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A REVIEW OF THE RELATIONSHIP BETWEEN ANTIDEPRESSANTS AND SUICIDE RISK

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ABSTRACT: There are a variety of causes of death, but one of the most common is a suicide, which has an annual global average rate of roughly 13 per 1000000 people. Men commit suicide at a higher rate than women. Suicide rates were reduced by prescribing higher doses of current antidepressants; however, multiple ecological, cohort, case-control, and controlled clinical trials in patients with acute affective disorder discovered that the risk of suicide ideation is higher in younger patients. As a result, this remains a matter of debate whether antidepressants enhance suicidal ideation in younger patients with acute affective illness. This review outlines the neuroscience of suicide and look into the link between antidepressants and suicide.

INTRODUCTION: Antidepressants, particularly Selective Serotonin Reuptake Inhibitors (SSRIs), are commonly prescribed due to the belief and understanding that they are generally safe and helpful for a wide range of diseases, including depression and anxiety. The question of whether certain antidepressant medicines (ADs), particularly Selective Serotonin Reuptake Inhibitors (SSRIs), induce the appearance or intensification of suicidal thoughts in sensitive individuals continues to be debated [1, 2]. Concerns about safety were first raised in the early 1990s, when reports suggested a link between the drug and suicidality [3].

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As a result, the link between antidepressant medication use and the risk of suicide has been a source of worry. The Food and Drug Administration (FDA) in the United States has been actively involved in giving guidelines and warnings regarding the use of these medications. In 1991, a public meeting was held to address concerns about anomalous behavior in patients who had been treated with fluoxetine. Suicidal conduct was reported by attendees immediately after they began using the drug [4, 5]. Different clinical research, such as case-control, cohort, ecological, and controlled studies, are aimed to gain additional information about the topic.

Neurobiology of Suicide: In the Neurobiology of Suicide, three neurobiological systems are engaged.

- ✓ First, urinary cortisol production, CSF investigations, DST non-suppression, and post-mortem brain studies all point to an HPA axis hyperactivity linked to suicidal conduct.

- ✓ Second, evidence of increased norepinephrine release and accompanying alterations in the noradrenergic system has been discovered.
- ✓ Third, a defective 5-HTergic system has been linked to suicidal behavior in a large number of investigations employing blood platelets, CSF, post-mortem brains, Functional Neuroimaging, and Genetics [6].

Patients who had recently attempted suicide had higher urine cortisol production for 24 hours than patients who did not have a history of suicidal conduct. The results of studies comparing plasma cortisol levels in suicidal and non-suicidal individuals following the administration of 1 mg dexamethasone (Dexamethasone suppression test, or DST) have been contradictory, but Coryell & Schlesser recently found that baseline dexamethasone non-suppression was associated with a fourteen-fold increase in the likelihood of suicide over a 15-year follow-up period [6].

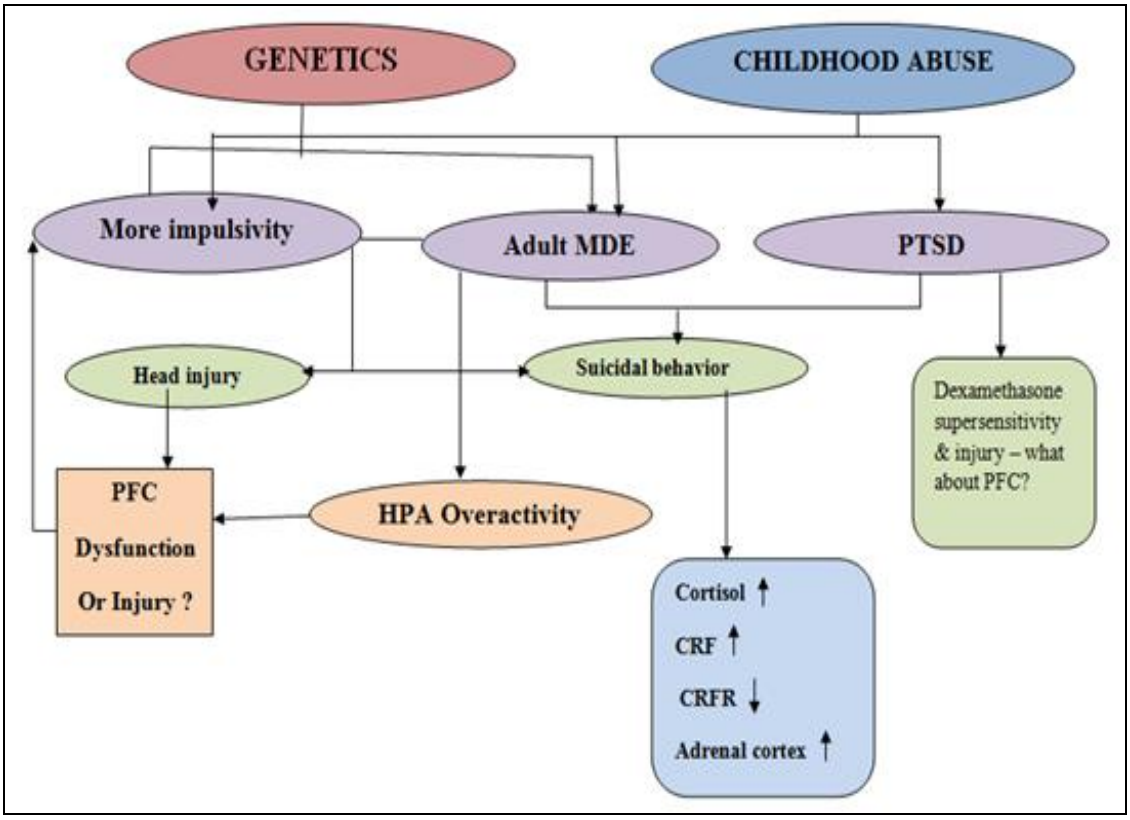

FIG. 1: NEUROBIOLOGY OF SUICIDE

Because AVP is an essential corticotrophin secretagogue, both AVP and Corticotropin Releasing Hormone (CRH) are found in the parvicellular neurons of the hypothalamic paraventricular nucleus. Inder & Others looked examined AVP concentrations in plasma and CSF and discovered that suicide attempters with depression had greater AVP concentrations in their plasma [8, 9].

Brunner and others, on the other hand, did not. There is a link between AVP and cortisol levels in both trials. The increased activity of the Hypothalamic-pituitary-Adrenal (HPA) axis associated with suicidal behavior was found in elevated CRH levels in the CSF of suicide victims [7]. Studies of the 5-HT metabolite 5-HIAA in the CSF have provided the first indication that the 5-HT neurotransmission system has a role in the pathogenesis of suicidal behavior.

The dopamine neurotransmission system has been implicated in the pathophysiology of suicidal behavior, according to CSF investigations. Patients with serious depression and a history of attempted suicide had a lower Prolactin response to a challenge with the 5-HT-releasing medication Fenfluramine [10, 11]. Reduced CRH binding sites have been discovered in the post-mortem brains of suicide victims.

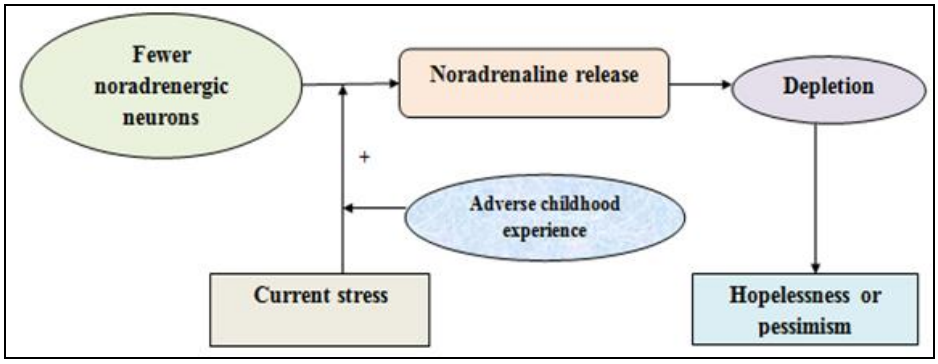

FIG. 2: EFFECT OF NOR-ADRENALINE DEPLETION ON THE BEHAVIOR

Suicide victims' locus coeruleus had fewer noradrenergic neurons, higher levels of tyrosine hydroxylase in the brain stem, and lower levels of postsynaptic adrenergic receptors in the cortex, according to post-mortem studies. These findings could be explained by an enhanced stress response before suicide, resulting in excessive NE release, a subsequent elevation in tyrosine hydroxylase biosynthetic activity, and downregulation of postsynaptic adrenergic receptors in the cortex [12, 13]. Farmer & Co-workers found no evidence of a genetic effect on the occurrence of suicidal ideation in recent sibling-pair research [14]. According to twin and adoption research, genetic variables are responsible for the majority, if not all, of suicide familiarity. At this time, it is unknown whether the genes that predispose to suicide are the same as those that predispose to depressive disorder, but the overlap appears to be incomplete. Completed suicide and psychiatric illness in relatives are risk factors for suicide, according to a recent large population-based case-control research, and the influence of family suicide history is independent of familial clusters of mental disorders [15]. Among other factors, this is owing to the difference in the phenotypic characterization of subjects about suicidal behavior & the accompanying psychiatric disorder. Moreover, it has recently been suggested that completed suicide & attempted suicide differ about genetic variability [16].

Parts of Brain Affected:

TABLE 1: PARTS OF THE BRAIN AFFECTED BY SUICIDE ATTEMPTERS [17]

Sr. no.	Parts of Brain	Functions in Normal Humans	Functions in suicide attempters
1.	Anterior Cingulate cortex	It maintains regional cerebral glucose metabolism. In BA-32 -Normal perfusion (Perfusion- arterial blood flow)	Regional cerebral glucose metabolism is decreased. In BA-32- Increased perfusion
2.	Posterior Cingulate cortex	Normal perfusion	Decreased Perfusion
3.	Thalamus	Normal alpha-[^{11}C] Methyl-L-tryptophan trapping	Increased alpha [^{11}C] Methyl-L-tryptophan trapping causes High lethality.
4.	Cerebellar pyramid	Normal perfusion	Decreased perfusion
5.	Parahippocampal	Normal alpha-[^{11}C] Methyl-L-tryptophan trapping	Increased alpha [^{11}C] Methyl-L-tryptophan trapping causes High lethality.
6.	Parietal	BA-40-Normal Perfusion	BA-40- Decreased Perfusion
7.	Temporal	Normal Perfusion Gray matter density is maintained	Decreased Perfusion Gray matter density is decreased
8.	Superior frontal	It maintains regional cerebral glucose metabolism	Regional cerebral glucose metabolism is decreased.
9.	Inferior frontal	It maintains regional cerebral glucose metabolism Normal volume of white matter	Regional cerebral glucose metabolism is decreased Increased volume of white matter
10	Amygdala	Normal volume	Increased volume
11.	Cerebellum	Normal reactivity towards mild angry faces	Increased reactivity towards mild angry faces
12.	Occipital	Normal alpha-[^{11}C] Methyl-L-tryptophan trapping	Increased alpha [^{11}C] Methyl-L-tryptophan trapping causes High lethality.

NT Disturbances in Suicide: The first studies of neurotransmitter metabolites in the cerebrospinal fluid (CSF) focused on depression. Although several studies have shown low concentrations of the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) and the dopamine metabolite homovanillic acid (HVA) in depressed patients, these early studies may have been skewed by the use of antidepressant drugs (which tends to lower CSF 5-HIAA), the amount of CSF drawn (both metabolites have a concentration gradient), and the use of control subjects. The differences between depressed patients and controls are underwhelming after these methodological aspects are taken into account. However, as evidenced by over 20 research, there is a strikingly consistent link between low CSF 5-HIAA concentrations and suicidal conduct. The link isn't just observed in depressive disorders; it's also been discovered in schizophrenia [18].

Impact of Social Isolation on Suicide: Many people view social separation and isolation as normal aspects of life. However, this may have an influence on your mental health. Distancing oneself from others may have the unintended consequence of raising the risk of suicide [19]. Moreover, the main tactic factors reported in the association between social isolation and suicide, such as temperament/ personality, low socio-economic status, abuse/life events, unemployment, low self-esteem, depression, medical conditions & loss, should be considered. Finally, it could be useful to distinguish between social isolation and deficits in social functioning present in some neuropsychiatric disorders, such as Alzheimer's disease and Schizophrenia, with specific pathophysiological mechanisms [20]. **Fig. 3** explains- When studying the association between social isolation and suicidal outcome, a number of tactic factors must be considered (*e.g.*, specific temperament/ personality, low socio-economic status, abuse/low self-esteem, psychiatric disorder, alcohol abuse. Social support is protective against suicidal outcomes [21].

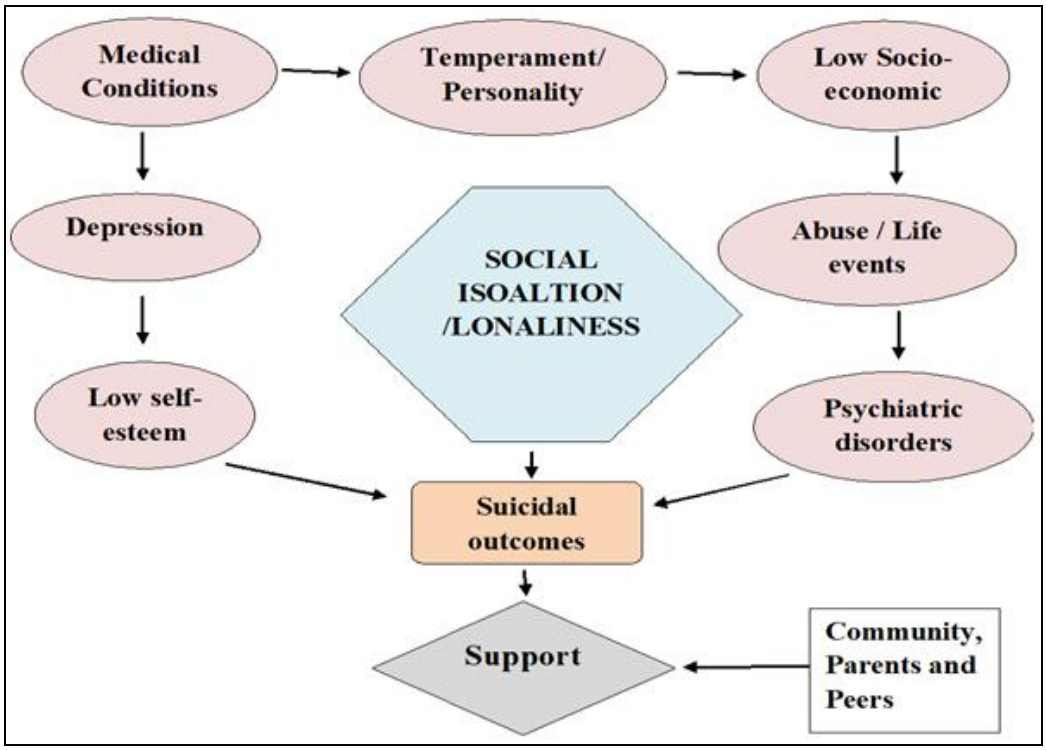

FIG. 3: IMPACT OF SOCIAL ISOLATION ON SUICIDE

Relationship between Antidepressants & Suicide: The link between antidepressant use and the risk of suicide is a topic of medical research that has sparked a lot of debate. The US Food and Drug Administration deemed this issue significant enough, marking a higher risk of suicide as a side effect of antidepressants [22]. According to several research, the use of certain antidepressants is linked to an increased risk of suicide in some patients when compared to the use of other antidepressants

[23]. The conclusions, on the other hand, have been subjected to much scrutiny and debate: Antidepressants reduce the risk of suicide in the general population, according to a multinational European study [24].

Youth: Antidepressants may raise the risk of suicidal thoughts and conduct in people under 25 who suffer from depression. The US Food and Drug Administration, in collaboration with the Neuro-Psychopharmacologic Advisory Committee and the Anti-Infective Drugs Advisory Committee, found in 2004 that there was a causal link between newer antidepressants and pediatric suicide [25].

Warnings: The Food and Drug Administration mandates "Black Box Warnings" on all SSRIs, stating that they double the prevalence of suicide ideation in children and adolescents (from 2 in 1000 to 4 in 1000) [26]. It's unclear whether the increased risk of suicide is due to the medication (a paradoxical effect) or a part of the depression itself (i.e., antidepressants allow those who are severely depressed who their depression would otherwise paralyze to become more alert and act out suicidal urges before fully recovering from their depressive episode to become more alert and act out suicidal urges before fully recovering from their depressive episode to become more alert and act out [27]. Suicidal ideation or behavior in young patients should be constantly observed, especially during the first eight weeks of treatment. Sertraline, tricyclic drugs, and venlafaxine have all been linked to an increased likelihood of attempted suicide in mentally ill people.

Increased Risk of Quitting the Medication: Following the introduction, titration, and removal of pharmaceuticals, a 2009 study discovered an increased risk of suicide [28, 29]. The risk of suicide increases in the first month after starting antidepressants, particularly in the first 1 to 9 days, according to a study of 159,810 adults who took amitriptyline, fluoxetine, paroxetine, or dothiepin [30].

WHO Response: Suicide is a public health priority, according to the World Health Organization (WHO). The first WHO World Suicide Report, "Preventing Suicide: A Global Imperative," was released in 2014 to raise public awareness about the public health implications of suicide and suicide attempts and make suicide prevention a top priority on the global public health agenda. It also intends to encourage and assist countries in developing or strengthening comprehensive suicide prevention plans as part of a multi-sectoral public health strategy.

Suicide is one of the priority conditions in the WHO mental health gap action program (mhGAP), which was created in 2008 and provides evidence-based technical recommendations to countries on improving service provision and care for mental, neurological, and substance use disorders. WHO member states committed to implementing the WHO mental health action plan 2013-2030.

Summary: Antidepressants appear to protect adults from suicidal behaviour, according to the findings. When compared to other antidepressant classes, SSRIs are linked to a reduced overall suicide rate (Example. TCAs). Antidepressants are helpful in reducing symptoms, which helps adults and the elderly avoid suicidal thoughts. This does not appear to be the case for children and adolescents, for whom antidepressant drugs can lower the intensity of depression but do not influence suicidal thoughts and actions. In contrast to what is seen in adults, aggressive-impulsive qualities may have a bigger role in teen suicide than depression. The effect of antidepressants on these characteristics is unknown. Illicit drugs may also play a role in teen suicide.

The black box warning and an earlier public health recommendation have demonstrated that deterring children from receiving medicine for depression is ineffective in reducing suicide conduct. Depression must be carefully monitored and treated, and the danger of suicide in youngsters must be closely monitored. Overall, clinical data suggest that antidepressants benefit the vast majority of patients, both young and elderly, with no increased risk of suicide.

Ten years after the introduction of the black box warning, it is time that the FDA reevaluates this decision and that the results be made public. Moreover, the labelling language should be rewritten to clearly delineate the risks of treatment compared with the risks of no treatment

CONCLUSION: We conclude that antidepressant drugs generally reduce suicidal ideation in depressed adults, but whether these agents impact suicidality in younger patients with major affective disorders is still a matter of debate. The possible increased suicide rate induced by the growing utilization of antidepressants remains one of the most important public health issues. Clinicians should be vigilant about the possible risk of iatrogenesis in prescribing potent drugs such as antidepressants. The possible existence, particularly in younger patients, of many unrecognized pseudo-unipolar mixed states, which can be a clinical substrate for suicidality, maybe one link to antidepressants in adolescent patients.

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