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Antidepressant Review

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Depression is the second leading cause of disability in the United States (US), following cardiovascular disease, and the leading cause of disability worldwide.[1] There have been many recent challenges which has resulted in rising incidences of depression. Examples of these include Coronavirus Disease-2019 (COVID-19), loss of employer-provided health insurance, the opioid pandemic, job termination and isolation. The Centers for Disease Control and Prevention (CDC) has reported increases in mental health challenges, with 40% of adults in the US reporting issues with mental health or substance abuse.[2] Depressive disorders were approximately four times higher in April-June of 2020 compared to the same time period in 2019.[2] Populations that have seen the largest increase in depressive disorders are younger adults, racial/ethnic minorities, essential workers and unpaid adult caregivers. The most recent report from the CDC on state specific rates found Oregon to be ranked the highest in the country in depression rates.[3] In Medicaid patients served by the Oregon Health Plan (OHP) there were over 133,000 patients with antidepressant claims in the second quarter of 2020.[4] Persons with mental health disorders are at least 10 times as likely to commit suicide or have a suicide attempt, emphasizing the importance of appropriate managment.[5] The combination of non-pharmacologic strategies, like behavioral counseling, with antidepressants can be important tools in optimizing patient care. This newsletter will focus on initiating, tapering, and switching antidepressants with a brief update on the use of esketamine.

Antidepressants

Providers are familiar with the classes of antidepressants that are available, which include: selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), atypical agents (bupropion and mirtazapine), serotonin modulators, tricyclic antidepressants and monoamine oxidase inhibitors (MAOIs). Classes of antidepressants are differentiated by their mechanisms of action, which corresponds to differing adverse event profiles. Food and Drug Administration (FDA) indications for antidepressants include depression, anxiety disorders and pain conditions. The National Institute for Health and Care Excellence (NICE) and American Psychiatric Association (APA) recommend second-generation antidepressants (SSRIs, SNRIs, or atypical agents) for initial treatment.[6,7] There is a lack of evidence from high quality systematic reviews that one second-generation antidepressant is superior to another; therefore, treatment selection should be based on adverse events, patient specific characteristics, tolerability and cost.

Antidepressant Adverse Events

Minimizing adverse events can increase adherence and treatment success of antidepressant therapy. Common antidepressant adverse reactions are sexual dysfunction, anticholinergic effects, drowsiness, insomnia/agitation, orthostatic hypotension, QTc prolongation, gastrointestinal adverse reactions and weight gain.[8] Antidepressants with a moderate to high risk of certain adverse reactions are presented in **Table 1.** Antidepressants in **Table 2** are associated with less risk of common adverse reactions to help providers select the most appropriate therapy. Boxed warnings are part of the prescribing information for all antidepressants due to the risk of suicidal thoughts and behaviors in pediatric and young adult populations and therefore, these populations should be monitored more closely.

Table 1. Antidepressants Associated with Moderate to High Levels of Certain Adverse Reactions*[8,9]

Antidepressant	Adverse Reaction	Level of Risk
Citalopram	QTc Prolongation	Moderate
Citalopram	Sexual Dysfunction	High
Escitalopram **Fluoxetine** **Paroxetine** **Sertraline**	Sexual Dysfunction	Moderate
Mirtazapine	Drowsiness	High
Mirtazapine	Weight gain	High
Venlafaxine	Sexual Dysfunction	Moderate
Trazodone	Drowsiness	High
Trazodone	Orthostatic Hypotension	Moderate
Trazodone	GI adverse reactions	Moderate
Vilazodone	GI adverse reactions	High
Vortioxetine	GI adverse reactions	Moderate

Key: * Other antidepressants may be associated with these adverse reactions but at slight or low risk.

Table 2. Antidepressant Recommendations for Minimization of Certain Adverse Reactions[8]

Adverse Reaction to be Avoided	Antidepressants with the Least Risk
Sexual Dysfunction	• Bupropion • Mirtazapine • Duloxetine • Vortioxetine • Nefazodone
Drowsiness	• SSRIs • SNRIs • Bupropion • Vilazodone • Vortioxetine
Anticholinergic	• SSRIs^ • SNRIs • Serotonin modulators* • Bupropion
Orthostatic hypotension	• Atypical agents† • SNRIs
QTc Prolongation	• SNRIs • Atypical agents† • Nefazodone • Vilazodone • vortioxetine
Weight gain	• Bupropion • Fluoxetine • SNRIs • Serotonin modulators*

Abbreviations: SNRIs – serotonin-norepinephrine reuptake inhibitors; SSRIs – selective serotonin reuptake inhibitors
Key: * Nefazodone, trazodone, vilazodone, vortioxetine; † Bupropion, mirtazapine; ^ Paroxetine is not recommended if anticholinergic adverse reactions are to be avoided

Switching Antidepressants

Antidepressant therapy should be tried for a minimum of 4 weeks after dose optimization to determine success of therapy. Remission of depressive symptoms with the use of an initial antidepressant treatment only occurs in around one-third of patients, thus necessitating switching to a different antidepressant.[10] There is limited evidence to guide changing antidepressants but in general, if two therapies from the same class have not been effective, it is recommended to try an option from a different class. Suggested guidance for switching antidepressants depends on the class, half-life and specific drug characteristics (**Table 3**). Caution is warranted due to lack of data on switching the following therapies: vortioxetine, vilazodone, desvenlafaxine, or levomilnacipran.[10]

Table 3. Key Strategies for Switching Antidepressants[10]

Strategies	Explanation	Recommended Classes	Examples
Abrupt switch	Stop the initial therapy and start the new one at a low dose	- SSRI to SSRI+ - SSRI to SNRI - SNRI to SSRI - SNRI to mirtazapine+	Citalopram to sertraline 25 mg/day
Cross-tapering*	Gradually increase the dose of the new therapy while decreasing the existing therapy	- SSRI to SSRI+ - SSRI to mirtazapine - mirtazapine to SSRI - SNRI to mirtazapine+ - Switching to or from bupropion	Sertraline 50 mg daily to mirtazapine 15 mg daily
Taper and switch	Taper high dose antidepressant to a low dose before starting new therapy	- High dose SSRI to new SSRI	Taper paroxetine by 25% every 4 to 6 weeks to 10 mg daily and then start sertraline 25 mg daily
Taper and switch with washout	Gradually taper dose, stop current medication and allow for washout	- Fluoxetine (4-7 day washout) to venlafaxine or duloxetine	Taper and stop fluoxetine. After washout start venlafaxine 37.5 mg/day

Abbreviations: SNRIs – serotonin-norepinephrine reuptake inhibitors; SSRIs – selective serotonin reuptake inhibitors
Key: * Not recommended with fluoxetine, which should be stopped and the new SSRI should be started after a 7-day washout; + Abrupt switch or cross-tapering can be used

When switching or discontinuing antidepressants there is a risk of discontinuation syndrome. Tapering antidepressants over 6-8 weeks is recommended to avoid this syndrome; however, it can still occur. Discontinuation syndrome can last up to 2 weeks and is due to the effects of decreasing levels of serotonin and down regulation of receptors. Discontinuation syndrome presents as gastrointestinal flu-like symptoms, irritability, insomnia, dizziness, vivid dreams and paresthesias.[11] The syndrome is most often seen when switching from a serotonergic antidepressant to a nonserotonergic treatment (e.g., switching from venlafaxine or paroxetine to buproprion) and with therapies with a shorter half-life.[10] Discontinuation syndromes can be treated by increasing the dose of the serotonergic agent, repeating the taper at a slower rate or switching the patient to an SSRI with a longer half-life.[11]

Esketamine

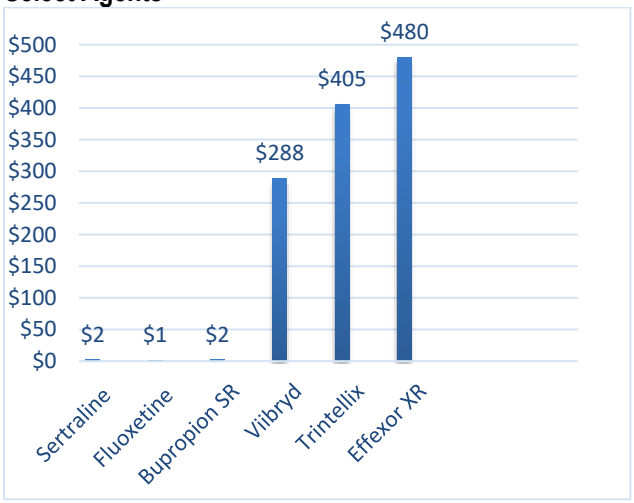
Esketamine is a non-competitive N-methyl-D-aspartate (NMDA) receptor blocker initially approved for treatment-resistant depression.[12] Esketamine must be given under the supervision of a provider and is only available through a Risk Evaluation and Mitigation Strategy (REMs) Program. It is indicated for use along with an oral antidepressant. Esketamine is associated with nausea, vomiting, dissociation, sedation, and misuse. Blood pressure should also be monitored as elevations have been seen for up to 4 hours. Esketamine, 56 or 84 mg, is given as a nasal spray twice weekly for the first month and then once weekly or every other week as maintenance therapy.[12] The cost for esketamine for a 30-day supply (given once weekly) is $1585.[13]

Esketamine received an expanded indication for major depressive disorder with suicidality in July of 2020.[12] Two, four-week randomized clinical trials demonstrated mean improvements in the Montgomery-Asberg Depression Rating Scale (MADRS) scale of 15.7-16.4 points with esketamine compared to 12.4-12.8 points for those treated with placebo, measured from baseline to 24 hours.[14,15] Patients with higher MADRS scores or those with prior suicide attempt demonstrated more improvement in depressive symptoms with esketamine use. The decrease in acute suicidality (median of 1 point on the Clinical Global Impression–Severity of Suicidality–revised [CGI-SS-r] scale) was the same in the esketamine group and placebo group.[14,15] Providers should be aware that although the new indication for esketamine would suggest an improvement in suicidal ideation, this was ***not*** demonstrated in the trials.

Comparative Antidepressant Costs

There are many antidepressant options available to choose from, with generic products representing the best value. A small selection of antidepressant comparative costs, based on average actual acquisition cost (AAAC), illustrate the dramatic differences in a 30-day supply (**Figure 1)**.

Figure 1. Comparative Antidepressant Monthly Cost for Select Agents



* Prices based on Myers and Stauffer Average Actual Acquisition Cost (AAAC) January 26, 2021. Available at: https://www.mslc.com/uploadedFiles/Oregon/AACArchive/OHA%20Generic%20Web%20Listing_20210126_State.pdf

Conclusion

In a time when many people are encountering depressive symptoms, optimizing antidepressant therapy is increasingly important. Choosing treatment options to minimize adverse reactions according to patient preferences and comorbidities will position patients to successfully adhere to therapy. Switching between antidepressants is common and can be done in a way to minimize unwanted symptoms and ultimately lead to an increased likelihood of treatment success.

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- For Oregon Health Plan (OHP) Fee-For-Service (FFS) patients ***there are voluntary preferred anti-depressants to promote cost-effective choices***
- Bupropion, bupropion ER, mirtazapine, venlafaxine and generic SSRIs are cost-effective options for OHP FFS patients
- Giving antidepressants as a single dose once daily improves costs and increases adherence

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References

1. National Institute of Mental Health. 2020 Mental Health Statistics. Available at: https://www.nimh.nih.gov/health/statistics/mental-illness.shtml. Accessed February 24, 2021.
2. Czeisler M, Lane R, Petrosky E, et al. Mental Health, Substance Use, and Suicidal Ideation During the COVID-19 Pandemic — United States, June 24–30, 2020. Morbidity and Mortality Weekly Report (MMWR). Centers for Disease Control and Prevention.2020. Available at: https://www.cdc.gov/mmwr/volumes/69/wr/pdfs/mm6932a1-H.pdf.
3. Johnson A. States with the Highest Rates of Depression. Quote Wizard. Available a: https://quotewizard.com/news/posts/states-with-highest-depression-rates. Accessed January 23, 2021.
4. Servid S. Drug Class Update: Antidepressants. Drug Use Research and Management Group. February 2021. Available at: https://www.orpdl.org/durm/meetings/meetingdocs/2021_02_04/finals/Antidepressant_ClassUpdate.pdf. Accessed January 25, 2021.
5. Bachmann S. Epidemiology of Suicide and the Psychiatric Perspective. *Int J Environ Res Public Health*. 2018;15(7). doi:10.3390/ijerph15071425
6. Posttraumatic Stress Disorder (PTSD). In: Dynamed [internet database]. Ipswich, MA: EBSCO Publishing, Inc. Updated December 21, 2020. Accessed February 10, 2021.
7. Major Depressive Disorder (MDD). In: DynaMed [internet database]. Ipswich, MA: EBSCO Publishing, Inc. Updated February 1, 2021. Accessed February 10, 2021.
8. Side Effects of Antidepressant Medications. In: UpToDate [internet database]. Waltham, MA: UpToDate Inc. Updated March 16,2020. Accessed February 10, 2021.
9. Hirsch M, Birnbaum R. Selective serotonin reuptake inhibitors: Pharmacology, administration, and side effects. In: UpToDate [internet database]. Waltham, MA. Updated March 16, 2020. Accessed February 10, 2021.
10. Choosing and Switching Antidepressants. In: Pharmacist's Letter [internet database]. Stockton, CA; Therapeutic Research Center. Updated July 2020 - Resource #360730. Accessed February 4, 2020.
11. Warner CH, Bobo W, Warner C, Reid S, Rachal J. Antidepressant discontinuation syndrome. *Am Fam Physician*. 2006;74(3):449-456.
12. Spravato (esketamine) [prescribing information]. Titusville, NJ. Janssen Pharmaceuticals. July 2020.
13. Spravato. Average Cash Price GoodRx. Available at: www.goodrx.com/spravato. Accessed February 1, 2021.
14. Fu D-J, Ionescu DF, Li X, et al. Esketamine Nasal Spray for Rapid Reduction of Major Depressive Disorder Symptoms in Patients Who Have Active Suicidal Ideation With Intent: Double-Blind, Randomized Study (ASPIRE I). *J Clin Psychiatry*. 2020;81(3). doi:10.4088/JCP.19m13191
15. Ionescu DF, Fu D-J, Qiu X, et al. Esketamine Nasal Spray for Rapid Reduction of Depressive Symptoms in Patients With Major Depressive Disorder Who Have Active Suicide Ideation With Intent: Results of a Phase 3, Double-Blind, Randomized Study (ASPIRE II). *Int J Neuropsychopharmacol*. 2021;24(1):22-31. doi:10.1093/ijnp/pyaa068