Psychiatric Treatment Options

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Brian.Miller@sharp.com Primary Care & Behavioral Health Integration Summit Nov 7, 2022 "I am now the most miserable man living. If what I feel were equally distributed to the whole human family, there would not be one cheerful face on the earth. Whether I shall ever be better I can not tell; I awfully forebode I shall not. To remain as I am is impossible; I must die or be better, it appears to me."

Abraham Lincoln in a letter to John T. Stuart, January 23, 1841.



This image is of 28-year-old identical twins, one with schizophrenia and the other well. It therefore clearly illustrates two points: (1) schizophrenia is a brain disease with measurable structural and functional abnormalities in the brain; and (2) it is not a purely genetic disease, and other biological factors play a role in its etiology.

SCHIZOPHRENIA IN IDENTICAL TWINS



Photo courtesy of Drs. E. Fuller Torrey and Daniel Weinberger.

MRI scans of 28-year-old male identical twins showing the enlarged brain ventricles in the twin with schizophrenia (right) compared to his well brother (left).

MRI Scan Showing Brain Tissue Loss in Schizophrenia



Healthy Subject

Schizophrenia Patient

http://www.schizophrenia.com/disease.htm

Dendritic Spine Reduction in Schizophrenia

Dendritic Spines: Area 46, Layer Non-Schizophrenic Individual



Schizophrenic Individual #1



Schizophrenic Individual #2



Glantz LA, et al. Arch Gen Psychiat 2000;57:65-73.

family studies



Antidepressants

- Response rate of 50% for first agent
- Up to 80% with additional trial and combination therapy
- Lay press popularized recent pooled data showing antidepressant response rate just slightly superior to placebo, but when controlled for mild depression response rate significantly increases



Antidepressants: Are They Effective or Just a Placebo? June 3, 2010

NEWSWEEK

The Depressing News About Antidepressants. Jan 28, 2010

Studies suggest that the popular drugs are no more effective than a placebo. In fact, they may be worse. Antidepressant Drug Effects and Depression Severity

A Patient-Level Meta-analysis

Randomized placebo-controlled trials of antidepressants between 1980-2009
Total of 6 trials
718 adult patients

JAMA 2010;303(16):1596

CONCLUSIONS:

The magnitude of benefit of antidepressant medication compared with placebo increases with severity of depression symptoms and <u>may</u> <u>be minimal or nonexistent, on average, in</u> <u>patients with mild or moderate symptoms.</u>

CONCLUSIONS:

For patients with <u>very severe depression</u>, <u>the benefit of medications over placebo is</u> <u>substantial.</u>

•Placebo ≠ No Treatment

Study trial design
treatment as usual
waitlist control
placebo controlled – regular clinical contact, rating scales, labs, hospitalization

Placebo Response

UCLA

- •89 patients with MDD
- •8 weeks of placebo controlled treatment
- •EEG used to study prefrontal cortical activity

•RESULTS:

- •Active treatment with antidepressant was associated with reduced brain activity in certain areas
- •Placebo was associated with increased brain activity in the same are

European Neuropsychopharmacology. March 23, 2012. online

Placebo Response

RESULTS: continued

If never treated with antidepressant

- Active treatment with antidepressant associated with reduced brain activity
- Placebo associated with increased brain activity
- Prior treatment with antidepressant
 - Active treatment with antidepressant associated with reduced brain activity
 - Placebo also associated with reduced brain activity

European Neuropsychopharmacology. March 23, 2012. online

Other Treatment Options

Ketamine

- FDA-approved in 1970 as an anesthetic
- Schedule III (Vicodin, anabolic steroids)
- Accumulating evidence since first being reported in 2000 to have a rapid antidepressant and antisuicidal effect
- glutamate N-methyl-D-aspartate (NMDA) receptor antagonist
- Novel mechanism targeting mood and psychotic disorders

Ketamine

- Randomized, double-blind. N = 73
- single intravenous infusion of ketamine or midazolam
- Response based on MADRS
 ketamine = 64%
 midazolam = 28%

James W. Murrough, et al. Am J Psychiatry 2013; 170:1134–1142

Similarly to ketamine, esketamine appears to be a rapid-acting antidepressant Available as a nasal spray 2013- received "breakthrough designation" from the FDA for treatment-resistant depression 2016- received "breakthrough designation" for major depressive disorder (MDD) with accompanying suicidal ideation

2019- approved for use with another antidepressant for the treatment of depression
Side effects

- dizziness, blurred vision, headache, nausea, vomiting, dry mouth
- poor coordination, poor concentration, restlessness, dissociative symptoms
- hypertension, tachycardia

Can only be given under medical supervion



- REMS- risk evaluation mitigation strategies
 Only available as a self-administered medication delivered at a registered Spravato treatment center
- Delivered directly to the treatment center
 Dispensing pharmacy, prescriber, patient all need to be registered and acknowledge requirements

Typical visit

- Arrival by usual means
- Blood Pressure checked before, during, and after treatment
- Released from treatment center after a minimum of two hours
- Must not drive for the remainder of the day
- Public transportation or ride share ok

Typical visit Reclining chair Dim lights Alone or with additional support Music or no music Set the tone ■ Relax and "lean in"



"Well, I do have this recurring dream that one day I might see some results."



Light Therapy

Procedure

- Sit in front of box with eyes open
- Do not look directly into light
- 2-3 feet max distance
- 30 minutes in the morning typical schedule

Light Therapy

Brightness Values: Standard Light Box 10,000 lux at 30 inches no sun tan, no UV exposure Comparisons: Street light 10-20 Lux Normal living room lighting 100 Lux Office fluorescent light 300-500 Lux Daylight, cloudy sky 5000 Lux Daylight, clear sky 10,000 Lux

Rapid Response

- 80 yo woman with chronic depression and SI
- In lieu of sleeping, she rode her bicycle throughout the night
- The next morning;

"was talking and moving around as if she were actually another person. She told me that at about two or three in the morning, she felt like a black cloud had been lifted from her shoulders."

Anna Wirz-Justice, MD

Sleep Deprivation

Total

- Keep awake all night
- Perform every other night

Partial

- Allowed to sleep 4 hours
- 12:00 to 04:00

Up to 60% response in Depression

- Improvement disappears after normal night's sleep
- Can be used to convince patient improvement is possible

Gorgulu. Rapid antidepressant effects of sleep deprivation. Brain Res Bull. Sept 2009; 80 (3): 158-162

Wirz-Justice. Biological Psychiatry. 15 August 1999; 46 (4): 445-453

Combining Sleep Deprivation, Light Therapy and Lithium

- 143 consecutively admitted pts with a MDE
- Sleep deprived every other day for one week
 - Awake from 07:00 until 19:00 every other day
 - Allowed to sleep 19:00-08:00 every other day
- Light Therapy
 - 10,000 lux everyday at 03:00 or between 08:00-09:00
- Lithium was continued in 49 pts, and added in remainderRESULTS:
 - 70% achieved a 50% reduction in HDRS within one week
 - 55% of responders maintained improvement at one month

Benedetti F, et al. Rapid Treatment Response of Suicidal Sxs to Li, Sleep Deprivation and Light Therapy in Drug-Resistant Bipolar Depression. J Clin Psych 2014;75(2):133-140

Exercise and Depression

- Aerobic better than anaerobic
- Can approach response rate seen with antidepressants in mild or moderate depression
- Additional benefits besides mood (cardiovascular)
- Releases endorphins (? Stimulates NE, 5-HT)
- 30 minutes three times a week at least, with dose response seen with longer duration or increased frequency
- 3 days/week = 30% reduction in HRSD-17
- 5 days/week = 50% reduction in HRSD-17

Dunn, AL, et al. Exercise treatment for depression: efficacy and dose response. Am J Prev Med 2005 Jan;28(1):1-8



Vagal Nerve Stimulation (VNS)

- Jack Zabara, while attending Lamaze classes with his wife, theorized that deep, regulated breathing lead to relaxation and pain control via the vagus nerve
- Demonstrated control of seizures by electrically stimulating the vagus nerve
- 1997 FDA approval for epilepsy
- 2005 FDA approval for treatment refractory depression
- May take several months for response
 - Pivotal study showed no benefit in first three months and 20-30% response after one year



DBS

FDA Appoved Parkinson's Disease (1997, 2002) Tremor (1997) Approved as a Humanitarian Device Exemption (intended for small populations/ rare disorders) Dystonia (2003) ■ OCD (2009) Under Investigation Depression, Schizophrenia, Dementia Chronic Pain, HA, Seizures, Tourette's Addiction, Obesity, Eating Disorders



Cranial Electrotherapy Stimulation (CES)

- FDA-approved for anxiety, insomnia, depression
 No large, controlled studies have been done, but was "grandfathered in" when already in use during Medical Device Act in 1979
- Low-amplitude, pulsed, alternating current passed between earlobes
- Battery powered
- Alpha-Stim available in US



Transcranial Direct Current Stimulation (tDCS)

- Passes electricity through the brain using Anode and Cathode leads attached to a battery
- Portable
- Inexpensive
- Easy to administer and use
- Current trials underway for FDA indications





A PET scan measures vital functions such as blood flow, oxygen use and blood sugar (glucose) metabolism.

Source: Mark George, M. D. Biological Psychiatry Branch Division of Intramural Research Programs, NIMH 1993

Transcranial Magnetic Stimulation (TMS)

- 2008- FDA approved for treatment of MDD
- 2018- FDA approved for OCD
- Standard protocol- 30 minutes a day, 5 days a week for 4-6 weeks
- Theta Burst- 3 mins for excitatory, 39 sec for inhibitory
- Side effects include HA, discomfort at treatment site
 - rarely syncope or sz (1/30,000 treatments)
- Other uses
 - Hallucinations and negative symptom's of SCZ
 PTSD, stroke, Parkinson's, migraines, tinnitus

Theta Burst Stimulation

10 bursts of three pulses at 50 Hz on a 5 Hz carrier wave for 2 seconds with an 8 sec intertrain interval

Blumberger DM, Vila-Rodriguez F, Thorpe KE, et al.: Effectiveness of theta burst versus high-frequency repetitive transcranial magnetic stimulation in patients with depression (THREE-D): a randomised noninferiority trial. Lancet 2018; 391:1683–1692

How it works

NeuroStar stimulates neurons in the prefrontal cortex to restore normal function in these local areas



Neurons in the prefrontal cortex communicate to deeper brain neurons



Stimulation of deeper brain neurons causes a secondary effect on remaining portions of the brain involved in mood

Number of TMS Publications



 Previously referred to as Stanford accelerated intelligent neuromodulation therapy, or SAINT

Accelerated iTBS protocol

- 90% of resting motor threshold
- left dorsolateral prefrontal cortex (DLPFC), localized by MRI
- 1,800 pulses per treatment (9 minutes)
- 50 minutes between treatment
- 10 times per day over the course of 5 days

Open-label treatment associated with a remission rate of ~90% after 5 days of treatment

Williams, Nolan R, et al. High-dose spaced theta-burst TMS as a rapid-acting antidepressant in highly refractory depression. Brain. 2018 Mar 1;141(3)

- Treatment Resistant Depression trial (N=21)
- Response and remission rates of 90% after 5 days
- 69.2% response rate and a 46.2% remission rate 4 weeks after treatment

Cole EJ, Stimpson KH, Bentzley BS, et al.: Stanford accelerated intelligent neuromodulation therapy for treatment-resistant depression. **Am J Psychiatry** 2020

- Double-Blind Placebo controlled trial
- 29 participants received either active (N=14) or sham (N=15) treatment under double-blind conditions
- 79% remission in the active treatment group and a 13% remission rate in the placebo/sham group
- Reduction in MADRS 4 weeks after treatment was 52.5% in the active treatment group and 11.1% in the sham treatment group

Cole EJ, Phillips AL, Bentzley BS, et al.: Stanford neuromodulation therapy (SNT): a double-blind randomized controlled trial. **Am J Psychiatry** 2022; 179:132–141



The Food and Drug Administration (FDA) has granted 510(k) clearance for the SAINTTM Neuromodulation System as delivered by Magnus Medical for the treatment of major depressive disorder (MDD) in adults who have failed to achieve satisfactory improvement from prior antidepressant medications in the current episode.



Electroconvulsive Therapy (ECT) aka "Shock" Treatments

- "Shock" was thought to be an essential component for improvement
- Induced with insulin, anesthesia, blood letting, camphor, electricity, magnets
- Determined that seizure was the essential component for improvement
- Method to initiate seizure not important for recovery
- Response rates approaching 90% for Depression and Catatonia
- Better effect against psychosis when given earlier in illness
- Requires general anesthesia
- Side effects include HA, short-term and rarely long-term memory impairment

Electroconvulsive Therapy (ECT)

- 1934 Hungary: Ladislas Meduna performs convulsive therapy using IM camphor to induce seizures. Later used metrazol, pentylenetetrazol
- 1938 Italy: First Electroconvulsive Therapy performed by Ugo Cerletti and his assistant Lucio Bini
- 1951: Muscle paralytic succinylcholine becomes available, leading to "modified ECT"
- Actions:
 - results in an overall decrease of brain electrical activity
 - increases Brain-Derived Neurotrophic Factor (BDNF)
 - suppresses seizures

ECT is a Small Piece of the Pie

____ ECT USA/Year 100,000

Depression USA/Year 21,000,000

Olfson et al., Am J Psychiatry, 1998

Proportions of Patients Remitting by ECT Number (n=341)



Husain MM, et al. J Clin Psychiatry 2004;65:485-491.

Relapse Status at 6 Months

Non-relapse Relapse Early Exit



Kellner CH, et al. Arch Gen Psychiatry, Dec 2006; 63: 1337 - 1344

Psychotherapy for Depression

Cognitive-behavioral therapy
Dialectical-behavioral therapy
Acceptance and commitment therapy
Interpersonal psychotherapy
Psychodynamic psychotherapy
Supportive psychotherapy

When to Choose Psychotherapy

- Motivated for change
- Willing to honestly examine oneself
- Cognitive ability to preservedNot too depressed
- Willing to make time commitment
- Mild to moderate symptoms
- Presence of complicating factors

"Remember in the depth and even the agony of despondency, that very shortly you are to feel well again."

Abraham Lincoln in a letter to Joshua Speed, February 13, 1842.



Questions?