**Major Depressive Disorder**

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The research and public knowledge involving mental health has greatly increased in the past few years. Major depressive disorder being one of the most impactful mental disorder due to the large number of adolescents and adults it affects. Recently, the number of patients being diagnosed has increased due to COVID-19 and the isolation many feel. This disorder is usually characterized depressed moods, anhedonia, or feelings of hopelessness that persist for at least two weeks (Hasin et al., 2018). This can have detrimental effects on a person’s social and physical life as many people diagnosed have trouble going out, can have more illnesses, and can sometimes have suicidal tendencies. However, even with all the growing recognition in major depressive disorder there are many who still have outdated stigmatizing ideas surrounding mental health that can include sexisms thoughts or things that lessen the impact of the disorder. There are many ways to help treat major depressive disorder such as medication, cognitive therapy, or the recently developed transcranial magnetic stimulation.

**Diagnosis**

The diagnosis of major depressive disorder comes from a patient having at least five of nine symptoms with one of the two core symptoms that persist for at least two weeks. The main symptoms that a patient can present with are insomnia or hypersomnia, psychomotor agitation, fatigue or anergia, guilt or worthlessness, and recurrent thoughts of death. One of the two core symptoms that a patient must have are either decreased mood or anhedonia which is the inability to feel pleasure. Due to the abundance of symptoms a patient may have, there are 227 possible combinations that can lead to a diagnosis of major depressive disorder (van Loo et al., 2012). The prevalence of MDD has been associated with poor health, low socio-economic stability, other psychiatric diagnoses, or the presence of mortality throughout a person’s life.

MDD has at least 11 subtypes that a patient could be diagnosed with that depends on the combination of symptoms (melancholic or psychotic), the onset (seasonal or postpartum), the course (single, recurrent, or chronic), and the severity (mild with 5 symptoms, moderate with 6 to 7 symptoms, or severe with 8 to 9 symptoms). The subtype MDD with anxious distress has at least two additional symptoms that include feeling keyed-up or tense, unusually restless, the inability to concentrate due to worry, fearing something awful may happen, and thinking that one may lose control. MDD with mixed features reports patients with at least three additional symptoms of elevated mood, inflated self-esteem, unusual talkativeness, flight of ideas, increased energy or goal-directed activity, and decreased need of sleep. Depending on the combination of these symptoms the patient can either have hypomania or mania and this must be present for almost every day for at least two weeks. The other subtypes of major depressive disorder that are not as prevalent are with melancholic features, atypical features, with psychotic features, with catatonia, with peripartum features, and with seasonal patterns (Hasin et al, 2018). The main approach to identifying and thus diagnosing these subtypes are using a latent factor model called the cluster analysis. This clusters individuals into homogeneous subgroups based on similarity across all variables and find pairs of similar individuals. The cluster approach mainly looks at factors involving depressed mood, loss of interest, worthlessness, concentration problems, suicide tendencies, fatigue, appetite or sleep problems in order to be diagnosed into one of the 11 subgroups (van Loo et al., 2012).

The DSM-5 had changed some of the major depressive disorder features from what can be found in the DSM-IV. One difference is the removal of MDD exclusion criteria for bereavement. In the DSM-IV a patient could no be diagnosed with MDD for at least two months following the loss of a loved one claiming that the depressive symptoms shown by a patient were due to the sadness of losing a loved one. The bereavement rule stated that there must be a two month wait period to see if these feelings of depressed moods or hopelessness were due to this loss. However, in the DSM-5 these researchers did not believe there was a need to treat people in mourning differently (Hasin et al., 2018).

A majority of those diagnosed with major depressive disorder are adults; however, most have symptoms start in adolescence with a few starting even earlier in childhood. The earlier onset of the disorder is associated with greater functional impairment, poorer quality of life, worse depressive episodes, and more suicidal tendencies. Most individuals diagnosed at a younger age are with the subtype of anxiety feature or a comorbid diagnosis of anxiety disorder. Research has shown that the children and adolescence that are diagnosed with MDD about 25-28% have also been diagnosed with anxiety disorder. These children have shown to have higher symptom severity, poorer academic performance, worse peer relationships, and less extra-curricular involvement than those not diagnosed with major depressive disorder. These individuals will have lifelong struggles with social, academic, and economic abilities as most people diagnosed young do not grow out of MDD (Haberling et al., 2019).

Recently, the public has been undergoing COVID-19 pandemic which has greatly impacted children and adults metal health with about 4 in 10 adults reporting depressive or anxiety like symptoms. Young adults are experiencing the closures of universities and loss of income which has been increasing the risk of reporting mental health to about half of the population. There has been reports of 11% of adults having suicidal thoughts due to financial and poor general health struggles. The disruption of daily schedules in parents with children have been effecting the emotional well-being of all parties involved as well which in turn is worsening the mental health. The school closure is severely impacting these children and adolescence as they have begun to feel isolated and lacking an understanding of general academic knowledge (Panchal et al., 2021).

**Neuroscience**

With almost 20% of American’s experiencing a major depressive episode in their lifetime the neuroscience behind MDD is becoming widely researched. The recent advances in brain imaging have allowed the expansion of understanding in cognitive and behavioral impairments associated with major depressive disorder. One of the main neuroimaging techniques is the use of magnetic resonance imaging (MRI) which have shown the specific brain regions in individuals diagnosed with depression by looking at the cortical thickness. This identified gray matter reduction in rostral anterior cingulate cortex (rACC), hippocampus, striatum, basal ganglia, insula, areas of the prefrontal cortex, and amygdala. Specifically, the reduction in gray matter from the hippocampus is involved in an increased number of depressive episodes and worse symptom severity with a longer duration. Some white matter has been found to be abnormal in association with gray matter in the prefrontal and subcortical areas. This has been shown to lead to early demyelination of the brain with greater clinical severity in MDD. There have also been reported lower levels of white matter in the limbic system, thalamic fibers, and corpus callosum in individuals who are depressed compared to nondepressed individuals. The other neuroimaging used for MDD is functional MRIs which view the magnitude of brain activation in specific regions by levels of oxygenated versus de-oxygenated hemoglobin. With the distress in emotion and cognition researchers focused on brain areas associated with dysfunction to emotional regulation. The frontal brain areas, subcortically the thalamus, were found to show both under and over activation of cognitive-emotional challenges. The rostral anterior cingulate cortex (rACC) was found to be significantly impacted. Researchers saw an inability to deactivate the rACC during cognitive processing and overall regulating. Some hyperactivity in the amygdala was found in depressed individuals as well in response to stimuli (Singh & Gotlib, 2014).

**Stigmatisms**

With research involving mental health increasing over the years the public’s knowledge has risen as well; however, the stigmatisms surrounding this has not decreased. Stigmatizations of mental health has been a prevalent social problem that has implications for personal as well as family well-being, finances, and the creation of a more just society. Stigmas attribute to discrediting their mental disorder and reduces someone from a whole person to a discounted one in labeling these individuals. There is also a separation of groups with a mentality of “us” versus “them” thinking claiming the symptoms or impairments warrant a distinct category. With depression, the thought is that patients diagnosed are in a group on the outside that lie beyond normal experiences on a categorical experience of symptoms that can be viewed as dimensional. Anti-stigma campaigns have been started to explain biogenetic causes of mental health by creating psychoeducational campaigns to reduce blame and increase perception to look at symptoms on a continuum rather than category. In looking at depressive symptoms on a spectrum there was a lower association of stigma and a greater understanding. Other methods the anti-stigma campaign has used are having individuals look at their willingness to interact with a person diagnosed with depression, assessing their emotional reaction to a person diagnosed with depression, and having the individuals recognize if someone has been treated for mental health in their immediate environment. This made individuals become more self-aware about how they treat others diagnosed with a mental health disorder for them to see if they fall in the stigmatizing group (Buckwitz et al., 2020).

Another common stigma in major depressive disorder is the sexism in diagnosing with women being twice as likely to be diagnosed than men. Even though men are less likely to be diagnosed they frequently experience higher rates of comorbid alcohol abuse and dependence and are four times more likely to have suicidal tendencies which have led to many damaged personal relationships. The two main theories for this gender gap are that men have an inability to recognize the symptoms of depression and that there is a possibility men perceive depressive symptoms as feminine. Men with depression typically present symptoms of major depressive disorder as having fatigue, irritability, loss of interest in work or hobbies, and sleep disturbances. There have also been reports of higher levels of externalizing behaviors like anger, impulse control, aggressive behavior, risk-taking, and avoidant behaviors. Men have also shown the internalization of emotions with depression that include numbness and an unwillingness to express emotion. This has created gender specific diagnosing criteria which includes social withdrawal, denial of pain, avoiding help, self-medicating behavior, denial of sadness with the inability to cry, harsh self-criticism, impulsive moods, changes to sex drives, and traditional symptoms of major depressive disorder. Men have a tendency to hide or feel ashamed of negative emotions and negative affect due to the pressure of social stigmas that lead to a reduction in self-reporting depression or seeking help. While men experience similar levels of depression, they might perceive this as weak and feminine which threatens their male gender role in society. This reinforces avoidance of feminine behaviors, with a hyper awareness of vulnerability, feelings, and emotions that are feminine to try and steer clear of these. These stigmas that men have led to the gender gap diagnosing of major depression (Cole & Davidson, 2018).

**Treatment**

Medication has been the primary treatment option in combating any depressive episode, major depressive disorder included, through the use of antidepressants. The first set of medications that were approved by the FDA for use were selective serotonin reuptake medications. The thought process behind this is that there is an abnormality in the serotonin levels available in the brain and these medications increase the availability at 5-HT type receptors. The first and most common type of SSRI being *fluoxetine* (Prozac) which was approved in the 1980s. This antidepressant action is very slow to take effect, starting in four to six weeks, and an even slower effect for the side effects to set in. The main side effects being anxiety, agitation, insomnia, and serotonin syndrome. The next SSRI released was *sertraline* (Zoloft) which proved to be four times more toxic than Prozac. The problem is that while it blocked the serotonin reuptake to increase the availability it also blocked dopamine reuptake producing dangerous levels and more side effects. Another SSRI is *paroxetine* (Paxil) which was also approved for generalized anxiety disorder. This has the highest rate of serotonin discontinuation syndrome and can produce psychosis as the levels of serotonin reuptake blockage is higher than all the rest. The serotonin syndrome is especially dangerous due to the cognitive disturbances that can include disorientation, confusion, and hypomania; as well as behavioral agitation, restlessness, autonomic nervous system dysfunctions, and neuromuscular impairments (Advokat et al., 2019). A different group of medications, that are termed norepinephrine and dopamine reuptake inhibitors (NDRI), have also been produced for major depressive disorder. *Bupropion* (Wellbutrin, Zyban, and Aplenzin) are in this category as they block the reuptake of both norepinephrine and dopamine. There are dangerous levels of these medications that depending on dosage due to the seizure threshold and increased risk of producing psychosis or myocardial infarction (Advokat et al., 2019). Another category of medications is serotonin and norepinephrine reuptake inhibitors as they block the presynaptic terminals of both these neurotransmitters; however, they can potentially block cholinergic and adrenergic receptors as well. *Venlafaxine* (Effexor) is in this category as with lower doses it has the reuptake of serotonin and norepinephrine; however, at higher doses it can inhibit the reuptake of dopamine. With this medication there is many potential risks that can come from the high dosages with triggering manic states and higher overdose fatality rates. The other medication in this group is *duloxetine* (Cymbalta) which has shown to greatly reduce physical symptoms of pain that include backaches, headache, muscle and joint pain, and back and shoulder pain. Although, common side effects are induction of manic or hypomanic episodes as well as nausea (Advokat et al., 2019). Finally, the most common medication group of antidepressants is noradrenergic or specific serotonergic antidepressants (NaSSA). *Mirtazapine* (Remeron) is in this category and acts as an antagonist at the postsynaptic 5-HT receptors, serotonin, and increases the presynaptic release of norepinephrine and serotonin. These medications have a faster activation but do not produce the side effects that SSRIs typically have. The side effects that are present are drowsiness and an increase in appetite or weight gain due to potential blockages in histamine receptors (Advokat et al., 2019).

A recently developed alternative treatment method for major depressive disorder is the repetitive transcranial magnetic stimulation (rTMS). This method is not used very frequently in clinical practice with more research needed and typically used with another treatment method. The process of rTMS has patients go through daily therapy treatments that last for 4 to 6 weeks. These therapy sessions have patients receive a large pulses that are applied to a defined cortical region, usually the dorsolateral prefrontal cortex, that involve large coils placed on the scalp to induce strong magnetic field electrical impulses. The magnetic field passes into the brain and induces electrical activity in cortical neurons that produce depolarization and repeated firing of neurons is used to induced changes in local and distal cortical activity. There are different frequencies that can be used during these sessions to affect different neurons and have different side effects. Low frequency stimulation has shown to have an approach in antidepressant efficacy and has the less risk of potential seizures. High frequency left sided rTMS was developed in attempt to produce a form of stimulation that might have greater efficacy than unilateral stimulation. Dorsomedial rTMS is a specific area of the prefrontal cortex that has 10 Hz intermittent theta burst stimulation. This does not produce cognitive side-effects but assists the neurons in the prefrontal and orbitofrontal cortex (Fitzgerald, 2020).

Major depressive disorder is extremely pervasive disorder in adolescents and adults that is characterized by depressed moods, anhedonia, or feelings of hopelessness that persist for at least two weeks. In order to be diagnosed a person must have at least five of nine symptoms with one of the two core symptoms. Due to the number of combinations of symptoms there are different subtypes people may be diagnosed with. The two most common being with anxious features or with mixed features. Even with major depressive disorder becoming more known and understood to the public there are still stereotypes and stigmas surrounding MDD. Mostly people being separated into an “us” versus “them” category and men believing that depressive symptoms are feminine. The main treatment for major depressive disorder is through the use of antidepressant medications. A newer and alternative treatment method that has surfaced is repetitive transcranial magnetic stimulation.

Resources

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