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Review Article

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MAJOR DEPRESSIVE DISORDER (MDD), ANTIDEPRESSANT AND OBESITY.

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ABSTRACT

Both Major depressive disorder (MDD) and obesity are common heterogeneous disorders with complex pathophysiology that have a major impact on public health, rising obesity rates have significant alarming health consequences. Despite the concomitant rise of antidepressant use and increased rates of obesity in the world especially in Western societies, the precise association & mechanism between the two underlying antidepressant-induced weight gain resulting in obesity still remained unclear. The Hypothalamic–pituitary–adrenal (HPA) axis activation occurs in the state of severe acute/ chronic stress leading to development of MDD & concurrently, the HPA axis also becomes deranged/ nonregulated in obesity attributing to share common pathophysiological pathway. In this review, we attempt to explore the complex relationships among antidepressants, MDD and obesity because several clinical studies have documented that obesity may increase the risk of developing MDD and vice versa.

KEYWORDS: Major depressive disorder, Hypothalamic–pituitary–adrenal.

INTRODUCTION

Weight gain resulting in Obesity, the complex phenomenon occurring in patients of major depressive disorders [MDD] using Antidepressants is a pronounced public health problem. The WHO has unveiled the data demonstrating that MDD is a second most prevalent cause of illness affecting 2 fold more women than males & two third of cases attempt suicide.[1-5]

Previous studies have already documented the positive relationship between obesity and MDD and vice versa, i.e. obesity could increase the risk of developing MDD and vice versa, suggesting common pathways for the mechanism of these two conditions, however, the exact /precise mechanism for causal association is yet to be explored.[6-13] Although, now a days, a number of different classes of antidepressants are available for therapy of MDD, their effects on the body weight leading to development of obesity still remains unsettled.

In this review, we examine the pathophysiology of MDD and obesity, and their complex interactions. More specifically, we discuss particularly the role of antidepressants' use in weight gain resulting in obesity and also the effects of interactions with environmental factors, such as stress if any.

The Concept of MDD

In this globally networked advanced era, Reactive, neurotropic or psychological depression associated with stressful events of life that alters emotional feelings with strong familial, social, environmental and financial burden predisposing a large population to suffer from mood swinging disorders or major disorder of mood (affective disorder) which may drive an individual to commit suicide in critical phenomenon state.

In general, this mood swinging disorder or mental depression are broadly classified as

1) Unipolar disorder (Major Depression)
2) Bipolar disorder [Manic Depressive Psychosis, MDP].

Unipolar disorder: it is the major disorder which will be discussed in this review.

Bipolar Disorder in which depression alternates with mania having strong hereditary background.[14]

Unipolar depression [MDD] is of two types such as [i] Reactive, neurotropic or psychological depression associated with stressful events of life which is an exaggerated reaction to adversity/ misery of life manifested as feeling of sadness, grief, unhappiness & ill luck, may be due to minor events like unsuccessful in examination or failure to procure a suitable job. The

emotional feelings are very intense & the person is used to find fault with others for the happenings instead of blaming himself for the same.

Usually, the middle aged & elderly individuals with genetic predisposition suffer from MDD with variety of bizarre symptoms such as anorexia, loss of weight, lack of interest, self- neglect, insomnia, loss of libido. Ultimately, the patient loses self- esteem & respect, blames himself with frustration, worthlessness & guilt feeling driving to commit suicide.[14]

Although, there is no definite BIOLOGICAL MARKER of such depression, there is certain biochemical basis [monoamine transmission hypothesis] involved i.e. decreased synthesis & turnover of brain neurotransmitter such as norepinephrine, dopamine & serotonin along with increased accumulation of Acetylcholine. The cerebrospinal fluid levels of the serotonin metabolite & 5-Hydroxyindolacetic acid [HIAA] are found to be decreased especially in patients who attempt to commit suicide than others.[15]

The Principle of pharmacotherapy

It is aimed to afford both symptom & relapse / recurrence free normal life [as far as possible] to the patients in rehabilitating them with marked improvement of cognitive & functional states as a whole.

Before introducing therapy, it is very essential & important to establish "doctor- patient" relationship for successful treatment of depression. The physician ought to gain the confidence of patients first in order to explore possible external triggering factors of illness & then, reduce the impact of such environment by means of COUNSELLING followed by specific antidepressants therapy. The newer antidepressants such as SSRIs etc are no way found to be consistently therapeutically superior to the decades old antidepressants TCAs like imipramine & amitryptiline except may be in some specific cases.[15]

Diagnosis criteria

The diagnosis of MDD is based on the presence of five or more of the following symptoms for a continuous 2-week period or longer, as described in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5): (i) depressed mood most of the day, nearly every day; (ii) significant weight loss/gain or decrease/increase in appetite; (iii) markedly diminished interest or pleasure in almost all activities; (iv) insomnia or hypersomnia; (v) fatigue or loss of energy; (vi) psychomotor retardation or agitation; (vii) feelings of worthlessness; (viii) diminished ability to concentrate or make valid decisions; (ix) recurrent thoughts of death-phobia.[16], feeling of guilt & self- blaming negative attitude of life.

Pathophysiology and relevant hypothesis underlying Biology of MDD

Being Complex disorder, the precise pathophysiology of MDD is still unsettled, alike of the mechanism of action of antidepressants, however, some hypothesis is considered on the basis of neurotransmitter monoamine reduction level in the brain is possible causative reason for MDD that is supported by the use of antidepressant MOAIs [hit & run drug], a class of antidepressant that restores physiological level of monoamine in the brain, however, this hypothesis is shaded due to gap of time period between immediate biochemical effects and delayed clinical response of the antidepressant, as the restoration duration is short but duration of action of this class of antidepressant is very prolonged about 3-4 weeks.[16]

Now, the theories of neuroendocrine, neuroimmune & neurotropic underlying biology of MDD are also in active consideration.[16,17] The immune mediators such as cytokines (e.g., interferons and interleukins) may have a positive role in MDD put forward the basis of neuroimmune theory(18). As those immune mediators modulate key functions such as sleep, appetite, cognition and temperature regulation, any alterations in those mediators can contribute indirectly to the pathogenesis of MDD, by disrupting vital functions.[18] as the innate immune system is altered in MDD towards a pro-inflammatory state and by the fact that some antidepressants act by reducing inflammation via cyclooxygenase inhibition. In addition, cytokines can contribute to HPA axis hyperactivity and affect the serotonergic, dopaminergic, glutamatergic and monoamonergic systems, contributing to MDD.[18-21] Accordingly, pro-inflammatory cytokines stimulate glucocorticoid release by acting at all three levels of the HPA axis: at the paraventricular nucleus level, they stimulate the release of corticotropin-releasing hormone (CRH); at the pituitary level, they stimulate the release of adrenocorticotropin; and at the adrenal glands, they stimulate the release of glucocorticoids.

The neuroendocrine theory proposes that the pathophysiological mechanism of MDD lies in the exaggerated response by hypothalamus–pituitary–adrenal (HPA) axis, whereby Cortisol levels are often increased in the plasma of MDD patients,[18-23] the logic lies in that antidepressant treatment down regulates the HPA axis response. Moreover, recent evidence points towards the importance of insulin-like growth factor 1 in MDD.[17-22] Furthermore, observation has documented that adipose tissue-derived hormone leptin has a potential role in MDD; circulating leptin levels are decreased in MDD patients especially in individuals who attempt to commit suicide in comparison with healthy controls.[23-26] In contrast, the relationship between antidepressant treatment and leptin levels remains less clear. Schilling *et al.* have shown that amitriptyline or mirtazapine antidepressant treatment increased plasma leptin concentrations, whereas the plasma leptin level remained unaltered with paroxetine and venlafaxine treatments.[27] Furthermore, intrahippocampal, [but not intrahypothalamic] administration of leptin led to antidepressant-like action in rodents, suggesting that

leptin-induced antidepressant actions were not secondary to leptin-induced metabolic effects.[28]

The chemical hypothesis of depression suggests that mood disorders are caused by a chemical imbalance in the brain, which can be corrected by antidepressant drugs. However, recent evidence indicates that problems in information processing within neural networks, rather than alteration in chemical balance, might underlie depression, and that antidepressant drugs induce plastic changes in neuronal connectivity, which gradually lead to improvements in neuronal information processing and recovery of mood.[29,30]

The Concept of Antidepressants Actions

Deficiency of brain neurotransmitters mainly norepinephrine & serotonin which can be restored by antidepressants that enhance monoamine availability & release. It is relevant to state that antihypertensive drugs e. g. reserpine & clonidine which reduce the availability of brain noradrenaline induce depression. Therefore, Antidepressant drugs are known to work primarily by modulating neurotransmitter levels in the brain in increasing the availability of neurotransmitters that includes MAOIs and TCAs as older generation of antidepressants, and newer generations include reuptake inhibitors such as SSRI(Selective Serotonin reuptake inhibitor, SNRI (selective norepinephrine reuptake inhibitor) and norepinephrine and dopamine reuptake inhibitors. Other antidepressants include tetracyclics and serotonin antagonist reuptake inhibitors.[31,32]

Currently, non-selective MAOIs available in the market include phenelzine (Nardil), isocarboxazid (Marplan) and tranylcypromine (Parnate)[33] Selective MAOIs include selegiline [MAO-B inhibitor] (Emsam) and clorgyline. However, now the use of such drugs has been declined because of their serious untoward effects, such as those related to food and drug interactions [cheese reaction]. MAOIs are used as a third or fourth line of the therapy when other types of therapy have failed.[33]

The therapeutic action of TCAs is known to occur via inhibition of brain serotonin and norepinephrine reuptake. These include imipramine (Tofranil), amitriptyline (Elavil), nortiptyline (Allegron), trimipramine (Surmontil), protriptyline (Concordin) and iprindole (Prondol).However, TCAs have multiple nonspecific actions that are associated with side effects.[34,35] These nonspecific actions include anticholinergic–antimuscarinic (M1), α-1 adrenergic antagonistic and antihistaminergic activities (H1 receptor blocking effect).[34] Furthermore, large doses of TCAs inhibit sodium channels, leading to lethal cardiac arrhythmias and seizures. For this reason, TCA antidepressants are used with great caution in patients with high risk of CVD.[36,37] Moreover, TCA-induced weight gain is one of the main reasons for the discontinuation of treatment within a month.[38]

Possible Mechanism of antidepressants mediated weight gain

The mechanism of actions of some Anorectics [Anorexiants] is first worth mentioning here in order to well understand & appreciate the possible mechanism of action of Antidepressants inducing weight gain.

1. Sibutramine inhibits reuptake of both NA & 5-HT & enhances their transmission in the brain resulting in inhibition of hypothalamic feeding centre leading to suppression of appetite & weight loss, it also increases thermogenesis inducing lipolysis in adipose tissues.

2. Fenfluramine & Dexfluramine inhibit reuptake of serotonin & enhance serotonergic transmission in hypothalamus leading to enhance satiety & decrease in appetite resulting in weight loss.[39]

3. Phentermine & Mazindol inhibit reuptake of NA & enhance noradrenergic transmission in brain causing inhibition of hypothalamic feeding centre resulting in suppression of appetite & loss of weight.[40]

In the light of the stated mechanism of anorectics, it now further seems clear that the antidepressants decrease the brain monoamine transmission resulting in activating hypothalamic feeding centre leading to increase appetite & weight gain.

Classification of Antidepressants

1. Trycyclic antidepressants[TCA]

Amitriptiline, nortriptyline, trimipramine, imipramine, protriptyline. They inhibit the reuptake of both NA & 5-HT into the neuron & increase their concentration & availability in brain.

2. Selective serotonin reuptake inhibitors [SSRIs]

Fluoxetine, fluvoxamine, paroxetine, citalopram, sertraline. They selectively inhibit reuptake of serotonin into the neurons & enhance its availability at the receptors in CNS.

3. Atypical antidepressants

Trazodone, bupropion, mianserin, mirtazapine, venlafaxine, amineptine, tineptine.

[a]. Trazodone blocks 5-HT reuptake & 5-HT2 antagonist, it is a Alpha-1 receptor blocker.[41]
[b]. Bupropion [DNRI] inhibits the reuptake of DA & NA.
[c]. Mitrazapine blocks Alpha-2 autoreceptor on nonadrenergic neurons & heteroreceptors on 5-HT neurons & increases release of both NA & 5-HT.
[d]. Venlafaxine [SNRI]: Inhibits the reuptake of both serotonin & noradrenaline.
[e]. Amineptine & tianeptine enhance reuptake of 5-HT.[42]

4. MAO-A inhibitors: Moclobemide, clorgyline: MAO-A is mainly involved in metabolism of NA, 5-HT & Tyramine, hence, they increase levels of norepinephrine

& serotonin in brain by inhibiting enzyme MAO. MAO-B [selegiline] is more selective for metabolism of dopamine.
5. Novel compounds [some are related to TCAs or SSRIs]: Venlafaxine, Duloxetine, Mirtazapine, Trazodone, Agomelatine, Milnacipran, Reboxetine, Trazodone & Nefazodone.[43]
Untoward effects of antidepressants:

1. SSRIs
They cause nausea, anorexia, dizziness, agitation, akathisia, anorgasmia & Serotonin Syndrome which although, rare but dangerous complication of SSRIs use manifested as restlessness, tremor, Shivering, myoclonous, hyperpyrexia, convulsion & delirium. The risk is increased by co-administration of MAOIs, triptan[antimigraine] & St John's Wort that also enhance serotonin transmission. The combination of fluoxetine or paroxetine with tramadol can cause serotonin syndrome by inhibiting metabolism of tramadol.[44]

2. TCAs
They cause dry mouth, constipation., blurring of vision, difficulty in accommodation, increased intraocular pressure [precipitates glaucoma], urinary retention in elderly males, Postural hypotension, sexual dysfunction, weight gain, prolongation of QT interval of ECG & precipitation of cardiac arrhythmia in over doses, hence, their use is contraindicated after myocardial infarction.[45]

3. MAOIs [Hit & Run drug]
They cause postural hypotension in elderly, dizziness, headache, irritability, apathy, insomnia, ataxia, dry mouth, constipation, sexual dysfunction especially anorgasmia, blurring of vision, peripheral oedema, tremor, restlessness, hyperthermia & weight gain. When a patient on MAOIs consumes food stuffs rich in tyramine, it may result in fatal hypertensive crisis & cerebrovascular accidents known as "CHEESE REACTION".[46,47]

In contrast to both TCAs & mirtazapine, SSRIs may induce weight loss by their anorectic effects when administered for a short term & they are also relatively safe in over doses.

Most of the antidepressants have quite similar therapeutic efficacy, hence, selection of drugs should be based on their adverse effect profiles & potential to cause serious toxicity.

CONCLUSION

The Antidepressant therapy in MDD could increase the risk of developing Obesity and *vice versa*. Several pathways certainly have definite role in this interaction, including neuroendocrine, neuro-immune and neurotropic mechanisms. Among those, activation of the HPA axis occurs both during MDD/stress and obesity, making it the most accepted shared common pathophysiological pathways in both the disorders. Moreover, Leptin and insulin resistance could be an alternative pathophysiological mechanism that needs to be further elucidated, along with the roles of the immune system and neurotropic factors.

Despite the concomitant occurrence of the frequent use of antidepressants and the high incidence of obesity in Western societies, further additional studies are required to establish & justify the proposed hypothesis that the rise in obesity rate is related at least in part to increasing use of antidepressants and moreover, to elucidate the mechanisms underlying antidepressant-induced weight gain resulting in obesity.

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