

Therapeutic Approaches for Treatment and Management of Depressive Disorder: A Comprehensive Review

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ABSTRACT

Depression, which is associated with high levels of cognitive and functional activity, melancholy, reduced activity, difficulty understanding, failure to focus, dietary abnormalities, sleep disturbances, and emotions of feelings of sadness, suicidal thoughts, and lack of hope are symptoms of a psychoneurotic disorder. It is a common and recurring disorder with a high morbidity and death rate throughout the world. Despite advances in depression treatment, such as selective serotonin reuptake inhibitors (SSRIs) and selective norepinephrine reuptake inhibitors (SNRIs), there remain several unmet clinical requirements in terms of effectiveness and adverse effects. These requirements range from enhanced to decreased side effects like emesis and erectile problems in treatment-resistant patients. There are a variety of combination therapies available to meet these needs. Several combination medicines and novel strategies have been found, all of which have the potential to improve one or so more areas. The kinds of targets and methods being used are extremely diverse. Therapeutic approaches, on the one hand, provide the benefits of SSRIs while including alternative routes in an attempt to improve efficacy or reduce undesirable effects. Neurotrophins (BDNF, IGF) are more novel targets on the other end of the spectrum, based on the most recent research suggesting antidepressants enhance neurogenesis. Antidepressants act by blocking many proteins, such as neurotransmitter transporters and G-protein coupled receptor families, in the brain. Some of the computational approaches that are useful for uncovering drug action mechanisms and are important for drug development are molecular docking, molecular dynamics, and drug candidates.

Keywords: Antidepressant effects, Depression, Disorders, Novel approaches of treatment.

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INTRODUCTION

Depressive can also be described as a state of being dissatisfied. It's also known as a psychoneurotic disorder, which is characterized *via* way of means of intellectual and practical hopelessness, depression, and technology of emotional distress, as well as difficulty understanding, loss of focus, disturbances in diet, sleepiness, and emotions of desperation, depression, and technology of suicidal tendencies.¹ It is a widespread disorder with a high frequency and severity that occurs often.² The arousal of grieving is a symptom of depression, which is a type of psychopathy that can affect the overall thinking method, behavior, and feelings.³ Such persons suffer from unbalanced sleep and sleeping disorders.⁴ There is meager data on the market concerning the underlying mechanisms of their laws. Abnormal neuronal structure in the brain is linked to severely insufficient or excessive sleep, neutrality in intercourse, and other extracurriculars. There are generally three classifications of depression: Clinical depression, which

is defined as serious depression. Changes in hormone levels and physical alternatives regarding the birth of a child define postnatal depression. A seasonal mental disease that occurs during the winter season when there is less daylight. In the ladies, the great depression arises additionally because of additional work overload, household chores, childcare services, relationship problems, elderly parents' care, and poverty, all factors to consider. In addition to all or any of these signs, psychological, biological, and secretion variables play a big part in depression.⁵ Premenstrual disorder (PMS) or pathological premenstrual depressive disorder (PMDD) in women will have a big impact on how depression develops. Depression in men may be linked to significant illnesses such as cancer and internal organ ailments, excessive exhaustion, irritation, loss of balance, lack of sleep, and becoming aggressive. Sclerosis depression affects older men (vascular depression) has been discovered. Time, which can result in suicide among children, is also associated with the rising sex and onset of puberty.⁶

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In women, good depression arises in addition as a result of additional job load, domestic duties, care for children, a challenging relationship, financial circumstances, and taking care of aging parents. Additionally, mental, biological, and secretion factors all have a key impact on depression in addition to all or any of these signs. PMS, PMDD, and pathology among women all play a significant part in the growth of depression.⁷ Depression in males could be related to suffering from serious diseases like cancer and internal organ disorder, excessive tiredness, aggravation, tolerance for previously joyful activities, dizziness, poor sleepiness, and becoming confrontational inducement depression (vascular depression) has already been observed in elderly males when the amount of your time which may end in suicide at intervals the kids are additionally associated to the rising sex and onset of pubescence.⁸

Antidepressants are those medicine that facilitates the reduction in symptoms of depressive diseases by correcting hormonal imbalances in the brain's neurotransmitters. A serotonin imbalance causes a change in personality and behavior. Neurotransmitters connect the brain's neurons. Vesicles are where neurotransmitters are stored in nerve cells. The axonic end of one neuron releases neurotransmitters such as 5-hydroxytryptamine, monoamine neurotransmitter, and vasoconstrictor, which are then taken up by a process called uptake. The antidepressants increase the concentration of particular neurochemicals near the neurons in the brain by inhibiting the reuptake of neurotransmitters through selective receptors.⁹

Depressive Illnesses Prevalence and Socioeconomic Consequences in India

The total weighted availability of lifetime depressive disorder was found to be 5.25% and it varies across the individual group of population samples collected. The lifetime prevalence of depressive disorder in the case of collected rural area populations was found to be 4.48%, whereas in populations collected from cities with strengths less than 1 million, the depressive disorder was found to be 4.93%, whereas in populations greater than 1 million strengths in cities was found to be 8.23%. When sampling was done from an educated mass population, it was found literate people with no formal education and a lifetime depression disorder of 6.04%. In contrast, the population with primary education was 5.76%. For the secondary education population, the data was 5.86%. In contrast, high school educated population, the lifetime dd was 4.67%, in preuniversity, it was 3.20%. when the sampling was done between the working and not working population, the lifetime dd figure was found to be 5.56 and 5.00%. While collecting the population considering marital status as a criterion, the lifetime depressive disorder for the married population was found to be 5.44%, and for the divorced and never-married population, the figure obtained was 11.23 and 2.87%. When considering the income group of the population, the figures obtained for the lowest, second, middle, fourth, and highest data obtained were 6.36, 5.68,

5.42, 4.21, and 4.76%, respectively. However, when the study population was taken considering states it was obtained, the lifetime depressive disorder of Gujarat was 1.9%, and Tamil Nadu 12.6%, respectively.¹⁰

While considering the current prevalence of depressive disorder from the study adult population, the statistical data obtained amongst the states, i.e., Gujarat 1.2%, Jharkhand 4.7%, west Bengal 4.3%, Manipur 3.7%. Whereas the rural population has 2.15% and cities with less than and more than 1 million population have 1.90 and 5.17% respectively.¹¹ While taking a population study considering education as a criterion, the data obtained for literate mass was 3.63%, primary educated mass 3.11%, secondary 2.70%, high school 2.26%, and pre-university 1.61%. When taking the working adult class population, it was found to be 2.70%, and not working class, it was 2.66%. The statistical data when considering marital status, the married group was 2.75%, never married was 1.70%, and the divorced adult population was 5.23%. When the income group was chosen, the statistical data for the lowest, second, middle, fourth, and highest was found to be 3.42, 3.14, 2.89, 2.20, and 1.91%, respectively.¹² When gender-based and age-based study population was taken into consideration adjusted percentage found in males was 1.0%, females was 1.23%, while the age groups (18–29, 30–39, 40–49, 50–59, and above 60) were 1.0, 1.45, 1.93, 1.87, and 1.72%, respectively (Sheehan DV 1998).⁸ The statistical data among the population is shown in Figure 1.

Approaches for the Treatment of Depression

Non-pharmacological approaches for the treatment of depression

The holistic approach to therapy, known as integrative medicine, incorporates both well-recognized complementary and alternative medicine (CAM) methods.¹² Integrative medicine (IntM), which is individualized and patient-centered, takes into account all environmental, economic, religious, and social elements that may have an impact on a patient's health.¹³ Integrative medicine philosophy places a strong emphasis on the relationship between the patient and the healthcare practitioner as well as on including the mind, body, spirit, and community to promote a natural healing response and the idea that healing is always possible even if the cure is not. The National Center for Complementary and Alternative Medicine classifies natural products (herbs, vitamins), manipulative and body-based activities (such as chiropractic and massage), and other alternative and complementary therapies treatments (such as energy therapies and entire medical systems) as complementary and alternative medicine (NCCAM). Yoga, acupuncture, and other body-based techniques are all included in memory medicine. As the corpus of research behind certain therapies expands and the practice is integrated into regular medical practice, complementary and alternative medicine (CAM) has an ever-expanding field of exercise. A well-liked and increasingly gaining medical trend is integrative medicine.¹³ Mostly as a result of demand in two nationally representative studies of more than 22,000 healthy individuals

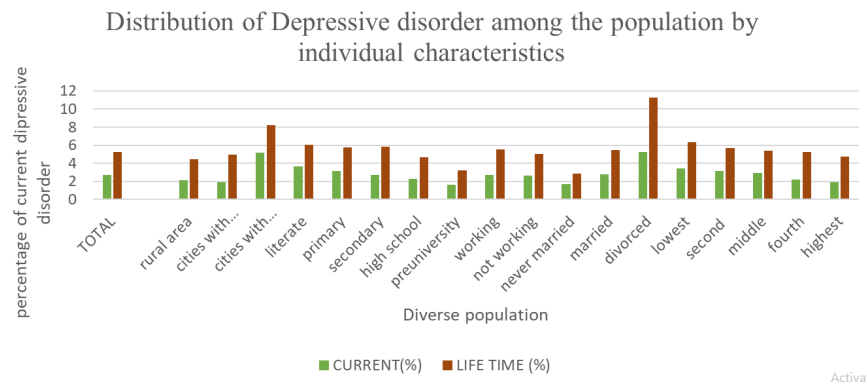


Figure 1: Statistically collected data among various adult populations suffering from a depressive disorder in India

and 2000 individuals suffering from depression, respectively, over 40 and 54% of participants reported using some type of integrative medicine in the previous year, with natural products and mind-body therapies being the most popular.¹⁴ Integrative medicine is commonly used for a variety of goals, including lowering sickness symptoms and the negative effects of traditional medical treatments, taking control of one’s health, and enhancing overall well-being. Numerous chronic diseases, including depression, may benefit from the use of integrative medicine, according to a growing body of research. St. John’s wort (SJW) and fitness were discovered to have the most proof at the time, whereas many other therapies (such as acupuncture and massage therapy) had little to no evidence. No embedded pharmaceutical therapies were as empirically well-supported as antidepressants or cognitive behavior therapy, according to a thorough evaluation of 37 integrative medicine techniques for treating depression published in 2002.¹⁵ St. John’s wort and exercise were shown to be beneficial in the treatment of depression in a 2011 assessment of many IntM methods.¹⁶

Medicine that treats both physical and mental health

Bringing physical and mental health together to improve your health and well-being, physical and mental health medicine is a group of techniques (e.g., yoga, meditation, and relaxation strategies).¹⁷

Insight meditation treatments

Insight meditation Treatments are a potential approach that focuses on the Latest evidence on meditation for depressive episodes has just about entirely focused on mindfulness meditation, a type of insight meditation that has its roots in Buddhist traditions.¹⁸ Insight meditation cognitive treatment and mindfulness-based stress reduction (MBSR) have received the most attention in research.¹⁹ Mindfulness-based cognitive therapy (MBCT) is an eight-week program that uses mindfulness meditation-based approaches to shorten the link between negative emotions and poor mood, as well as increase the conscious experience of shifts in physiological reactions, emotional feelings, and thought patterns from one moment to the next moment (For instance, body scan and attentive breathing). This idea can help patients recognize the first indications of depression and take proactive measures to

prevent mood swings. Mindfulness-based reducing stress is an eight-week structured therapy for chronic pain sufferers.²⁰ According to various published research and concepts, mindfulness-based approaches appear to be effective and promising treatments for depression. The results show that mindfulness-based interventions have relatively large treatment effects for lowering symptoms of depression and recurrence frequencies (reduced risk to 34%) for up to a year.²¹ Insight meditation methods have no significant differences from antidepressants or cognitive behavioral therapy. Patients who achieved incomplete recovery following antidepressant therapy, for example, exhibited considerably reduced and identical recurrence rates, whether mind fullness-based cognitive therapy (28%) or antidepressants (27%) were used in comparison to placebo (71%). In addition, the study was judged to be of excellent quality, with the use of well-validated methods, no signs of reporting bias, or study heterogeneity. More research is required on procedures and dosing in mindfulness-based treatment. Whether mindfulness training is more successful in preventing depressive recurrence among those who have previously undergone more depressive episodes is one key subject in this field. According to mindfulness-based cognitive therapy theory and early research, individuals with a history of three or more depressive episodes should react better to therapy since there is a larger association between negative thinking and depressive symptoms.²² Although the majority of studies’ incoming evidence supports this notion and demonstrates that mindfulness-based cognitive therapy is helpful independent of a person’s level of depression.²³

Techniques for relaxation

Almost limited study has concentrated on stress relief interventions for depression in the current history. For stress relief, more therapy alternatives are available. If efficient, then there will be no or very little therapy for reducing signs of depression. In 2009, 15 quasi-randomized controlled studies on stress reduction were reviewed, and the Cochrane Collaboration published relaxation therapy and relaxation methods (imagined sensory relaxation, heaviness, and stress relief in the body).²⁴ Since then, we’ve only found one research on relaxing for depression. This study looked at an 8-week relaxation program based on cognitive behavioral therapy

(CBT) that was given to 133 young adults who were depressed but didn't have a history of mental illness.²⁵

Yoga

Yoga is viable for depressed patients, and the first findings are encouraging; nevertheless, severe methodological shortcomings and variability within yoga regimens limit decisive conclusions.²⁶ In four out of five randomized controlled trials, meditation was discovered to be more helpful than either therapy or certain active treatments (Examples include psychosocial support and progressive muscular relaxation). The validity of these findings was nevertheless constrained by the fact that active monitoring groups weren't typically connected in terms of time or other general criteria and that overall outcome assessments weren't frequently conducted without disclosing the experimental group. Using several methods, yoga dramatically reduced symptoms to the same degree as a placebo in the currently limited investigation. Yoga dramatically lowered depressive symptoms to a level comparable to health education. However, subjective explanations for recovery varied, with only the yoga group in a recent study's research techniques reporting acquiring the new defensive approach.²⁷ To comprehend the workings of yoga treatment as well as its safety and dosage, much study is required.

Natural goods

Natural goods are biologically based compounds that aim to improve general health. Examples include herbal remedies or botanicals, minerals, vitamins, and dietary supplements (e.g., probiotics). Therefore, these strategies can be used in addition to or as a supplement to a whole-food diet.

Exercise and movement therapies

Exercise has a large effect size compared to no treatment or placebo controls and may be a useful alternative to standard care when paired with antidepressants, cognitive behavioral therapy, and other physical activities.²⁸ However, more extensive investigations had less of an impact. To enhance motivation, healthcare professionals should tailor prescription drugs for exercise to the patient's degree of activity and chosen type of activity.²⁹ Given that many international health organizations, such as the American Psychiatric Association, advise exercise as an adjunctive treatment for depression and that this recommendation holds for other forms of physical activity, suppliers should take a proactive stance and customize activity prescription medications to the individual's activity level and preferred type of activity.

Pharmacological Approaches for the Treatment of Depression

Strategies for monoaminergic

As per the monoamine hypothesis of depression, serotonin deficiencies in the brain produce the genesis and pathophysiology of depression, norepinephrine, and/or dopaminergic. Consequently, modern pharmacotherapies (e.g., selective

serotonin reuptake inhibitors (SSRIs), selective norepinephrine reuptake inhibitors (SNRIs)) have been created in an attempt to correct these changes in dopamine receptors systems. The 3- to 5-week wait period needed to reach therapeutic effectiveness is a drawback of all commercially available antidepressants, regardless of their mode of action. This recovery period is assumed to represent the time necessary for the adaptation of monoamine receptors (for example, 5-HT1A, 5-HT2C, and -2 adrenergic receptors). Current drug discovery strategies have focused on producing innovative antidepressants with double and/or triple action to potentially speed up the onset of antidepressant function while reducing unwanted side effects. The sections that follow will address three methods of action for these approaches, as well as data from preclinical and clinical studies.³⁰

SSRI/ 5-HT1A antagonists are medications that inhibit the function of the SSRI/5-HT1A receptor

The deferred therapeutic relevance of SSRIs is thought to be largely due to the implicit Somatosensory 5-HT1A auto receptors being activated. In numerous brain regions, including the dorsal raphe nuclei, acute SSRI medication raises serotonin levels. According to a preclinical study, by activating inhibitory 5-HT1A autoreceptors in the dorsal raphe, this increase in serotonin prevents 5-HT cells from firing and dampens further 5-HT releases in the brain's terminal serotonergic regions. Long-term SSRI use impairs 5-HT1A auto receptor function (14–21 days).³¹ Acute treatment is less likely to result in substantial serotonin surges than this. These results imply that SSRIs and 5-HT1A receptor antagonists may raise central serotonin levels more strongly and quickly, producing a faster-acting antidepressant.³² Numerous recent non-invasive studies indicate that WAY-100635 and other selective 5-HT1A antagonists ameliorate SSRI and SNRI-induced neuronal serotonin alterations.³³ These findings are confirmed by novel experimental models susceptible to serotonergic behavioral consequences since 5-HT1A antagonism has been demonstrated to increase serotonergic effects. In rats and mice, SSRIs show antidepressant-like effects, and they commonly cause long-term harm in lab testing.³⁴ According to medical studies, when taken with the 5-HT1A/adrenoceptor antagonist pindolol, the antidepressant effect of selective serotonin reuptake inhibitors is increased and/or improved.³⁵ There is enough evidence to suggest that using SSRIs in combination with 5-HT1A receptor antagonists may help treat severe depression, despite the conflicting results of this research. Similar to this, several companies have lately released research on the creation of dual-acting medications that function as SSRIs and full or partial 5-HT1A receptor antagonists, some of which are successful in investigations on experimental depression.³⁶ In preclinical depression animals, some of these dual-acting SSRI/5-HT1A medications are helpful. As more dual-acting SSRI/5-HT1A drugs enter clinical trials, it could not be long before we learn if this strategy represents the next step in the development of antidepressant drugs.

Antagonists of the SSRI/ 5-HT2C

Treatment with selective serotonin can be modest or severe, and it binds to 5-HT_{2C} receptor sites, which are frequently discussed. The significance of this biochemical alteration in the antidepressant effects of selective serotonin reuptake inhibitors is likewise unknown. Recent studies suggest that inactivating the 5-HT_{2C} target point may boost the neurobiological and behavioral effects of antidepressants. In rodents used for *in vivo* microdialysis, Cremer *et al.* found that SB242084 and RS102221 significantly increase the monoamine effects of selective serotonin reuptake obstructions on the serotonin conditions of hippocampal and pyramidal neurons. These compounds also significantly increase the effects of the nonselective 5-HT_{2C} binding site inhibitors ketanserin and irindalone.³⁷ Despite the reality that both drugs have considerable neurochemical effects when combined, 5-HT_{2C} receptor antagonists have little consequence on extracellular serotonin. In concepts of depression and anxiety, such as the rodent tail suspension test (TST) and schedule-induced fluid retention, this serotonergic step generates pronounced additions to the antidepressant. These additions include products of selective serotonin reuptake impediments that are analogous to the reported neurochemical products. Complementary scars from 5-HT_{2C} enhanced neurochemical and behavioral (TST) responses to fluoxetine were seen in null genetically altered mice.³⁸ When compared to the offspring of their wild type. Although the precise brain mechanisms underlying these enhanced behavioral and neurochemical responses are unknown, it is most probable that altered negative feedback processes at the postsynaptic site are the mechanism by which they are mediated. The native infusion of RS102221 on a serotonergic regular basis, according to the findings, generates effects on selective serotonin neurochemistry that are equivalent to systemically given 5-HT_{2C} antagonists. According to this preliminary research, blocking 5-HT_{2C} enhances the neurochemical and behavioral effects of SSRIs. Similarly, our findings point to a unique depressive disorder therapeutic method that integrates both targets, either as a distinct molecular reality or as a backup treatment to existing well-known selective serotonin reuptake inhibitors.³⁹

Adrenergic antagonists of SSRIs and α -2 adrenergic receptors

A system that targets noradrenergic auto receptors may have the potential to broaden the synaptic effects of traditional antidepressants. Antidepressants, particularly norepinephrine reuptake inhibitors (SNRIs) like reboxetine (Edronax), elevate extracellular norepinephrine concentration significantly. Norepinephrine may activate presynaptic α -2 advancement adrenergic autoreceptors on both norepinephrine and dopamine cells, resulting in weakened noradrenergic and dopaminergic responses. Furthermore, because neighboring α -2 adrenergic receptors suppress serotonin efferent from the dorsal nerve, inhibiting α -2 receptors may also affect serotonergic transmission α -2 adrenergic antagonists may increase the neurochemical effects of antidepressants and

may affect antidepressant effects in people, despite the lack of evidence that this particular mix approach has any effect on animal models of depression. A few facts support this idea, including the fact that drug interactions of antidepressant medications with adrenergic blockers result in a faster dysregulation of cerebral cortex-adrenergic receptors. It is also known that nonselective α -2 adrenergic receptor antagonists, including mirtazapine (Remeron), have marginally stimulating effects on the right.⁴⁰ Last but not least, clinical evidence shows that SSRIs and nonselective α -2 blockers work more quickly to produce an antidepressant effect. These study findings have stimulated significant chemical work to create and manufacture improved antidepressant drugs that combine monoamine reuptake inhibitory action with antagonistic activity at the α -2 adrenergic receptor.

Supplements, vitamins, and minerals

S-adenosylmethionine, an amino acid typically found in humans, is a physiological molecule that spontaneously generates from adenosine triphosphate and methionine and is essential for some metabolic processes in the brain. (J. 2011) Numerous studies have shown that SAM-e as a monotherapy for depression offers significant benefits over placebo, with quite large effect sizes for mild depression.⁴¹

Folate

Low folate levels have been related to depression because there is some evidence that folate can be used as an antidepressant supplement, particularly in patients with low folic acid levels. Folic acid treatment is probably going to enhance how well antidepressant medications work because folic acid insufficiency is likewise connected to poor antidepressant effectiveness. The results were not as remarkable since so few of this research were double-blind, placebo-controlled investigations. Since, few of these studies were double-blind and placebo-controlled, the outcomes weren't as impressive. There is an increasing focus on the role of L-methyl folate in depression since folate is physiologically inactive and must be changed into L-methyl folate to cross the blood-brain barrier and encourage the creation of neurotransmitters.⁴² Only accessible with a prescription, l-methyl folate tablets have FDA approval. L-methyl folate supplements, which are sold as pharmaceutical medical meals, are meant to increase folate levels and an individual's receptivity to antidepressants. These supplements are tolerable and might be utilized as antidepressant supplements, according to a preliminary study. There is no proof to support the benefits of taking a folate supplement.

Vitamin D

The majority of controlled studies have either focused on affective disorders, used healthy persons, or had considerable technical obstacles (such as an inactive control group), whereas the majority of vitamin D research has been cross-sectional or epidemiological. Due to the limited study design, the existing results do not support vitamin D as a cause or potential cause of depression or as a workable therapy for depression. Vitamin

Table 1: List of GPCR receptors, antidepressant medications, and signaling cascades induced by target proteins

| <i>Receptors</i> | <i>Transduction mechanism</i> | <i>Examples</i> |
|--|--|--|
| (5-HT1A) Serotonin receptors | Gi/Go pathway (cAMP pathway) | Buspirone, Tandospirone, F-15599, F-13714 |
| Dopamine receptors (D2, D3) | Gi/Go pathway (cAMP pathway) | Aripiprazole, Brexipiprazole, Cariprazine |
| Opioid receptors like (μ -opioid receptor, κ -opioid receptor, γ -opioid receptor) | Gi/Go pathway (cAMP pathway) | Buprenorphine, Nalmefene, Tianeptine, BTRX-246040 |
| (mGlu2, mGlu3) Glutamate receptors | Gi/Go pathway (cAMP pathway) | MGS0039, LY341495, RO4491533 |
| Orphan receptors like (GPR26, GPR56, GPR158,) | Gs pathways Ak strain transforming signaling pathway, GSK3, Upregulation of EIF4 Regulation of RGS7 | P7, P19 |
| Cannabinoid receptors-like (CB1, and CB2) | Gi/Go pathway (cAMP pathway) | Tetrahydrocannabinol, Rimonabant, Terpineol, β -caryophyllene |
| Cholinergic receptors (M1, M2) | Gi/Go pathway Gq pathway | Scopolamine, VU0255035 |
| GABA receptors (GABA B) | Gi/Go pathway | CGP 56433A, CGP 36742, CGP 51176, CGP 7930 |
| Neurokinin receptors (NK1) | Gs pathway (cAMP pathway) | Aprepitant, L-759274 |
| The receptors for cholecystokinin (CCK2) | Gq pathways | L-365,260, CI-988 |

D intake shows that taking fluoxetine together with vitamin D greatly reduces the symptoms of depression.⁴³

Antidepressants' Action on Neurotransmitter

Possessing seven membrane-spanning helices, GPCRs are the biggest class of membrane receptors in humans. They activate many signal transduction and link to heterotrimeric G proteins to transmit extracellular signals into the inside of the cell (Table 1). GPCRs from various receptor groups have been connected to stress.⁴⁴

CONCLUSION

Although depression is a grave mental disorder, it can be treated using current medicines. Antidepressants are widely available and can be used to treat depression without danger or side effects. The most appropriate course of therapy is chosen for each patient based on their clinical-physiological characteristics, including their illnesses, potential illness, medication interactions, status as pregnant or nursing, and mental health. Depending on the kind and degree of the depression, several antidepressant classes are employed. Antidepressants come in a variety of forms, such as tricyclic antidepressants (imipramine, nortriptyline, amitriptyline,

and doxepin), SSRIs, SNRIs (bupropion), and atypical antidepressants (trazodone, mirtazapine, and vortioxetine). The creation of novel therapies, which have the potential to modify cutting-edge therapeutic procedures, will be made possible by the correct identification of the factors that accurately predict treatment outcomes.

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