Major Breakthroughs in the Medication Treatment of Depression

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Today's Objectives

- Examine depression as a syndrome and gain a clear understanding of what antidepressant medications – as well as non-pharmacological interventions – can objectively manage and treat
- Address the limitations of today's most often prescribed antidepressants, and why they fail to deliver positive results for most users
- Describe the characteristics, benefits, risks, side effects, cost factors, and effectiveness of new, novel, breakthrough agents in depression treatment

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Your Role in Combined Psychosocial and Pharmacological Treatments

- Collaboration and communication with prescribing professionals
- Managing the combined treatments
  - Referrals for medication
  - Client psychoeducation
  - Monitoring drug effects and side effects
  - Promote adherence to combined treatments
  - Too often, nonmedical professionals are reluctant to get involved with medication issues, believing it is beyond their knowledge and not within their scope of expertise
  - The reality: Medication and psychotherapy are not mutually exclusive, so therapists and counselors MUST be attuned to the reactions and results patients are having with medication, to best direct and advise them regarding future appointments with prescribers

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Neurotransmitters

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Norepinephrine

- Regulates arousal, attention, cognitive function, stress reactions
- Most often associated with the "fight – flight response
- Low levels of norepinephrine are continuously at work in our brains and bodies, levels increase when we're faced with threat, danger, or stress

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Serotonin

- Regulates mood, anxiety, appetite, sleep, sexual functioning, states of consciousness
- Most often implicated in depressive states
- Linked to the development of a popular class of antidepressants know as the SSRIs

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Dopamine

- A primary role is regulation of the “pleasure principle”
- Also relevant in many other functions including memory, movement and motivation
- Four prominent dopamine pathways

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Glutamate

- Glutamate is the brain’s primary excitatory neurotransmitter
- It is a basic building block of proteins and plays an important role in learning, memory, and mood regulation
- Research consistently shows that people with depression have lower glutamate levels in their brains compared to healthy subjects

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Unipolar Depression

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Understanding Depression

- Depression is likely many illnesses, when we use the term “depression” with a client, it’s a bit like a car mechanic saying you have engine trouble
- On first visits with a client, assess for a need for emergency hospitalization, pursuant to psychotic features or suicide risk; then move on to an acute or comorbid medical or substance-related condition needing attention (acute stroke, for example)
- Next, look at whether the depressive episode has “mixed” hypomanic/manic features
- Consider the term “bipolar-ish” to describe patients whose depressive syndrome skews toward the bipolar side: Clues include family history of bipolar, psychomotor retardation
- Most useful indicator of bipolar is the complaint that antidepressants make the patient feel worse – antsy, agitated, wired, insomnia

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Understanding Depression (cont)

- There are circumstances where depression is NOT an illness; we sometimes attribute "depression" to people experiencing, demoralization, grief, or despair – these are not "illnesses" but rather normal parts of the human condition subjected to adverse circumstances
- What do patients need to know about "depression?" Start by telling them what depression ISN'T – it is not caused by a chemical imbalance in the brain and that it's an "umbrella" diagnosis – a group of related conditions under a "tent"
- Discuss the benefits and risks of medication and discuss the need for MORE than just medication – virtually all depressive syndromes have a psychosocial component, and sometimes a cultural and spiritual component as well
- "Medication is potentially a bridge between feeling terrible and feeling better, but you still need to walk across that bridge"

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Understanding Depression (cont)

- Depression can be often misunderstood as sadness; most people who are chronically depressed aren't sad, instead they feel nothing because their bodies are stuck in survival mode.
- Commercials for depression in the 90s named the cause as low levels of serotonin, with no mention of toxic marriages, unhealthy workplaces, financial stress, or unresolved trauma, a natural reaction to unnatural environments.
- Their bodies are stuck in a "freeze" protective state – a cocoon like existence; this is why we need to understand depression as a RESPONSE, rather than a disease or a disorder
- This results in a state of defeatism – manifesting in an inability to handle uncertainty, feeling powerless, unable to protect boundaries and maintain control
- "Why do anything, I can't live life like I want to"

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Influences on Clinical Depression

- Inflammatory
- Demoralization
- Biological
- Medical
- Medication
- Substance abuse
- Chronic pain
- Chronic Insomnia
- Hormonal

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Antidepressants: An Overview

- Antidepressants have been available since the 1950s, but psychiatry was reluctant to prescribe them believing they robbed patients of their autonomy
- So, depression was allowed to run its course, and many people moved from mild to moderate to severe depression to immobilizing despair
- Antidepressants, however, are controversial – particularly the more contemporary SSRIs and SNRIs. Do they really help users achieve symptom remission, and if so, to what extent? Is improvement mostly placebo-related?
- We do know this: Antidepressants improve FUNCTIONING, not FEELINGS, so its important for the client to understand what these drugs are able to provide and for how long

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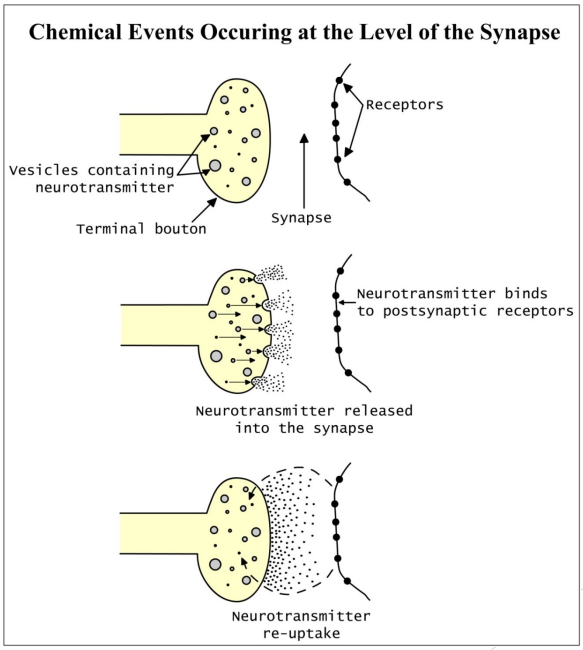

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How Conventional Antidepressants Work

- Inherent to this mechanism of action is that in depressed individuals a chemical imbalance exists, which antidepressants aim to rebalance
- Thus, the longer chemicals remain in the synapse, the greater the possibility the individual's depression will normalize through this chemical restoration process
- This chemical imbalance theory was vogue up to the early 2000s - when science acquiesced and changed its mind and embraced research that better explains these complex mechanisms
- It is now believed depression reduces brain-derived neurotrophic factor (BDNF), which causes nerve cells to shrink. Antidepressants then activate BDNF
- This better explains why it takes antidepressants so long to take effect; antidepressants don't just fill up the neurotransmitter 'tank," instead it takes time (at least 2-4 weeks) for them to stimulate nerve growth and exert a positive effect on mood

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How to Explain Antidepressant Actions to Clients

- Keep explanations simple, try this: "Nerve cells control brain function, so your depression is likely happening because of some shrinkage of these cells. Lexapro, or (any other antidepressant) can have a fertilizing effect by stimulating your nerve cells to grow and strengthen, helping you to feel better."
- Antidepressants of course, aren't fertilizer but the use of metaphor, or example helps the client form a picture of what's going on
- Sobering news about SSRIs and SNRIs from the *Lancet* medical journal in 2018: "These antidepressants do outperform placebo, but these agents have only modest to small efficacy in the treatment of adults with unipolar depression, but are not totally useless
- My experience: I rarely see debilitating depression like I used to; as many of those who would have exhibited very severe symptoms were started on SSRIs or SNRIs which slowed the progression of symptoms due to this broad "fertilizer" effect

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Classes of Antidepressants

- First came the Opiates and Opioids
- Cyclics: Elavil; Pamelor; Anafranil;
- Trazodone – antidepressant effects; weight neutral; improves sleep; cognitive issues; orthostasis
- NRI: Strattera – blocks norepinephrine exclusively; classified as as an antidepressant, but approved only for ADHD
- SSRIs: Prozac Family
- SNRIs: Effexor; Cymbalta;
- Atypicals: Wellbutrin (DNRI); Remeron
- Wellbutrin – No weight gain or sexual side effects, seizure risk at higher doses
- Remeron – norepinephrine and serotonin effects, powerful blocker of histamine contributing to its sedative effects
- Approved: MDD; OCD; GAD; PTSD; SAD; Chronic Pain (Cymbalta)

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Next Came…

Viibryd (vilazodone)

- Combines the mechanism of action of SSRIs like Prozac with that of the anti-anxiety drug Buspar
- Targets the anxiety symptoms that often accompany depression
- Purports minimal weight gain and sexual dysfunction

Trintellix (vortioxetine)

- This is essentially a Viibryd copycat.
- It's claim to be effective in managing the cognitive symptoms of depression, particularly poor concentration didn't materialize

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The "Newest" Breakthroughs

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Ketamine Infusion Therapy

- Ketamine is classified as a preoperative general anesthetic for both human and animal use
- No serotonin, norepinephrine or dopamine effects but instead is an NMDA receptor antagonist, like dextromethorphan and methadone
- If you remember the days of the "rave" phenomenon, ketamine was a popular psychedelic going by the moniker "special K"
- Touted as possessing rather fast-acting antidepressant properties, with many clinicians, predominately psychiatrists, offering ketamine infusion therapy as a alternative for treatment-resistant depression, particularly for those with suicidal tendencies
- Because ketamine is not FDA approved for depression and is therefore considered an off-label procedure, free market forces enter the picture. Upfront fees can run up to $500 per infusion.
- Side effects: Possible acute hypertensive crisis; free-floating, hallucinatory sensations, elevated blood pressure
- So is it possible that dissociation is either a predictor or even possibly responsible for its antidepressant effect? What then? Will the goal be to induce a psychedelic experience to maximize ketamine's benefits?

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Spravato (esketamine)

- On March 5, 2019, the FDA approved Spravato (esketamine) nasal spray as additive treatment with antidepressants for treatment-resistant depression
- Overall response rates after a month of treatment were much higher for esketamine plus an antidepressant, when compared to placebo plus an antidepressant. Also in a long-term maintenance trial, the midpoint time to relapse in stable responders to the esketamine-antidepressant combination was a whopping 635 days
- Providers of this agent must sign up with the REMS (Risk Evaluation and Mitigation Strategy) system, and the Drug Enforcement Administration (DEA) performs an inspection of a provider's office. A provider is mandated to supervise a patient while the intranasal dose is self-administered, and the supervision must be ongoing for at least 2 hours afterward to monitor for side effects
- Esketamine is the first, really new and original antidepressant to reach the U.S. market in over 30 years
- $600 for each 56mg dose and nearly $900 for each 84mg dose
- Side effects: Bitter aftertaste; elevated BP; dissociation
- There is an URGENT need for something new for those suffering from depression – particularly treatment-resistant depression

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Auvelity (dextromethorphan/bupropion)

- At its core this is a Robitussin and Wellbutrin combination
- "Augment with velocity"
- Like ketamine, dextromethorphan increases glutamate transmission through NMDA antagonism
- Pairing it with bupropion accomplishes another goal: it increases the half-life of dextromethorphan extending the excitatory glutamate effect
- And since bupropion increases norepinephrine and dopamine, we have a triple action – glutamate, norepinephrine, and dopamine
- What stands out in trials is speed of onset, with separation from placebo in one (1) week
- Side effects: dizziness, headache, diarrhea
- Pricing: $1,200 per month minimum, without generic substitution
- Potential for misuse: "Robotripping"
- Generic substitution

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The Psychedelic Psilocybin

- Want to go a trip?
- All psychedelics render an altered state of consciousness in users, and there is evidence that the brain becomes more pliable or flexible post psychedelic use
- Psychedelics are challenging the scientific gold standard
- The most salient clinical term for this is *neuroplasticity* – whereby individual cells can sprout new connections and reorganize in response to different types of experiences.
- In other words, this is a neural response to learning, which psychedelics can enhance. Neuroplasticity then, means that our brains and minds are cast into a state whereby they are more readily influenced.
- In the best-case scenario, psychedelics can potentially be terrific for accelerating the treatment of depression – which we desperately need
- Side effects: altered sense of consciousness, anxiety, tachycardia, sensory manifestations, seeing bright colors

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Exxua (gepirone ER)

- Powerful serotonin 5-HT1A partial agonist (similar to Buspar)
- Rejected by the FDA in 2002, 2004, 2012
- Gained FDA approval after 25 years of rejections as 13 clinical trials for depression were negative
- Its efficacy is comparable to other lower performing antidepressants
- Another "me-too" poised to go down the road of serotonin failure
- Improved sexual function in both men and women with depression and a lack of weight gain
- **Significant cardiac risks associate with QT wave prolongation, requiring an ECG before and during treatment which will likely deter prescribers**
- Also, in the $1,000 price range per month
- This is a loser – if I ever saw one!!

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Side Effects

SSRIs and SNRIs

- Increased anxiety or an "activated" feeling
- Sedation
- Insomnia
- Weight gain (Avg: 4 pounds over six months)

Wellbutrin

- Prominent for anxiety and insomnia
- Little, if any weight gain
- No sexual side effects

Remeron

- Weight gain can be a monster

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Other Often Prominent Side Effects of SSRIs and SNRIs

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Emotional Blunting

- Flattening of feelings, or "flat effect" is a potentially serious side effect of SSRIs and SNRIs
- Approximately half of SSRI and SNRI users report some degree of blunted emotions
- For people with depression, some emotional blunting can be a blessing, in that the medications remove some of the emotional pain associated with depression; however, the drugs also erase some of the enjoyment of feeling less depressed
- As a result of this blunting, things, issues, etc., that once provoked strong emotional responses now leave the individual unaffected or even apathetic
- "Reinforcement learning"
- How to best manage: Dose reduction; switching; taking the medication every 2nd or 3rd day if possible;
- NEVER abruptly stop

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Managing Sexual Dysfunction

- Consider medical possibilities first. Also rule out hormonal issues in both men and women
- Dosage reduction.
- Take antidepressant after sexual activity when blood levels are at their lowest
- Periodic respite from antidepressants
- Switch
- Augmentation

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Managing Antidepressant Withdrawal

1. **Think it through**. Are you clear about what you want the drug to do and for how long? Are your expectations regarding improvement realistic? You may not have to start them in the first place
2. **Put yourself in competent hands**. Seek the services of psychiatry – they do this all the time
3. **Tapering**. Tapering is generally not difficult to manage. It begins with tapering the dose of the existing AD, then if withdrawal symptoms emerge, switching to Prozac can ease the process because of its long half-life. Known as "micro-tapering." The toughest: Paxil, Effexor and Cymbalta (all have short half-lives)
4. **Go slow**. What's the rush? You've been on the drug for 10 years
5. **Think it through, Act II**. What about relapse to depression? If stopping is plan A and it doesn't work, is there a plan B? If not, there really wasn't a plan A

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"Cuddling" is an Antidepressant!

- Cuddling is an antidepressant especially for those with physical abandonment childhood wounds
- Cuddling releases oxytocin the "love" hormone, which improves mood and reduces stress
- Cuddling and other affections such as physical touch, (not exclusively sex) are also super antioxidant boosters – promoting emotional regulation and lowering stress hormones
- No partner? Give it a try with a pet

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Other Antidepressants

- Any form of regular exercise
- Talking regularly with supportive friends
- Resolving complex trauma
- A stroll through a botanical garden; a walk on a beach
- Avoiding aloneness
- Not fixing everyone else's issues
- Regular participation in a book club, camera club, any club
- Boosting self-esteem
- Laughing at oneself
- Avoiding "doomscrolling"
- Prayer regular meditation, self care
- Daily acts of kindness and generosity
- Faith

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Repetitive Transcranial Magnetic Stimulation (rTMS)

- Electrical activity in the brain is influenced by a pulsed magnetic field passed through a coil of wire encased in plastic and held close to the head
- The magnetic field painlessly penetrates the scalp and skull – focusing on specific areas of the brain associated with mood disorders
- rTMS likely stimulates underactive neurons and restores them to normal functioning
- A full course of treatment runs five days a week, 20-40 minutes per day for 6 weeks.
- Since FDA approved, it is covered by most insurance

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One Of The Best-Known Psychiatrists Of The 20th Century

Charlie Brown asks Lucy, "what can you

do when you feel lonely and depressed and don't fit in?" Lucy says, "see how big this

world is and how much room there is for everyone?" "You were born to live in this world, right?"

Charlie, "right."

Lucy, "well live in it then!" "Five cents, please"

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Resources

Dr. Nicole LePera on X: "Depression is misunderstood as sadness. Most people who are chronically depressed aren't sad at all. They feel nothing. Their bodies are stuck in a freeze protective state. This is why we need to understand depression as a response, rather than a disease." / X

Dr. Nicole LePera on X: "Unresolved complex trauma, economic stress, toxins in the environment, lack of connection to each other and nature." / X

Dr. Nicole LePera on X: "Cuddling is an antidepressant." / X

Dr. Nicole LePera on X: "Commercials for depression in the 90s named the cause as low levels of serotonin. With no mention of toxic marriages, unhealthy workplaces, financial stress, or unresolved trauma. Depression is a response. A natural response to unnatural environments." / X

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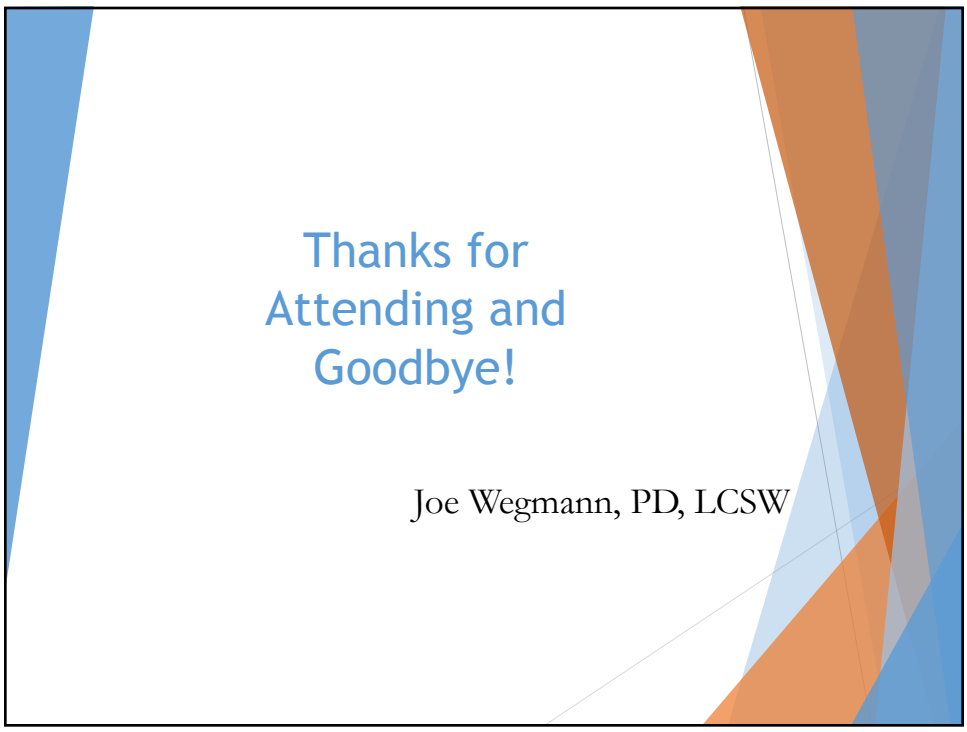

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