CONNECTICUT MEDICAL ASSISTANCE PROGRAM DEPARTMENT OF SOCIAL SERVICES
&
HEALTH INFORMATION DESIGNS

New Frontiers in Treatment Resistant Depression

Major Depressive Disorder (MDD) affects approximately 7% of the US population and is a leading cause of disability worldwide.[1,2] MDD can be a chronic disease with half of patients who experience one depressive episode experiencing future episodes.[3] Patients with a first degree relative with MDD are twice as likely to develop depression themselves.[4] Depression can have an impact on all aspects of life including family and social interactions, career, education, and overall health. During 2020 13% of the Connecticut Medical Assistance Program received a diagnosis of depression. While psychiatric disorders are more prevalent in patients with poor socioeconomic standing[5], the larger percentage of patients diagnosed in the CT Medicaid population compared to the national average may also be due to COVID-19.

A major depressive syndrome or episode manifests with **five** or more of the following symptoms, present most of the day nearly every day for a minimum of two consecutive weeks. At least one symptom is either depressed mood or loss of interest or pleasure.[6]

- Depressed mood most of the day, nearly every day. (NOTE: In children and adolescents, can be irritable mood.)
- Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day.
- Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month) or decrease or increase in appetite nearly every day.
- Insomnia or hypersomnia nearly every day.
- Psychomotor agitation or retardation nearly every day (observable by others).
- Fatigue/loss of energy nearly every day.
- Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day.
- Diminished ability to think or concentrate, or indecisiveness, nearly every day.
- Recurrent thoughts of death, recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

Approximately one third of patients who are diagnosed with MDD fail to respond to antidepressant therapy.[7,8] These patients are termed to have Treatment Resistant Depression (TRD). While there is no universal definition for TRD, literature often defines this as the trial and failure of 2 or more antidepressants of adequate dose and duration. Difficult to treat depression (DTD) is sometimes used in place of TRD to demonstrate that treating this disorder is not hopeless. DTD has been defined as "depression that continues to cause significant burden despite usual treatment efforts.[9]" While the TRD definition has a place in defining the pharmacological approach to treatment, the DTD definition is more acceptable for clinical practice.

Patient specifics that can predict poor response to antidepressant therapy include childhood trauma, stressful life events, early onset depression, family history of psychiatric illness, and comorbid health disorders.[5,9,10] TRD/DTD is associated with higher rates of comorbid psychiatric disorders, increased hospitalizations, higher rates of suicide attempts, and an increased demand on health care costs and resources.[11]

Treatment of comorbid disorders and symptoms such as anxiety, pain, insomnia as well as other health disorders such as diabetes often result in a better response to depression treatment. Lifestyle modifications, diet, exercise, good sleep hygiene, managing stress, managing thoughts of hopelessness, and engaging in psychotherapy are also good approaches to treating the whole patient.

Antidepressant medication is the cornerstone of treating depression. Oral antidepressant therapy should be started at the lowest effective dose with slow titration occurring every 1-4 weeks until the patient has an optimal response. If the patient does not respond to typical dosing after 6-12 weeks, switching antidepressant agents is appropriate.[8] SSRIs or SNRIs are usual first line therapy for MDD and older classes are typically used when failure to first line therapy occurs.[12] Table 1 includes utilization data for antidepressant therapies prescribed to the Connecticut Medical Assistance population during 2020. Table 2 includes first line, second line, and augmentation therapies for MDD.[13]

Adding additional medications such as adjunctive therapy to the first line agent can benefit patient response, however, adding medications also increases the risk of side effects. Switching antidepressants altogether can diminish any partial effect from the first agent used. Consideration when switching or adding additional agents include assessment of the patient's tolerance and response to their current therapy, prior failed therapies, severity of illness, patient preference, and clinician judgement.

When multiple treatment failures occur, other interventional options for treatment should be considered, however, often times these options are not explored until much later in the treatment path. Interventional options do not necessarily exclude pharmacotherapy. In fact, many of these options recommend or require the patient to be receiving an oral antidepressant concurrently. Below are some interventional FDA approved treatments for TRD/DTD.

Electroconvulsive therapy (ECT) is a procedure performed on patients while under general anesthesia in which repetitive electrical pulses are delivered to the cortex, increasing

pyramidal cell and cortical activity, and ultimately producing a tonic-clonic seizure.[12] ECT treatments are typically performed 2-3 times per week for a total of 6-12 treatments. Therapy can either be administered unilaterally or bilaterally. Different forms of ECT include bitemporal standard pulse ECT (most common) and right unilateral ultra-brief ECT.[12]

ECT is an effective option for treating depression and has shown rates of 50-60% remission after treatment.[8,12] Despite its effectiveness, ECT utilization for depression is low which may be due to several different factors such as patient accessibility, stigma surrounding use, adverse effects associated with treatment, and cost.[14] Side effects can include headache, nausea, cognitive impairment, and memory loss. Less than 1% of TRD patients end up receiving ECT despite its efficacy.

ECT is considered first line treatment for depression with psychotic or suicidal features and is considered the gold standard for TRD/DTD. ECT has the most evidence in the literature for maintenance therapy for TRD and is the most effective therapy for TRD.[12] ECT is also associated with decreased hospitalizations, suicide, and general mortality.[15,16]

Repetitive Transcranial Magnetic Stimulation (rTMS) is FDA approved for TRD and can be used as monotherapy or adjunct to antidepressant medications. Unlike ECT, patients do not require general anesthesia for the procedure and remain awake through the process. Repetitive TMS is not intended to induce seizures. rTMS works by sending a pulsed magnetic field to brain region(s) via a coil placed on the scalp, causing a change in excitability. Repetitive TMS (rTMS) is delivered to the brain by "trains" or a sequence of pulses to the brain followed by periods of rest . Standard of care for rTMS is currently 20-30 sessions given over the course of 4-6 weeks.[17] The dorsolateral prefrontal cortex is the most common area of the brain targeted by rTMS because it is thought to promote the regulation of human emotions.[18] The most common types of rTMS include: unilateral high frequency left sided (HFL), unilateral low frequency right sided (LFR), and bilateral LFR immediately followed by HFL.[18] Another option for rTMS is known as theta burst stimulation (TBS). Regular rTMS treatments take approximately 30 minutes, however, TBS treatments are much quicker, lasting approximately 3 minutes.[19] Deep rTMS is also another option or approach which targets deeper into the cortex compared to the other options.

Approximately 25-40% of patients receiving rTMS will respond to therapy.[18,20-22] A third of patients who respond to rTMS will require more treatments within a year to circumvent relapse.[17] Treatments will vary based on the type of coil and modality for therapy .[17] Side effects tend to be mild and can include headache, muscle twitching, and pain at the site of administration. Repetitive TMS could be considered as an option for non-FDA approved treatment in pregnant patients.

Vagus Nerve Stimulation (VNS) is FDA approved as adjunctive therapy for TRD in adults and is recommended as an option for therapy after trial and failure of 4 or more medications.[23] VNS requires surgical implantation of a generator which delivers pulses of electrical energy via bipolar electrodes to the left cervical vagus nerve. The vagus nerve is a target for TRD due to 80% of its function being to carry sensory afferent information to the brain.[23]

VNS is an effective treatment option in this extremely hard to treat population. Aaronson et al reported a 50% reduction in depressive symptoms and a decrease in suicide rates in patients who received VNS in combination with other antidepressant treatment compared to standard treatment alone.[24] Another study found that 32% of patients showed a response to therapy and 14% experienced remission after approximately 2 years of treatment.[25]

Risks associated with VNS device implantation are relatively low but may include postoperative infection and, in rare cases, vocal cord paralysis. VNS is considered long term therapy which may require multiple procedures throughout the years to replace electrodes and batteries of the device. Adverse events associated with stimulation of the vagus nerve include hoarseness, coughing, and vocal changes.[26]

Other non-FDA approved brain stimulating techniques that have been used for TRD include:

- Magnetic Seizure Therapy (MST) – similar to ECT in that patients must be under general anesthesia for procedure and a seizure is induced. Also similar to rTMS in that magnetic pulses are used.
- Deep Brain Stimulation (DBS) – requires brain surgery and a permanent implant placed directly into the brain. FDA approved to treat Parkinson's disease, epilepsy, and obsessive compulsive disorder
- Transcranial Direct Current Stimulation

Ketamine is a schedule III controlled substance available as oral, intravenous (IV), and intranasal formulations. While the IV formulation is FDA approved as an anesthetic in both humans and animals, it is not FDA approved for TRD. The intranasal form, esketamine, received FDA approval in 2019 as adjunctive therapy in adults for TRD and the treatment of patients with MDD with acute suicidal ideation.[27,28] Additionally, it should be noted that ketamine has the potential for abuse and dependence and has a history of being used illegally under the street name "Special K."

Ketamine is a N-methyl-D-aspartate (NMDA) receptor antagonist. While there are many theories on how ketamine exerts its antidepressant effects, the exact mechanism is

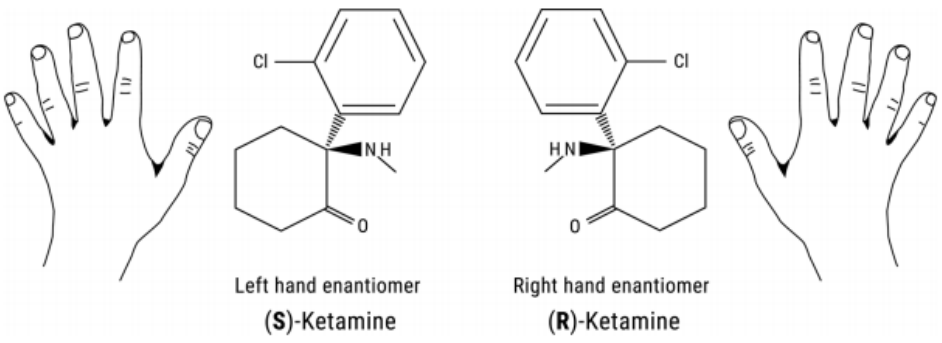

Figure 1. Chemical structure of the (S) - ketamine and (R) - ketamine enantiomers. Mirror image stereoisomers.

unknown.[29,30] Racemic mixtures of ketamine contain both the left handed (S) and right handed (R) enantiomers of the drug. IV ketamine is a racemic mixture of both enantiomers. Intranasal esketamine is the S enantiomer of the drug which has been shown to have higher affinity for NMDA receptors as well as a more powerful effect when compared to the R enantiomer, arketamine.[29] Recent studies have shown that arketamine may have a better safety and side effect profile.[31] Both enantiomers undergo extensive hepatic metabolism by cytochrome P450 enzymes 3A4 and 2B6. S-norketamine, the active metabolite of S-ketamine, is also thought to have antidepressant effects.[29]

Intranasal esketamine must be administered to the patient under direct supervision of a health care provider which includes 2 hours post administration observation due to the risk of sedation and dissociation. Due to the risk of serious adverse events and the potential for abuse, the FDA requires esketamine to be monitored by a Risk Evaluation and Mitigation Strategies (REMS) program. Dosing recommendations for induction and maintenance phases of treatment can be found by accessing the package insert.[28]

Side effects include dizziness, headache, dissociation, perception disturbance, depersonalization, hallucination, and derealization.[32] Psychomimetic side effects are more prominent with the IV formulation, although do still occur with the intranasal formulation.[27] Risks and safety concerns associated with long term ketamine use include memory impairment, cognitive impairment, bladder toxicity, interstitial cystitis, hepatoxicity, and risk of patient addiction/dependence.[32,33] Ketamine is contraindicated in patients with aneurysmal vascular disease and intracerebral hemorrhage. Concurrent use of medications that cause sedation such as benzodiazepines, opioids and other CNS depressant medications with ketamine is not recommended.

Single dose infusion (2 mg/kg) of IV ketamine has rapid antidepressant and anti-suicidality effects that are sustained for approximately 1 week.[34] While Singh et al showed that IV ketamine administered 2-3 times a week sustains antidepressant activity in patients with TRD[35] Lonescu et al reported that 6 ketamine infusions over the course of 3 weeks "failed to demonstrate a significant difference in depression severity or suicidality.[36]" At this time, IV ketamine does not carry an FDA approval for treatment of acute depressive episodes or TRD. Overall efficacy from different trials showed that intranasal esketamine reduces risk of suicidal depressive symptoms.[33,37]

While there are a number of different options, there is no "right" method or combination of therapies when addressing TRD. Each patient is unique and responds differently than the next. The majority of patients with TRD will require a blend of psychological, pharmacological, alternative therapies, and other approaches to work toward remission and prevent relapse. Consideration of tolerability, side effects, and response time to each therapy is paramount. Addressing non-adherence, cognitive behavioral therapy, lifestyle modifications, and treating the whole patient is fundamental. There remains a disconnect between how TRD is defined in research and how it is evaluated in practice. Labeling a patient treatment resistant based on the number of pharmacologic trials and failures does not necessarily take into account the individual characteristics of the patient, root cause or longevity of the depression, and how the patient defines or determines their own remission. While there are many nonconventional and alternative options when deciding the best course of treatment, additional trials are needed to help guide best practices for treatment of TRD.

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Table 1. Connecticut Medical Assistance Program Antidepressant Utilization during 2020

Drug Name/Class	Number of Prescriptions Filled	Number of Units Dispensed	Number of Unique Recipients	Percent of Population Receiving Therapy
SSRIs	373,601	18,377,018	69,496	7.84%
SNRIs	121,508	5,889,298	20,138	2.27%
Mirtazapine	45,016	1,537,369	8,859	1.00%
Bupropion	105,334	4,810,235	19,661	2.22%
TCAs	52,661	2,785,027	11,758	1.33%
MAOIs	262	27,500	46	0.01%
Esketamine	1,627	4,454	102	0.01%

SSRI (Selective Serotonin Reuptake Inhibitor, SNRI (Serotonin Norepinephrine Reuptake Inhibitor, TCA (Tricyclic Antidepressant), MAOI (Monoamine Oxidase Inhibitor)

Table 2. First Line Antidepressants for MDD			
Class	**Other Indications**	**Adverse Effects**	**Clinical Pearls**
SSRIs: citalopram escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline	Panic disorder, OCD, PTSD	Weight gain, sexual dysfunction, hyponatremia in the elderly, abnormal bleeding, QTc prolongation (citalopram higher doses)	Safe in pregnancy (sertraline), benefit in patients with comorbid anxiety
SNRIs: desvenlafaxine, duloxetine, levomilnacipran, venlafaxine	Fibromyalgia, panic disorder, hot flashes, musculoskeletal pain	Diaphoresis, headache, GI bleeds, hyponatremia in the elderly, hepatoxicity (duloxetine)	Caution in uncontrolled hypertension, can cause discontinuation syndrome
Mirtazapine	Insomnia	Increased cholesterol, headache, GI bleeds	Safer in overdose, does not cause sexual dysfunction, increases appetite
Bupropion	Smoking cessation	Hypertension, seizure, agitation	Increases energy and concentration, causes less weight gain and sexual dysfunction, contraindicated in patients with seizure and anorexia/bulimia
Second Line Antidepressants for MDD			
TCAs: amitriptyline, clomipramine, imipramine, doxepin, nortriptyline	Neuropathic pain, insomnia, panic disorder	Anticholinergic effects, orthostatic hypotension, increased falls, seizure	Increased risk of cardiac events, do not use in the elderly population (Beers drugs), lethal in overdose, weight gain
MAOIs: selegiline, phenelzine, tranylcypromine, isocarboxazid	Parkinson's disease	Hypertensive crisis, myoclonus, organ dysfunction	Do not combine with other antidepressants, tyramine food contraindicated
Augmentation therapies for MDD			
Lithium	Bipolar disorder	Sedation, hypothyroidism, polyuria, hypercalcemia, progressive chronic renal disease	Requires monitoring, contraindicated in renal impairment, narrow therapeutic index
2nd generation antipsychotics: aripiprazole, olanzapine, quetiapine, brexipiprazole	Schizophrenia, Bipolar disorder	Cerebral vascular events, metabolic changes, diabetes, tardive dyskinesia	Aripiprazole is activating, olanzapine and quetiapine are the most sedating
Triiodothyronine (T3)	Hypothyroidism	Anxiety, chest pain, decreased bone mineral density	Less monitoring and better tolerated compared to other augmentation therapies
Esketamine	MDD with suicidal thoughts or actions	Dissociation, sedation, increased blood pressure	Must be administered under supervision of a healthcare professional, REMS program medication

SSRI (Selective Serotonin Reuptake Inhibitor, OCD (Obsessive Compulsive Disorder, PTSD (Post Traumatic Stress Disorder), SNRI (Serotonin Norepinephrine Reuptake Inhibitor, GI (gastrointestinal), TCA (Tricyclic Antidepressant), MAOI (Monoamine Oxidase Inhibitor)