The Modern Face of Depression: A Comprehensive Review

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Abstract

Depression is one of most widespread disabling and one of most important global mental health problems among the main causes of disability, affecting more than 332 million people worldwide. The incidence has dramatically increased, especially among youths, who showed a clinically elevated symptom range, and who were in their environment stressed by the COVID-19 pandemic and consequently were around 25.2% more depressed. Depression is not just related to mental health, but also cardiovascular disease, immunological deficit and suicide – finally the biggest killer of the young adult population (15-29 years). In addition to the depression and apathy symptoms, numerous individuals with depression or apathy will have more irritability, numbness, brain fog, notification fatigue, and sleep difficulties due to tech-neglect, just to name a few. Mechanistically, it's now understood that depression involves dysfunction in multiple systems such as neuroinflammation (elevated blood markers of inflammation like C-reactive protein [CRP], interleukin [IL] 6, and tumor necrosis factor [TNF] α), dysfunction of the HPA-axis, dysfunction of the fronto-limbic circuit, and a disrupted circadian rhythm. Therefore, the informal workers face a more high risk of depression symptoms, 27% more likely than the formal workers in LMICs. With available effective treatments ranging from pharmaceutical, from psychosocial to neuromodulatory, over 75% of people who are affected in low to middle income countries do not receive treatment partly due to any combination of stigma, and lack of resources. Innovation in recent approaches, such as digital biomarkers, app-based cognitive behavioral therapy (CBT), ketamine-esketamine, closed-loop neurostimulation, and others is making it apparent once again that novel methods for directly intervening with precision are being born. This paper draws together the latest global statistics, common symptom domains, possible origins, and emerging interventions for digital-age depression, aiming to promote a multidisciplinary approach that integrates psychology, behavioural factors, digital and biological treatments to combat the emerging and escalating worldwide burden of digital-age depression.

Keywords: Depression; teens, digital health, neuromodulation, depression, the digital era, neuroinflammation, the HPA axis and circadian disruption.

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1. Introduction

Depression—or major depressive disorder—is a common condition that impacts numerous people and occurs again and again. Susceptibility to other forms of depression such as mourning, suicidal ideation or low self-esteem is well described; when diagnosed, it is considered to be an enduring case of low spirits and loss of enjoyment of fun activities that can impact other areas of life including social and employment activities [1]. The indirect consequences of depression, such as decreased productivity, increased morbidity, mortality and suicide, contribute significant numbers of disability-adjusted life years (DALYs) to the global burden of illness, and depression is a major cause of DALYs [2]. Population-based studies [3] revealed that there is significant regional and sociodemographic variation in the recent decades in the increased rates among young and teens.

Depression is one of the most critical health problems in the world due to its pervasiveness, severity and effect on normal functioning. More than 300 million people throughout the globe suffer from depression, making it one of the most common mental health disorders. Burgeoning prevalence of this disease is especially noticeable in the youngest and youngest adult age groups [4] and correlates with the stress, social isolation, and life changes.

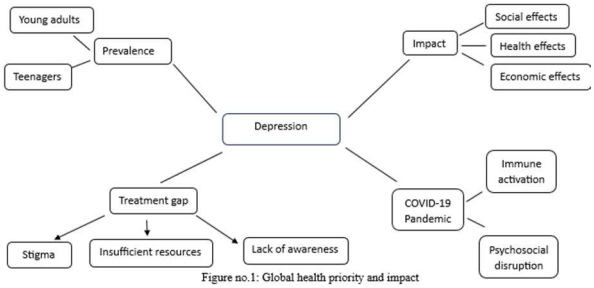


Figure no.1: Global health priority and impact

Depression also has emotional consequences, and studies have associated depression with higher rates of acquiring other illnesses, including diabetes, heart disease, and weakened immune system [5]. Desperation sometimes may cause suicide, one of the most significant causes of death, particularly in the ages group of 15-29. This is a great public health issues due to the high association it has with suicidal ideations and suicidal action.

A third is there is a "gap" in treatment for depression. Despite the availability of synthetic drugs at an affordable price, more than half of the people who require medications don't take action to begin. There are various factors which can contribute to this, such as a lack of health-care resources, lack of adequate knowledge and stigma [6].

The COVID-19 pandemic has contributed to these processes in several ways in increasing and intensifying them. A synergic contribution of all these factors, together with the onset of viruses, immune activation and social changes, can be seen in the particularly common mood disorder that is represented by both the presence of viruses in PnWS and their contribution to the increased immune tone, such as depression, which is experienced by up to 23% of the entire world (see meta-analysis [7]).

2. Global epidemiology of Depression

2.1 Sharp rise in youth depression after COVID-19

This has been consistently reported in abundance in literature since the onset of the COVID-19 epidemic, with an increase in clinical suffering and symptoms in youth and young adults. According to World Health Organization [8] the number of cases of depression has increased by 25% worldwide in the first year of the pandemic. The severe impact of the COVID-19 epidemic on the mental health of children and teens throughout the world is well-documented. All around the globe, it has a devastating effect on the emotional well-being of young people. A review of the world literature suggests that there has been an uptick globally in symptoms of clinically elevated depressive disorder in youth during the early years of the COVID-19 pandemic [9].

Epidemiologic evidence from the world demonstrated that social and environmental factors play a role in causing depression in the youths. Financial issues were precarious as many families were struggling with finances and some were losing jobs and increasing the probability of symptoms in adolescents. This increased mental strain and strained relationships with members of one's family, creating an increased risk that the adolescent could become depressed [10].

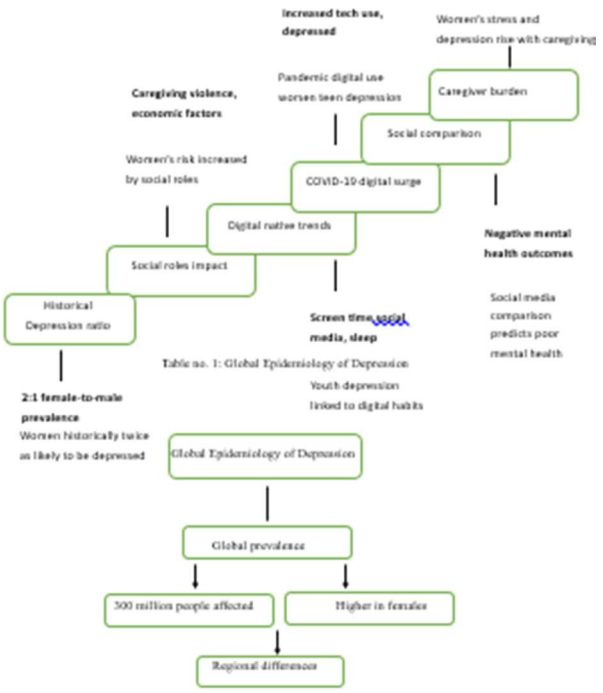
Another important factor was trauma exposure. Many of the youngsters had fear and a feeling of existential vulnerability as a result of COVID-19 related illness and death of family members. The likelihood of developing depression was greatly enhanced by this emotional stress [11].

2.2 The Gender gap- not only biological but shaped by social roles

potential differences in learning styles, abilities, and interests—how many of these differences are biological and how many are cultural/social and how many reflect norms surrounding children and adolescents?

Women have approximately twice the prevalence as men (about 2:1) but more recent studies have shown that this is much higher. Women have a significantly higher risk of involvement in caregiving responsibilities, more contact with interpersonal violence and also economic fragility [12].

Stress, burnout and depressive symptoms can be a serious risk for women, as they often take on many roles as caregivers for the children or others already in their lives who have chronic conditions, such as long-term time consuming care, which may not be paid. National surveys and population studies show that the stress of caregiving and depression level are higher in women than men [13].



2.3 Depression in digital native populations

Just as with any group of young people, there's a definite epidemiology among children who've grown up in a society dominated by social media. longitudinal studies have found numerous factors including sleep disturbances and too much screen time and late night use of smartphones to be associated with adolescent depression.

A new long-term study of cohorts of adolescents demonstrated that as adolescents' digital technology use increased, so did their depressive symptoms during the COVID-19 global pandemic [14]. Social media comparison tendencies is one of the good predictors regarding the negative aspect of mental health [15].

2.4 Hidden burden in informal workers and low income populations

The unorganized sector workers, such as low paying workers, domestic workers have to bear a very high psychological burden in terms of depression which is not very well recognized. Unstable work situations, lack of social supports, mental health services and job insecurity are some of the factors linked to these increased risks of suicide. A multi cities study conducted in Latin America showed that in informal jobs, people had 27% greater odds of having major depression symptoms as those in formal jobs [16].

The depression symptoms rate was found to be much higher among informal workers than official workers in China in 2018 China Family Panel study, which was related to lower family income and poorer physical health scores [17]. Researches [18] found that rates of depression and mental health problem appear to be more common in the youth in the informal sector of Nigeria construction industry. Among other things, it stems from the precariousness of the economies and from unsafe working conditions and ineffective protection of workers that are not legislated.

2.5 Global mental health gap

In some low income countries, treatment rates can reach as low as 25%, with only 50-90% of patients in a patient sample with depressive disorder receiving minimal adequate treatment in a 12 months period and only a small proportion of patients with severe depression receive treatment for depression. For the significant part of the world depressed population, there is no therapy, although there are promising options available [19].

3 Pathogenesis- Modern, Multisystem Mechanisms

3.1 Inflammation and Immune Activation

The results suggest that some chronically depressed persons have increased peripheral levels of pro-inflammatory cytokines, including C-reactive protein (CRP), interferon-gamma (IFN-γ), and interleukin-6 (IL-6), and tumor necrosis factor- alpha (TNF- α) [20]. Some of the ways in which these cytokines could interact with the brain include a way to alter the permeability of the BBB, by saturaible transport across BBB, and another way by inducing the activation of endothelial cells of BBB by vagal afferent signaling [21].

In CNS, pro-inflammatory mediators activate the microglia and astrocytes. Such cells are subsequently shown to inhibit synaptic pruning, alter glutamatergic transmission, down regulate a number of neurotrophic factors like brain derived neurotrophic factors (BDNF) and influence tryptophan metabolism to shift indoleamine 2,3-dioxygenase (IDO) towards Kynurenine pathway. This metabolic rerouting results in the production of neuroactive metabolites like quinolinic acid, some of which could be toxic to neurons, as well as reduce the availability of serotonin precursors [22].

In the clinic, this immune action is manifested as "sickness-behavior" symptoms including lethargy, insomnia, loss of appetite and loss of pleasures [23].

3.2 HPA- Axis Dysregulation

A dysfunction of the Hypothalamic-Pituitary-Adrenal-axis (HPA-axis) is one of the best-described biological markers of Major Depressive Disorder (MDD). This is a maladaptive mechanism of response to stress, which is genetically influenced as well as impacted by years of stress psychological and social effects. In terms of physiology, the HPA axis is important for normal diurnal decreases in cortisol (high in the morning and lower into the afternoon).

In the majority of patients with depression, this rhythm is flattened; in many patients, the evening or afternoon cortisol level is raised, while in some it is normal (as well as the level in the early morning is reduced); some patients even experience an irregular cortisol rhythm, a weaning off of those 'morning cortisol powers' or both; changes in one or more of these patterns are highly correlated to long-term stress and childhood trauma [24]. Glucocorticoid negative feedback also is impaired in some MDD patients (cortisol being the hormone, and glucocorticoid receptors in the hippocampus being the circuits) such that they are not effective in stopping the secretion of cortisol downstream [25].

On the molecular level, elevated levels of cortisol over a prolonged period of time alter the structure of the neural network and promote greater neuroinflammation, which results in cognitive, emotional, and memory deficits associated with MDD [26]. This is because increased glucocorticoid signalling leads to a deficit in neurogenesis in the hippocampus, loss of synapses and reduced connectivity between the PFC.

3.3Neural circuit Dysfunction

Brain imaging assessments revealed that those with MDD struggle with communicating in the “fronto-limbic” circuitry that regulates these processes of emotional control, critical thinking, stress responses, and memory integration. High-resolution magnetic resonance imaging (MRI) studies show a depression is associated with decreased executive function, such as attention shifting and problem solving, [27] .

Unlike the hypoactive and structurally damaged prefrontal hippocampus areas, the amygdala is overactive, characterized by increases in emotional outbursts, fear-based neurological event interpretation and negative bias [28]. The changes at the circuit level are not specific to any given setting, but rather emerge in the context of neurochemical dysregulation/neuro-inflammatory stress, which together constitutes the MDD symptom profile [29].

3.4 Mitochondrial Dysfunction and Oxidative Stress

In recent years, mitochondrial dysfunction has been recognised as an important mitochondrial sign of depression. Multiple physiological changes have been associated with clinical depression, in humans as well as animals, including: reduced ATP production, abnormal mitochondrial morphology and function, impaired mitophagy, increased oxidative stress (ROS), and impaired electron transport chain (ETC) function. Increased general inflammation from damage-associated molecular patterns (DAMPs) that activate the immune system, and decrease energy supply from mitochondrial failure further damages neurons.

This energy deficiency may be expressed as a cognitive slowing leading to fatigue, diminished motivation and emotional instability, especially in the neurons that are energy demanding in the cortex and limbic systems [30].

3.5 Circadian and sleep disruption

There are numerous abnormalities in major depression, the most prominent being that of the circadian rhythm. This is reflected in molecular clocks as well as neuroendocrine rhythms, behavioral sleep-wake cycles, and physiological oscillations which control emotional stability. SA Node coordinates peripheral clocks, and regulation is disturbed in depressed subjects, both peripheral and SA Node hormones are less intense (absent: cortisol, less intense: melatonin) in flatter waves of diurnal variation [31].

These have been correlated with other symptoms including decreases in slow-wave sleep and an increased REM latency followed by decreased mood instability, cognition, therapeutic response and risk of suicide [32].

When the circadian rhythm is disrupted, it disrupts both neurochemical and neuroimmune balance that contributes to the heightened feelings of depression. Immune activity, synaptic plasticity and monoamine neurotransmission are regulated by the circadian clock. A low-risk, high-yield approach that is gaining traction is chronotherapy (CT), for use in the treatment of depression in particular, particularly among individuals with circadian/sleep disturbance [33]. These can involve techniques like cognitive

behavioral therapy for insomnia, structured sleep-wake schedule, use of melatonin agonists and bright light therapy.

3.6 Social, Behavioral and Digital Environmental Factors

A growing focus on social, behavioral and digital environmental factors that promote the biological and psychological dimensions of MDI. These factors exert effects via a pathway that collectively involves the stress physiology, immune activation and circadian rhythm. Stressful interpersonal situations including social isolation and loneliness, bullying, family conflict and discriminatory experiences are chronically activating the HPA axis and SNS. This, in turn, leads to higher levels of cortisol, higher output of the catecholamines, higher inflammatory signaling, and in the long-term to neurotoxic side effects on the prefrontal and hippocampus circuits that are involved in emotional regulation [34].

Besides oxidative stress, aggravation of the circadian misalignment and diminished neurotrophic signaling, the behavioral lifestyle factors not only make inactive people more vulnerable to current lack of physical activity, irregular daily rhythms, poor sleep habits and unhealthy eating habits, but also can increase it. Several aspects have been associated with excessive or acute social media consumption in today's society such as reduced total sleep time, night exposure to social media, emotional overstimulation, and electronic contexts [35]. Feedback between digital and social stressors and biological mechanisms, such as inflammatory response, deficit in synaptic plasticity and impairment of top-down prefrontal circuits, as well as feedback between stressors with negative circadian timing, are all important contributing factors to depression vulnerability. It is found that social disadvantage, unhealthy lifestyle and being exposed to digital presence all contribute to a lowered capacity of youth to cope with depression. This again highlights the importance of comprehensive approaches to social disadvantage, behaviour, and use of digital technologies, which may help to reduce stress and biological resilience.

4 Modern symptoms domain in Depression

4.1 Emotional symptoms

- **Irritability:** In recent years irritability is an increase of this emotion that is considered as one of the symptoms of depression, many more common in young adults or adolescents. There are many people who don't exhibit any of the symptoms of depression; however, they are very sensitive to the smallest irritation and cannot take much stress.
  Every patient will have an alteration in behavior and self-control, clinically speaking. An increase in symptoms of irritability in the youth could indicate an increased risk for mixed affective disorder or suicidal behaviours and research findings are in support of the association between functional impairment and anhedonia and emotional dysregulation.
  According to neuroscientific research, present-day irritability is indicative of dysregulation of fronto-limbic networks, most especially of impaired prefrontal cortisol regulation of an overactive amygdala. Some evidence indicates that in the case of highly irritable adolescents connections between emotional influence from the amygdala, the ventral striatum, and prefrontal regions of the brain are abnormal [37].

- **Emotional numbing:** For those who use the Internet, particularly the younger developed, who are fully immersed in this virtual world, a diffuse depression, not the severe depression characteristic of “major depression,” is setting in. For example, statements in a patient's clinical history are frequently: "I don't feel anything most of the time" and "Even when things are going well, it's not making me feel like I'm excited" [38]. Repeated exposure to novelty seeking and repeated exposure to rewards can result in a similar decrease in dopaminergic responding to standard rewards and an attenuation of emotional responding, respectively [39].

4.2 Cognitive symptoms

- **Brain fog:** Brain fog is a phenomena that is becoming quite well known for today's depression found in 4.2 Signs of cognitive impairment: Slow thinking, diminished mental clarity, mental tiredness after a few minutes of concentration. Many will have problems that are having slower thoughts and that things are a lot harder for them than before. The symptom occurs more often in these people who experience chronic stress reactions, disrupted sleeping patterns and/or metabolic problems. Brain fog is linked to decreased efficiency of brain functions – cognitive processing and working memory – and is caused by neuroinflammatory activity

as well as circadian rhythm, according to studies.

4.3 Somatic symptoms

- **Fatigue:** Fatigue is a common aspect of modern depressive illnesses, often is profound, enduring and is generally unresponsive to sleep or rest. Common complaints are a decrease in daily physical stamina, an increased tendency to snooze and low effort activities. It is this type of exhaustion that is connected with many of the modern physiological or behavioural stresses as opposed to a normal sleep state. The main causes of this increased sleep fragmentation are disturbances in the circadian rhythm and evening use of electronic devices which cause daytime tiredness and associated mood dysregulation [41].
- **Chronic pain:** Chronic pain has emerged as a somatic symptom of today's modern depressive disorders and has come into increasing recognition. Tension type headache, neck and shoulder pain due to poor posture and high screen time use, etc. are commonly reported. Depression exacerbates the intensity (and persistency) of perceived pain and therefore increases emotional suffering and functional disability due to chronic pain [42].

4.4 Digital era symptoms

- **Notification fatigue:** In today's digital age there has been a new phenomenon that arose that is known as "Notification Fatigue" – human mind is having to work too hard and is getting overstimulated by the new notifications. When the alerts are short and frequent, there are repetitive sympathetic surges that each time result in a short increase in heart rate, and the production of cortisol. These chronic high functioning activities of the HPA axis and alterations in sleep secondary to microarousal accumulate to become a problem of cognitive recovery and chronic high functioning activities of the HPA axis and disturbances of sleep. Research shows that digital disruption, if it occurs on a regular basis, leads to impairment of working memory and to heightened stress reactivity [43].
- **Tech driven insomnia:** This is a major issue and has been associated with overuse of electronics devices, in the hours leading up to sleep. A common complaint from patients is a lengthened time it takes for them to fall asleep or stay asleep.

It is established that the use of a smart phone or LED screen, reduces the natural release of the hormones synthesized by the body and advances the natural cycle to later times of the day, making it much harder to sleep at an ornate and natural time [44].

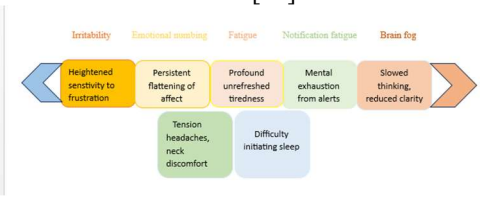


Figure no. 4: Modern symptoms domain in depression

5 Screening and Diagnosis

The current diagnostic frameworks, DSM-5-TR and ICD-11, remain widely used in the world today. Listed in these guides, chronic sorrow and anhedonia are some of them. Current research suggests that rating scales standardized to the same scale and objective digital biomarkers could help in the identification of individuals sooner in the detection system, as well as reducing underdiagnoses. This is particularly the case for younger generations whose first exposure to technology will be what has come to be known as the digital native generation [45].

There are a number of validated depression rating instruments available, such as the PHQ-9, HAM-D, MADRS and the Beck Depression Inventory. The PHQ-9 is widely used in primary care and platforms utilized in telemedicine and may be used to gauge the effectiveness of a therapy [46].

The advent of digital mental health biomarkers, which provide passive, continuous, and ecological data, is a big change in the current period. Research reveals that there's been a change in how people utilize their smartphones with some experiencing less mobility and using their phones more throughout the night. Wearable technology that measures sleep quality, heart rate variability, stability of the circadian cycle and physical activity. More and more, telepsychiatry is using digital screening technologies. Quick and real-time data on emotional state, cognitive decline, and psychomotor changes are provided via cognitive tests that are based on automated text or voice-based sentiment analysis apps [47].

6 Management and Treatment Approaches

6.1 Pharmacological Approaches

Research has been targeted at more expedient treatments, due to their inability to be as effective as some would like and their relatively slow onset of action, yet SSRIs and SNRIs are still considered first-line drugs. Ketamine and intranasal esketamine are important steps forwards as NRD positively influences synaptic plasticity by modulating NMDA receptors, resulting in clinically meaningful betterment in hours, particularly in patients who failed to benefit with previous treatments [48]. We should expect to see further research look at drugs that target the immune system, for instance anti-inflammatory drugs (including IL-6 and TNF-α modulators) and microbiome therapies in the future, as this is an exciting area of research that reflects the involvement of the immune system and gut brain processes in depression.

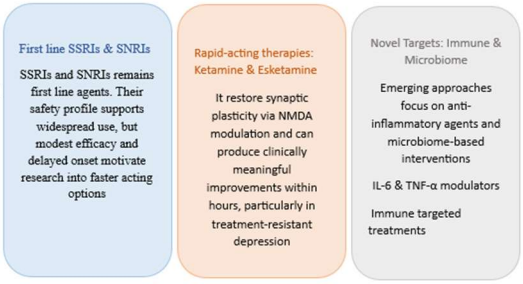


Figure no. 5: Management &

6.2 Psychological and Digital interventions

Evidence-based psychotherapies such as Mindfulness-Based Cognitive Therapy (MBCT) and Cognitive Behavioral Therapy (CBT), which target maladaptive thinking and stress reactivity, are still important.

A unique trait of today's mental health services is the widespread use of digital health systems. For young people, there is evidence to support the use of app-based CBT and AI-assisted mood tracking and app-based teletherapy for monitoring and detection of early relapse [50].

6.3 Neuromodulation Techniques

Today, technology in the field of neuromodulation has largely enabled such circuit-specific therapies. The two types of stimulation, theta-burst stimulation (TBS) and repetitive transcranial magnetic stimulation (rTMS), both offer non-invasive modulation of impaired cortical networks and increase reaction rates and delivery speed [51].

For more severe and/or psychotic depression, the most effective, quickest acting antidote is referred to as electroconvulsive treatment (ECT). Customized neuromodulation technologies, including the less commonly used deep transcranial magnetic stimulation (TMS), vagus nerve stimulation (VNS), and/or trigeminal nerve stimulation (TNS) and the recently developed, as yet experimental, approach of closed loop neurofeedback, and approaches guided by brain-computer interfacing fall at the frontier of customized forms of neuromodulation [52].

Conclusion

Depression is one of the most impacting public health problems internationally, and it is a growing issue in the lives of people everywhere, irrespective of their socio-economic, cultural, ethnic or religious backgrounds. In recent years several incidents of depression have been reported, including a significant increase among young adults and adolescents, following the COVID-19 epidemic. This has been driven by a number of factors, such as a myriad of problems in the family, a sense of being disconnected, economic difficulties, and the increasingly heavy reliance on technology. This increase is the result of a variety of complex biological processes, such as altered brain circuits involved with mood, hormonal changes due to stress and inflammation.

Stigma, ignorance and resource scarcity are all apart of the underserved depressed people. The proper medical treatment, digital wellness techniques, psychological help and succour, and healthy conduct routines are all essential components of a proper treatment strategy for depression. To mitigate the effects of depression and improve the world's wellbeing, improving public health awareness and the mental health system is essential.

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