

Update on Antidepressants

Connecticut Academy of Family Physicians

September 29, 2023

Jeffrey Shelton, M.D.
Chair, Department of Psychiatry
Middlesex Health





FINANCIAL DISCLOSURE

I do not have any financial affiliations which may have direct or indirect connection to the content of this presentation



Update on Antidepressants

Objectives

- Understand the incidence and prevalence of Major Depressive Disorder
- Review antidepressant medications and the STAR*D study
- Understand the definition and incidence of Treatment Resistant Depression
- Review current therapies for Treatment Resistant Depression
- Overview current trends in psychiatric research



Update on Antidepressants

Major Depressive Disorder (MDD)

“People often think the opposite of depression is happiness. It’s not. The opposite of depression is vitality”

- Andrew Solomon, author of *The Noonday Demon: An Atlas For Depression*



Update on Antidepressants

Major Depressive Disorder (MDD)

- Prevalence: 1:5 Americans will experience MDD at least once during their lifetime
- Incidence: Recent estimates show 16 million American adults had an episode of depression over the course of a year
- According to World Health Organization - leading cause of disability worldwide

Update on Antidepressants

Development Timeline

1950's	1960's	1970's	1980's	1990s	2000's	2010's
Imipramine	Amitriptyline	Doxepin	Fluoxetine	Paroxetine	Duloxetine	Vortioxetine
MAOIs Vilazodone	Nortriptyline			Bupropion	Sertraline	Aripiprazole
Citalopram						
Venlafaxine						

Question:

After imipramine came to market - which antidepressant was an



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Answer - None

SSRIs, SNRIs, and other antidepressants represented improvement in tolerability and safety but not efficacy.

What does that mean?

There was no improvement in the efficacy of the medications for depression from 1959 until 2019.



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What happened from 1959 until 2019?

- 1) Major advancements in neuroscience.
- 2) Growth of effective, evidenced-based psychotherapies - particularly Cognitive Behavioral Therapy CBT (Beck), Dialectical Behavioral Therapy DBT (Linehan), and trauma focused therapies such as Cognitive Processing therapy CPT (Resick).
- 3) Research in algorithms for patients who did not respond to first trial of antidepressants (STAR*D study).
- 4) Electroconvulsive Therapy (ECT) became the gold standard for the treatment of MDD.



Update on Antidepressants

Sequenced Treatment Alternatives to Relieve Depression (STAR*D)

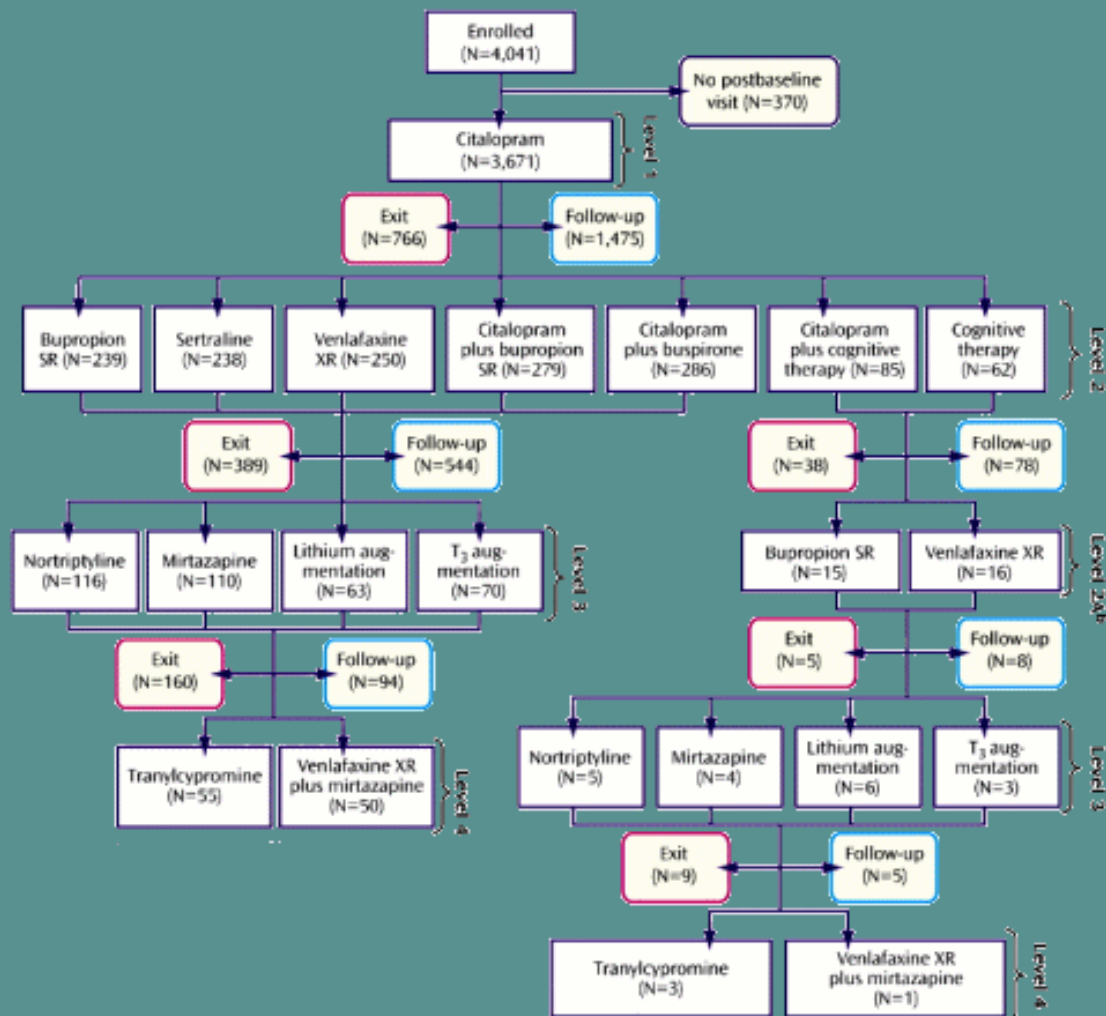
Funded by the NIMH

Focused on treatment of patients who did not respond to first trial of antidepressant

Four-phase protocol

Over 3,000 patients at 23 different sites

Trivedi MH, Rush AJ, Wisniewski SR, et al. Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. *Am J Psychiatry*. 2006;163:28-40





Update on Antidepressants

STAR*D Take Homes

- No clear medication “winner”
 - Bupropion was slightly more effective as augmentation than lithium and buspirone however not statistically significant
 - Switching to different monotherapy or augmentation with another medication were equally effective.
- 50% of patients who achieved remission in Phase One did so after 6 weeks.
- Rate of remission decreased with every phase.
 - If no or minimal response after 2 antidepressant trials - likelihood of remission decreases is very low (15%)



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Treatment Resistant Depression (TRD)

- Treated with 2 or more antidepressant medications with minimal to no response (less than 50% reduction in symptoms)
- About 30% of patients with MDD have TRD
 - >30% will attempt suicide
 - Decreased life expectancy
 - Significant functional loss



Update on Antidepressants

Ketamine

- Approved by FDA in 1970 as anesthetic
- Low incidence of respiratory depression and hypotension
- Neuropharmacology

Stimulates release of glutamate via antagonism of the NMDA receptor on the inhibitory neuron



Update on Antidepressants

Ketamine

- Research with ketamine for TRD began in early 2000's.
- Results were remarkable.
- Patients who had not responded to numerous med trials and are normally excluded from antidepressant research showed fast and dramatic improvement



Update on Antidepressants

Ketamine

Initial Study at Yale. Published in 2000

- 9 patients with Treatment Resistant Depression
- Received low dose IV ketamine (0.5mg/kg) vs IV saline
- Saline patients had no response
- Ketamine patients had dramatic reduction in depressive symptoms within 72 hours

Berman RM, Krystal JH, et al. Antidepressant effects of ketamine in depressed patients. *Biological Psychiatry*. 2000;47:351-354



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Research of Ketamine for Depression

- Subsequent two decades saw an explosion of research on ketamine
- Studies involving thousands of patients across the world showed ketamine to be safe and effective.
- Overall, at least 70% of patients with TRD had clinically meaningful response.



Update on Antidepressants

Ketamine

- Increases transmission of glutamate through NMDA receptor antagonism however so do other medications, including memantine, which do not offer antidepressant effects
- Challenged monoamine theory of depression which had predominated psychiatry for decades
- Redefined depression as illness of neuronal atrophy
- Ketamine causes neurogenesis in prefrontal cortex through increased expression of BDNF



Update on Antidepressants

Esketamine

- FDA approved intranasal esketamine (Spravato) in 2019 for treatment resistant depression as well as MDD with acute suicidality.
 - S-enantiomer of ketamine
- Only medication FDA approved to treat suicidality



Update on Antidepressants

Esketamine

- Eligibility
 - Diagnosis of Major Depressive Disorder
 - Persistent symptoms despite trial of 2 or more medication trials despite sufficient duration and dosing.
 - Does not have active substance use disorder
 - Does not have uncontrolled HTN
 - Must be prescribed antidepressant



Update on Antidepressants

Esketamine

- Medication given directly to patient at time of treatment (not dispensed to patient from pharmacy)
- Patients are observed taking dose
- Must be monitored for 2 hours after dose
- Monitored for elevated blood pressure



Update on Antidepressants

Esketamine

- Administered twice a week for 4 weeks
- Then once a week for 4 weeks
- Then every other week for 8 weeks
- Then assess need for maintenance treatment



Update on Antidepressants

Esketamine

- Side Effects
 - Dissociation
 - Hypertension
 - Hyperacusis
 - Photophobia
 - Sedation



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Esketamine

- What is Dissociation?
 - Derealization
 - Feeling detached from surroundings
 - Objects may change shape or color
 - Depersonalization
 - Feeling detached from self
 - Feel like a spectator/watching a movie of yourself



Update on Antidepressants

Esketamine

- Dissociation
 - Most severe during initial treatment
 - Music helps
 - Environment (quiet and dimmed lighting)
 - Staff present to monitor and provide reassurance



Update on Antidepressants

Esketamine at Middlesex

- Started March 2022
- Over 80 patients treated
- Ages range from 22-86
- Results encouraging



Update on Antidepressants

Esketamine

- S.W.
 - 22 year year Caucasian male
 - Dropped out of college in 2020 due to severity of depression
 - Multiple medication trials with minimal response



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Esketamine

- S.W.
 - Prior to starting esketamine - PHQ-9 25/27*
 - 2 days after 1st dose - PHQ-9 12/27
 - 10 days after 1st dose - PHQ-9 6/27
 - Most recent treatment was 2 weeks ago - PHQ-9 6/27

* Metric- Based Care



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Esketamine

- J.A.
 - 73 year old Caucasian woman
 - Decades long struggle with depression with numerous prior medication trials



Update on Antidepressants

Esketamine

- J.A.
 - PHQ-9 prior to starting esketamine 18/27
 - “Feeling down, depressed, or hopeless”
 - *Nearly every day*
 - “Little interest or pleasure in doing things”
 - *Nearly every day*



Update on Antidepressants

Esketamine

- J.A.
 - 5 days after initial treatment - PHQ-9 was 10
 - “Feeling down, depressed, or hopeless”
 - *Not at all*
 - “Little interest or pleasure in doing things”
 - *Not at all*



Update on Antidepressants

Esketamine

- J.A.
 - 5 days after initial treatment - PHQ 9 was 10
 - “Feeling down, depressed, or hopeless”
 - *Not at all*
 - “Little interest or pleasure in doing things”
 - *Not at all*

Update on Antidepressants





Update on Antidepressants

What's new in psychiatry?



Update on Antidepressants

Psychedelic Psychiatry

- What is “Psychedelic”?
 - Loosely grouped class of drugs which can induce altered thoughts and sensory perception.
 - Includes LSD (Acid), Psilocybin (Magic Mushrooms), MDMA (Ecstasy & Molly), Ayahuasca, DMT, Mescaline, and Ketamine.
 - At sufficient doses, can cause hallucinations and paranoia.
 - In the 1950’s and early 1960’s - thought to be wonder drugs in psychiatry. Became associated with 1960’s counterculture leading to “moral panic” so became schedule 1 substance.



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Psychedelic Psychiatry

- In The News:
 - WSJ 2021
 - *“Silicon Valley and Wall Street Elites Pour Money Into Psychedelic Research”*
 - NYT 2022
 - *“The Psychedelic Revolution is Coming. Psychiatry May Never Be the Same”*



Update on Antidepressants

Psychedelic Psychiatry

- JAMA Psychiatry 2021

“This randomized clinical trial found that psilocybin-assisted therapy was efficacious in producing large, rapid, and sustained antidepressant effects in patients with major depressive disorder.”

Davis AK, et al. Effects of Psilocybin-Assisted Therapy for Major Depressive Disorder. *JAMA Psychiatry*. 2021 May; 78:1-9



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Psychedelic Psychiatry

NEJM 2021

Psilocybin (25mg) vs. escitalopram (20mg) for patients with Major Depressive Disorder. No placebo arm. Psilocybin was as effective as escitalopram for primary outcome (improvement in QIDS-SR-16 score at 6 weeks). Psilocybin was twice as effective than escitalopram for secondary outcomes (change in HAM-D and MADRAS at 6 weeks). No serious adverse events. Side effects occurred at equivalent rate.

Carhart-Harris R, et al. Trial of Psilocybin versus Escitalopram for Depression. *NEJM*. 2021; 394:1402-1411



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Psychedelic Psychiatry

Nature 2021

“MDMA-assisted therapy is highly efficacious in individuals with severe PTSD, and treatment is safe and well-tolerated.”

Mitchell JM, et al. MDMA-assisted therapy for severe PTSD: a randomized, double-blind, placebo-controlled phase 3 study. *Nature*. 2021; 27: 1025-1033



Update on Antidepressants

**I do not recommend patients use
psychedelic drugs.**

**However, we need more effective medications and research
into certain psychedelics is promising**



Update on Antidepressants

Take homes

- **SSRIs remain the first line treatment for MDD**
- **Different traditional antidepressants have roughly equivalent efficacy**
- **If patients do not respond to trial of one medication - switching to different medication or augmenting with another medication (bupropion, mirtazapine, buspirone, or aripiprazole) are both effective options**



Update on Antidepressants

Take homes

- About 30% of patients will have no response and 30% will have only partial response with first medication trial
- Subsequent trials with augmentation, switching antidepressants, and/or psychotherapy is effective for about 60-70% of patients



Update on Antidepressants

Take homes

- Esketamine is a safe and effective medication for patients with Treatment Resistant Depression
- There is promising research into the use of psychedelics for different mental disorders including Major Depressive Disorder and Posttraumatic Stress Disorder however no FDA approved treatments as of yet.



Update on Antidepressants

“We always overestimate the change that will occur in the next two years and underestimate the change that will occur in the next ten. Don’t let yourself be lulled into inaction”

- Bill Gates

Thank you

