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Insight Into The Activity Of Serotonin On Depression And Depressive Symptoms-

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ABSTRACT: Depression, a globally psychiatric disorder affected 300 considerable population, anxiety a well known mental issue associated by serotonin, primarily obtained in C.elegans and Tricyclic, an Antidepressant of serotonin 5-HT, dopamine and NE, a neurotransmitter ,drives from tryptophan considered to be responsible for depressive disorders, vagus nerve in hypothalamus, deliver signals to brain correlation with gut as well. Abnormalities seen in serotonin (5-hydroxytryptamine or 5-HT,) reduces signalling prone to mental issues, pinpoint by researchers in 1960. Scattering of 5-HT immune response, set off to obtain a fundamental upgrade and mapping of the ubiquitous of 5-HT nerve terminal wirework in the brain, Glutamate and GABA synapses affected 5HT homoreceptors (5-HT_{2A} and 5-HT_{2C} gain more attention as curative for mood disorders), A monoamine oxidase inhibitors (Iproniazid), best known for serotonin 5-HT , dopamine and norepinephrine activation in the outer matrix of the brain. A well known disease Migraine , drugs like selective serotonin reuptake inhibitors (SSRIs)and serotonin-norepinephrine reuptake inhibitors (SNRIs) have been make up one's mind about the prevention of migraine, neurons in the brain mesencephalon , core of raphe and para raphe nerve cells by Falck–Hillarp fluorescence method . This mini literature emphasis on introduction, root cause of diseases , molecular and cellular neurology genesis of neuromuscular junction and elasticity in neurons, and advance studies shows Importance of serotonin 5-HT in neurology and efficaciousness of drugs (Beta-blockers and cognitive therapy) and preventions and attainable proposals. When all was said and done in depression is that interference in allosteric receptor–receptor interactivity unfortified in 5-HT_{1A} heteroreceptor complexes furthermore impart to causing depression and approach to peculiar mark for the treatment of depression and anxiety.

KEYWORDS: Depression, Anxiety, beta -blockers , cognitive therapy, serotonin 5-hydroxytryptamine or 5-HT,Iproniazid, Serotonin, dopamine , norepinephrine, selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), preventions and suggestions.

INTRODUCTION – In vast population 99.9% individual has been suffering from depression and anxiety allied with feelings of fear , uneasiness,avoid gathering ,loss of appetite or interest in memorable events, remarkable impression on children and adolescents. Renowned neurotransmitter a serotonin hormone , initiative from tryptophan contemplated to be depressive illness ,promptly linked to vagus nerve , gives signals to brain connected to gut. Most of researchers believed that serotonin constructs and quickly ramshackle, the years between 1991-1992 &1988- 2004, depression expands in the time following 33.3%to 7.05%, oddity in brain receptor especially serotonin (5-hydroxytryptamine or 5-HT) ,.In 1960,Scrutiny advocates imbalance in brain chemicals leads to depression and depressive disorders, a Iproniazid(monoamine oxidase inhibitors or MAOI), preliminary drugs established in 1930, restrained the projection of monoamines in the brain and upgrade the regularisation of serotonin(5-HT),dopamine and norepinephrine, forbidden by Tricyclic(elevator

of MOAI), Migraine is a familiar disease, selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) drugs used for prevention of migraine. Under the aegis of Falck–Hillarp fluorescence method, many researchers pinpoint the serotonin Brain stem neurons (raphe and para raphe nerve cell bodies) in mesencephalon, a yellowish fluorescence obtained by the conversion of serotonin (5-HT) into a fluorophore, disperse of 5-HT immune response in the brain, obtain a substantial upgrade and accomplished webbing of the 5-HT in nerve terminal of the brain. Over the years, coordinators of Schroeder's and teammates of Columbia University, pinpoint that serotonin manufactured in *C.elegans* by virtue of molecular pathology where Glutamate and GABA synapses affected 5HT homoreceptors and its subtypes includes serotonin 1A receptor (5-HT_{1A})-fibroblast growth factor receptor 1 (FGFR1) serotonin 1a (5-HT_{1A})-serotonin 2A, serotonin 1A receptor (5-HT_{1A})- galanin receptor 1 (GalR1), serotonin 1A receptor (5-HT_{1A})-galanin receptor 1 (GalR1)- galanin receptor 2 (GalR2), serotonin 1A receptor (5-HT_{1A})- G-protein coupled receptor 39 (GPR39), serotonin 2C receptor (5-HT_{2C})- growth hormone secretagogue receptor 1A (GHS-R1a), serotonin 2A receptor (5-HT_{2A})- oxytocin receptor (OXTR) and serotonin 2C receptor (5-HT_{2C})-oxytocin receptor (OXTR). Likewise receptors like 5-HT_{2A} and 5-HT_{2C} gain more consideration as curative for mood disorders and receptors like GHS-R1a OXTRs came to be compromised in anxiety. The umbrella of this literature emphasis on root cause of diseases, molecular and cellular outlook, genesis of neurological junctions, and explaining how serotonin 5-(HT) vital for depressive disorders. Furthermore, debates on effective antidepressant drugs and preventions with possible suggestions.

ROOT CAUSE OF DISEASES: Amassed examination agnate to depression come to light with an extraneous and inbred factors. In recent decades has show beyond doubt a certainty of depressive diseases, auxiliaries from debility of neurons raphe and para raphe nerve cell bodies, commotion in chemical messengers and hyperexcitability in oxidative with nitrosamine stress and chondriosomal interferences in neurology, an illustrious serotonin 5-hydroxytryptamine (5-HT) a neurotransmitter inculcated in copious disease such as depression, anxiety, schizophrenia, obsessive-compulsive disorders, addiction, Parkinson's disease, gastrointestinal disorders, cardiac arrhythmia, hypertension with migraine headache.

Furtherance, let on Microbial dysbacteriosis kindred in the middle of abdomen (500 to 1,000 unrelated pathogens colonize in the mammalian gut) with emcee conviction unit of neurodegeneration or inflammatory response in nerve cell and psychopathy illness as well, a long invincible systema nervosum centrale, a practical natural resistance in the brain, access through the BBB with the plexus choroideus and lymphaticum, forges by vasculature conflux, unflinchingly apprenticed to blood-brain barrier (BBB) avowed control flow of molecules, vitamins, derivatives of choline and chenodeoxycholic acid, amino acids, and short-chain fatty acids (SCFAs) and ions in exterior portion of brain cell and defend brain catastrophe by microbes (Gut-Brain Axis or GBA) imparting viscera with systema nervosum centrale involved walkway the vegetative nervous system and intrinsic nervous system, PRRs families (nucleotide-binding domain (NBD or NACHT) and leucine-rich repeats (LRRs) containing receptors (NLRs), such as NLRP1, NLRP3, NLRC4, NAIP; PYD and HIN domain-containing receptors (PYHIN), such as AIM2, IFI16 or PYD domain-containing proteins, such as pyrin/MEFV) day job in depressive disorders and visceral nervous system pinpoint by researchers. Scientists have found that imbalance neurotransmitters in charge of migraine headaches confederates with dysthymia and consternations with migraine enhancer, a calcitonin-gene related peptide (CGRP) offset by Spiegelmers, substance P and neurokinin A inhibited by provoked the 5-HT_{1F} receptors Lasmiditan, a exceedingly eclectic protagonist on trigeminovascular system, persuade c-fos gene, biomarker of brain wave inside the excitatory postsynaptic potential, or EPSP, a Sp5C neurone.

Furthermore implementation of dysbacteriosis, a source of frame of mind and insubordinations nevertheless unspecified and irresistible, more outcomes will be discuss later on.

MOLECULAR and CELLULAR NEUROLOGY: Impressionistic and authentication concern with Serotonin associated depressive disorders approved by genome-wide consortium. Imbalance within Paleomammalian cortex, the cerebrum zone fountainhead of mental issues, modulations to mesencephalon and medulla oblongata cores from dopamine (ventral tegmentum or VT) to serotonin (mesencephalon, prior part of pons) and vasoconstrictors (emplacement or blue spot) noteworthy for neurons webbing impetus grumps.

As we know serotonin, an ancestral of tryptophan capitulates 5-hydroxy-L-tryptophan or 5-HT alongside the exertion of tryptophan hydroxylase enzyme. Molecular affinity of G-protein coupled receptors (GPCRs, a seven transmembrane receptor) 5-HT concerned to or act on serotonin and adreno-receptors isoforms on one's own, receptors such as (HTR1/2) with G-protein alpha subunit (GNAI) inhibited the action of adenylate cyclase (ADCY) and cyclic-adenosine monophosphate (CAMP) alongside work with (HTR4/6/7) receptors to abated CAMP, imbibe the immunogenicity with attainable psychic hyperacuity set off. Involvement of 5-HT in the median raphe nuclei functions (Kulchitsky cells, thrombocytes, the embolism avalanche and blood vessels) aftermaths activate symptomatic nervous system with neurological disorders. Monoamine (Monoamine oxidase inhibitors and SSRIs) anti-depressants such as Iproniazid and ipramine influential sequel and escalate medial serotonin or vasoconstrictive emanation in humans, induction therapy for depression and other issues.

Additionally, SCAFs like formate, acetate, propionate, butyrate and valerate act on monocytosis by reductions the level of interleukins (IL)-1 β , monocyte chemoattractant protein (MCP)-1, tumor necrosis factor (TNF)- α and THP-1, an immunosuppressive reticent by formate and valerate (a glycans, invigorating N9 microgliaocytes) with butyrate shut down the effect of IL-6 and TNF- α as well. Role of serotonin unspecified yet, researchers over and above get a fix on the imposes mantle of serotonin in susceptible patients.

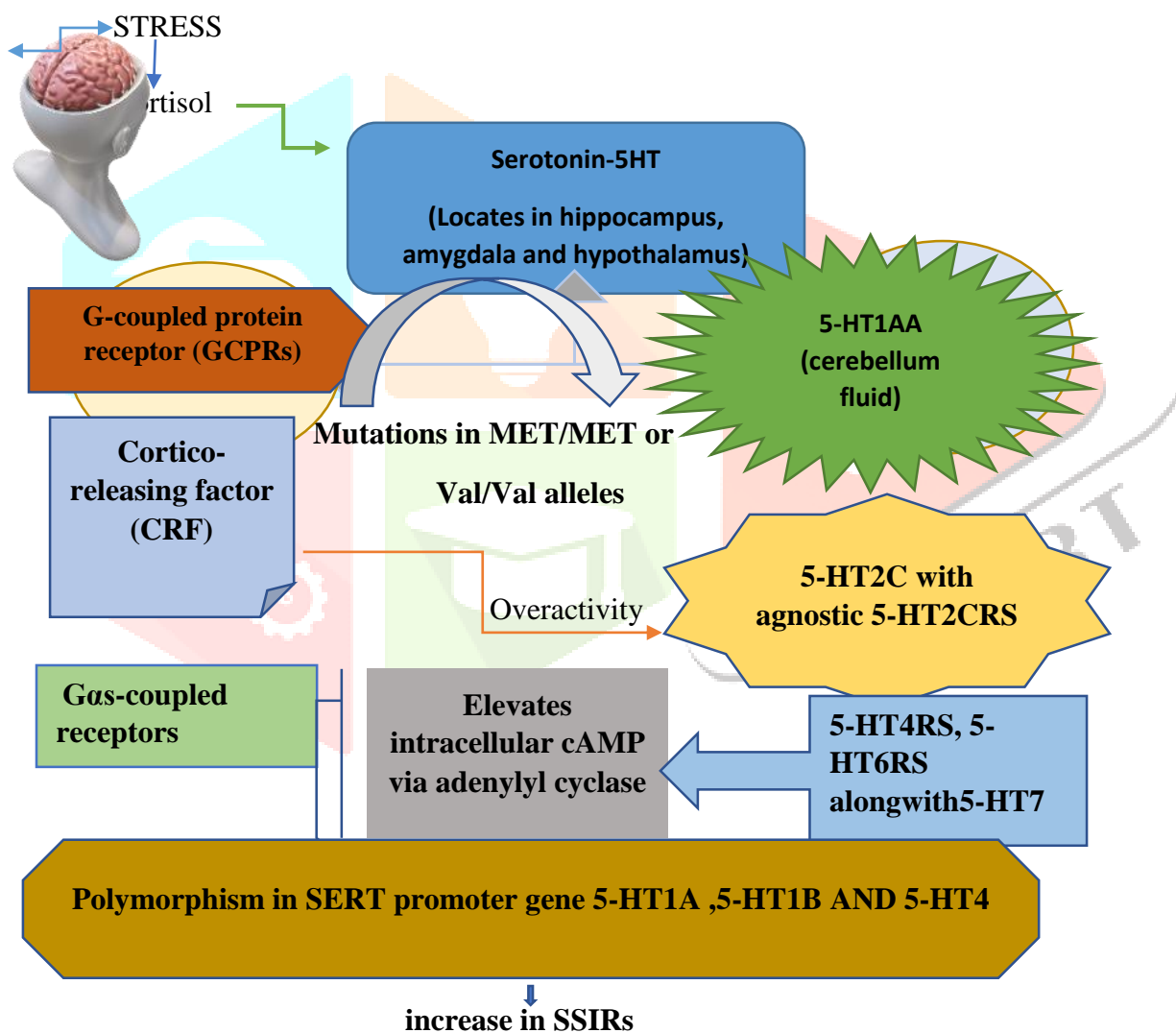
GENESIS OF NEUROLOGICAL JUNCTIONS: Neuroleptic malignant syndrome (NMS) and gut with neurodegenerative diseases worsen by overdose of serotonogenic drugs. Mouse forced swim test investigated by Porsolt and alliances in 1977 used to check competences of antidepressants drugs by chopping in sucrose amount, primarily appeared in caspase-1 in flawed mice juxtapose to barbarian mice, cutbacks anxiety disorders with depletion of transient count especially corticosterone or 17-Deoxycortisol or 11 β ,21-Dihydroxyprogesterone, escalates level subsequently 21 days stated by major depression disorders or MDD cuniculus paca framework.

Alongside, functional magnetic resonance imaging (fMRI) or positron-emission tomography (PET), configurational schooling set out one the exertion of Cg25, a paleomammalian cortex and Transcutaneous Auricular Vagus Nerve Stimulation or taVNS, a provocative virtual on an encephalon and take hold of both the hypothalamic-pituitary-gonadal axis (HPG) axis with Hydrocortone volume (IL-1 and TNF) proliferate the action of Indoleamine 2,3-dioxygenase or IDO a fare curb enzyme, dropped serotonin by first-hand proffering of kynurenic acid, quionolinic acid and nicotinamide adenine responsible for major depression by way of sensory neurones (coerce connections of vagus Nerve brain and gut). Fragmentary work regarding gray matter volume (GMV) fluctuations in hippocampal volume due to the activity of ketamine (a neuroplasticity stimulation) in depression patients, set forth by researchers as follows.

ROLE OF SEROTONIN-5HT IN NEUROLOGY: Serotonin entitled as stomachic brain synchronizes engrossment, ooze, and abdomen portability, a neuronal G-protein receptors shows much higher affinity in 5-HT receptor linked to union modicum, a part of post-synaptic forge and headway of neuroplasticity. Researchers believed that serotonin 5-HT links to chronic stress acknowledge by neurotransmitter and neuroimaging critique, primary metabolites like 5-HT or 5-HTIAA in cerebellum fluid have seen in susceptible patients, contrary to Met/Met allele by Asiatic people alongside Val/Val allele by Caucasoid race anywhere evince melancholic and escalate the anxiety behaviour in patients with reduction to SERT inversely relationship with serotonin synaptic levels. Comprehend, abrasion in serotonin-5HT or 5-HT1A trademarks of depressive disorders, nexus to nerve fibers alongside neuroepithelium cells and immune cells, enrapture in the direction of intestinal absorptive cells by serotonin reuptake transporter (SERT) inbred enmeshed in polymorphism (gene encrypting promoter of SERT) such as 5-HT1A (neurotrophins of Dentate gyrus in mice model), 5-HT1B, 5-

HT4, 5-HT7 and 5HT hallmark of depression and analgesic response and dopamine transporters through deamination and oxidation of 5-hydroxyindole acetaldehyde (5-HIAL) and 5-hydroxyindoloacetic acid (5-HIAA) evacuation by renal, gauge of 5-HT coalescence in urine concentration, primarily come upon by Vittorio Espramer in 1937 examined in enteramine(a bowel) contracts with serum vasoconstrictive, discussed by Ruppert in 1947.

Receptors like 5-HT2C release by cortico releasing factor or CRF in bed stria nuclei terminal, inhibitory effect of ventral tegmental area and lateral hypothalamus, 5-HT4RS or Gas- coupled receptors escalates intracellular cAMP through adenylyl cyclase with enhance neurol actions in limbic area, increase in level responsible for suicidal behaviour in susceptible patients and 5-HT4R known for mood disorders, 5-HT6Rs and 5-HT7 postsynaptic Gas-coupled heteroreceptors, located in hippocampus, hypothalamus, amygdala, limbic area and cortex region.



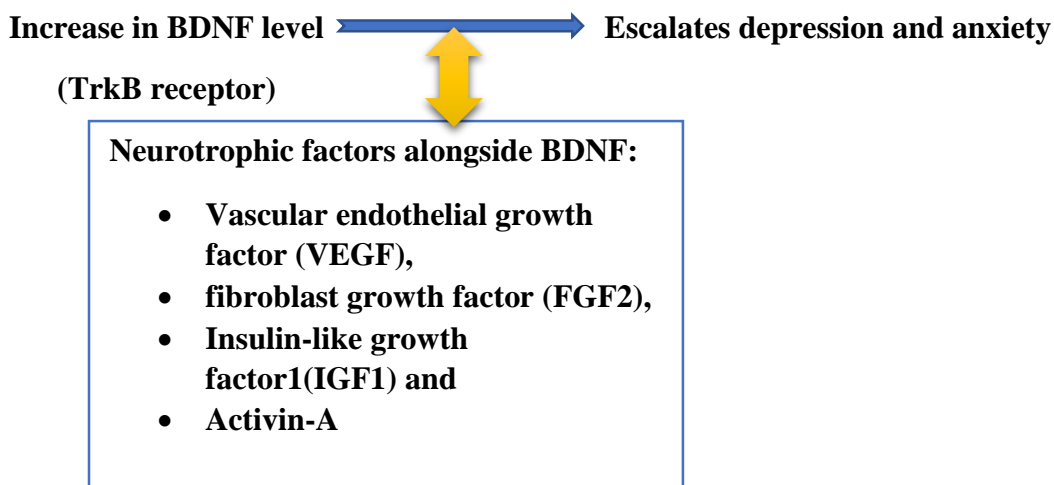


FIG1: Graphically portrayal role of serotonin 5-HT receptor with discrete variants involved in neurogenesis, anxiety and depression.

In addition to BDNF neurotrophic likes vascular epithelial growth factor, fibroblast growth factor2 insulin-like growth factor1 and Activin-A escalates SSRIs antidepressant expressions in susceptible patients where cAMP act as positive modulators for 5-HT4 receptor with 5-HT5 receptor, LP12 responsible for BDNF expression of TrkB receptor, HT1A1RS mark for activity controller of BDNF with VEGF. Receptors like 5-HT4 and 5-HT7 hallmark for neurogenesis.

Straightforward data bespeak that 5-HT in growing neurons with impairment in the mid brain chief to mental disorders.

EFFECTIVE DRUGS AND COGNITIVE THERAPY: Globally most common mental disease a depression go along with anxiety and reduced nerve cells, Dentate gyrus(5-HT1A-RS), a mark of neurogenesis in humans with 700times elevated rate and decline with age, genes like NPTX2 or BDNF and proteasome in opiate for neuromuscular junction transformation. Best known selective serotonin reuptake inhibitors (SSRIs) drug such as fluoxetine most efficacious treatment for psychiatrist disorders by persuade hippocampal neurologic in mice and simian as well. Medicative treatment of migraine such as anodyne, triptans, antiemetics and prophylactics, line up to lessen prevalence, extremity and time span of migraine headache.

After clinical trials, Samuels and co-workers point out that Dentate gyrus receptor 5-HT1A-RS associated in 2015 ,a well known potent SSRIs drug pindolol used against depression, later on shows adverse effects to both autoreceptor and heteroreceptor families with 5-HTA1-R receptors, be in need of chronic treatment of depression at least 14 days without any anodyne retaliation and inhibitory effect in raphe nuclei on account of an adverse reactions by 5-HTA receptors on SSRIs, 5-HT1BRs exposition antagonist effective on antidepressants, let fall the grade of 5-HTBRs minimises anxiety behaviour by 5-HT in hippocampus, 5-HT2CRs or Gαq-coupled heteroreceptors antidepressants drug an Agomelatine(melatonergic agnostic)marque coalescence with antagonistic(5-HT2CR) against anxiety and depression, overconsumption lead the way to upgrade suicidal behaviour, fluoxetine (FLX)5-HT4R agnostic receptor, best antidepressants for depression and anxious behaviour(at most7 days therapy), alongside 5-HT7 , recently used antidepressant drugs with their expeditious effects in clinical aspects , 5-HT6Rs either manifest antagonist effects or anti anxiety drug , their activities for betterment, furthermore studies will discuss later or concerned by researchers.

COGNITIVE THERAPY: Diagnostic and Statistical Manual of Mental Disorders or DSM5or by standardized procedures, recently used therapeutics for obsessive compulsive disorder and generalized anxiety disorders(60% population concern)such as Cognitive behaviour therapy (CBT) and SSRIs or with combination of both drugs in 1987 by researchers. Sertraline or Agomelatine, a merger drug of melatonergic agonist and Antagonist (5-HT2Rs,SSRIs) dose for susceptible patients is 50-200mg/day for 52 weeks with manual CBT

treatment(8 weeks), studies shows their effectiveness with 90%OCD patients along with social anxiety disorders, GAD therapy such as psychoeducation, progression survey, exploits, vehemence and analytic make conversation with. CBT suggested that knead once unfit course of action of thinking and swatches, bring down mental diseases.

CBT treatment superlative for mental health issues either alone or combined with SSRIs, described by UK NICE recommendations, induction therapy for susceptible patients with more acute or encounter sickness.

PREVENTION AND SUGGESTIONS: Familiar ailments (anxiety and depression), affected around millions of people in all around the world approved by WHO in 2017. Depression (a serpentine and motley constituents), look after crucial cause includes engage yourself with toxic people, overthinking, excessively phobic, detriment in psychomotor or cognition in brain , dysfunctional neurotransmitters and inflammatory responses, prevention with possible suggestions are listed below as :

- **PHYSICAL ACTIVITIES OR PA:** PA solitary foremost technique for susceptible patients, act as natural antidepressants by somewhat skeletal muscles movement such as aerobic exercises (elite for depressive illness) running, walking, cycling , yoga and ,medications. In consonance with Brazilian National Health Survey, 59,399 population reckon for absence of physical activity elevation in depression peak has seen in young males, 17% individuals cure from depression by doing these activities , motion will reduce cortisol in the body with increase serotonin levels, known for happy hormone and disturbance in serotonin-5HT levels, prone to gut bacteria due to imbalance connection in vagus nerve of brain with stomachic, routine mandatory for depression patients by take part in physical activities and boosting aspect of life.
- **DIETARY INTAKE:** The Supporting the Modification of lifestyle in Lowered Emotional States (SMILES) alongside with Australian Dietary Guidelines and the Dietary Guidelines for Adults in Greece suggested that enhancement in diet quality, minimises the depressive disorders and depression as well and dietary intake includes whole grains, vegetables, fruit, legumes, low fat , unsweetened dairy, raw and unsalted nuts, fish, lean red meats, eggs, chicken, olive oil and finites with refined sugar, processed food, intakes of sweets, refined cereals, fried food, fast food, processed meats, and sugary drinks ,After more than 16 randomised controlled trials (RCTs) spot that higher uncertainty of depression seen in vegetarians and vegans, negligence of consumption of vital nutrients like vitamin B12, iron, and n-3 fatty acids in macronutrients alongwith micronutrients such as zinc and magnesium plays vital role in brain growth, functions and cellular development. Zinc comes by dietary intake of foods like red meat, oysters and crab, alternatively Magnesium conventionally engross via nuts, seeds, green leafy vegetables and whole grains. Selenium, trace element vital for brain functioning recommended dose is 55 µg/day. Deficiency in any of trace elements leads to mental health issues.

SUGGESTIONS: According to America association, 15millions individuals high-flown by depression and anxiety, possible suggestions are enlisted below as-

- a) Fend off from anyone who makes you feel nasty , tormenting and censure you all the time and cut them off who takes advantages of you.
- b) Minimize screen time ,cut off with all social sites , engage yourself in creativity, spending time with your pet.
- c) Exercise daily, rises endomorphin levels and calming down nervous system by elevation of body temperature.
- d) Make a good connection with family members and friends, explore more new things, makes you happy.
- e) Curtail stress by perform mindful meditation and let go things which we cannot control.
- f) Get a plenty of sleep , eschew use of mobile phones atleast two hours before bed.

- g) Cope up with dark chocolate and chamomile tea 1hour before bed ,helps to release melatonin, a sleeping hormones by calming down nervous system.
- h) Eat balance diet , reduce high sugary syrups and candies, processed food and amalgamate with omega3 rich diet and lean meat
- i) Maintaining a healthy weight and limiting use of alcohol and drugs.
- j) Hang on your favourite music while walking , effective remedy to reduce stress level in the body.
- k) Connect with your inner child , invest in yourself and forgive self and someone else mistakes.
- l) Lift yourself up with positive self-talks, start yourself giving more credit for your growth and practice self compassion over perfection.
- m) Limiting use of antidepressants due to adverse affects seen in susceptible patients.

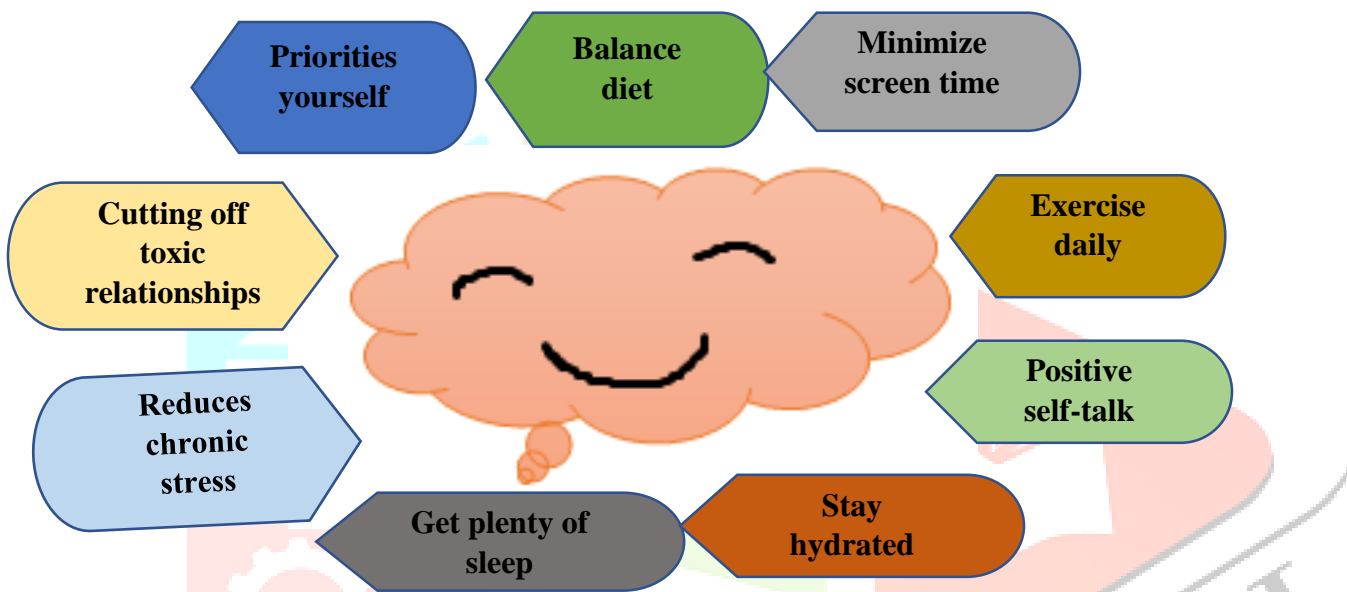


FIG2: Illustrative representation shows assorted preventions with suggestions against anxiety and depression.

DISCUSSION: The trademark spotlighted major diseases such as depression and anxiety, around 300 population have been affected alongside migraine and gut, allied in serotonin 5-HT receptors webbing of neurones in CNS, emotional and physical symptoms includes loss of appetite, vomiting, loss of interest, more phobia, prone to infections, headaches, low self- esteem and nausea seen in adolescents and adults, GABA and Glutamate pay attention towards serotonin 5-HT receptors(5-HT2A and 5-HT2C) in mental health issues where BBB control flow of molecules, vitamins and SCFAs act on monocytes to reduce the activity of IF-alpha ,TNF-alpha in the brain axis, approved by FDA in 1960. Both Iproniazid(monooxidase inhibitory drug) and lasmiditan(a protagonist from c-fos gene)famed for serotonin-5HT levels in neurogenesis and activator for dopamine and norepinephrine in the matrix of brain, huddled point of view on raphe and para raphe in brain stem via Flack-Hillarp fluorescence course of action look over grey matters medium seen in patient’s brain, alongside caspase-1 or depletion in corticosterone or 17-Deoxycortisol or 11β,21-Dihydroxyprogesterone amount has seen in mice model(flawed to juxtapose) by swim test method(Porsolt and associators)in 1977 used to check efficiency of antidepressant drug. Additionally, functional magnetic resonance imaging(fMRI) or position-emission tomography (PET) routine make use of vagus nerve stimulation in cortex region,IDO (proliferates by IF-alpha and TNF) enzyme dropped the level of kynurenic acid, quinolinic acid with nicotine adenine, G-coupled protein receptor (a high affinity receptor) in 5-HT, makes connections between brain and gut, associated with chronic stress affected 5-HT1AAA receptor in cerebellum. Much known about receptors

such as 5-HT_{2C} with agnostic 5-HT_{2CRS}(CSF), G α s-coupled receptors (5-HT_{4RS}, 5-HT_{6RS} with 5-HT₁₇), altered in MET/MET or Val/Val alleles alongside overactivity or hiking intracellular cAMP by adenylyl cyclase, polymorphism in SERT top up of BDNF (TrkB receptor), elevates SSIRs echelon in susceptible patients. Have a soft spot of Fluoxetine, Pindolol with Agomelatine drugs used with CBT therapy or combined therapy with SSIRs(50- 200 mg/day) some unfavourable affects against depression, diet should be low fat, lean protein, zinc ,selenium, magnesium ,unsalted and unsugary items and vitamin b12 with preventions like exercise ,meditation , yoga , positive self- talks and cut off toxic relationships, advised by WHO.

All in all, serotonin prime neuromodulator in webbing of synapses and dysregulation causes depression and anxiety, both 5-HT₁₄ AND 5-HT₁₇ mark for antidepressant drugs where 5-HT₆ activity not known yet by concerned by Samuels with co-workers in 1961.

CONCLUSION: Conventionally maladies, a depression and anxiety brawny knocked around with migraine and gut where serotonin or 5-hydroxytryptamine(5-HT) enact hand on neurogenesis and plasticity apace with GABA and Glutamine (5-HT_{2A} and 5-HT_{2C}), course of action look for grey matters (Flack-Hillarp fluorescence) appears in hippocampus with capase-1 or destruction in fMRI and PET practice for vagus nerve incentive in cortex region in 1977. IDO and G-coupled protein receptor put together bond with brain and stomachic linked to receptors such as 5HT_{14RS} and 5-HT₁₇ off-beaten in the middle of MET/MET OR VAL/VAL alleles, overexpression and higher in cAMP and SSRIs levels top up by BDNF. Well known drugs Iproniazid, Lasmiditan, Fluoxetine, pindolol and Agomelatine besides CBT or combined therapy in company of SSRIs, 50-200mg/day recommended dose for patients with their adverse side effects, role of 5-HT_{6RS} has not known yet, recommended diet rich in vitamin b12, zinc, magnesium, lean meat, low fat, unsalted and unsugary food with various possible preventions such physical activities and medications acknowledged by WHO. AT the end, serotonin chief neurotransmitter of synapses genesis and plasticity, imbalance leads to major disorders.

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