Emerging Pharmacologic Therapies for Treatment Resistant Depression

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Purpose:
Treating mental health disorders can be complex. Treatment options for patients struggling with depression that do not respond to traditional antidepressant medications are limited. This presentation will review possible therapies for patients experiencing treatment resistant depression and examine the efficacy/safety data available for these agents in current literature.

Objectives:

- Describe the presentation, incidence and treatment of unipolar depression.
- Define Treatment Resistant Depression (TRD) and its impact on society.
- Discuss existing and emerging pharmacological options for the treatment of TRD.

Self-Assessment:
(Q1) What are the preferred first line agents used for treatment of unipolar depression?

A. Selective Serotonin Reuptake Inhibitors (SSRIs)
B. Serotonin-Norepinephrine Reuptake inhibitors
C. Tricyclic Antidepressants
D. Both A and B
E. All of the above

(Q2) How many failed antidepressant courses are needed to meet criteria for the most commonly accepted definition of TRD?

A. One
B. Two
C. Three
D. TRD is not defined by the number of failed antidepressant trials.

(Q3) What agent, brought to the market in 2019, carries an indication for the adjunctive treatment of TRD with an oral antidepressant?

A. VRAYLAR® (cariprazine)
B. TRINTELLIX (vortioxetine)
C. SPRAVATO™ (esketamine)
D. None of the above

Major Depressive Disorder (MDD)

What is unipolar depression?

- A complex and highly heterogeneous condition[1].
- Several models have been developed in an attempt to better understand the causes and mechanism of depression but fail to explain the condition fully.
    - Many medications shown to be effective in treating major depressive disorder act on monoamine pathways[2,3].
        - The monoamine-deficiency hypothesis posits that impaired noradrenergic and serotonergic signaling pathways cause depression. However, this hypothesis fails to explain why some patients do not respond to therapy and why some patients may have a delayed response to antidepressant medications[2,3].

Diagnosing Major Depressive Disorder (MDD)[4]

- DSM-5 criteria requires at least 5 symptoms of depression to be present over a 2-week period to define a “Major Depression Episode” with anhedonia (loss of interest in previously enjoyable activities) or depressed mood being at least one of the symptoms. Other symptoms can be found below:

Table 1: DSM-5 Criteria for Major Depressive Disorder[4]

At least one required symptom	Other defining depression symptoms
Depressed mood	Changes in appetite/weight
Anhedonia	Difficulty in sleeping
	Psychomotor agitation/retardation
	Loss of energy or fatigue
	Inability to concentrate or focus
	Feelings of guilt or worthlessness
	Suicidal thoughts or ideation

Depression’s Impact on Society

- In the United States, an estimated 16.9% of patients will meet criteria for a depression diagnosis sometime in their lifetime[5].
    - A study published by the CDC showed that 8.1% of Americans met depression criteria within a specified 2-week period[6].

- Economic Burden:
    - Greenberg et al., found that patients with MDD spent approximately $210.5 million more than patients without MDD on direct or indirect costs related to their condition[7].

Measuring Treatment Severity[8]

- There are many tools available to quantify depression symptoms and assess the severity of the conditions:

Table 2: Depression Severity Scoring Tools[8]

● Beck Depression Inventory (BDI) ● Center for Epidemiologic Studies Depression Scale (CES-D) ● EQ-5D ● ***Hamilton Depression Rating Scale (HAM-D)**** ● ***Montgomery-Åsberg Depression Rating Scale (MADRS)**** ● Social Problem-Solving Inventory-Revised (SPSI-RTM) ● Beck Hopelessness Scale	● Quick Inventory of Depressive Symptomatology-Self-Report (QIDS-SR) ● ***Patient Health Questionnaire (PHQ-9)**** ● Reminiscence Functions Scale (RFS) ● Short Form Health Survey (SF-36) ● Social Adjustment Scale-Self Report (SAS-SR) ● Social Functioning Questionnaire (SFQ)
*indicates the most common severity scoring tools.	

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Treating Depression

First Line[9,10]

- Psychotherapy or second-generation antidepressants are generally regarded as preferred treatment options for MDD.
    - Second generation antidepressants refer specifically to selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs)[11]. A table of antidepressants can be found in Appendix-1 at the end of this handout.
    - Psychotherapy with a psychiatrist can be used alone or in combination with pharmacotherapy.

Second Line[12]:

- If psychotherapy was used as monotherapy for initial treatment, it is recommended to add on a second-generation antidepressant.
- If a second-generation antidepressant was used for initial treatment, it is recommended that the patient switch to an antidepressant of a different class, augment with an antidepressant of a different class, or augment with psychotherapy.

About half of all patients seeking treatment for MDD will not have an adequate response to their first trial of ADT therapy[13]. Up to **30%** of patients will not respond to conventional antidepressant treatments and meet criteria for Treatment resistant depression[12].

Treatment Resistant Depression (TRD)

While there are no official guidelines defining what constitutes treatment resistant depression, many studies regard it as depression with little or no response to at least two trials of preferred antidepressant treatments[12].

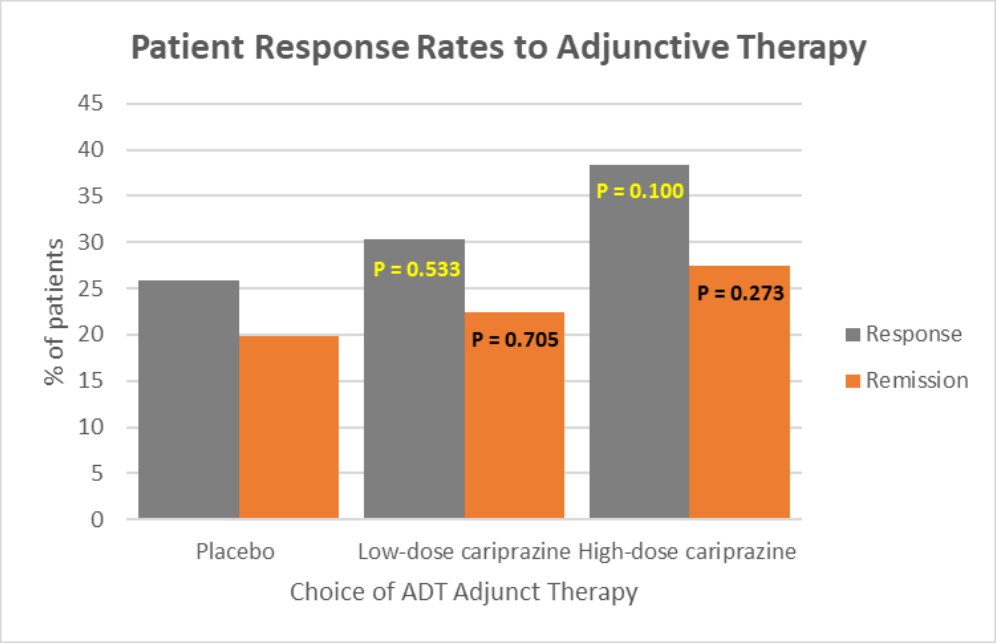
Treatments for TRD[12]

- Augmentation is commonly recommended for patients who fail at least two preferred antidepressant regimens (SSRIs or SNRIs).
    - In some cases, medications that are not traditionally used as antidepressants can be an effective adjunct treatment option (see **Table 3**).

Table 3: Adjunct Medication Options for Treatment Resistant Depression[12]	
Lithium	• A mood stabilizer commonly used for the treatment of bipolar disorder. • Recommended as adjunct therapy by multiple guidelines including the American Psychological Association. • Robust evidence showing efficacy when used in combination with other antidepressants. ○ Many studies showing efficacy as adjunctive therapy were conducted with Tricyclic Antidepressants (TCAs) and not first-line therapies.
Thyroid Hormone (T3)	• Evidence showing efficacy when used in combination with other antidepressants. ○ Many studies showing efficacy as adjunctive therapy were conducted with TCAs and not first-line therapies.

Other Antidepressants	● For patients who have failed two courses of an SSRI/SNRI, switching to a medication in a different antidepressant class may increase the likelihood of a response. ● TCAs and monoamine oxidase inhibitors (MAOis) are generally less tolerable than SSRIs/SNRIs, but may be a good option for those who do not respond to preferred agents.
2nd-generation antipsychotics	● *Good quality research showing that certain antipsychotics (olanzapine, aripiprazole, risperidone, lurasidone, and quetiapine) are effective as adjunctive treatment for TRD with SSRIs and SNRIs.*
Cariprazine (VRAYLAR®)[13]	
Title: Efficacy of adjunctive low-dose cariprazine in major depressive disorder: a randomized, double-blind, placebo-controlled trial. **Objective:** To assess the efficacy, safety and tolerability of cariprazine as adjunctive therapy for the treatment of MDD in patients who have previously failed traditional antidepressant treatment. **Primary Endpoint:** Change from baseline in the Montgomery–Åsberg Depression Rating Scale (MADRS) total score. **Methods:** ● 19-week, multicenter, randomized, double blind, placebo controlled, parallel group study. ● Patients were randomized in a 1:1:1 ratio to receive oral antidepressant medication with placebo, cariprazine 0.1-0.3 mg/day, or cariprazine 1.0 - 2.0 mg/day.	

Results:



*Response was defined as at least a 50% reduction from baseline MADRS score. Remission was defined as an MADRS score of 10 or less.

Conclusion:

- Cariprazine has antidepressant properties that could make it a good option for patients with MDD, but more studies are needed.

Citation:

Fava, M., Durgam, S., Earley, W., Lu, K., Hayes, R., Laszlovszky, I., & Németh, G. (2018). Efficacy of adjunctive low-dose cariprazine in major depressive disorder: a randomized, double-blind, placebo-controlled trial. *International clinical psychopharmacology, 33(6)*, 312.

Ketamine[16,17]

- Used traditionally for anesthesia.
- Available as IV or nasal formulations.
- Mechanism of Action: non-competitive antagonist of glutamate N-methyl-D-aspartate (NMDA) receptors.
    - Its function as an antidepressant is unknown, but may be from downstream effects of glutamatergic pathway regulation.
    - S-Ketamine is most potent at these receptors.

Spravato™ (esketamine)[18]

- Nasal formulation of esketamine approved by the FDA in 2019.
- Approved for TRD and MDD symptoms with suicidal thoughts/ideation.
- Contraindicated in cases of aneurysmal vascular disease, arteriovenous malformation, and Intracerebral hemorrhage.
- Side Effects: dissociation, dizziness, nausea, sedation, vertigo, hypoesthesia, anxiety, lethargy, blood pressure increased, vomiting, feeling drunk, and euphoria.
- Must be dispensed through a Risk Evaluation and Mitigation Strategy (REMS) program due to the associated risk of sedation and dissociation.
    - Requires Spravato™ to be dispensed/administered under the direct supervision of a Healthcare provider. **It should never be dispensed to a patient for home use.**
    - Patients should be monitored by a healthcare provider for at least two hours after administration.
    - Pharmacists have the primary responsibility of ensuring a prescriber is enrolled in the REMS program prior to dispensing.
- Spravato™ was approved primarily based off safety and efficacy data from 6 clinical trials.

Ketamine Efficacy[19]

Title:
Efficacy and safety of flexibly dosed esketamine nasal spray combined with a newly initiated oral antidepressant in treatment-resistant depression: a randomized double-blind active-controlled study.
 	
Objective:
Evaluate the safety/efficacy of switching a patient with TRD on a failing antidepressant regimen to esketamine with a new antidepressant.
 	
Endpoints:
• Primary: Change in the MADRS Score.
• Secondary:
  ○ Proportion of patients with onset of clinical response, defined as at least a 50% reduction in MADRS score by day 2.
  ○ Change from baseline in the Sheehan Disability Scale score.
  ○ Change from baseline in the PHQ-9 score.

Methods/Randomization:

- This was a randomized, placebo-controlled, double blind, multicenter phase III study.
- 227 patients were randomized at the start of the trial, but 4 patients never received an assigned trial drug. 223 patients were randomized in a 1:1 fashion so that 114 patients received esketamine adjunct treatment and 109 patients received placebo adjunct treatment.
- Phase 1:
    - Prospective observation phase to assess efficacy of current antidepressant treatment.
- Phase 2:
    - Treatment phase with patients receiving a new oral antidepressant with either placebo or esketamine adjunctive therapy.
- Phase 3:
    - Follow-up phase.

Inclusion/Exclusion Criteria:

Inclusion	Exclusion
• Documented failed therapy with at least one antidepressant. • Age 18-64. • Diagnosed single episode or recurrent MDD without psychotic features. • IDS-C score of 34+ consistent with moderate or severe depression. • Previous non-response to at least two antidepressants in their current episode.	• Current/recent homicidal ideation or suicidal ideation with intent. • History of certain psychiatric conditions. • Intellectual disability or autism spectrum disorder. • Uncontrolled hypertension. • Seizures. • A recent history of moderate/severe substance use disorder. • Positive urine test results for drugs of abuse.

Statistical Analysis:

- All statistical analyses were done in SAS statistical software.
- Sample size was determined via a previous Stage II trial.
- 98 patients in each cohort were needed to achieve 90% power.
- The primary efficacy endpoint (change in MADRS score) was measured via a mixed-effects model using repeated measures (MMRM).
- A MMRM model was also used to measure the change from baseline in the Sheehan Disability Scale and PHQ-9 scores. Baseline values were used as covariates.
- A Cochran-Mantel-Haenszel chi-square test was used to evaluate the proportion of patients with onset of clinical response by day 2.

Results:

	Antidepressant + Esketamine	Antidepressant + Placebo
Baseline MADRS Score	37.0	37.3
Change from baseline MADRS score at day 28	-21.4	-17.0
95% CI on difference = [-7.31, -0.64] P-value = 0.020		

- The proportion of patients with at least a 50% decrease in their MADRS score by day 2 with maintained reduction was higher in the esketamine group compared to the placebo group, but was not statistically significant.
- Because the above result was not significant, comparison analyses of the Sheehan Disability Scale score and PHQ-9 score was not evaluated.

Adverse Effects:

The following adverse events occurred in greater than 10% of patients in their respective cohorts:

- <u>Placebo Cohort:</u>
  - Dysgeusia (11.9%)
  - Headache (17.4%)

- Esketamine Cohort:
    - **Dissociation (26.1%)**
    - **Nausea (26.1%)**
    - **Vertigo (26.1%)**
    - Anxiety (10.4%)
    - Somnolence (13.0%)
    - Dysgeusia (24.3%)
    - Dizziness (20.9%)
    - Headache (20.0%)
    - Blurred Vision (12.2%)
    - Paresthesia (11.3%)

Conclusions:

- Author's conclusions**:**
    - Patients who were administered esketamine nasal spray with a new antidepressant had a greater decrease in their MADRS score compared to those who received a placebo nasal spray with a new antidepressant.
    - More adverse effects were seen in the esketamine cohort.

- Presenter's conclusions**:**
    - Patients taking esketamine showed a larger decrease in the depression severity symptoms.
    - Results indicate that esketamine may be an effective antidepressant agent, but many people may not have a response.

Strengths/Weaknesses:

- Strengths:
    - Large sample size.
    - Measureable, objective outcomes.
- Weaknesses:
    - No way to determine significance in the real-world setting.

Citation:

Popova, V., Daly, E. J., Trivedi, M., Cooper, K., Lane, R., Lim, P., ... & Singh, J. B. (2019). Efficacy and safety of flexibly dosed esketamine nasal spray combined with a newly initiated oral antidepressant in treatment-resistant depression: a randomized double-blind active-controlled study. American Journal of Psychiatry, 176(6).

Investigational Agents for TRD

Minocycline[14]

Title:
Augmentation therapy with minocycline in treatment-resistant depression patients with low-grade peripheral inflammation: results from a double-blind randomised clinical trial.

Objective:
To assess the efficacy of minocycline as an adjunctive treatment option for patients on antidepressant therapy with inflammatory markers.

Primary Endpoint:
- Change from baseline in the Hamilton Depression Rating Scale (HAM-D-17) score at week 4.

Methods:
- A single center, randomized, placebo controlled, parallel group trial consisting of patients who had failed at least one traditional antidepressant therapy and had a CRP level ≥1 mg/L.
- Patients were randomized in a 1:1 fashion with 18 patients receiving minocycline and 21 patients receiving placebo adjunctive therapy.
- The primary outcome was evaluated after receiving 4 weeks of therapy**.**

Results:
- Change in HAM-D-17 score was not significant when comparing the placebo group to the minocycline group.
- Subanalysis examining patients with CRP levels ≥ 3 mg/L found that a statistically significant number of patients on minocycline had a greater change in HAM-D-17 score compared to placebo.

Conclusion:
- Minocycline may be an effective add-on therapy for patients with TRD with an inflammatory component.

Citation:
Nettis, M. A., Lombardo, G., Hastings, C., Zajkowska, Z., Mariani, N., Nikkheslat, N., ... & Mondelli, V. (2021). Augmentation therapy with minocycline in treatment-resistant depression patients with low-grade peripheral inflammation: results from a double-blind randomised clinical trial. *Neuropsychopharmacology, 46(5),* 939-948.

Psilocybin[15]

Title:
Trial of psilocybin versus escitalopram for depression.

Objective:
Determine the utility of psilocybin as an antidepressant agent.

Primary Endpoint:
- Change from baseline in the 16-item Quick Inventory of Depressive Symptomatology–Self-Report score at week 6.

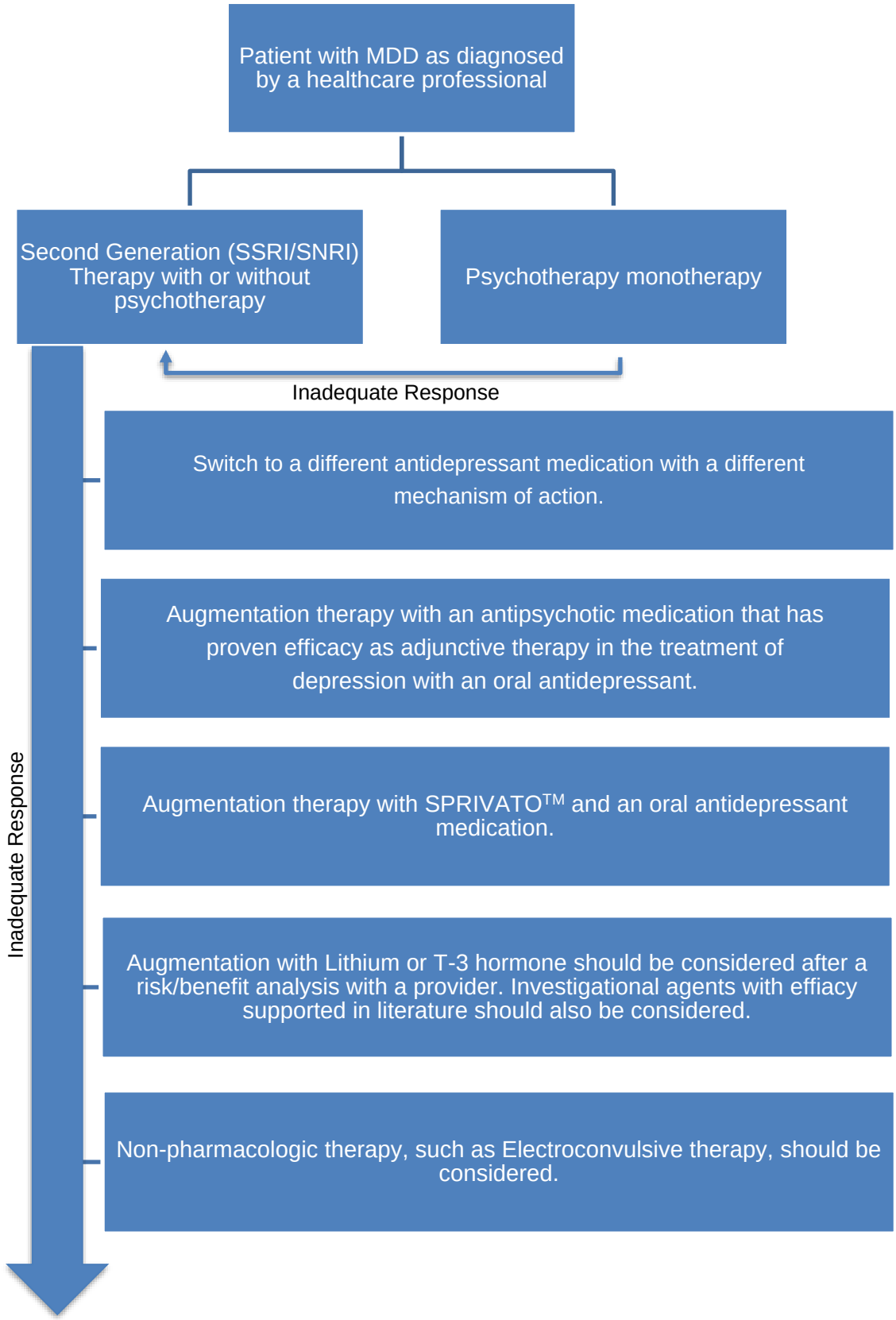
Methods:
- A phase 2, double-blind, randomized, controlled trial consisting of patients diagnosed with moderate/severe MDD.
- Patients were randomized in a 1:1 fashion with 30 patients receiving psilocybin therapy and 29 patients receiving escitalopram therapy.
- The primary outcome was evaluated after receiving 6 weeks of therapy.

Results:
- Change in the QIDS-SR-16 was not significant when comparing the escitalopram group to the psilocybin group.
- Adverse effect profiles generally favored psilocybin compared to escitalopram.

Conclusion:
- Psilocybin has antidepressant properties that could make it a good option for patients with MDD, but more studies are needed.

Citation:
Carhart-Harris, R., Giribaldi, B., Watts, R., Baker-Jones, M., Murphy-Beiner, A., Murphy, R., ... & Nutt, D. J. (2021). Trial of psilocybin versus escitalopram for depression. *New England Journal of Medicine, 384(15)*, 1402-1411.

Recommended Treatment Algorithm:



Pharmacist's Role:

- As medication and drug billing experts, pharmacists are essential to ensure the Spravato™ is dispensed legally and billed appropriately.
    - As part of the REMS programs, we are required to verify providers' enrollment.
- Pharmacists are readily available and well equipped to judge efficacy and tolerability of medications used for depression and TRD.

Key Takeaways:

- Depression is a heterogeneous condition that is difficult to characterize.
- A high percentage of patients may not respond to traditional antidepressant treatments.
- Therapy for Treatment Resistant Depression (TRD) should be individualized based on a patient's comorbid conditions and other medications.
- Esketamine may be a good option for patients who do not respond to traditional therapy.

Resources

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20. Lexicomp.

Abbreviations

MDD – Major Depressive Disorder or unipolar depression

TRD – Treatment Resistant Depression

MADRS – Montgomery–Åsberg Depression Rating Scale

SSRI – Selective Serotonin Reuptake Inhibitor

SNRI – Serotonin and Norepinephrine Reuptake Inhibitor

TCA – Tricyclic Antidepressant

MAOi – Monoamine Oxidase inhibitor

Appendix A1

Selective Serotonin Reuptake Inhibitors (SSRIs)[2]			
Mechanism of Action: Selective inhibition of the serotonin (SERT) transporter, blocking reuptake.			
Agents	**Dosage Forms**	**Reported Adverse Effects (Incidence >10%)**	**Major Drug Interactions**
Fluoxetine (PROZAC™)	Capsules:10mg, 20mg, 40mg, 90mg Tablets: 10mg, 20mg, 60mg	Decreased libido, anorexia, diarrhea, nausea, xerostomia, sexual disorder, anxiety, drowsiness, headache, insomnia, nervousness, yawning, asthenia, tremor, pharyngitis.	Drugs that are substrates of CYP2D6 and 2C19, Antiplatelet medications, other serotonergic drugs.
Sertraline (ZOLOFT™)	Capsules: 150mg, 200mg Tablets: 25mg, 50mg, 100mg Oral sol: 20mg/mL	Diarrhea, nausea, xerostomia, dizziness, drowsiness, fatigue, insomnia.	Drugs that are highly protein-bound, drugs that are substrates of CYP2D6, antiplatelet medications, products containing alcohol, other serotonergic drugs.
Citalopram (CELEXA™)	Capsules: 30mg Tablets: 10mg, 20mg, 40mg Oral sol: 10mg/5mL	Diaphoresis, nausea, xerostomia, drowsiness, insomnia.	Antiplatelet medications, QT-prolonging agents, other serotonergic drugs.
Paroxetine HCl (PAXIL™)	Tablets: 10mg, 20mg, 30mg, 40mg, 12.5mg CR, 25mg CR, 37.5mg CR Oral sol: 10mg/5mL	Diaphoresis, decreased libido, constipation, decreased appetite, diarrhea, dyspepsia, nausea, xerostomia, ejaculatory disorder, dizziness, drowsiness, headache, insomnia, asthenia, tremor.	Drugs that are substrates of CYP2D6, antiplatelet medications, other serotonergic drugs.

Escitalopram (LEXAPRO™)	Tablets: 5mg, 10mg, 20mg Oral Sol: 5mg/5mL	Diarrhea, nausea, ejaculatory disorder, drowsiness, headache, insomnia.	Drugs that are substrates of CYP2C19, antiplatelet medications, QT-prolonging agents, other serotonergic drugs.
Fluvoxamine (LUVOX™)	Capsules: 100mg ER, 150mg ER Tablets: 25mg, 50mg, 100mg	Headache, insomnia, drowsiness, dizziness, nervousness, nausea, diarrhea, xerostomia, anorexia, ejaculatory disorder, weakness.	Drugs that are substrates of CYP1A2 or CYP2C19, antiplatelet medications, other serotonergic drugs.
Serotonin and Norepinephrine Reuptake Inhibitors (SNRIs)[2]			
<u>Mechanism of Action</u>: Binds the serotonin (SERT) and norepinephrine (NET) transporters, blocking reuptake.			
Agents	**Dosage Forms**	**Common Adverse Effects (Incidence >10%)**	**Major Drug Interactions**
Venlafaxine HCl (EFFEXOR™)	Capsules: 37.5mg ER, 75mg ER, 150mg ER Tablets: 25mg, 37.5mg, 50mg, 75mg, 100mg, 37.5mg ER, 75mg ER, 150mg ER, 225mg ER	Diaphoresis, weight loss, anorexia, nausea, xerostomia, dizziness, drowsiness, insomnia, asthenia.	Antiplatelet medications, other serotonergic drugs.
Desvenlafaxine (PRISTIQ™)	Tablets: 25mg ER, 50mg ER, 100mg ER	Hyperhidrosis, nausea, xerostomia, dizziness, insomnia.	Antiplatelet medications, other serotonergic drugs.
Duloxetine (CYMBALTA™)	Delayed release capsules: 20mg, 30mg, 40mg, 60mg	Weight loss, abdominal pain, decreased appetite, nausea, vomiting, xerostomia, drowsiness, fatigue, headache.	Antiplatelet medications, drugs that are substrates of CYP2D6 or CYP1A2, other serotonergic drugs.

Tricyclic Antidepressants (TCAs)[2]			
<u>Mechanism of Action:</u> Binds the serotonin (SERT) and norepinephrine (NET) transporters, blocking reuptake. TCAs also have affinity for other monoamine receptors.			
Agents	**Dosage Forms**	**Common Adverse Effects (Incidence >10%)**	**Major Drug Interactions**
Imipramine (TOFRANIL™)	Pamoate formulation, tablets: 75mg, 100mg, 125mg, 150mg HCl formulation, capsules: 10mg, 25mg, 50mg	Incidence not specified, but patients may experience various cardiovascular, central nervous system, dermatologic, endocrine, gastrointestinal, genitourinary, hematologic, hepatic neuromuscular, ophthalmic, otic, and hypersensitivity adverse reactions.	Anticholinergic agents, CNS depressants, QT-prolonging agents, other serotonergic agents.
Amitriptyline HCl (ELAVIL™)	Tablets: 10mg, 25mg, 50mg, 75mg, 100mg, 150mg	Incidence not specified, but patients may experience various cardiovascular, dermatologic, endocrine, gastrointestinal, genitourinary, hematologic, nervous system, hepatic neuromuscular, ophthalmic, otic, and hypersensitivity adverse reactions.	Anticholinergic agents, CNS depressants, other serotonergic agents.
Doxepin (SILENOR™)	Capsules: 10mg, 25mg, 50mg, 75mg, 100mg, 150mg Concentrate: 10mg/mL Tablets: 3mg, 6mg	No adverse reactions occurring in >10% of patients.	Anticholinergic agents, CNS depressants, QT-prolonging agents, other serotonergic agents.

Nortriptyline (PALMELOR™)	Capsules: 10mg, 25mg 50mg, 75mg Solution; 10mg/5mL	Incidence not specified, but patients may experience various cardiovascular, dermatologic, endocrine, gastrointestinal, genitourinary, hematologic, hepatic neuromuscular, nervous system, ophthalmic, otic, renal and hypersensitivity adverse reactions.	Anticholinergic agents, CNS depressants, other serotonergic agents.
Desipramine HCl (NORPRAMIN™)	Tablets: 10mg, 25mg, 50mg, 75mg, 100mg, 150mg	Incidence not specified, but patients may experience various cardiovascular, central nervous system, dermatologic, endocrine, gastrointestinal, genitourinary, hematologic, hepatic neuromuscular, ophthalmic, otic, and renal adverse reactions.	Anticholinergic agents, CNS depressants, other serotonergic agents.
Clomipramine HCl (ANAFRANIL™)	Capsules: 25mg, 50mg, 75mg	Dizziness, drowsiness, headache, fatigue, insomnia, nervousness, myoclonus, diaphoresis, weight gain, change libido, xerostomia, constipation, nausea, dyspepsia, anorexia, diarrhea, abdominal pain, increased appetite, impotence, tremor, myalgia, visual disturbance, pharyngitis.	Anticholinergic agents, CNS depressants, QT-prolonging agents, other serotonergic agents.
Protriptyline HCl (VIVACTIL™)	Tablets: 5mg, 10mg	Incidence not specified, but patients may experience various cardiovascular, central nervous system, dermatologic, endocrine, gastrointestinal, genitourinary, hematologic, hepatic, neuromuscular, ophthalmic, otic, and renal adverse reactions.	Anticholinergic agents, CNS depressants, other serotonergic agents.

Trimipramine (SURMONTIL™)	Capsules: 25mg, 50mg, 100mg	Incidence not specified, but patients may experience various cardiovascular, central nervous system, dermatologic, endocrine, gastrointestinal, genitourinary, hematologic, hepatic, neuromuscular, ophthalmic, otic, hypersensitivity and renal adverse reactions.	Anticholinergic agents, CNS depressants, other serotonergic agents.
Monoamine Oxidase Inhibitors (MAOis)[2]			
<u>Mechanism of Action:</u> Binds monoamine oxidase, preventing the degradation of monoamine molecules.			
Agents	**Dosage Forms**	**Common Adverse Effects (Incidence >10%)**	**Major Drug Interactions**
Phenelzine (NARDIL™)	Tablets: 15mg	Incidence not specified, but patients may experience various cardiovascular, dermatologic, endocrine, gastrointestinal, genitourinary, hepatic, nervous system, and ophthalmic adverse reactions.	Anticholinergic agents, CNS depressants, other serotonergic and dopaminergic agents.
Isocarboxazid (MARPLAN™)	Tablets: 10mg	Dizziness, headache	Blood pressure lowering agents, anticholinergic agents, CNS depressants, other serotonergic and dopaminergic agents.
Selegiline HCl (ZELEPAR™)	Capsules: 5mg Tablets: 5mg	Hypotension, nausea, dizziness, headache, insomnia.	Blood pressure lowering agents, anticholinergic agents, CNS depressants, other serotonergic and dopaminergic agents.

Tranylcypromine (PARNATE™)	Tablets: 10mg	Incidence not specified, but patients may experience various cardiovascular, dermatologic, endocrine, gastrointestinal, genitourinary, hematologic, neuromuscular, otic, nervous system, and ophthalmic adverse reactions.	Anticholinergic agents, CNS depressants, other serotonergic and dopaminergic agents.
Other Antidepressants[2]			
Mechanism of Action: Varies between agents.			
Agents	**Dosage Forms**	**Common Adverse Effects (Incidence >10%)**	**Major Drug Interactions**
Bupropion HCl (WELLBUTRIN™)	Tablets: 75mg, 100mg, 100mg SR, 150mg SR, 200mg SR, 150mg ER, 300mg ER, 450mg ER	Tachycardia, diaphoresis, weight loss, constipation, nausea and vomiting, xerostomia, agitation dizziness, headache, insomnia, migraine, tremor, blurred vision, nasopharyngitis, pharyngitis, rhinitis.	Drugs that are substrates of CYP2D6.
Mirtazapine (REMERON™)	Tablets: 7.5mg, 15mg, 30mg, 45mg	Elevated cholesterol, weight gain, constipation, increased appetite, xerostomia, drowsiness.	Drugs that are substrates of CYP3A4, CNS Depressants, other serotonergic agents.
Amoxapine (ASENDIN™)	Tablets: 25mg, 50mg, 100mg, 150mg	Drowsiness, xerostomia, constipation.	Anticholinergic agents, CNS depressants, other serotonergic agents.
Vilazodone HCl (VIIBRYD™)	Tablets: 10mg, 20mg, 40mg	Headache, diarrhea, nausea.	Drugs that are substrates of CYP3A4, other serotonergic agents.

Nefazodone HCl (SERZONE™)	Tablets: 50mg, 100mg, 150mg, 200mg, 250mg	Headache, drowsiness, dizziness, insomnia, agitation, xerostomia, nausea, constipation, weakness.	Drugs that are substrates of CYP3A4, serotonergic agents.
Vortioxetine (TRINTELLIX™)	Tablets: 5mg, 10mg, 20mg	Nausea, sexual disorders.	Antiplatelet agents, other serotonergic agents.
*Agents listed in Appendix A1 do not represent all agents used in the treatment of Major Depressive Disorder (MDD). *Proper trial for antidepressant medications should be 30 days. Some patients may need 2-4 weeks of therapy for a response. *All data was retrieved via *Lexicomp*			