EXPERIENCE the Nineteenth

Innovations in Managing Depression

Monday, October 25, 2021

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Recent Innovations for Treatment of Depression

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Nineteenth Century Charitable Association
October 25, 2021

Global Burden of Mental Health Disorders

Rank	Cause	DALYs* (millions)
1	**Unipolar depressive disorders**	**65.5**
2	Alcohol-use disorders	23.7
3	Schizophrenia	16.8
4	Bipolar affective disorder	14.4
5	Alzheimer's and other dementias	11.2
6	Drug-use disorders	8.4
7	Epilepsy	7.9
8	**Migraine**	**7.8**
9	**Panic disorder**	**7.0**
10	**Obsessive-compulsive disorder**	**5.1**
11	**Insomnia (primary)**	**3.6**
12	**Posttraumatic stress disorder**	**3.5**
13	Parkinson's disease	1.7
14	Multiple sclerosis	1.5

*Disability-adjusted life years

Collins et al. *Nature*, 2011

Clinical Challenges of Depression

- Clinical depression common but often misdiagnosed

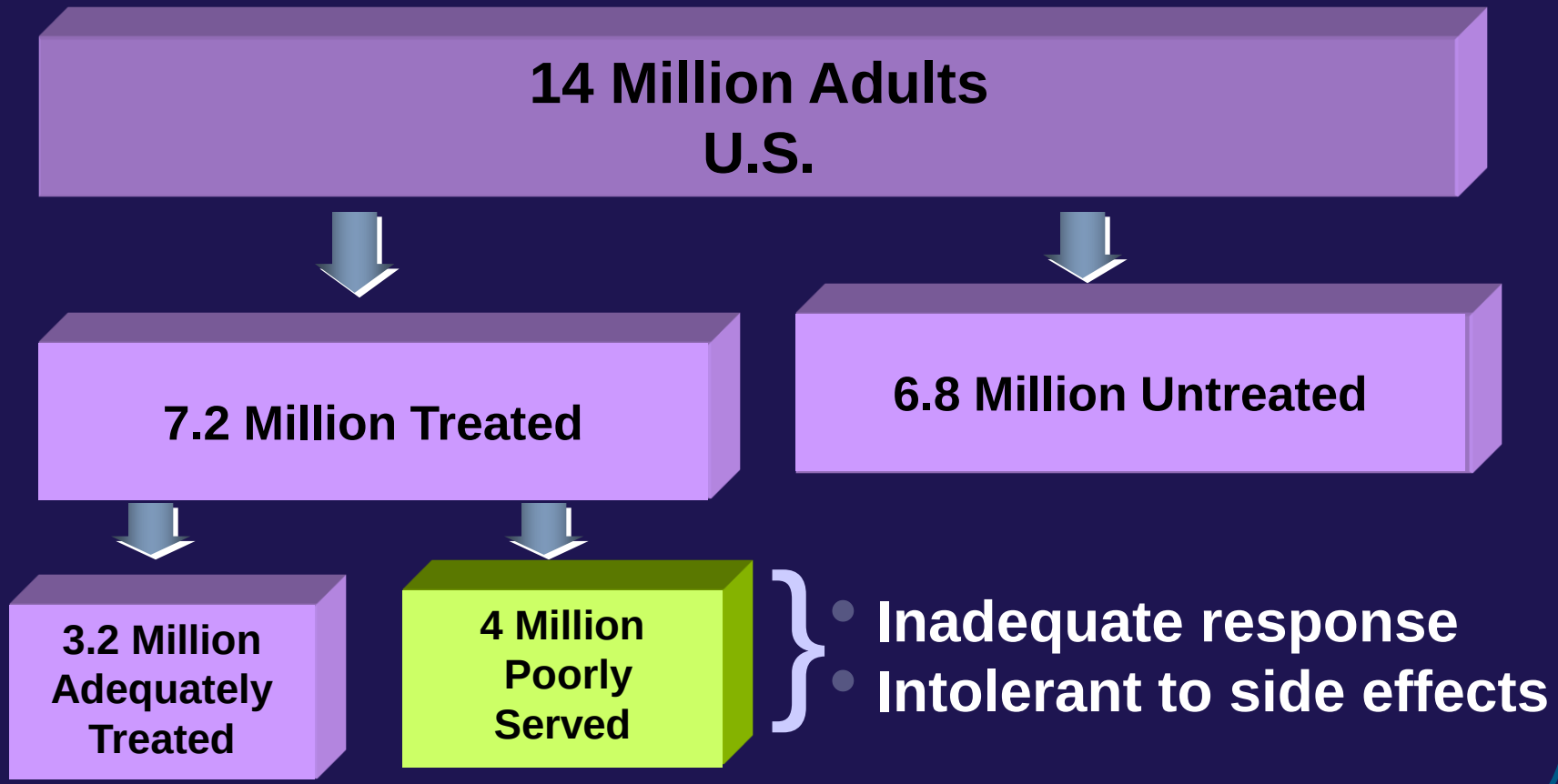
- ~ 50% of suicides are associated with depression
- Comorbid anxiety frequent and increases suicide risk

- Bidirectionally, depression and medical conditions (e.g., ACS; diabetes; stroke; cancer) adversely impact each other

- While majority of depressions respond to medications, psychotherapy or both, many patients do not receive an adequate trial

Pan et al *JAMA,* 2011

Major Depression: A Significant Unmet Need



Kessler et al *JAMA*, 2003

Symptoms of Depression

- **Mood changes**
  - Sad, empty or irritable mood
  - Diminished interest or pleasure (anhedonia)
- **Somatic changes**
  - Weight or appetite
  - Sleep disturbance
  - Fatigue or loss of energy
- **Cognitive changes**
  - Worthlessness/guilt/psychosis
  - Diminished attention, concentration or indecisiveness
  - Hopelessness; ”nothing to live for”
  - Suicidal ideation/intent/behavior

McIntyre RS et al *J Clin Psychiatry*, 2017

Suicide: Epidemiology

- In 2019, 47,500 Americans died by suicide

  - Tenth leading cause of death for all ages

  - Second leading cause for ages 10-34

  - 70% visit a physician within two months preceding their death

Therapeutic Options

Pharmacotherapy

- Antidepressants
- Antianxiety agents
- Mood stabilizers
- Antipsychotics

- Glutamatergic agents
- GABAergic agents

- Psychedelics

Psychotherapy

- Psychoeducation
- Cognitive behavioral therapy
- Interpersonal therapy
- Family focused

Neuromodulation

- Electroconvulsive therapy
- Transcranial magnetic stimulation
- Chronotherapy

Antidepressants I

Class	Generic Name	Trade Name	Daily Dose (mg/day)
Serotonin Reuptake	Citalopram	Celexa	20-40
Inhibitors (SSRIs)	Escitalopram	Lexapro	10-20
	Fluoxetine	Prozac	10-60
	Fluvoxamine*	Luvox	100-300
	Paroxetine	Paxil	10-50
	Sertraline	Zoloft	50-200
Serotonin Modulators	Vilazodone	Viibryd	10-40
	Vortioxetine	Trintellix	10-20
Selective Norepinephrine	Atomoxetine*	Strattera	60-120
Reuptake Inhibitors			
Serotonin/ Norepinephrine	Duloxetine	Cymbalta	30-60
Reuptake Inhibitors (DSNRIs)	Venlafaxine	Effexor	75-375
	Desvenlafaxine ER	Pristiq	50-100
	Levomilnacipran	Fetzima	40-100
Aminoketones	Bupropion	Wellbutrin	150-450
Triazolopyridines	Nefazodone	Serzone**	100-600
	Trazodone	Desyrel	150-600

*Not approved by FDA for depression; **No longer available except in generic formulation

Janicak PG, Marder S, Pavuluri M. *Principles and Practice of Psychopharmacotherapy*. 5th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2011.

Antidepressants II

Class	Generic Name	Trade Name	Daily Dose (mg/day)
Tetracyclics	Amoxapine	Ascendin	200-600
	Maprotiline	Ludiomil	75-225
	Mirtazapine	Remeron	15-45
Tricyclics (TCAs)	Amitriptyline	Elavil	75-300
	Clomipramine	Anafranil	100-250
	Desipramine	Norpramine	75-300
	Doxepin	Sinequan	75-300
	Imipramine	Tofranil	75-300
	Nortriptyline	Pamelor	75-300
	Protriptyline	Vivactil	20-60
	Trimipramine	Surmontil	75-300
Monoamine Oxidase Inhibitors (MAOIs)	Isocarboxazid	Marplan	40-60
	Phenelzine	Nardil	30-90
	Selegiline***	Emsam	6-12
	Tranylcypromine	Parnate	30-60

***Transdermal system approved for depression

Janicak PG, Marder S, Pavuluri M. *Principles and Practice of Psychopharmacotherapy*. 5th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2011.

Cognitive Behavioral Therapy

- CBT is a process that uses incremental steps toward a behavioral change:
  - Goal-oriented and problem-focused therapy
  - How we think (cognition), how we feel (emotion) and how we act (behavior) are linked and impact each other
  - Promote self-awareness and emotional intelligence
  - Helps recognize and stop negative cycles that worsen symptoms

Treatment-Resistant Depression

- Failure to respond to an adequate, continuous dose of two different antidepressants from the same or different classes for at least 6–8 weeks
- ~ 30% of patients diagnosed with MDD
- Factors accounting for lack of adequate response
  - Inaccurate diagnosis and/or assessment of response
  - Failure to improve functionality
  - Psychosocial factors
  - Comorbid SUD (eg., alcohol)

Glutamatergic Strategy: Ketamine

- Anesthetic and analgesic which acts at the glutamate NMDA receptor
- Single subanesthetic dose can lead to rapid antidepressant and anti-suicidal effects
- Unipolar and bipolar depression
- Repeated doses may cause more sustained benefit

Anand A, Matthews SJ *Psychopharm Rev,* 2011

Glutamatergic Strategy: Esketamine

- S (+) enantiomer of ketamine

- 5, phase III trials: 3 short-term; one maintenance of effect; one assessing long-term safety

- Nasal administration (56 or 84 mg) produced a rapid reduction in symptoms when used to augment an oral antidepressant
- Schedule: twice a week for first month; once a week for second month; then, once every one to two weeks.

- Most common AEs were sedation, dissociation and increased BP (typically within 2 hours of dosing; requires REMS protocol)

Janssen *FDA NDA,* 2018

GABAergic Strategies: Neurosteroids I

- Postpartum depression (PPD)
- Brexanolone is an IV formulation of the neuroactive steroid hormone, allopregnanolone (metabolite of progesterone), acts as a $GABA_A$ receptor–positive allosteric modulator
- 2 large, phase III RCTs (n= 246) found that a sing dose produced rapid, sustained (up to 30 days) improvement in women with PPD
- AEs include excessive sedation and possible loss of consciousness (4% vs 0% with placebo) requiring a REMS

Meltzer-Brody S et al. *Lancet*, 2018

GABAergic Strategies: Neurosteroids II

JAMA Psychiatry

RCT: Effect of Zuranolone vs Placebo in Postpartum Depression: A Randomized Clinical Trial

POPULATION

150 Women

Women ages 18-45 y with postpartum depression and Hamilton Rating Scale for Depression (HAMD-17) score ≥26

Mean (SD) age, 28.3 (5.4) y

INTERVENTION

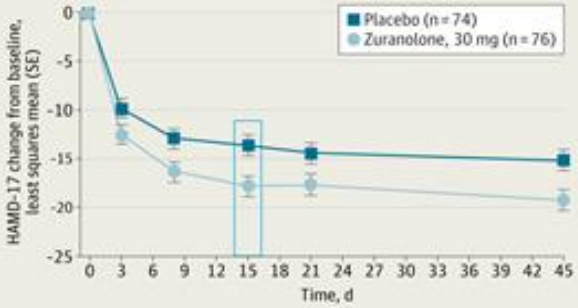
153 Individuals randomized

76 Zuranolone
Oral zuranolone, 30 mg, every evening with food for 14 d

74 Placebo
Oral placebo capsule every evening with food for 14 d

FINDINGS

Individuals with postpartum depression who received zuranolone for 2 wk displayed significantly greater reductions in depressive symptoms compared with placebo at day 15



Difference in change in depressive symptoms at 15 wk, zuranolone vs placebo:
−4.2 (95% CI, −6.9 to −1.5); *P* = .003

SETTINGS / LOCATIONS

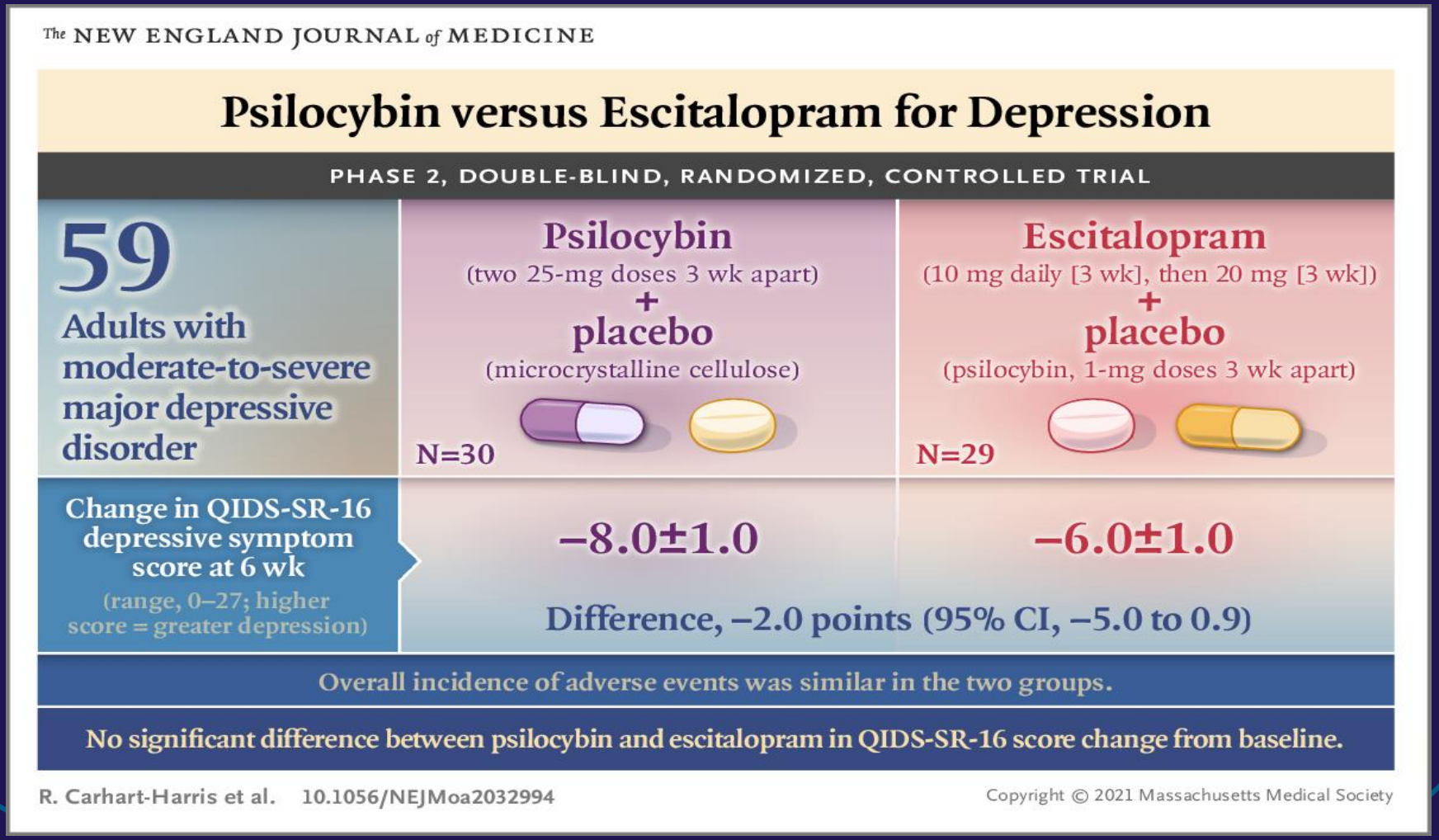
27 Clinical sites in the US

PRIMARY OUTCOME

Change from baseline in depressive symptoms at day 15, as measured by HAMD-17 score (range, 0-52, with higher scores indicating more severe depression)

Deligiannidis KM, Meltzer-Brody S, Gunduz-Bruce H, et al. Effect of zuranolone vs placebo in postpartum depression: a randomized clinical trial. *JAMA Psychiatry*. Published online June 30, 2021. doi:10.1001/jamapsychiatry.2021.1559

Psilocybin versus Escitalopram



Neuromodulation Techniques

NON-INVASIVE

SEIZURE

- Electroconvulsive therapy (ECT)*
- Magnetic seizure therapy (MST)
- Focal electrically administered stimulation (FEAST)

NO SEIZURE

- Transcranial magnetic stimulation (TMS)*
- Transcranial direct current stimulation (tDCS)
- Transcutaneous auricular VNS (tVNS)
- Transcranial focused/unfocussed ultrasound

- Deep brain stimulation (DBS)
- Vagus nerve stimulation (VNS)*
- Epidural cortical stimulation (EpCS)

* FDA-cleared

INVASIVE

ECT: Advantages

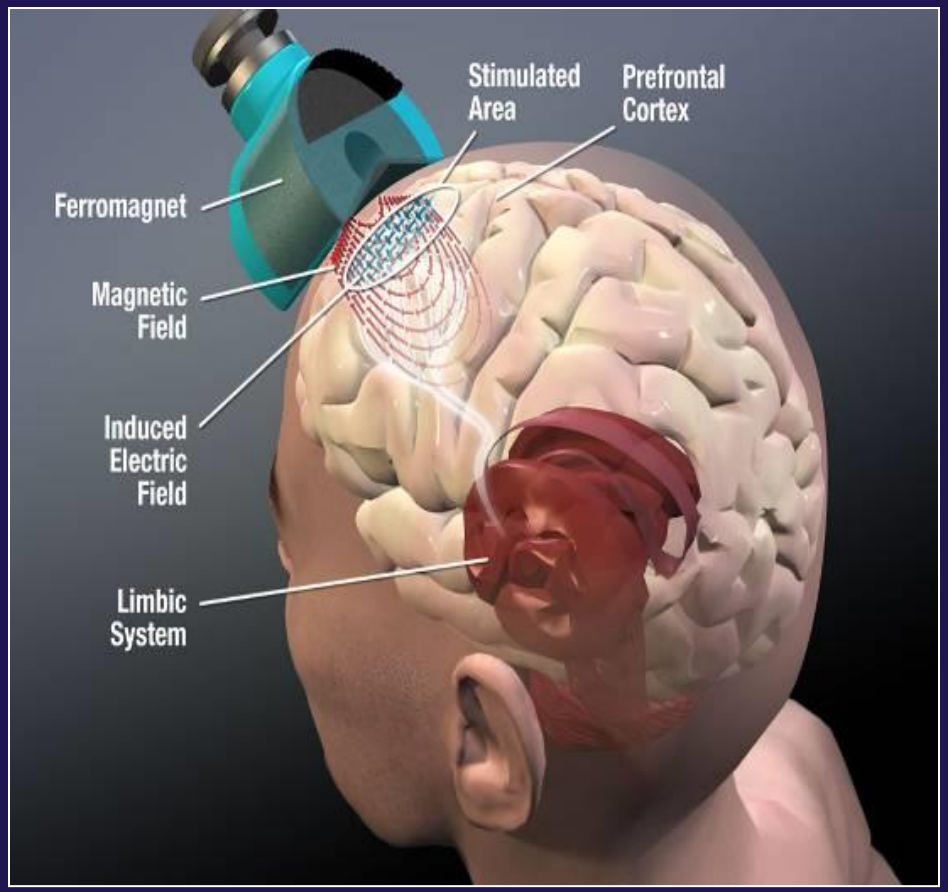
- 80 years of clinical and research experience
- Often rapidly effective for more severe episodes of depression (psychosis, catatonia, suicidality *)
- Effective for various disorders (unipolar and bipolar depression; mania; schizophrenia)
- Minimal systemic effects

ECT: Disadvantages

- Access
- Patient acceptance/stigma
- Optimal administration
- Cost
- Relapse rates
- Adverse effects (eg., cognitive)

*Gaynes BN. *JAMA Netw Open.* 2021

Transcranial Magnetic Stimulation



- Pulsed magnetic fields of ~1.5 Tesla in strength
- Magnetic fields pass unimpeded approximately 2–3 cm into cortex
- Induces a focal electrical current in cortical tissue
- Produces local and distal functional changes in targeted neural circuitry

TMS: Advantages

- No seizure necessary
  - No anesthesia
  - Pro-cognitive (?)
    Working memory/attention
- No drug interactions
- Minimal systemic effects
- Subjects remain independent
- Patient preference

TMS: Disadvantages

- Limited clinical experience
- Time intensive
- Relatively slow onset of efficacy
- Application site pain/discomfort
- Potential for seizure
- Cost

Magnezi R et al *Patient Prefer/Adherence, 2016*
Begemann MJ et al *Psychological Med,* 2020

Chronotherapy

- Bright light therapy (eg., SAD; BPD)
- Sleep deprivation
- Sleep phase advance/delay

Srinivasan et al *Exp Opin Investigation Drugs,* 2011; Boland et al *J Clin Psychiatry*, 2017
Martinez K et al *J Clin Psychiatry,* 2012