Wyoming Drug Utilization Review

Treatment of Refractory/Treatment Resistant Depression

Written by Beth Withrow, PharmD Candidate 2022

Major depressive disorder (MDD) is a leading cause of disability in the United States, affecting about 6.7% of adults in any given year (1). MDD can occur at any age, but the median age at onset is 32.5 (1). MDD presents in a myriad of ways, with no consistency in risk factors, comorbidities, or symptomatic presentation from patient to patient. Depression exists on a spectrum that can range from minimal impact on quality of life to life threatening, and people with depression can move in both directions along this spectrum.

Treatment of MDD generally involves a combination of psychotherapy and pharmacotherapy, though patients and practitioners may opt to use either of these as monotherapy (2). Selection of first line pharmacotherapy involves consideration of patient specific factors and side effect profiles, because no one drug has been shown to be more effective than the others. Treatment most commonly begins with an SSRI because they are generally tolerable for most people (2).

Approximately 30% of people with MDD are resistant to treatment, defined as "inadequate response to at least 2 trials of antidepressant therapy" (3). A trial of antidepressant therapy is considered adequate if the patient trialed the medication at therapeutic dosage for at least six to eight weeks; determining an "inadequate response" is more challenging as response to treatment for antidepressant medications can be subjective. Objective clinical scales, including the Hamilton Depression Rating Scale and the Inventory of Depressive Symptomatology, used both prior to initiation of therapy and periodically during treatment can more clearly establish response or non-response to treatment (3).

When evaluating MDD for treatment resistance, it is important to consider other possible causes of treatment failure (3). Drug trials that were ended because of tolerability issues, were prescribed or taken at suboptimal doses, or that were complicated by comorbidities like substance use disorder or a personality disorder, should not be classified as treatment resistant until the complicating factors have been mitigated and the drug has been rechallenged (3).

Once a determination of treatment resistance has been made, treatment options fall into two general categories: pharmacotherapy or brain stimulation (3). Brain stimulation is generally reserved for refractory cases after pharmacotherapy has failed, and includes electroconvulsive therapy (ECT), repetitive transcranial magnetic stimulation (rTMS), magnetic seizure therapy, deep brain stimulation, and vagus nerve stimulation. Current data best supports ECT and TMS, and studies have shown that pharmacotherapy post-brain stimulation can prolong remission if it is achieved (3).

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Pharmacotherapy for treatment resistant depression involves optimizing, combining, switching, or augmenting the antidepressant regimen (3). Medications currently considered appropriate and effective for augmentation in refractory depression include lithium, triiodothyronine, and second generation antipsychotics (3). When considering these augmentation strategies, second generation antipsychotics are generally trialed first due to their efficacy and tolerability (8).

The second generation antipsychotics (SGA) quetiapine, aripiprazole, olanzapine, and risperidone have been tested as adjunct therapy with SSRIs and SNRIs for the treatment of resistant depression and shown good efficacy (3). A combination of olanzapine and fluoxetine in particular has demonstrated a 60% response rate (3). Pimavanserin, a SGA approved for the treatment of psychosis in patients with Parkinson's disease, has also been studied as an add-on to an SSRI or SNRI for treatment resistant depression with some success (8).

Lithium has been used as a psychiatric medication since the 1960s and has been most-studied as an augmentation agent with tricyclic antidepressants (3). However, recent studies have shown a benefit in using lithium to augment SSRIs in patients with treatment-resistant depression. While lithium augmentation has been shown to be effective, the toxicity and monitoring requirements can make its use less desirable (9).

The thyroid hormone triiodothyronine (T3) has also been used to augment antidepressants since the 1960s (3). In some studies it has been shown to be as efficacious as lithium when used for augmentation (10). While it has been primarily studied as an augmenting agent with tricyclic antidepressants, recent studies have paired it with SSRIs and SNRIs as well. T3 doesn't require the clinical monitoring that lithium does, so may be a better initial strategy. T3 has shown effectiveness in patients who are euthyroid in addition to those with hypothyroid conditions (10).

Other, more novel therapeutics have also been investigated for use in treatment resistant depression (3).

Ketamine, which in sub-anesthetic doses is a rapid acting antidepressant, has shown efficacy in treatment resistant depression, though it does come with an increase in dissociation for some patients (4). Esketamine, an enantiomer of ketamine, has recently become available in an intranasal form that is FDA approved as an augmentation agent for treatment resistant depression when used in combination with another antidepressant (3). When used for treatment resistant depression, dosing starts at 56 mg twice weekly, increases up to 84 mg twice weekly if needed to control symptoms, and then is decreased to once weekly at 4 weeks, and potentially every other week at 9 weeks (5).

Psilocybin, a plant alkaloid known to be a psychedelic, has been researched in small, open label trials and has shown up to a 58% response rate up to three months after a series of two doses – a low safety dose and then a high treatment dose (3). Nineteen participants in one study received an initial 10 mg oral dose followed by a 25 mg oral dose 7 days later (6). At the end of the six month follow up period, six of the participants were still experiencing remission from depression with no additional supportive measures. The trial indicated that 14 participants reported paranoia and "autobiographical visions" during the acute drug phase, (6) which generally lasted for about 6 hours with a peak at 2-3 hours post-ingestion (7).

For many patients with treatment resistant depression, bloodwork shows elevated C-reactive protein and cytokine levels (3). In these patients, IV infusion of the TNF antagonist infliximab lowered their CRP levels, (3) but a meta-analysis of studies failed to show a significant difference in depressive symptoms from placebo when using infliximab to augment standard antidepressant therapy (11). Celecoxib and minocycline have likewise been studied, but also without current evidence to support that they are more effective than placebo in the treatment of depression (12).

Other novel compounds are being considered for therapeutic use in patients with treatment resistant depression. Targets such as the delta opioid receptors and GABA system as well as anticholinergic agents have all shown effectiveness in small trials and are currently undergoing additional investigation (3).

Treatment of treatment-resistant depression is a complex process, with patient-specific factors guiding selection of treatment modalities and pharmacological options. Augmentation of an existing, optimized regimen if the patient is experiencing partial

response appears to be the preferred first step, with changes in pharmacotherapy regimen or progression to brain stimulation followed by pharmacotherapy reserved for those patients who do not respond to augmented therapy alone.

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The P&T Committee met for its quarterly business meeting on May 11, 2023

Highlights of this meeting include:

The University of Wyoming School of Pharmacy was awarded the contract for DUR services for a ten-year term, ending June 30, 2033. Dr. Tracy Caller, neurologist from Cheyenne, has replaced Dr. Paul Johnson on the P&T Committee.

Pharmacists received provider status in the last legislative session. The Department of Health is now working through the rule process and system changes required to implement this change.

The buprenorphine dosing limit was increased to 24 mg per day. All doses above 24 mg will require prior authorization.

The prior authorization requirement limiting to indication was removed for the anticoagulant class and the anticonvulsant class with the exception of gabapentin, pregabalin, clonazepam, topiramate and Epidiolex. Gabapentin will now be allowed for use in alcohol abuse disorder and alcohol withdrawal. Pregabalin will be allowed for anxiety and restless leg syndrome.

Filspari, Skyclarys and Lamzede were reviewed. All were limited to indication. Spravato is covered by the Medicaid program as a buy and bill product through the Medical Benefit. It is not covered through the Pharmacy Benefit. Kesimpta will be approved first-line for MS patients with highly active disease.

All prior authorization criteria are open for public comment. Comments can be sent by email to alewis13@uwyo.edu. All comments should be received by June 30, 2023. The next P&T Committee meeting will be held August 10, 2023 in Cheyenne. An agenda will be posted approximately two weeks prior to the meeting.

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