergic, adrenergic and dopaminergic systems with the aim of accelerating serotonin, dopamine and nor-epinephrine<sup>6</sup>

### **Epidemiology**

Stroke may be a major explanation for death and disability in many countries. It had been reported that, in 2013, globally, there have been nearly 25.7 million stroke survivors, 6.5 million deaths thanks to stroke, 113 million disability-adjusted life-years (DALYs) lost due to stroke and 10.3 million new occurrences of stroke<sup>7</sup>. The prevalence and severity of depression in stroke patients is highly increased between six months and two years after a stroke. Consistent with the epidemiological studies, nearly 30% of stroke patients develop depression, either within the first or late stages after stroke. Both major and minor depression are reported in stroke patients, with a better prevalence of major depression occurring soon after a stroke. The prevalence of major depression changes over time, with the very best rates from three to 6 months after stroke and later declines to 50% of initial frequency at one year<sup>8</sup>. Two meta-analyses determined the prevalence at 29% (20, 293 patients) in 43 studies over a period of 5 years post stroke and 31% (25,488 patients)

in 61 prospective studies over 5 years post-stroke. Within the current study, depression was diagnosed in about 37% of patients<sup>9</sup>.

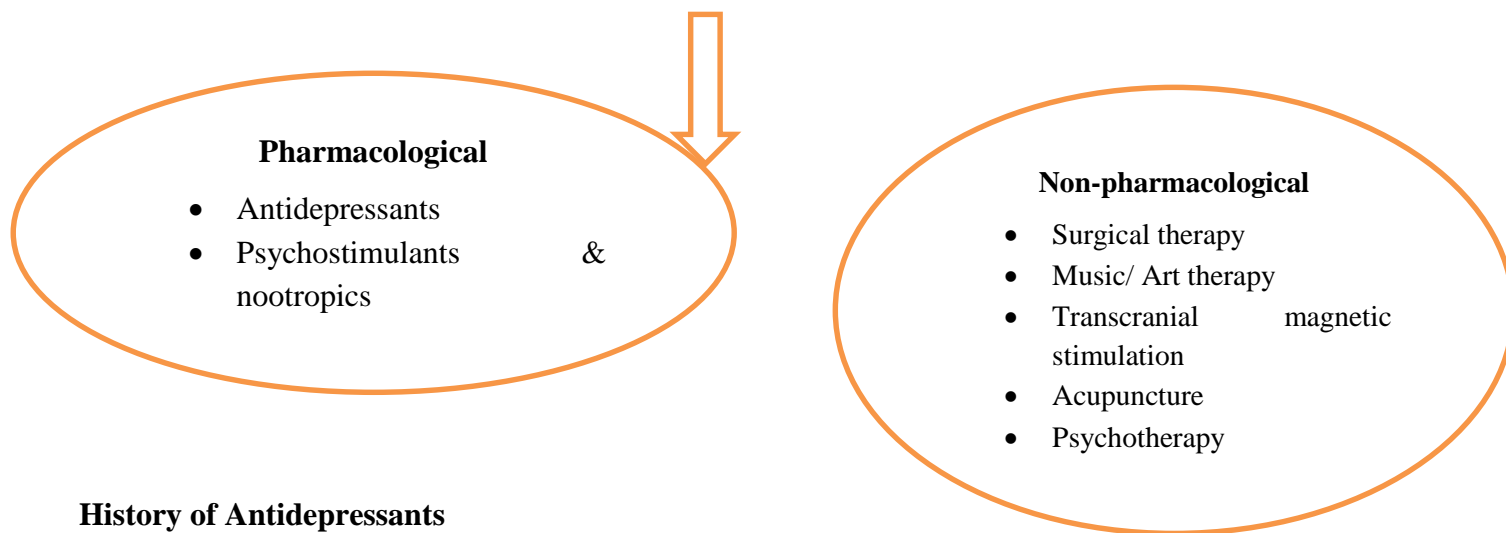
### Mechanism of Antidepressants

The different therapeutic approaches to treat PSD include Antidepressants, psychotherapy, surgical therapy, Transcranial magnetic stimulation, acupuncture, music therapy<sup>2</sup>. Most of the antidepressant influences the serotonergic, adrenergic and dopaminergic systems with the aim of accelerating serotonin, dopamine and nor-epinephrine<sup>5</sup>.

### The Various Treatment Options Available For Post-Stroke Depression

Antidepressants, psychotherapy, surgical therapy, Transcranial magnetic stimulation, acupuncture, music therapy are often used<sup>2</sup>.

### POST STROKE DEPRESSION THERAPY



### History of Antidepressants

Year of approval	Dominant drugs utilized in the treatment of depression
1952	IPRONIAZID It is the primary MAOI developed, it inhibits several neurotransmitters within the brain, including serotonin
1957	IMIPRAMINE It is the primary TCA introduced for medical use, enhances the level of neurotransmitters within the brain
1988	FLUOXETINE It is the primary SSRI, even most of ordinarily prescribed today. Reduces reuptake of serotonin and increases the concentration of neurotransmitters.
1993	VENLAFAXINE It is the primary SNRI, it inhibits reuptake of serotonin and norepinephrine
2013	VORTIOXETINE It is an atypical antidepressant, increases the amount of serotonin and modulates the discharge of other neurotransmitters.
2019	KETAMINE

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It is the primary of latest wave of medicine within the underlying circuitry of depression, which is approved to be used within the market.

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## PHARMACOLOGICAL TREATMENT

### ANTIDEPRESSANTS

#### Selective Serotonin Reuptake Inhibitors (SSRIs)

The most commonly used/ first line choice is SSRIs (selective serotonin reuptake inhibitors). The various SSRIs are Citalopram, Fluoxetine, Paroxetine, Sertraline. It works by increasing level of serotonin in brain by blocking the reuptake of serotonin by neurons. A significant improvement in motor functions was seen in patients taking SSRIs, this in turn improves the quality of life in stroke patients. Another type of medication used to treat PSD is SNRIs, however SNRIs should be carefully used because of their side effects (Irritability, insomnia, nausea, vomiting, cardiovascular responses<sup>1</sup>. SSRIs are relatively safer with better tolerability<sup>10</sup>. Since antidepressants can cause a series of adverse events and result in poor patient compliance, it is crucial to explore other treatment which has least side effects for the management of PSD<sup>11</sup>. Paroxetine ranked the highest in SSRIs as it is one of the most potent inhibitor of selective serotonin reuptake inhibitors, it works by selectively inhibiting the neuronal presynaptic uptake of serotonin for facilitating the neuronal transmission. Paroxetine improves the cognitive and functional performance of post stroke depressive patients, as well as their quality of life. However the male sexual dysfunction is more common with paroxetine than fluoxetine. Paroxetine should be used cautiously in stroke, especially in patients with cognitive confusion and compromised sexual dysfunction<sup>12</sup>. When compared with others, paroxetine could be the potential choice for treatment of PSD, because it features a good balance between the efficacy, acceptability and tolerability. In addition to this it is also safe<sup>13</sup>. Vortioxetine was approved for the treatment of Major depressive disorder (MDD) in 2013 by the FDA. Vortioxetine's therapeutic effects are through modulation of the 5-HT receptors and an inhibition of the 5-HT transporters. The antidepressant effect of the vortioxetine is mainly through its antagonist effect on the 5-HT<sub>3</sub>, 5-HT<sub>7</sub>, and 5-HT<sub>1D</sub> receptors, partial agonist activity on the 5-HT<sub>1B</sub> receptor, agonist effect on the 5-HT<sub>1A</sub> receptor, and inhibition of the 5-HT transporter<sup>14</sup>. It enhances the extracellular concentration of various neurotransmitters such as dopamine, histamine, noradrenaline, and acetylcholine.

#### Serotonin/ Nor-Epinephrine Re-uptake Inhibitors (SNRIs)

The various SNRIs which can be used for treating PSD are Venlafaxine, Duloxetine, Desvenlafaxine, Desulepin. PSD patients on duloxetine improved faster than the patients treated with SSRIs. The most commonly seen side effects are nausea, somnolence, insomnia, dizziness, dry

mouth, headache. Duloxetine can be used as an alternative to other agents in treating post stroke depression<sup>15</sup>.

An intriguing fact is that duloxetine, an SNRI is superior to SSRI because of its faster and significant reduction in depressive symptoms in stroke patients<sup>16</sup>.

While SSRIs inhibit serotonergic receptors, SNRIs acts on noradrenergic receptors as well and thereby increases the nor-epinephrine level. Duloxetine is the better choice for early improvement in aged patients with underlying diseases. Prescribing of antidepressants in stroke survivors with Post stroke depression should be done very carefully as they are vulnerable to adverse effects<sup>11</sup>.

Desvenlafaxine, a lively metabolite of venlafaxine, is an SNRI approved by the Food and Drug Administration (FDA) for the treatment of MDD in adults in 2009. Desvenlafaxine results in selective reuptake inhibition at the serotonin (5-HT) and norepinephrine (NE) transporters, leading to an enhanced extracellular concentration of 5-HT and NE. Desvenlafaxine also affects hypothalamus which is a crucial regulator of biological functions like mood, sleep cycle, stress response, sexual behaviour, temperature, and pain sensations. It lacks affinity for a number of receptors, including muscarinic cholinergic, histaminergic, and  $\alpha_1$ -adrenergic receptors, and monoamine oxidase (MAO) receptors, possibly reducing the risk of undesired side effects which may be related to these receptor sites. In pregnant rats and rabbits, desvenlafaxine causes a decrease in foetal weight with no evidence of teratogenicity. However, there are not adequate studies in pregnant women<sup>13</sup>.

#### **Mono amine oxidase inhibitors (MAOIs)**

The different MAOIs include Isocarboxiazid, Phenzelzine, Moclobemide(reversible), Tranylcypromine. The mechanism of action of antidepressant drugs like monoamine oxidase inhibitors (MAOIs), phenelzine and tranylcypromine is the inhibition of the enzymatic conversion of 5HT and NE into their metabolites. It is usually given in cases of atypical or drug resistant depression. These compounds contain a certain level of toxicity, however moclobemide is found to be more safe and effective. The MAOIs block the metabolism of neurotransmitters such as NE, DA and 5-HT and cause increase within the concentration of monoamine transmitters. The traditional MAOIs (tranylcypromine) act in irreversible and non-selective manner unlike the recently investigated MAOIs are reversible in binding and selective for either MAO-A or MAO-B. The commonly seen side effects include Dizziness, Headache, Drowsiness, Sleep Disturbances (Including Insomnia, Hypersomnia, Fatigue, Weakness, Tremors, Twitching, Myoclonic Movements)<sup>13</sup>.

Because of potentially lethal dietary and drug interactions, monoamine oxidase inhibitors have been reserved as a last line of treatment, used only when other classes of antidepressant drugs (for example selective serotonin reuptake inhibitors and tricyclic antidepressants) fails<sup>17</sup>.

### **Tricyclic Antidepressants (TCAs)**

Amitriptyline, Imipramine, Des-imipramine, Nortriptyline are the TCAs which can be used for PSD. Both SSRIs and TCAs have significant effect in relieving major depressive symptoms in stroke patients<sup>18</sup>. They block the re-uptake of serotonin and Nor-epinephrine in presynaptic terminals, which leads to increased concentration of the neurotransmitters. The antidepressant use increases the gastrointestinal and central nervous system side effects. Psychological therapies cannot be used alone for the treatment of Post stroke depression, antidepressant and physical therapy is also required<sup>19</sup>. TCAs have also been reported to block muscarinic,  $\alpha_1$ -adrenergic and histaminic receptors<sup>10</sup>. Although TCAs are having high efficacy, their anticholinergic effects (confusion, urinary retention, glaucoma) and antiadrenergic effects (hypotension and dizziness) would not make them a first line treatment. But the response in PSD patients with the same cannot be ignored<sup>11</sup>.

### **Nor-Epinephrine Re-uptake inhibitors (NRIs)**

Reboxetine, viloxazine, teniloxazine and atomoxetine belongs to NRI class of antidepressant<sup>16</sup>. The Hamilton depression score in PSD is reduced by the use of reboxetine, an NRI which has high selective affinity for nor-epinephrine transporter, it works by increasing the Nor-Epinephrine level. Reboxetine shows minimal cardiovascular risk unlike TCAs. As authors argues that in the treatment of major depression, reboxetine is having only little effect, more RCTs are required on reboxetine in-order to provide treatment recommendations. Commonly seen side effects include insomnia, dizziness, dry mouth and excessive sweating<sup>11</sup>. At moderate dose, the NRIs selectively inhibit the norepinephrine reuptake transporters (NET) at the terminal presynaptic membranes of the noradrenergic nerves within the CNS resulting in selective accumulation of norepinephrine within the synaptic clefts. But at high doses the NRIs significantly inhibit dopamine reuptake via NET, especially in areas of the brain such as the prefrontal cortex (neo-cortex) that are significantly lacking dopamine reuptake transporters (DAT). Off-label this is used for panic disorder, attention deficit hyperactivity disorder (ADHD), bulimia nervosa, narcolepsy, and treating therapy-resistant paediatric nocturnal enuresis. They are approved for use in many countries worldwide including the United Kingdom, but have not been approved for depression treatment in the United States<sup>16</sup>.

### **PSYCHOSTIMULANTS AND NOOTROPICS**

Citicoline is one of the most abundant endogenous nucleotide compound and cell membrane lipid in animal and human tissues, it works by increasing the phosphatidyl choline synthesis. Citicoline reduces the cognitive deficit and increases the neuronal functions and memory. Certain studies show that citicoline increases the level of neurotransmitters: dopamine, nor-epinephrine, serotonin thereby reduces neuronal degeneration and manages neurodegenerative disorders. It also improves cognitive impairment by its neuro-protective and neuro-restorative effects<sup>1</sup>. The side effect which are mainly seen includes insomnia, headache, diarrhea). To sum up all the points, these are the various pharmacological approaches to treat the stroke induced depression/ post-stroke depression.

## **NON-PHARMCOLOGICAL TREATMENT**

### **ACUPUNCTURE**

Acupuncture is having a gradually increasing attraction, as it is a non-drug therapy. A Complete remission of PSD using antidepressants may result in adverse effects including sexual dysfunction, sleep disturbances, GI side-effects. Multiple targets and multi-level effects may be the mechanism of action of acupuncture. Acupuncture increases the level of monoamines 5-HT, Dopamine, nor epinephrine and acetylcholine. However, medication therapy combined with acupuncture was not found to be effective, it may be because of underlying reasons or because of the short duration of most of the studies<sup>20</sup>.

The risk of PSD was shown reduced after stroke by treating patients with acupuncture. Acupuncture treatment relieves pain, spasticity, physical functions, improves quality of life and cognitive functions. As the depression after stroke is highly correlated with physical disabilities, acupuncture is useful; however acupuncture doesn't help with depression symptoms. The positive side of acupuncture treatment is that, it is a low cost treatment and has no potential side effects. But the limitation is that the acupuncturist uses different acupoints in different patients, and it is hard to define the acupoints<sup>21</sup>.

By far the acupuncture treatment is safe and efficacious for PSD, but due to limited number of studies on the same, it is not possible to recommend acupuncture for the treatment of PSD<sup>19</sup>.

### **HYPERBARIC OXYGEN THERAPY + ANTIDEPRESSANTS**

PSD results in long term disability change in quality of life and significant increase in socio-economic costs. Cerebral hypoxic ischemia affects the brainstem, thalamus, frontal cortex, and other areas and causes depression. Hence an improvement in the oxygen supply to brain in stroke patients can reduce the secondary damage to cerebral cortex as well as nerves. Combination of hyperbaric oxygen therapy and fluoxetine is highly effective, improves the post-stroke deprived with psychological and acupuncture helps to improve the depression in stroke patients<sup>22</sup>.

## **PSYCHOTHERAPY AND SURGICAL THERAPY**

Psychological therapy shows promising results in both prevention and treatment of post stroke depression and has been established as an effective treatment of choice. However the literature regarding the efficacy of psychological therapy for post stroke depression is limited and further studies are required.

High grade stenosis in ischemic stroke patients showed that carotid angioplasty stent was associated with lower depression scores than antidepressant treatment<sup>2</sup>.

In patients who received carotid angioplasty stenting, significant improvement in depression and neurological abnormality was seen than in patients who were treated with SSRIs.

## **TRANSCRANIAL MAGNETIC STIMULATION**

It is a non-invasive brain stimulation therapy. In this, the electromagnetic coil is placed over the dorsolateral prefrontal cortex area, which then generates a magnetic field and subsequently electrical current in the brain<sup>23</sup>.

Even if the mechanism of TMS on PSD is unknown, its effectiveness can't be denied. Usually 1000rTMS pulses (5-10 Hz) over the left DLPFC and 1000rTMS Pulses over the right DLPFC are used to treat depression after stroke. But it should be further studied in-order to provide a strong theoretical basis for clinical application<sup>24</sup>. The rTMS is not having any serious adverse events, only occasional effects such as headache, scalp discomfort at stimulation site following treatment sessions are present. The major disadvantage of rTMS is the 4-6 week timeline for the clinical benefit. rTMS is safe as well as effective for the depressive symptoms in stroke patients<sup>25</sup>.

## **MUSIC/ ART THERAPY**

Psychological disabilities can be overcome with the help of art therapy. Art therapy causes sensory stimulation, rhythms, colors which can address the patient's psychological issues. Stroke patients having chronic depression may have loss of appetite, insomnia, excessive eating or sleeping, low self-esteem. Thus physical therapy alone is not sufficient, psychological therapy is also required along with it in-order to address all these issues of depression in stroke patients. The stroke patients can gain the ability to look inside themselves through art activities, form relationship with therapist, and communicate easily with others<sup>26</sup>.

As a treatment for various diseases, standardized music therapy is being used. It helps to improve communication, linguistics, emotional response and behavioral adjustments. The effect of music therapy on psychological status of stroke patients is highly encouraging. One of the main advantages of music therapy is that its low possibility of side effects because it is non-invasive and it doesn't use drugs. By inspiring motivation for rehabilitation, music can enhance functional

abilities through improvement of depression and anxiety. Music can significantly improve quality of life and reduce the depressed mood in post stroke patients<sup>27</sup>.

### **RECENT ADVANCES IN PSD PHARMACOLOGICAL TREATMENT**

The treatment given by combining amphetamine and focused activity has been shown to improve forelimb motor function after stroke as a long term effect by the axonal sprouting from contralesional neurons. The use of dopamine has shown positive result in language outcome. The use of glutamate and acetylcholine has shown promising results, i.e. brain plasticity modulation using pharmacological intervention has the potential to assist recovery after stroke<sup>28</sup>.

It is a paradoxical agent which doesn't fit into any of the existing classes of antidepressants. The questionable antidepressant activity of agomelatine must be from the sedative action via the melatonergic MT<sub>1</sub> and MT<sub>2</sub> receptors agonistic action along with its anxiolytic effect action via 5-HT<sub>2c</sub> receptor antagonism<sup>16</sup>. Hence it is thought to increase the level of neurotransmitters dopamine and nor-adrenaline. The commonly seen side effects of agomelatine include weight gain, Insomnia, dizziness, abdominal pain, tiredness. From the psychopharmacological point of view, agomelatine is efficacious as an adjunct-augmenting pharmacotherapeutic agent for the treatment of patients with anxious depression disorders (i.e., either major depression disorder [MDD] or bipolar depression or schizoaffective depression associated with anxiety disorder component). Agomelatine alone might not be effective as a monotherapy for the treatment of major depressive episode or bipolar depression or schizoaffective depression due to its unique mechanism of action as a melatonergic MT<sub>1</sub> and MT<sub>2</sub> receptors agonist and a selective serotonergic 5-HT<sub>2c</sub> receptor antagonist<sup>16</sup>.

### **EMERGING GLUTAMATE RECEPTOR BLOCKERS**

Currently researches are focused on finding novel, non-monoaminergic based drugs for the treatment resistant depression. The glutamatergic neurotransmitter pathway appears to be important in the pathophysiology of depressive disorders<sup>16</sup>. Ketamine is one such drug under study. In the study with ketamine, it has shown that it is safe for treating depressive patients. A concern regarding the use of rapid acting antidepressants are whether there will be worsening or rebound of suicidal ideation as the antidepressant effects of ketamine dissipate. Ketamine administration remains a research procedure with significant potential risks and further research is needed before considering it as a routine treatment for depression<sup>29</sup>. Reports show that intravenous administration of ketamine has potent antidepressant effects in treatment-resistant depression<sup>30</sup>. Further, ketamine and the putative antidepressants that have followed it have clearly demonstrated that antidepressants need not produce their therapeutic effects via direct effects on monoamine

receptors, ketamine should be limited predominately to research contexts to insure that adequate review of risks and benefits has occurred before ketamine infusion, enhance the consent process before ketamine infusion, protect individuals patients undergoing ketamine treatment, and increase the likelihood that the growing experience with ketamine infusion informs the sector of depression research. An alternative strategy would be to employ ketamine to induce remission and then to prevent depressive relapse using other medications or psychotherapeutic approaches<sup>29</sup>. Ketamine may be a better inexpensive, less strenuous and simpler substitute for Electroconvulsive therapy/ electro shock (ECT) within the management of treatment-resistant MDD or bipolar depression or schizoaffective depression. The sub-anaesthetic low dose-ketamine and ECT produced antidepressant effects; however, ketamine produced superior antidepressant effects in terms of fast response onset. For example, ketamine produced rapid antidepressant effects starting at 24 h; whereas, the antidepressant effects of ECT weren't expressed until after 48 h. The antidepressant effects of both ketamine and ECT lasted for a minimum of seven days. This shows that ketamine is more efficacious than ECT for treating MDD or bipolar depression or schizoaffective depression<sup>16</sup>.

In this review we are compiling the different treatment options available for post stroke depression. Both non-pharmacological and pharmacological therapies are required for providing a proper care of treatment to the post stroke depressive patients. The pharmacological treatment includes SSRIs, SNRIs, NRIs, TCAs, MAOIs and Citicholine for post stroke-depression. The non-pharmacological treatment includes psychotherapy, surgical therapy, Transcranial magnetic stimulation, acupuncture, music and art therapy. The combination of both pharmacological and non-pharmacological therapy has the potential to increase the effectiveness.

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