Resistant Depression

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Treatment-resistant depression (TRD) affects millions worldwide and is the leading cause of disability and suicide. Relatively, TRD is common in treated major depressive disorder patients. To diagnose TRD, physicians need to look for primary and secondary causes of depression and recognize standard failures that lead to misdiagnosis.

We present a case of TRD where not much benefit was achieved from pharmacological and psychological treatment; other treatment modalities such as focal brain stimulation techniques and ECT were considered.

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Major depressive disorder (MDD) is a common and serious medical illness. Signs of MDD include feelings of sadness and/or a loss of interest in activities. MDD affects a person both emotionally and physically. To diagnose depression, symptoms should last for no less than two weeks, varying from mild to severe. Medical conditions such as thyroid problems, brain tumor or vitamin deficiency could mimic symptoms of depression; therefore, it is important to exclude general medical causes[1]. Depression affects approximately 6.7% of adults per year[2]. In the general population, one in six people would have depression once in their lifespan.

Depression could occur as early in life as the late teens and mid-20s. Females are more prone to depression than males. One-third of females will have an episode of depression once in their lifetime[2]. Compared to other psychiatric disorders, treatment for depression shows promising results. Between 80-90% of people with depression eventually respond well to treatment[2]. Depression could even affect a person who lives under ideal circumstances[2]. It is caused by changes in certain chemicals in the brain, stress or continuous exposure to violence, neglect, abuse and/or poverty[2]. Depression could be genetically inherited. Treatment of depression includes the use of antidepressants, psychotherapy, or electroconvulsive therapy (ECT)[2].

TRD is a common clinical incidence amid patients being treated for major depressive disorder[3]. Some of these cases are misdiagnosed or not adequately treated. An accurate diagnosis is made by examining all possible causes and accepting the model failures that lead to misdiagnosis.

The aim of this presentation is to report a case of TRD and the possibilities of other lines of treatment.

THE CASE

A thirty-six-year-old male presented in 2013 with a history of low mood, anhedonia, feelings of guilt, insomnia, poor appetite and social withdrawal. He was anxious and complained of poor concentration; he had been experiencing these symptoms for approximately three months.

He had no other mood or anxiety symptoms, such as fatigue or loss of energy. No death wishes or suicidal ideation. His medical history revealed that he has been suffering from gastric pain and discomfort for three years. The patient has been married for twelve years and is a father of two children. He is a secondary school graduate and working as a clerk. The patient was assessed using the Hamilton Depression Rating Scale (HAM-D)[4]. The patient is a smoker and not known to use or abuse alcohol or any other illicit drug. Complete blood count, renal function test, liver function test, vitamin B12, vitamin D, and thyroid function test were within normal.

Physical examination was normal. The patient presented to the clinic with fair grooming, but poor eye contact and had tearful eyes. His speech during the interview was of low volume and with long pauses. Assessment revealed low mood, obvious feelings of worthlessness and poor concentration. No delusions, suicidal thoughts or hallucinations were reported.

The patient was started on Escitalopram (10mg/day) and Quetiapine (25mg/day). Six months later, he reached the maximum recommended dose of 20mg/day of his antidepressant, but only showed a slight improvement in mood.

The patient was then switched to Paroxetine (12.5mg), which was gradually increased to the highest dose of 50mg/day after nine months. In addition, he was prescribed Mirtazapine (15mg/day) to improve his sleep. The patient remained on these medications for one year; however, the symptoms (loss of appetite and weight, depressed mood, social withdrawal, tiredness) persisted and no improvement was noted.

The patient was advised to attend Cognitive Behavioral Therapy (CBT) sessions with a clinical psychologist. The patient attended eight months of CBT with no improvement;

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his symptoms seemed to worsen over time. Therefore, the patient was advised to start Electro-Convulsive Therapy (ECT) sessions. However, the patient refused. The patient discontinued psychotherapy but continued to take Paroxetine (50mg/day) for another year. The patient continued having depressed mood, insomnia, feelings of worthlessness and feelings of hopelessness. In addition, the patient presented with symptoms of irritability. He was then started on Venlafaxine (75mg/day), which was increased gradually; Paroxetine (50mg/day) was stopped. He reached the maximum dose of Venlafaxine (225mg/day) and Zopiclone (7.5mg HS) was added to improve quality of sleep. Pregabalin (75mg/day) was prescribed as an adjuvant agent.

The patient showed partial remission (feeling of worthlessness and hopelessness, irritability) after one year of this regimen.

DISCUSSION

TRD is a major depressive disorder that shows resistance to remission after numerous trials of treatment[5].

The DSM-5 criteria for major depressive disorder are as follows[1]:

A. Over 2 weeks, five of the following features should be present most of the day, or nearly every day (must include the first two): depressed mood, anhedonia, significant weight loss or gain or an increase or decrease in appetite, insomnia or hypersomnia, psychomotor agitation or retardation (observed by others), fatigue or loss of energy, feelings of worthlessness or excessive or inappropriate guilt (not merely self-reproach about being sick), diminished ability to think or concentrate, or indecisiveness (either by subjective account or observation of others), recurrent thoughts of death (not just fear of dying), or suicidal ideation, a suicide attempt, or a specific plan for committing suicide.
B. The symptoms cause clinically significant distress or impairment in functioning.
C. The symptoms are not due to a medical/organic illness.

Episodes are categorized as: mild (presented with few symptoms and mild functioning impairment); moderate (minimum symptoms and functional impairment); severe (includes most symptoms that are present with severe functional impairment)[1].

A persistent depressive disorder is defined as low mood throughout the day, almost daily for two years and accompanied with two or more of the following: change in appetite, disturbed sleep, low self-esteem, inability to concentrate or make decisions and hopelessness[1].

Several clinical studies have investigated TRD through trials focusing on N-methyl-D-aspartate receptors (NMDAR)[6]. In these studies, NMDAR inhibitors ketamine and nitrous oxide were used to treat TRD patients[7]. The results of these studies revealed that inhibition of NMDAR plays a role in the behavioral aspect[8]. However, these open a new avenue for other therapeutic in TRD cases[5].

Monoamine hypothesis is based on the hypothesis that increasing levels of monoamine neurotransmitters can treat depression, which is what the current antidepressant is based on[9]. Recent studies focus on using the stress model of depression: a form of reducing neuroplasticity by producing mild insult to the brain. This will reduce dendrites, length and complexity and the neurogenesis[9].

Focal brain stimulation techniques (including transcranial magnetic stimulation (TMS), vagus nerve stimulation (VNS) and deep brain stimulation (DBS)) are designed to provide direct, modifiable stimulation to a specific brain region with the goal of modulating function throughout a particular neural system. Over the last several years, these techniques have been used increasingly to study the neurobiology of depression and as potential antidepressant therapies.

Ketamine is a potent selective N-methyl-D-aspartate (NMDA) receptor antagonist, has emerged as a promising agent in the treatment of patients with depression[10].

Deep brain stimulation (DBS) of the subcallosal cingulate gyrus (SCG) is an experimental approach in treatment-resistant depression (TRD)[15]. Clinical studies indicate a significant antidepressant effect of Photo-Bio-Modulation and good tolerability. It enhances the mitochondrial metabolism after absorption of near-infrared energy by cytochrome c oxidase[12]. With regards to new antidepressant treatments, researchers are working on expanding the elements of the biological data for depression[13].

CONCLUSION

TRD is challenging. Little benefit was achieved from both pharmacological and psychological treatment; focal brain stimulation techniques and ECT should be considered.

Over the next several years, we expect significant advances in the understanding and treatment of depression.

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